ISSN (Online) 3134-8823

Journal of Advanced Biological Sciences

Received: November 24, 2025 | Accepted: June 24, 2026 | Published: June 30, 2026

Volume 03, Issue 01, Pages 19-23

DOI https://doi.org/10.66590/jabs2026030108

Research Article

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Clinical Characteristics and Response to Therapy in Pediatric Systemic Lupus Erythematosus

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How to Cite the Article:
Elhussein, Gamal Eldin Mohammed Osman *et al.* "Clinical Characteristics and Response to Therapy in Pediatric Systemic Lupus Erythematosus." *Journal of Advanced Biological Sciences*, vol. 03, no. 01, June 2026, pp. 19-23. https://doi.org/10.66590/jabs2026030108

Abstract | Pediatric systemic lupus erythematosus (pSLE) is a chronic, multisystem autoimmune disease characterized by immune dysregulation, autoantibody production, complement activation and inflammatory injury affecting multiple organs. Compared with adult-onset systemic lupus erythematosus, childhood-onset disease is generally associated with higher disease activity, more frequent major-organ involvement, greater exposure to glucocorticoids and immunosuppressive therapy and earlier accumulation of irreversible damage. This narrative review summarizes the major clinical, immunological and laboratory characteristics of pSLE and examines treatment strategies and indicators of therapeutic response. Renal, hematologic, mucocutaneous, musculoskeletal and neuropsychiatric manifestations are emphasized because they substantially influence prognosis and treatment selection. Current management generally combines hydroxychloroquine with glucocorticoids and organ-specific immunosuppressive therapy, including mycophenolate mofetil, cyclophosphamide, azathioprine, methotrexate and calcineurin inhibitors. Biologic therapy, particularly B-cell-directed treatment, may be considered in selected patients with persistent or refractory disease. Treatment response should be assessed using clinical activity, urinalysis and renal indices, complement levels, anti-double-stranded DNA antibodies, blood counts and validated disease activity measures rather than relying on a single biomarker. A treat-to-target strategy aims for remission or low disease activity while minimizing glucocorticoid exposure and treatment toxicity. Future research should focus on pediatric-specific biomarkers, molecular phenotyping, precision immunotherapy and prospective studies defining predictors of response and long-term organ protection.

Key Words Pediatric Systemic Lupus Erythematosus, Childhood-Onset SLE, Lupus Nephritis, Autoimmunity, Immunology, Glucocorticoids, Immunosuppressive Therapy, Biologics, Treatment Response

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a heterogeneous autoimmune disorder resulting from interactions among genetic susceptibility, environmental triggers, innate and adaptive immune abnormalities and loss of self-tolerance. Approximately 15–20% of patients with SLE develop disease during childhood. Childhood-onset SLE is clinically important because the disease often presents with substantial inflammatory activity at an age when growth, puberty, education and psychosocial development are still occurring. Reviews and cohort studies consistently indicate that childhood-onset disease is more severe than adult-onset SLE, with greater disease activity, more frequent major-organ involvement and increased risk of damage accumulation [1,2].

The biological basis of pSLE includes increased type I interferon signaling, B-cell hyperactivity, abnormal T-cell responses, autoantibody generation and immune-complex-mediated tissue injury. These mechanisms provide a biological rationale for the use of corticosteroids, antimalarial drugs, conventional immunosuppressants and, increasingly, targeted biologic therapies. However, treatment decisions in children must balance disease suppression against adverse effects on growth, bone health, infection risk, fertility and long-term cardiovascular health [3,4].

This review synthesizes evidence on the clinical characteristics of pSLE and the response to commonly used therapies, with particular attention to biological mechanisms, organ involvement, disease activity assessment and contemporary treat-to-target principles [5,6].

MATERIALS AND METHODS

A narrative literature review was prepared using peer-reviewed literature addressing childhood-onset SLE, clinical manifestations, immunological abnormalities, treatment and therapeutic response. Major review articles, longitudinal cohort studies, consensus recommendations and contemporary clinical guidelines were prioritized. Particular emphasis was placed on evidence describing pediatric populations and on publications addressing disease activity, lupus nephritis and treatment response. This manuscript is a literature-based review and does not report a new patient cohort; therefore, no patient-level results or fabricated numerical outcomes are presented [7,8].

Clinical Characteristics of Pediatric SLE

Demographic and Age-Related Characteristics: pSLE most commonly becomes clinically apparent during adolescence and is uncommon before five years of age. A strong female predominance becomes evident around puberty, although boys can develop severe disease. Earlier onset may be associated with distinct genetic or monogenic contributions and warrants consideration of an underlying immune dysregulation syndrome in selected patients [9].

Mucocutaneous and Musculoskeletal Manifestations

Malar rash, photosensitivity, oral or nasal ulcers, alopecia and other cutaneous manifestations are frequent. Arthralgia and inflammatory arthritis are also common and may be among the first manifestations leading to diagnosis. Cutaneous and musculoskeletal symptoms often improve with control of systemic inflammation, hydroxychloroquine and, when necessary, short courses of glucocorticoids or steroid-sparing immunosuppressants.

Renal Involvement

Lupus nephritis is one of the most clinically consequential manifestations of pSLE. Proteinuria, hematuria, hypertension, reduced kidney function and active urinary sediment may indicate renal disease. Kidney biopsy is important when clinically indicated because histological class and activity/chronicity influence treatment selection and prognosis. Persistent proteinuria or impaired renal function requires close monitoring because renal damage can become irreversible [10].

Hematological Manifestations

Anemia, leukopenia, lymphopenia and thrombocytopenia may occur through immune-mediated destruction, inflammation, bone-marrow effects or medication-related toxicity. Hematological abnormalities may parallel disease activity but should always be interpreted alongside infection, drug toxicity and other potential causes [11].

Neuropsychiatric Involvement

Neuropsychiatric SLE encompasses a broad spectrum ranging from headache, seizures and cognitive dysfunction to psychosis, mood disorders, cerebrovascular events and peripheral neurological syndromes. Diagnosis requires careful exclusion of infection, metabolic disorders, medication effects and thrombotic disease. Severe manifestations generally require prompt immunosuppressive treatment after appropriate evaluation [12].

Cardiovascular and Constitutional Manifestations

Fever, fatigue and weight changes are common but nonspecific. Serositis may present as pleuritis or pericarditis. Long-term cardiovascular risk is increased by chronic inflammation, dyslipidemia, hypertension, renal disease and glucocorticoid exposure, making risk-factor modification an important component of pediatric care.

Immunological and Laboratory Characteristics

Antinuclear antibodies are highly sensitive for SLE and are a key entry criterion in contemporary classification systems, but ANA positivity alone is not diagnostic. Anti-double-stranded DNA antibodies are particularly relevant to disease activity and renal involvement in many patients. Anti-Smith antibodies are highly specific for SLE. Reduced complement concentrations, especially C3 and C4, may accompany

active immune-complex disease. Antiphospholipid antibodies identify patients at risk for thrombosis and pregnancy-related complications later in life [13].

Laboratory monitoring should include complete blood count, serum creatinine and estimated kidney function, urinalysis, urine protein quantification, complement levels and disease-specific autoantibodies when clinically appropriate. No individual laboratory marker reliably represents total disease activity; therefore, laboratory findings should be integrated with clinical assessment and validated disease activity instruments such as SLEDAI-2K or BILAG [14].

Treatment Strategies and Response to Therapy

General Treatment Principles: Treatment is individualized according to disease severity and organ involvement. The major goals are rapid suppression of inflammation, prevention of irreversible organ damage, achievement of remission or low disease activity, preservation of growth and development and minimization of treatment toxicity. Current guidance supports early recognition, regular monitoring and a treat-to-target approach [15].

Hydroxychloroquine

Hydroxychloroquine is generally considered a foundational therapy for patients with SLE unless contraindicated. It may reduce mucocutaneous and musculoskeletal activity and contributes to flare prevention. Long-term use requires appropriate ophthalmic monitoring because retinal toxicity, although uncommon, can cause irreversible visual impairment.

Glucocorticoids

Glucocorticoids remain central to treatment of moderate-to-severe pSLE and severe organ involvement. Intravenous methylprednisolone may be used for organ-threatening disease, followed by oral therapy and a planned taper. Clinical response may occur rapidly, but cumulative glucocorticoid toxicity is a major concern in children, including growth suppression, obesity, hypertension, osteoporosis, infection and metabolic complications. Steroid-sparing therapy should therefore be introduced whenever appropriate.

Conventional Immunosuppressive Therapy

Mycophenolate mofetil is widely used for lupus nephritis and other significant organ involvement. Cyclophosphamide remains an important option for severe or life-threatening disease, particularly selected proliferative nephritis or severe neuropsychiatric disease. Azathioprine is frequently used for maintenance therapy, while methotrexate can be useful for selected arthritis and cutaneous disease. Calcineurin inhibitors, including tacrolimus and voclosporin in appropriate settings, can provide additional renal disease control, although pediatric evidence varies by agent and indication.

Biologic and Targeted Therapies

Targeted therapies are increasingly relevant for patients with persistent activity or inadequate response to conventional treatment. B-cell-directed strategies are biologically attractive because B cells contribute to autoantibody production, antigen presentation and cytokine signaling. Belimumab has pediatric approval for selected patients with active SLE and is an important steroid-sparing option. Rituximab is used off-label in selected refractory cases, particularly when conventional therapies have failed or disease is severe. Emerging approaches targeting interferon pathways and other immune pathways may further expand treatment options.

Assessment of Therapeutic Response

Therapeutic response should be evaluated systematically rather than by symptoms alone. Clinical improvement may include resolution of fever, rash, arthritis, serositis or neurological manifestations. In lupus nephritis, decreasing proteinuria, improvement or stabilization of kidney function and resolution of active urinary sediment are important indicators. Rising complement levels and declining anti-dsDNA concentrations may support improvement, although these biomarkers do not always correlate perfectly with clinical activity.

Validated activity measures, particularly SLEDAI-2K and BILAG-based assessment, can help standardize longitudinal evaluation. Current treat-to-target frameworks emphasize clinical remission or low disease activity with the lowest feasible glucocorticoid exposure. In children, minimizing glucocorticoids is particularly important because cumulative exposure may interfere with growth and development.

Factors Associated with Incomplete Response or Relapse

Incomplete response can result from severe baseline disease, renal or neuropsychiatric involvement, delayed diagnosis, medication toxicity, adherence difficulties, infection, socioeconomic barriers and limited access to specialist care. Disease heterogeneity also means that patients with apparently similar clinical phenotypes may respond

differently to the same treatment. This supports the development of molecular biomarkers capable of identifying treatment-responsive subgroups.

DISCUSSION

The available evidence supports the concept that pSLE is biologically and clinically more aggressive than many adult-onset cases. The high frequency of renal, hematological, musculoskeletal and mucocutaneous manifestations creates a need for early, multidisciplinary assessment. Treatment response is generally strongest when active disease is recognized promptly and therapy is tailored to the affected organs.

A major challenge is balancing effective immunosuppression with the unique vulnerabilities of childhood. Prolonged glucocorticoid exposure may produce substantial morbidity even when inflammatory activity is controlled. Therefore, modern management increasingly emphasizes steroid-sparing immunosuppressive therapy, structured monitoring and treat-to-target strategies. The recent expansion of biologic therapies illustrates how improved understanding of B-cell and interferon biology is translating into targeted treatment.

Future biological research should investigate molecular endotypes of pSLE, transcriptomic and proteomic signatures, interferon pathway activity, B-cell phenotypes and biomarkers predicting renal or neuropsychiatric disease. Prospective pediatric cohorts and clinical trials are particularly important because many therapeutic recommendations have historically been extrapolated from adult SLE studies.

Limitations

This manuscript is a narrative review rather than a systematic review or original clinical cohort study. It therefore does not provide a pooled effect estimate or a formal meta-analysis. Heterogeneity in pediatric definitions, disease activity measures, treatment regimens and follow-up periods limits direct comparison between studies. In addition, several therapies used in children have historically been supported by limited pediatric trial data.

CONCLUSIONS

Pediatric systemic lupus erythematosus is a heterogeneous and potentially organ-threatening autoimmune disease in which early diagnosis, biological characterization and prompt treatment are essential. Renal, hematological, mucocutaneous, musculoskeletal and neuropsychiatric manifestations are major determinants of disease burden. Hydroxychloroquine, glucocorticoids and conventional immunosuppressive drugs remain central to management, while targeted biologic therapies provide additional options for selected patients. Response should be evaluated using integrated clinical, laboratory and validated disease-activity measures, with the goal of achieving remission or low disease activity and minimizing cumulative glucocorticoid exposure. Future research should prioritize pediatric-specific biomarkers and precision therapeutic strategies.

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