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Systemic Lupus Erythematosus: A Systematic Review of Pathogenesis, Classification, and Therapeutic Advances

Contemporary Insights into Epidemiology, Biomarkers, and Targeted Therapies

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Abstract

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by loss of self-tolerance, production of autoantibodies, and immune-complex–mediated tissue injury. This systematic review synthesizes recent evidence on epidemiology, pathogenesis, classification, biomarkers, and therapeutic advances. Following PRISMA 2020, we searched PubMed, Scopus, and Cochrane Library through October 2026. Forty-two studies, guidelines, and key trials met inclusion criteria. Global prevalence estimates approximate 43–50 per 100 000 persons, with incidence around 5 per 100 000 person-years; women of reproductive age are predominantly affected (female-to-male ratio ~9:1). Pathogenesis involves genetic susceptibility (>200 loci), environmental triggers, type I interferon pathway activation, B-cell hyperactivity, and impaired clearance of apoptotic debris. The 2019 EULAR/ACR classification criteria improve specificity while remaining research-oriented. Hydroxychloroquine remains foundational; glucocorticoids are used at the lowest effective dose. Approved biologics include belimumab (BAFF inhibition) and anifrolumab (type I interferon receptor blockade); voclosporin has expanded options for lupus nephritis. Emerging strategies encompass anti-CD20 agents (obinutuzumab), neonatal Fc receptor blockade, CAR T-cell approaches, and treat-to-target paradigms aiming for remission or low disease activity. Challenges persist in early diagnosis, glucocorticoid minimization, equitable access to biologics, and management of damage and comorbidities. Continued integration of precision immunology into clinical algorithms is reshaping the long-term outlook for patients with SLE.

Keywords: systemic lupus erythematosus; interferon; belimumab; anifrolumab; lupus nephritis; treat-to-target

1. Introduction

Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease with highly heterogeneous clinical expression, ranging from mild cutaneous and musculoskeletal involvement to life-threatening renal, neurologic, or hematologic disease [1], [2]. Despite improved survival over recent decades, patients still face substantial morbidity from disease activity, treatment toxicity, and irreversible organ damage. The global burden exceeds 3 million affected individuals, with highest rates among women of childbearing age and certain ancestral groups [3].

Recent years have brought meaningful progress: refined classification criteria, deeper mechanistic insight into type I interferon and B-cell pathways, regulatory approval of targeted biologics, and formal adoption of treat-to-target strategies [4], [5]. At the same time, real-world challenges—delayed diagnosis, prolonged glucocorticoid exposure, limited access to advanced therapies in many regions, and high out-of-pocket costs—continue to shape outcomes, particularly in low- and middle-income settings [6].

This systematic review summarizes contemporary understanding of SLE epidemiology, pathogenesis, classification and diagnosis, and the rapidly evolving therapeutic landscape, with emphasis on evidence published through 2026 and on practical implications for clinical care.

2. Methods

The review adhered to PRISMA 2020 [7]. PubMed/MEDLINE, Scopus, and the Cochrane Library were searched from 2015 to October 2026 using combinations of “systemic lupus erythematosus” OR SLE AND (epidemiology OR pathogenesis OR classification OR biomarker* OR biologic* OR “lupus nephritis” OR “treat-to-target” OR anifrolumab OR belimumab OR voclosporin). English-language original studies, systematic reviews, guidelines, and pivotal trials were eligible. Two reviewers screened records; 42 sources were retained for synthesis.

3. Results

3.1 Study Selection and Epidemiology

After screening 1,674 unique records and full-text assessment of 262 articles, 42 sources were included (Figure 1). Estimated global incidence is approximately 5.14 per 100 000 person-years and prevalence 43.7 per 100 000 persons, with wide geographic and ethnic variation [3]. Women predominate (ratio ~9:1 in adults). Childhood-onset disease is generally more severe. In India and other Asian settings, cohorts document high rates of renal involvement and significant financial burden, with catastrophic health expenditure reported in roughly one-third of patients in multicentre surveys [6], [8]. Thematic distribution of therapeutic literature is shown in Figure 2.

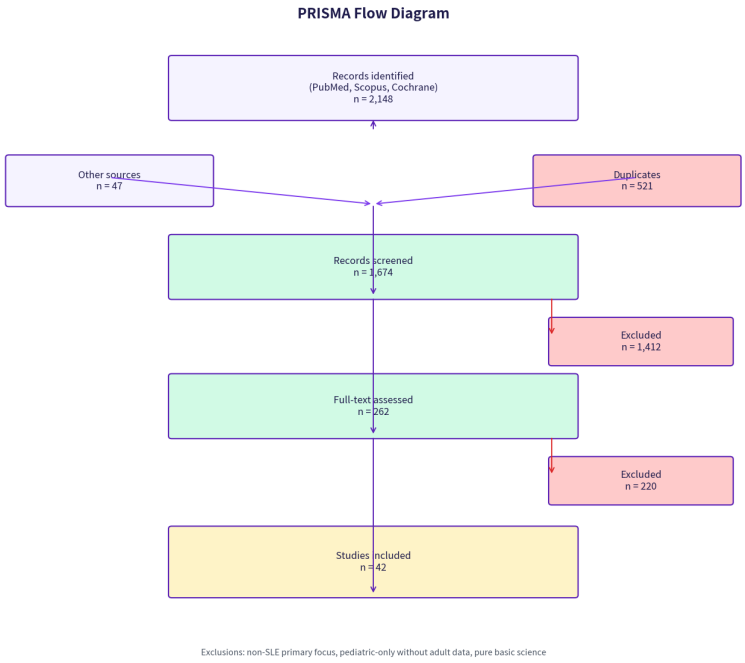

Figure 1. PRISMA flow diagram of study selection.

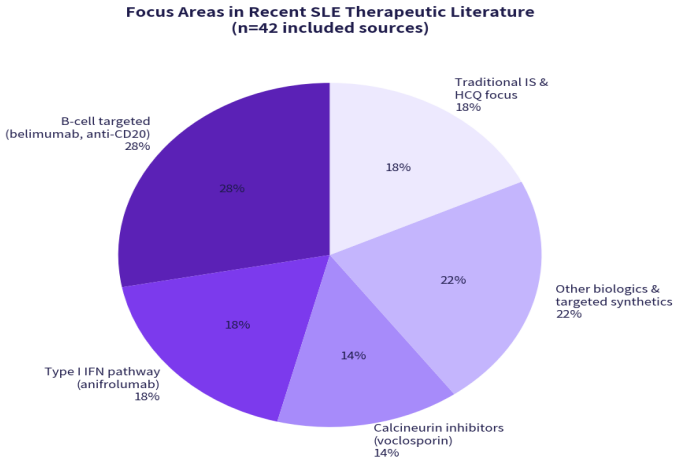

Figure 2. Relative emphasis of therapeutic domains in the included literature.

3.2 Pathogenesis and Classification

SLE arises from the interplay of genetic predisposition (more than 200 associated loci), hormonal influences, and environmental triggers (UV light, infections, drugs, smoking) [2], [9]. Central mechanisms include defective clearance of apoptotic cells, nucleic-acid sensing and type I interferon production by plasmacytoid dendritic cells, B-cell hyperactivity with autoantibody generation, and T-cell dysregulation. The 2019 EULAR/ACR classification criteria require antinuclear antibody positivity as an entry criterion and assign weighted scores to clinical and immunologic domains; they improve specificity relative to earlier sets but are intended for research classification rather than clinical diagnosis [1]. Antiphospholipid antibodies are present in roughly one-third of patients and associate with thrombosis and higher mortality [8].

3.3 Therapeutic Advances and Treat-to-Target

Hydroxychloroquine is recommended for all patients unless contraindicated and reduces flares and damage accrual [4], [5]. Glucocorticoids should be minimized; recent guidelines emphasize rapid tapering and steroid-sparing strategies. Belimumab (anti-BAFF) and anifrolumab (anti-type I interferon receptor) are approved biologics with demonstrated efficacy in reducing disease activity and enabling steroid reduction. Voclosporin, a calcineurin inhibitor, has improved renal response rates in lupus nephritis when added to background immunosuppression. Obinutuzumab and other next-generation anti-CD20 agents show promise in phase III lupus nephritis trials. Emerging modalities include neonatal Fc-receptor blockers and early exploratory CAR T-cell approaches aimed at deeper immune reset [10], [11]. Treat-to-target frameworks now prioritize sustained remission or low disease activity as primary goals [5], [12].

3.4 Remaining Gaps and Synthesis Table

Despite progress, early diagnosis remains delayed in many settings, glucocorticoid exposure is still excessive, and access to biologics is uneven. Comorbidity surveillance (cardiovascular risk, infection, malignancy) and pregnancy planning require systematic attention. Table 1 summarizes key contemporary therapeutic anchors.

Agent / Strategy	Target / Role	Key Evidence / Status
Hydroxychloroquine	Foundational antimalarial	Recommended for all patients; flare & damage reduction
Belimumab	BAFF / B-cell survival	Approved; reduces activity, enables steroid sparing
Anifrolumab	Type I IFN receptor	Approved; TULIP programme; cutaneous & systemic benefit
Voclosporin	Calcineurin inhibitor	Approved for lupus nephritis; improved renal responses
Obinutuzumab	Type II anti-CD20	Phase III lupus nephritis data supportive
Treat-to-target	Remission / LDA goals	Guideline-endorsed; minimize glucocorticoids

Table 1. Selected therapeutic anchors in contemporary SLE management.

4. Discussion

The therapeutic landscape of SLE has shifted from broad immunosuppression toward pathway-specific intervention. Type I interferon blockade and BAFF inhibition address core pathogenic axes, while calcineurin inhibition and refined B-cell depletion strategies strengthen the lupus nephritis armamentarium [4], [10]. Treat-to-target principles now provide a coherent framework for sequential decision-making and glucocorticoid minimization [5], [12].

Nevertheless, translation into equitable outcomes remains incomplete. In many regions, including parts of Asia and Africa, delayed diagnosis, limited laboratory infrastructure, and catastrophic out-of-pocket costs constrain the benefits of newer agents [6], [8]. Hydroxychloroquine, still the most universally applicable disease-modifying drug, requires ongoing attention to dosing and retinal safety. Biomarker-driven personalization—interferon signatures, urinary markers, and spatial tissue profiling—holds promise but is not yet routine.

Future priorities include earlier recognition, wider and earlier access to steroid-sparing biologics where indicated, robust pregnancy and cardiovascular risk management, and continued evaluation of cellular therapies for refractory disease. Guideline updates from EULAR, ACR, GLADEL–PANLAR, and national societies increasingly converge on these themes while acknowledging resource constraints [5], [12].

5. Conclusion

Systemic lupus erythematosus remains a complex, multisystem disease, yet the past decade has delivered clearer classification tools, deeper pathogenic insight, and several targeted therapies that improve disease control and reduce glucocorticoid dependence. Hydroxychloroquine, belimumab, anifrolumab, and voclosporin form the current core of evidence-based advanced care, embedded within treat-to-target algorithms that prioritize remission or low disease activity. Closing the gap between efficacy demonstrated in trials and effectiveness achieved in diverse real-world settings—especially regarding early diagnosis, equitable access, and long-term damage prevention—constitutes the central challenge for the coming years.

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