SYSTEMIC LUPUS ERYTHEMATOSUS: AUTOIMMUNE MECHANISMS AND ORGAN DAMAGE

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Abstract: Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by loss of self-tolerance, production of pathogenic autoantibodies, and immune complex-mediated inflammation that can affect the skin, joints, kidneys, blood cells, nervous system, and serosal surfaces. This narrative review synthesizes current evidence on the immunopathogenesis and organ-specific manifestations of SLE, drawing on the 2019 EULAR/American College of Rheumatology (ACR) classification criteria, the 2023 EULAR management recommendations, and recent trial data on biologic and targeted therapies. Disease pathogenesis reflects a self-amplifying cycle in which genetic susceptibility and environmental triggers impair clearance of apoptotic debris, promote loss of tolerance in autoreactive B and T lymphocytes, and drive immune complex deposition, complement activation, and a dominant type I interferon signature that sustains tissue inflammation and progressive organ damage. Lupus nephritis and neuropsychiatric involvement remain the principal drivers of morbidity and require prompt, biopsy- or presentation-guided treatment. Management has shifted toward early, individualized combination therapy — hydroxychloroquine as a foundation for nearly all patients, glucocorticoid minimization, and earlier introduction of immunosuppressive or biologic agents such as belimumab, anifrolumab, and voclosporin — aimed at achieving sustained remission or low disease activity while limiting cumulative organ damage. A mechanism-based understanding of SLE, combined with structured classification and severity assessment, is central to improving long-term outcomes, including within the healthcare system of Uzbekistan.

Keywords: Systemic lupus erythematosus, autoimmunity, autoantibodies, lupus nephritis, type I interferon, complement, organ damage, belimumab, anifrolumab.

Methods

This work was prepared as a narrative literature review. A literature search was conducted in August 2026 using PubMed, the EULAR and ACR publication databases, and the websites of major rheumatology societies, with the search terms "systemic lupus erythematosus," "autoimmune mechanisms," "lupus nephritis," "type I interferon," and "organ damage," combined with filters for publication in English between 2016 and 2026. Priority was given to the 2019 EULAR/ACR classification criteria, the 2023 EULAR management recommendations, systematic reviews, and peer-reviewed original research; narrative summaries from established clinical reference sources were included for foundational background. Case reports and articles without accessible full text were excluded. A total of twelve sources meeting these criteria were selected and synthesized for this review.

Introduction

Systemic lupus erythematosus is a chronic autoimmune disease of heterogeneous clinical expression, in which loss of immune tolerance to nuclear self-antigens leads to the production of pathogenic autoantibodies, immune complex formation, and inflammatory damage across multiple organ systems. The disease disproportionately affects women of reproductive age and follows a relapsing-remitting course, with clinical severity ranging from mild mucocutaneous and articular disease to organ- and life-threatening involvement of the kidneys, central nervous system, and hematologic system.

SLE is now understood not as a single pathogenic pathway but as the convergence of genetic susceptibility, hormonal influence, and environmental triggers on a common final pathway of defective clearance of apoptotic material, autoreactive lymphocyte activation, and sustained type I interferon-driven inflammation. This mechanistic understanding has directly informed the expansion of targeted biologic therapies over the past decade, including agents directed against B-cell survival signals and the type I interferon receptor.

The aim of this review is to summarize current evidence on the autoimmune mechanisms, organ-specific manifestations, classification, and stepwise management of systemic lupus erythematosus, with particular emphasis on recently updated international recommendations and their relevance to clinical practice.

Understanding the modern approach to SLE is relevant across several areas of clinical practice, including:

- Rheumatology (diagnosis, classification, disease activity and damage assessment, long-term management)
- Nephrology (recognition and staged treatment of lupus nephritis)

- Neurology and psychiatry (evaluation of neuropsychiatric lupus)
- Dermatology (classification and treatment of cutaneous lupus)
- Hematology (evaluation of autoimmune cytopenias and antiphospholipid syndrome)
- Obstetrics (management of pregnancy in patients with SLE and antiphospholipid antibodies)

Autoimmune Mechanisms

The pathogenesis of SLE begins with a genetic and environmental predisposition — polygenic risk involving interferon-pathway and immune-regulatory genes, combined with triggers such as ultraviolet light exposure, Epstein-Barr virus infection, and hormonal factors — that impairs the physiological clearance of apoptotic cell debris. Persistence of nuclear antigens (double-stranded DNA, ribonucleoproteins) in this setting provides a sustained source of self-antigen available to the immune system.

This defective clearance permits the breakdown of self-tolerance in autoreactive B and T lymphocytes, resulting in the production of specific autoantibodies, most notably anti-double-stranded DNA (anti-dsDNA) and anti-Smith (anti-Sm) antibodies, which are highly specific for SLE and correlate with disease activity, particularly renal involvement. Autoantibody-antigen complexes deposit in tissues and activate the complement cascade, consuming C3 and C4 and generating anaphylatoxins and membrane-attack complexes that amplify local tissue injury.

A dominant type I interferon signature, driven in part by plasmacytoid dendritic cells activated through nucleic acid-sensing Toll-like receptors, further amplifies this cycle by upregulating antigen presentation, promoting autoreactive lymphocyte survival, and sustaining a pro-inflammatory state across affected tissues. This self-perpetuating cycle — summarized in Figure 1 — explains both the multisystem nature of SLE and the rationale for therapies directed at B cells, complement, and the interferon pathway.

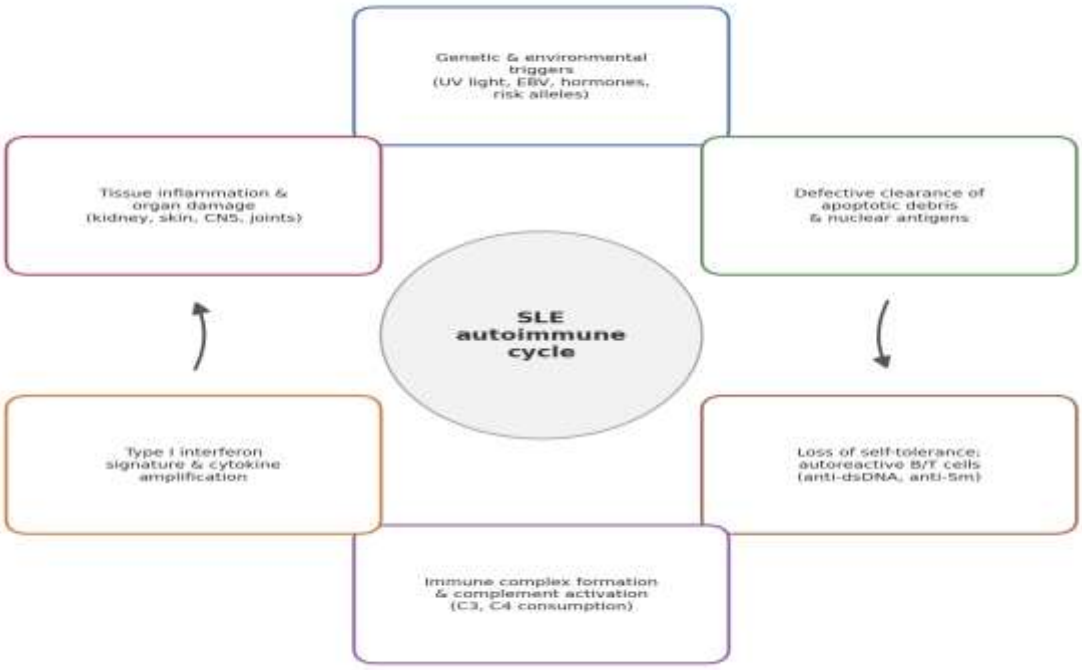

Figure 1. The self-amplifying autoimmune cycle of systemic lupus erythematosus: genetic and environmental triggers, defective apoptotic clearance, loss of self-tolerance, immune complex and complement activation, and type I interferon signaling converge to drive tissue inflammation and organ damage, which in turn releases further autoantigen.

The specific organs affected, and the severity of involvement, reflect where within this cycle disease activity is most concentrated in a given patient: immune complex deposition predominates in lupus nephritis, autoantibody-mediated cytotoxicity predominates in hematologic manifestations, and interferon- and antibody-mediated neuroinflammation contributes to neuropsychiatric disease. Organ damage accumulates both from active inflammation and, over time, from the cumulative toxicity of therapy, particularly prolonged glucocorticoid exposure.

Organ Involvement and Manifestations

SLE can affect virtually any organ system, and the pattern and severity of involvement vary widely between patients and over the course of disease. Renal and neuropsychiatric involvement are associated with the greatest risk of irreversible organ damage and require the most intensive evaluation and treatment. The principal organ systems and representative manifestations are summarized in Table 1.

Table 1. Major Organ Systems Affected by Systemic Lupus Erythematosus

Organ System	Representative Manifestations	Key Immune Mediators
Mucocutaneous	Malar rash, discoid lesions, photosensitivity, oral ulcers, subacute cutaneous lupus	Anti-Ro/SSA, type I interferon, complement
Musculoskeletal	Non-erosive polyarthritis, arthralgia, myalgia	Immune complexes, pro-inflammatory cytokines
Renal (lupus nephritis)	Proteinuria, hematuria, active urinary sediment, ISN/RPS classes I–VI on biopsy	Anti-dsDNA, immune complex deposition, complement (C3, C4) consumption
Hematologic	Autoimmune hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia	Autoantibodies against blood cell antigens
Neuropsychiatric	Seizures, psychosis, cognitive dysfunction, cerebrovascular disease, peripheral neuropathy	Anti-neuronal and antiphospholipid antibodies, cytokine-mediated neuroinflammation
Serosal / cardiopulmonary	Pleuritis, pericarditis, accelerated atherosclerosis, pulmonary hypertension	Immune complex deposition, chronic inflammation
Vascular	Raynaud phenomenon, vasculitis, thrombosis (with antiphospholipid antibodies)	Anticardiolipin, anti-β2-glycoprotein I, lupus anticoagulant

Classification

The 2019 EULAR/ACR classification criteria, jointly developed for research and clinical trial purposes, use a positive antinuclear antibody titer of at least 1:80 on HEp-2 cells as an obligatory entry criterion, after which weighted points are assigned across seven clinical domains (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal,

musculoskeletal, and renal) and three immunologic domains (antiphospholipid antibodies, complement proteins, and SLE-specific antibodies). Within each domain, only the highest-weighted criterion present is counted, and classification as SLE requires at least one clinical criterion together with a cumulative score of ten or more points out of a theoretical maximum of fifty-one. In the original validation cohort, these criteria demonstrated a sensitivity of 96.1% and a specificity of 93.4%, an improvement over both the 1997 American College of Rheumatology criteria and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria. Representative domains and weights are summarized in Table 2.

Table 2. Selected Domains of the 2019 EULAR/ACR Classification Criteria for SLE

Domain	Representative Criterion	Weight (points)
Entry criterion	Antinuclear antibody titer ≥1:80 on HEp-2 cells (required to proceed)	—
Constitutional	Fever	2
Hematologic	Thrombocytopenia	4
Mucocutaneous	Acute cutaneous lupus	6
Serosal	Acute pericarditis	6
Musculoskeletal	Joint involvement	6
Renal	Biopsy-confirmed class III or IV lupus nephritis	10
Immunologic — antibodies	Anti-dsDNA or anti-Sm antibody positivity	6
Immunologic — complement	Low C3 and low C4	4
Classification threshold	**≥1 clinical criterion plus total score**	**≥10**

These criteria are intended primarily to identify homogeneous patient groups for research and clinical trials rather than to replace individualized clinical diagnosis, and biopsy-confirmed lupus nephritis in the presence of antinuclear or anti-dsDNA antibodies is sufficient for classification independent of the additive point total.

Treatment

Management follows an individualized, treat-to-target approach aimed at achieving remission or, when remission is not attainable, the lowest possible level of disease activity, while minimizing glucocorticoid exposure and preventing accrual of irreversible organ damage.

The updated 2023 EULAR recommendations affirm hydroxychloroquine as a foundation of therapy for essentially all patients with SLE, at a target dose of 5 mg/kg real body weight per day, balanced against individual risk of flare and retinal toxicity. Glucocorticoids are used as bridging therapy during periods of active disease and should be minimized to 5 mg per day or less (prednisone equivalent) for maintenance, and withdrawn entirely when possible.

A key shift in the updated recommendations is earlier and less hierarchical use of immunosuppressive and biologic agents: methotrexate, azathioprine, or mycophenolate, and/or biologic therapy with belimumab or anifrolumab, should be considered promptly in patients who do not adequately respond to hydroxychloroquine alone or who cannot reduce glucocorticoids below the recommended maintenance threshold, rather than only after failure of conventional agents. Anifrolumab, a monoclonal antibody targeting the type I interferon receptor subunit 1, directly addresses the interferon-driven component of disease and has become an option particularly for patients with prominent mucocutaneous and musculoskeletal activity.

For lupus nephritis, treatment is guided by biopsy class and combines high-dose glucocorticoids with mycophenolate mofetil or cyclophosphamide as induction therapy; the 2023 recommendations support combination regimens incorporating belimumab or a calcineurin inhibitor such as voclosporin alongside standard induction therapy in appropriate patients, reflecting trial evidence of improved renal response rates. Maintenance therapy typically continues mycophenolate or azathioprine for a prolonged period, with careful monitoring for relapse.

Neuropsychiatric, hematologic, and severe cutaneous manifestations are managed according to the attributable mechanism and severity, ranging from topical or antimalarial therapy for limited cutaneous disease to high-dose glucocorticoids and cyclophosphamide for life-threatening central nervous system involvement. Patients with concurrent antiphospholipid antibodies require individualized assessment for thromboprophylaxis or anticoagulation. Comorbidity management — cardiovascular risk reduction, bone health, infection prevention through appropriate vaccination, and psychosocial support — is recommended as an integral part of long-term care for every patient with SLE.

Conclusion

Systemic lupus erythematosus arises from a self-amplifying autoimmune cycle in which defective clearance of apoptotic debris, loss of tolerance in autoreactive

lymphocytes, immune complex and complement activation, and a dominant type I interferon signature converge to produce multisystem inflammation and progressive organ damage.

Accurate classification using validated, weighted criteria and systematic assessment of organ involvement — particularly renal and neuropsychiatric disease — are essential to guide individualized, treat-to-target management. Contemporary therapy combines hydroxychloroquine, judicious glucocorticoid use, and earlier introduction of immunosuppressive or targeted biologic agents such as belimumab and anifrolumab.

Continued application of mechanism-based classification and guideline-directed, individualized treatment holds the potential to increase rates of sustained remission, reduce cumulative organ damage, and improve long-term outcomes for patients with systemic lupus erythematosus.

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