Scientific Research Publishing

Journal of Biosciences and Medicines, 2026, 14(4), 278-305
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Optimizing Cytopenia Treatment in Systemic Lupus Erythematosus: Insights from a Systematic Review

Omar Alrashed[1], Mahdi Grashi[1], Noura Alforaih[2], Ghaydaa Aldabie[3*], Munther Khamashta[4,5]

[1]Internal Medicine Department, Mubarak Alkabeer Hospital, Kuwait City, Kuwait
[2]Rheumatology Department, Amiri Hospital, Kuwait City, Kuwait
[3]Rheumatology Department, Farwaniya Hospital, Kuwait City, Kuwait
[4]Emeritus Professor of Medicine, King's College, London, UK
[5]GSK Scientific Director, Immunology, Dubai, United Arab Emirates
Email: Alrashed117@hotmail.com, Mahdigrashi@gmail.com, *Dr_ghaydaa@yahoo.com, Munther.khamashta@kcl.ac.uk

How to cite this paper: Alrashed, O., Grashi, M., Alforaih, N., Aldabie, G. and Khamashta, M. (2026) Optimizing Cytopenia Treatment in Systemic Lupus Erythematosus: Insights from a Systematic Review. *Journal of Biosciences and Medicines*, **14**, 278-305.
https://doi.org/10.4236/jbm.2026.144022

Received: March 10, 2026
Accepted: April 26, 2026
Published: April 29, 2026

Abstract

Introduction: Hematologic abnormalities affect many patients with systemic lupus erythematosus (SLE). Despite their clinical relevance, standardized treatment guidelines remain limited, and management strategies rely heavily on observational evidence. This systematic review synthesizes current evidence on treatment strategies for hematologic cytopenias in adults with SLE and identifies key gaps in the literature. **Methods:** A systematic review was conducted in accordance with PRISMA guidelines. Searches of Embase, MEDLINE, and the Cochrane Library (from database inception to March 31, 2025) identified 15,197 records. Following screening and eligibility assessment, 37 studies evaluating anemia, leukopenia, thrombocytopenia, or bi-/pancytopenia in SLE were included. Treatment strategies were analyzed by cytopenia subtype and categorized according to line of therapy. **Results:** Management strategies varied according to cytopenia subtype. Anemia was treated with corticosteroids for autoimmune hemolytic anemia and pure red cell aplasia, with rituximab or immunosuppressants for refractory cases. Iron deficiency was managed with oral or intravenous iron; anemia of chronic disease responded to lupus control and erythropoiesis-stimulating agents. Leukopenia was observed if asymptomatic, but corticosteroids, immunosuppressants, or granulocyte-colony stimulating factor were used when clinically indicated. Thrombocytopenia treatment was tiered by severity and bleeding risk, using corticosteroids, rituximab, thrombopoietin receptor agonists, or splenectomy. Bi-or pancytopenia required urgent intervention based on underlying etiology (e.g., thrombotic thrombo-

cytopenic purpura, hemophagocytic lymphohistiocytosis, marrow failure), often involving corticosteroids combined with intravenous immunoglobulin, rituximab, or cytotoxic agents; plasma exchange was reserved for conditions such as thrombotic thrombocytopenic purpura. **Conclusion:** Cytopenias in SLE require subtype-specific management strategies tailored to the underlying mechanism and disease severity. This review summarizes current therapeutic approaches and highlights the need for prospective studies to establish standardized treatment strategies.

Keywords

Systemic Lupus Erythematosus, Cytopenia, Anemia, Thrombocytopenia, Leukopenia, Immunosuppressive Therapy

1. Introduction

Hematologic abnormalities are among the most common and clinically significant manifestations observed in systemic lupus erythematosus (SLE), affecting up to 83% of patients at the time of diagnosis [1]. These manifestations include anemia, leukopenia, thrombocytopenia, and, less frequently, bi- or pancytopenia. They may arise from multiple mechanisms, including immune-mediated peripheral destruction, bone marrow suppression, medication toxicity, or secondary complications such as infection or nutritional deficiency [2].

Importantly, cytopenias are not merely laboratory abnormalities but are increasingly recognized as markers of disease activity, treatment response, and long-term prognosis. For instance, severe thrombocytopenia has been linked to a nearly threefold increase in mortality among newly diagnosed SLE patients [3].

Despite their clinical relevance, therapeutic approaches for managing cytopenias in SLE remain heterogeneous. Current management strategies are generally extrapolated from broader SLE treatment guidelines, with no standardized treatment protocols. Furthermore, the available literature predominantly consists of observational studies, including retrospective cohorts and case series, with a relative paucity of randomized controlled trials evaluating treatment efficacy in this setting.

While conventional therapies such as corticosteroids and other immunosuppressants remain the cornerstone of treatment, the emergence of newer biologic agents has introduced additional therapeutic options for managing refractory or severe cytopenias. Nevertheless, robust evidence to guide their optimal use in hematologic manifestations of SLE remains limited.

In this review, we provide a structured synthesis of existing evidence on the management of cytopenias in SLE, organized according to the affected hematologic lineage. Therapeutic approaches are summarized across cytopenia subtypes to provide a clinically oriented framework for treatment selection and to highlight key gaps for future research.

2. Methods

2.1. Study Design

This study was conducted as a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [4]. This review evaluated treatment strategies for cytopenias in SLE, including anemia, leukopenia, thrombocytopenia, and bi-/pancytopenia. Clinical studies involving adult patients with SLE were identified through a comprehensive literature search. Data were extracted and categorized according to cytopenia subtype to assess therapeutic approaches, treatment thresholds, and reported clinical outcomes. A formal review protocol was not registered prior to study initiation; however, the eligibility criteria, outcomes of interest, and synthesis approach were prespecified prior to study screening, and no post hoc modifications were made during the review process.

2.2. Eligibility Criteria

Eligibility criteria were established using the population, intervention, comparison, and outcome (PICO) framework [5], an approach commonly used to structure systematic reviews and particularly useful in areas where randomized evidence is limited.

The population of interest comprised adult patients (≥18 years) with SLE and at least one associated cytopenia. The interventions included pharmacologic or procedural treatments used for the management of SLE-related cytopenias. Eligible study designs included randomized controlled trials, non-randomized trials, cohort studies, case-control studies, and case series including five or more patients, provided that they reported therapeutic interventions and relevant clinical outcomes. Conference abstracts were included if they provided sufficient clinical and outcome data, with greater emphasis placed on evidence from larger cohort studies and registry analyses.

Studies were excluded if cytopenias were attributed to unrelated causes, such as hematologic malignancies, infections, or medication toxicity. Additional exclusions included animal or *in vitro* studies, editorials and opinion articles. Conference abstracts lacking sufficient data were excluded, as were non-English publications without reliable translation. Given the predominantly observational nature of the available literature, the presence of a comparator group was not required for study inclusion.

Outcomes of interest included hematologic response, relapse, adverse events, and reported treatment thresholds or treatment indications.

2.3. Search Strategy

A systematic search of MEDLINE (via PubMed), Embase, and the Cochrane Library was conducted from database inception to March 31, 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to SLE, hematologic cytopenias (e.g., anemia, leukopenia, thrombocytopenia), and

therapeutic interventions.

Named therapies such as corticosteroids, hydroxychloroquine, rituximab, belimumab, anifrolumab, mycophenolate mofetil, azathioprine, cyclophosphamide, calcineurin inhibitors, cyclosporine, tacrolimus, intravenous immunoglobulin (IVIG), granulocyte colony-stimulating factor (G-CSF), thrombopoietin receptor agonists (TPO-RAs) and plasma exchange were included, along with broader treatment concepts (e.g., "management," "treatment indication," "thresholds for therapy"). Search syntax was adapted for each database. The full search strategies for all databases are provided in the Supplementary Material (Table S1).

2.4. Study Selection

Search results were imported into Covidence systematic review software for screening. Duplicate records were removed using both automated and manual methods. Two reviewers independently screened titles and abstracts, followed by full-text assessment for eligibility. Any discrepancies were resolved through discussion with a third reviewer (principal investigator). The study selection process is summarized in the PRISMA flow diagram (Figure 1).

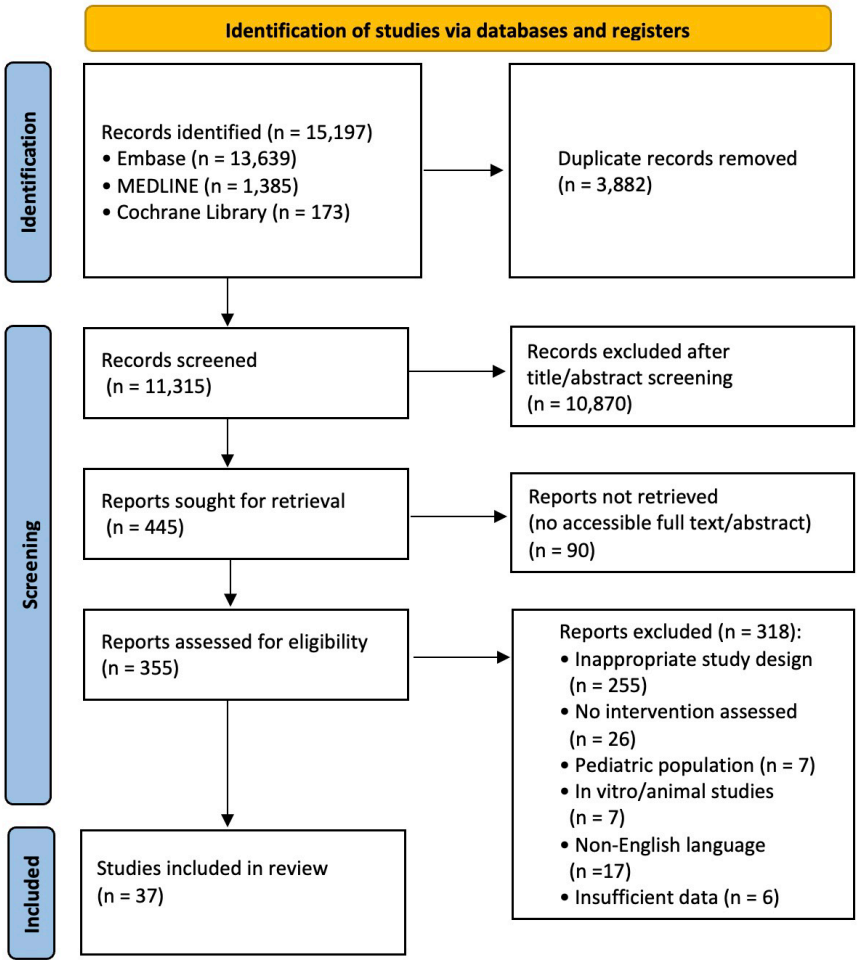


Figure 1. PRISMA flow diagram showing the selection process for included studies.

2.5. Data Extraction

Data were extracted by one reviewer using a standardized data extraction form and independently verified by a second reviewer to ensure accuracy. Extracted variables included study design, publication year, country, sample size, inclusion criteria, and duration of follow-up. Clinical data included SLE diagnostic criteria, patient demographics, and cytopenia subtype. Treatment-related variables included therapeutic class, individual agents used, treatment context (monotherapy or combination therapy), and dosing information when available. Reported outcomes included hematologic response (complete or partial), time to response, relapse rates, adverse events, and effects on SLE disease activity. Definitions of key outcome measures, including complete response, partial response, relapse, refractory disease, and severe cytopenia, were heterogeneous across studies, with no universally accepted or standardized criteria identified in the available literature. Consequently, outcomes were interpreted according to the definitions applied in the individual studies, where available.

2.6. Quality Assessment

A formal risk-of-bias assessment was conducted using the National Institutes of Health (NIH) Study Quality Assessment Tools [6], selected according to study design. The NIH tool for Observational Cohort and Cross-Sectional Studies was applied to cohort studies, while the NIH tool for Case Series Studies was used for case series. Each study was evaluated according to predefined methodological criteria, and an overall rating of good, fair, or poor quality was assigned. Two reviewers independently performed the quality assessments, and disagreements were resolved through discussion to reach an agreement. The resulting quality ratings were incorporated into the interpretation of the findings and are reported in the Supplementary Material (**Table S2**) [7]-[43].

2.7. Data Synthesis

Given the heterogeneity of study populations, interventions, and outcome measures, quantitative meta-analysis was not considered appropriate. Therefore, a structured narrative synthesis was performed. Studies were grouped by cytopenia subtype (anemia, leukopenia, thrombocytopenia, or bi-/pancytopenia) and organized by treatment category, including corticosteroids, immunosuppressive agents, biologic therapies, IVIG, splenectomy, and hematopoietic growth factors. Therapies were classified as first-, second-, or third-line based on reported clinical effectiveness, frequency of use across included studies, and consistency with prior literature; this classification reflects a structured synthesis of the available evidence and expert-informed clinical judgment, rather than formal evidence-graded guideline recommendations. For subtypes excluded due to secondary etiologies (e.g., iron deficiency anemia), treatment strategies were drawn from prior reviews and expert consensus. Extracted outcomes included treatment response, time to improvement, remission durability, adverse events, and, when available, treat-

ment thresholds, such as cell counts or bleeding risk. Recurrent treatment patterns and gaps in evidence were highlighted to inform future research priorities.

2.8. Ethical and Data Protection Considerations

As this study involved the synthesis of data from previously published literature, formal ethical approval was not required. No individual patient-level data were collected or analyzed. The study adhered to the ethical principles outlined in the Declaration of Helsinki [44].

3. Results

3.1. Study Selection Results

A total of 15,197 records were identified through database searches, including Embase (n = 13,639), MEDLINE (n = 1385), and the Cochrane Library (n = 173). After removing 3882 duplicate records, 11,315 unique studies remained for title and abstract screening. Of these, 445 articles were retrieved for full-text review, and 355 were assessed for eligibility. Ultimately, 37 studies met all inclusion criteria and were included in the final synthesis (Supplementary Material, **Table S2**). Reasons for exclusion at the full-text stage included: inappropriate study design (n = 255), lack of intervention data (n = 26), pediatric populations (n = 7), *in vitro* or animal studies (n = 7), non-English language without reliable translation (n = 17), and insufficient outcome data (n = 6). The study selection process is summarized in the PRISMA flow diagram (**Figure 1**).

3.2. Anemia management in SLE

Anemia is a common hematologic manifestation of SLE, with a reported prevalence of up to 50% [45]. Hemoglobin (Hb) level has been shown to negatively correlate with SLE disease activity [45]. Since different types of anemia occur in SLE, treatment strategies must be tailored according to the underlying etiology (**Figure 2**).

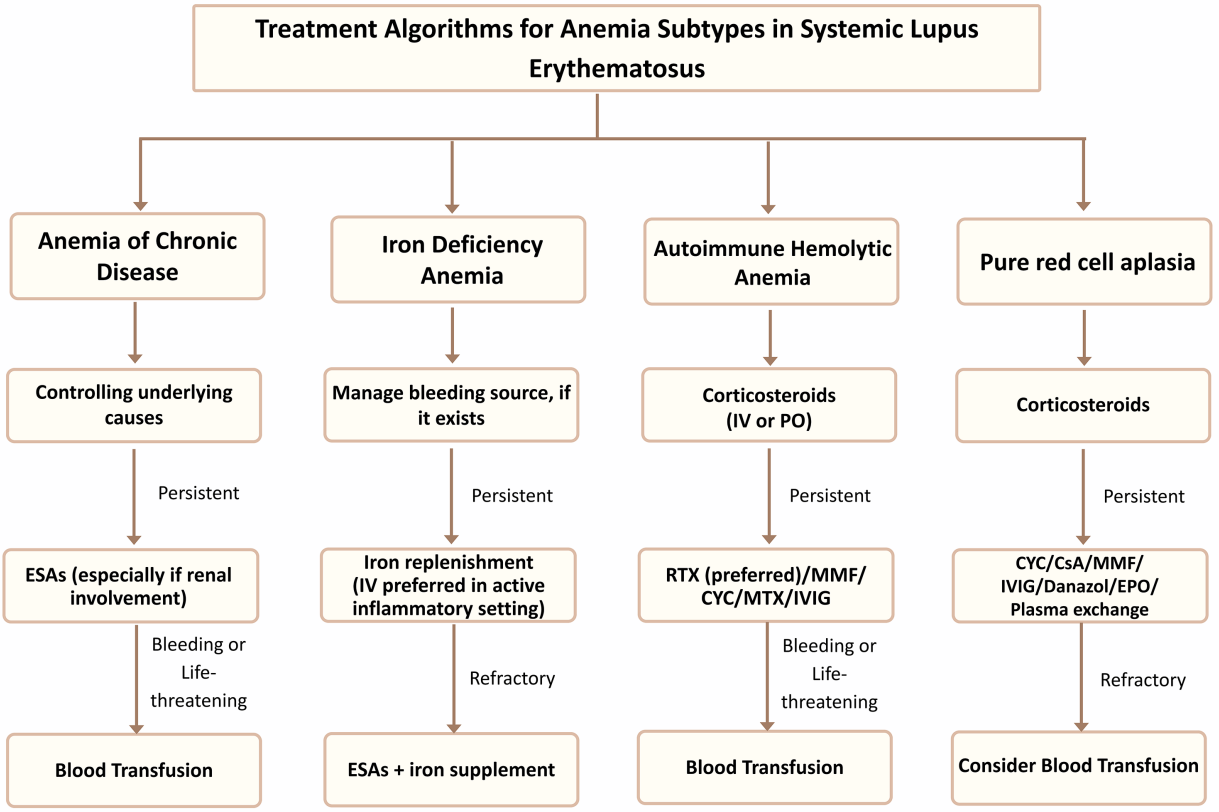
- **Anemia of chronic disease (ACD)**

ACD is the most frequent subtype of anemia in SLE, with a reported prevalence of approximately 41% in observational studies [45]. Management of ACD primarily focuses on controlling underlying inflammation [46]. In patients with persistent anemia despite adequate disease control, particularly in the setting of renal involvement, erythropoiesis-stimulating agents (ESAs) may be considered. Blood transfusions are generally reserved for severe or life-threatening anemia, particularly when bleeding is also present [46]. Despite the clinical importance of ACD, no studies in this review specifically evaluated treatment outcomes for ACD in adult patients with SLE, highlighting an important evidence gap.

- **Iron deficiency anemia (IDA)**

IDA is another frequent anemia subtype in SLE, reported in approximately one-third of patients with anemia [45]. Recognition and accurate diagnosis are essential, as concurrent inflammation can obscure traditional iron parameters. Like

ACD, no formal treatment thresholds or SLE-specific guidelines exist. Management follows general IDA principles: first, identify and address bleeding sources, if they exist; second, initiate iron supplementation, with intravenous iron preferred in the setting of active inflammation [46]. ESAs may be used in combination with iron supplementation to optimize response, with reassessment of Hb levels following treatment initiation [47].



Abbreviations: ESAs = erythropoiesis-stimulating agents; IV = intravenous; PO = oral; RTX = rituximab; MMF = mycophenolate mofetil; CYC = cyclophosphamide; MTX = methotrexate; IVIG = intravenous immunoglobulin; CsA = cyclosporine; EPO = erythropoietin.

Figure 2. Treatment Algorithm for Anemia Subtypes in Systemic Lupus Erythematosus.

- **Autoimmune hemolytic anemia (AIHA)**

AIHA typically accounts for approximately 10% of anemia cases in SLE [47]. While no specific Hb threshold has been defined to initiate treatment, the American College of Rheumatology (ACR) conditionally recommends initiating glucocorticoid therapy for symptomatic patients, particularly when ischemic manifestations or hemodynamic instability are present [48]. Furthermore, they recommend the addition of IVIG and/or anti-CD20 therapy (e.g., Rituximab) over conventional immunosuppressive agents [48]. These recommendations are based on very low-quality evidence.

High-dose corticosteroids, such as oral prednisone or intravenous methylprednisolone, remain the first-line therapy, with clinical response typically observed

within approximately three weeks [47]. Upon stabilization, tapering is usually initiated over two to three months. In a French case series involving 26 patients, corticosteroid therapy achieved an 85% complete response rate [16]. However, subsequent studies have shown that long-term remission following steroid withdrawal occurs in only about one-third of patients, and approximately 20% - 30% require second-line therapy [47]. Second-line options for steroid-refractory or steroid-dependent disease include rituximab, mycophenolate mofetil, cyclophosphamide, methotrexate, danazol, and IVIG. Rituximab has become the preferred second-line agent, particularly in relapsing or severe disease, due to its favorable efficacy and safety profile [47].

Evidence supporting the efficacy of anifrolumab and belimumab in SLE-associated AIHA remains limited, and further research is needed to evaluate their potential role [49] [50].

Blood transfusions should generally be avoided, when possible, as they may induce alloantibody formation against red blood cell antigens in SLE patients. However, it should not be delayed in life-threatening anemia, even when crossmatching interference is present, as ABO- and Rh-compatible units can generally be administered safely using least-incompatible transfusion protocols under expert hematologic guidance [51]-[53]. The roles of splenectomy and whole-blood exchange transfusion in refractory SLE-associated AIHA remain inconclusive [31] [47] [51].

- **Pure red cell aplasia (PRCA)**

PRCA is a rare hematologic complication, and its association with SLE is even more uncommon, with most evidence derived from case reports [51]. PRCA may occur even in patients with otherwise inactive SLE, often presenting as an isolated hematologic abnormality [51]. Due to its rarity, the true prevalence remains unknown, and diagnosis is frequently delayed. Treatment is generally recommended for all confirmed cases, regardless of Hb level. Corticosteroids are considered first-line therapy and typically induce a response within one to four weeks [51]. In refractory disease, second-line options include cyclophosphamide, cyclosporine, mycophenolate mofetil, IVIG, danazol, Erythropoietin (EPO), or plasma exchange [51]. Supportive transfusion can be considered while awaiting treatment response [33] [47].

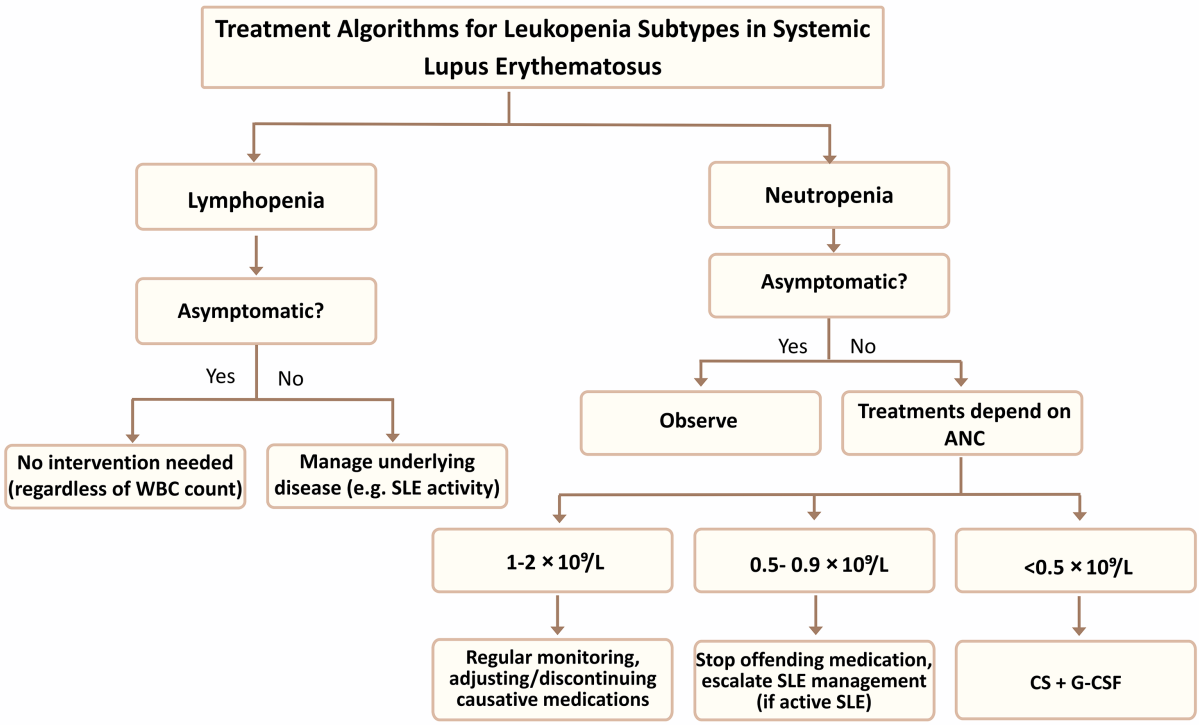
3.3. Leukopenia Management in SLE

Leukopenia is a well-recognized hematologic manifestation of SLE, with a reported prevalence ranging from approximately 22% to 41.8% [54]. White blood cell counts below 4000 cells/μL are usually seen in nearly 50% of patients, although only 20% develop counts below 1000 cells/μL [47]. Leukopenia is included in the 1997 ACR and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria, highlighting its diagnostic relevance [55] [56]. Although leukopenia is not considered a validated prognostic marker, persistent leukopenia in the absence of alternative explanations, such as infection, medications,

or ethnic neutropenia, may reflect underlying disease activity and influence clinical decision-making, particularly when accompanied by systemic disease flares. The most common subtypes, lymphopenia and neutropenia, differ in prevalence, pathophysiology, and therapeutic implications.

- **Lymphopenia**

Lymphopenia is the most common subtype of leukopenia in SLE, reported in up to 37% of patients [57]. Several studies indicate a positive correlation between lymphopenia and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores, suggesting that lymphocytopenia may help reflect SLE disease activity [46]. Although often asymptomatic, persistent or severe lymphopenia increases infection risk. Merayo-Chalico *et al.* identified lymphopenia < 1.0×10^9/L, low C3, and corticosteroid use (even < 7.5 mg/day) as independent predictors of infection, most commonly urinary tract, skin, lungs, and bloodstream [58]. Similarly, Ng *et al.* reported that lymphopenia at diagnosis predicted major infections during the first year of disease, independent of immunosuppressive therapy [59]. Despite these associations, isolated asymptomatic lymphopenia generally does not require specific treatment. The 2025 ACR guidelines for SLE management conditionally recommend against initiating immunosuppressive therapy solely for isolated lymphopenia, even when lymphocyte counts fall below 1.0×10^9/L, in the absence of other signs of active disease (**Figure 3**) [48]. Instead, management should focus on treating underlying SLE activity when present [46].



Abbreviations: WBC = white blood cell; SLE = systemic lupus erythematosus; ANC = absolute neutrophil count; CS = corticosteroids; G-CSF = granulocyte colony-stimulating factors.

Figure 3. Treatment Algorithms for Leukopenia Subtypes in Systemic Lupus Erythematosus.

- **Neutropenia**

Neutropenia occurs less frequently than lymphopenia in SLE, with a prevalence of approximately 12.5% in a large multinational cohort [57]. In most cases, neutropenia is mild, while moderate-to-severe neutropenia (Absolute Neutrophil Count (ANC) < 1000/μL) is relatively uncommon [51]. Several mechanisms have been proposed to explain neutropenia in SLE, including peripheral destruction of granulocytes mediated by antineutrophil antibodies**,** increased margination or alterations in the marginal and splenic granulocyte pools, and reduced granulocyte production within the bone marrow [60]. Additional contributors may include disease activity and medication-related toxicity [51].

Management of neutropenia in SLE depends on severity, symptoms, and disease activity. Similar to lymphopenia, the 2025 ACR guidelines recommend against initiating immunosuppressive therapy for asymptomatic neutropenia, even when the ANC is below 1000/μL, provided that other manifestations of active SLE are absent (**Figure 3**) [48]. Initial management of mild neutropenia (ANC 1.0 - 2.0 × 10^9/L) without infection or flare involves observation, regular blood monitoring, and, if indicated, adjusting or discontinuing potential causative medications such as azathioprine, methotrexate, or cyclophosphamide. Additional preventive measures may include vaccination and infection prophylaxis when clinically indicated [2].

When moderate neutropenia (ANC 0.5 - 0.99 × 10^9/L) persists despite discontinuation of potential causative medications, escalation of SLE-directed therapy may be considered, particularly when neutropenia is associated with active disease [61].

Severe neutropenia (ANC < 0.5 × 10^9/L) is less common but may be associated with a significant risk of infection. In such cases, treatment typically includes high-dose corticosteroids, and G-CSF may be administered to accelerate neutrophil recovery [21] [62].

Evidence supporting the use of anifrolumab and belimumab in the treatment of neutropenia or lymphopenia remains limited, and further research is needed to clarify their role in this setting [49] [50] [63].

3.4. Thrombocytopenia Management in SLE

Mild thrombocytopenia (platelet count 100,000 - 150,000 cells/μL) is a common hematologic manifestation of SLE, occurring in approximately 25% - 50% of patients [47]. It frequently coexists with other cytopenias, such as leukopenia or AIHA, and is associated with increased morbidity and mortality [51]. In the INSPIRE cohort, thrombocytopenia was identified in 10.4% of newly diagnosed SLE patients [3]. Among these patients, those with severe thrombocytopenia (platelet count < 20 × 10^9/L) had a threefold higher mortality rate than those with moderate (platelet count 20 - 50 × 10^9/L) or no thrombocytopenia [3]. Thrombocytopenia in SLE may result from multiple mechanisms, including immune thrombocytopenia (ITP), antiphospholipid antibodies (aPL) or antiphospholipid syndrome

(APS)-associated thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), or medication-related thrombocytopenia [64].

- **Immune thrombocytopenia (ITP)**

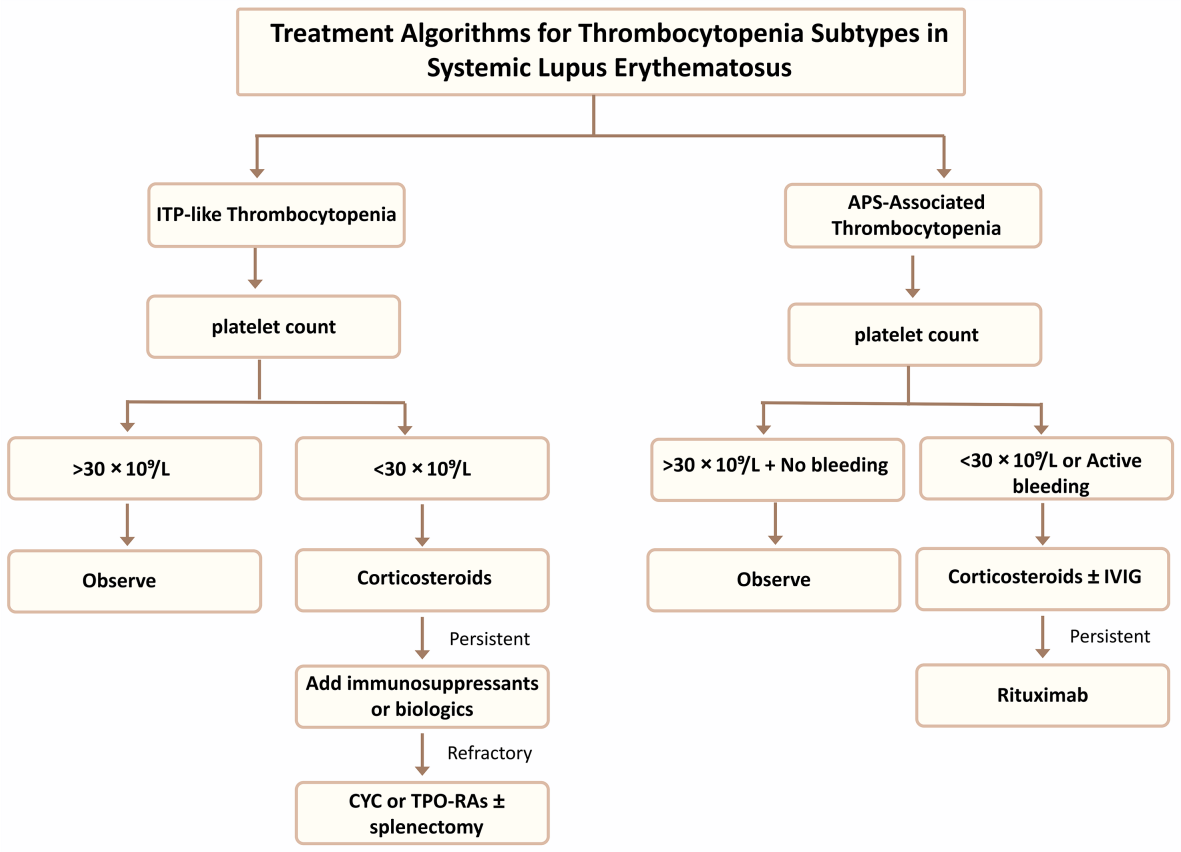
ITP-like thrombocytopenia may precede the diagnosis of SLE in up to 16% of patients and sometimes may occur up to 10 years before the development of other clinical manifestations [64].

The 2025 ACR guidelines recommend initiating treatment when platelet counts fall below 30,000/μL [48]. In asymptomatic patients, therapy typically consists of glucocorticoids combined with immunosuppressive agents such as mycophenolate mofetil, azathioprine, calcineurin inhibitors, anti-CD20 therapy, belimumab, or IVIG. In patients with active bleeding, treatment generally includes glucocorticoids together with IVIG and/or anti-CD20 therapy, although these recommendations are based on low-quality evidence [30] [48].

Corticosteroids remain the cornerstone of first-line therapy [20] [29] [32] [48] [65]. In a study by Arnal *et al.*, prednisone at 1 mg/kg/day produced an early response in approximately 80% of patients, although only 22% achieved sustained remission. When prednisone was combined with danazol or hydroxychloroquine, long-term response rates increased to 50% and 64%, respectively, allowing tapering and discontinuation of corticosteroids in some cases [20]. Adjunctive therapies, including hydroxychloroquine, azathioprine, calcineurin inhibitors, cyclophosphamide, mycophenolate mofetil, and IVIG, have frequently been used to maintain remission [19] [20] [23] [24] [36] [48] [65]. Rituximab is the most extensively studied second-line therapy [7] [12]-[14] [34] [42] [65]. In a retrospective cohort study, Roussotte *et al.* reported that 73% of patients responded to rituximab, with 90% achieving complete response and relapse-free survival extending up to 53 months [32]. Other immunosuppressive agents, such as azathioprine and mycophenolate mofetil, have demonstrated pooled response rates of 65% - 88%. TPO-RAs, including eltrombopag, have also shown rapid platelet responses within days and relatively low relapse rates [8] [9]. Splenectomy is generally reserved for highly selected refractory cases after failure of medical therapy [25] [27] [41]. Evidence regarding the use of danazol and sirolimus in SLE-associated thrombocytopenia remains limited [22] [26] [35].

These findings are consistent with the narrative review by Bashyal *et al.*, which identified corticosteroids as first-line therapy, followed by immunosuppressive agents or biologics as second-line treatments, with TPO-RAs or splenectomy reserved for refractory disease [66]. Additional therapies, such as calcineurin inhibitors (e.g., tacrolimus), have reported response rates exceeding 70%, while fostamatinib has demonstrated modest efficacy. IVIG or cyclophosphamide may be used in acute bleeding episodes, and hydroxychloroquine may contribute to relapse prevention [66].

Overall, current evidence supports a tiered treatment strategy, with corticosteroids as first-line therapy, immunosuppressive agents or biologics as second-line treatments, and TPO-RAs or splenectomy for refractory disease (**Figure 4**).



Abbreviations: ITP = idiopathic thrombocytopenic purpura; CYC = cyclophosphamide; TPO-Ras = thrombopoietin receptor agonists; APS = antiphospholipid syndrome; IVIG = intravenous immunoglobulin.

Figure 4. Treatment algorithms for thrombocytopenia subtypes in systemic lupus erythematosus.

- **APS-Associated thrombocytopenia**

aPL are detected in approximately 30% - 40% of patients with SLE, and a subset of these individuals subsequently develop APS [67]. Thrombocytopenia is a recognized manifestation of APS and is included in the clinical domain of the ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria for APS. In affected patients, platelet counts typically range from 20 to 130 × 10^9/L [68].

The 2025 ACR guidelines do not provide specific treatment recommendations for APS-related thrombocytopenia; therefore, management generally follows approaches used for SLE-associated thrombocytopenia [48]. When platelet counts fall below 30 × 10^9/L or in patients with active bleeding, glucocorticoids with or without IVIG are typically used as first-line therapy (**Figure 4**) [48].

No APS-specific trials were identified in this review. However, Bashal *et al.* suggested that Rituximab may have a potential role in refractory disease, and in rare cases, hematopoietic stem cell transplantation has been considered [64]. These recommendations are largely extrapolated from small observational studies and case series, underscoring the need for prospective studies to establish evidence-based management strategies.

3.5. Bi/Pancytopenia Management in SLE

Bicytopenia and pancytopenia are uncommon but important hematologic manifestations of SLE, as they may reflect underlying bone marrow pathology. Bone marrow examination in these cases may reveal abnormalities such as hypocellularity, dyserythropoiesis, stromal alterations, or increased reticulin, suggesting a central immune-mediated mechanism [69]. However, findings may also be normal or nonspecific, particularly when cytopenias result from peripheral immune-mediated destruction. Bone marrow disorders, including myelofibrosis, aplastic anemia, and pure red cell aplasia, have been described as part of the hematologic spectrum of SLE [46].

- **Bone marrow failure (BMF) syndromes**

BMF syndromes, though rare, are serious intrinsic causes of bi- or pancytopenia in SLE, with subtypes such as aplastic anemia (AA), autoimmune myelofibrosis (AIMF), and marrow hypocellularity, most often reported in small case series and case reports. In a prospective biopsy study of 41 patients with SLE and cytopenia, Wanitpongpun *et al.* found marrow abnormalities in nearly half, including hypocellularity (50%), plasmacytosis (35%), haemophagocytosis (30%), dyserythropoiesis (10%), aplastic anemia (10%), and myelofibrosis (5%), although only 9.8% had true pancytopenia [70]. These findings underscore that marrow involvement is not uncommon in cytopenic SLE and emphasize the diagnostic value of bone marrow biopsy, particularly in cases of unexplained f bi-/pancytopenia or treatment resistance.

No standardized ACR guidelines exist for SLE-related BMF, and evidence remains limited to case-based reports. Glucocorticoids are the most commonly used first-line therapy in AIMF, with frequent hematologic improvement when initiated early [46] [47]. Unlike primary myelofibrosis, which is typically resistant to immunosuppression, AIMF may respond favorably to immune-modulating therapy, although outcomes tend to be poorer in fibrotic or established disease. IVIG has shown benefit in selected immune-mediated cases, while combination therapy with glucocorticoids and mycophenolate mofetil has achieved recovery in some patients, suggesting a potential steroid-sparing role [46] [71]. Overall, management should be tailored to the underlying marrow pathology, disease activity, and clinical severity, with early recognition and initiation of immunosuppression offering the greatest likelihood of hematologic recovery.

- **Macrophage activation syndrome (MAS)/Hemophagocytic lymphohistiocytosis (HLH)**

MAS and HLH are rare but severe complications of SLE. Although HLH can occur as a familial or sporadic disorder, it can also be triggered by disruption of the immune system from infections, malignancy or rheumatic diseases [72] [73]. Secondary MAS is a potentially life-threatening condition. While it is more frequently observed in the pediatric age group, it can also occur in adults, often presenting with greater severity [46]. Because features such as persistent fever, cytopenias, and systemic inflammation overlap with lupus flares, diagnosis is often

delayed, contributing to under recognition and poor outcomes. No formal guidelines exist for MAS treatment in SLE, and current practice relies on observational data and expert opinion. Therapy is generally initiated when patients develop sustained fever, worsening cytopenias, hyperferritinemia, or organ dysfunction [46]. High-dose glucocorticoids remain the cornerstone of first-line treatment, particularly when infection is excluded, with agents such as cyclosporin or cyclophosphamide reserved for MAS driven by active SLE [46]. Among included studies, only Lambotte *et al.* systematically evaluated treatment, reporting 15 MAS episodes in 12 adults with SLE: 12 responded to glucocorticoids alone, while two required cyclophosphamide, illustrating the effectiveness of this stepwise approach [17]. Overall, early recognition and prompt initiation of immunosuppressive therapy are essential to prevent progression to multiorgan failure and reduce mortality in SLE-associated MAS.

- **Myelodysplastic syndrome (MDS)**

MDS are rare clonal marrow disorder that typically presents with persistent cytopenias. In a cohort of more than 15,000 patients with rheumatologic diseases followed for 55,841 person-years, SLE was associated with a significantly increased risk of developing MDS (adjusted hazard ratio, 2.61; P = 0.01) [74]. The median age at diagnosis among SLE patients was 38.5 years, and the majority were classified as refractory cytopenia with multilineage dysplasia [74]. Patients who subsequently developed MDS had significantly lower baseline Hb (median 9.5 vs 12.2 g/dL) and higher mean daily glucocorticoid exposure (14.0 vs 4.8 mg/day), both of which were independently associated with increased risk [74]. These observations highlight the need for early marrow evaluation in SLE patients with disproportionate anemia or refractory bi-/pancytopenia.

Currently, no disease-specific guidelines exist for the management of MDS in the context of SLE, and therapeutic strategies are largely extrapolated from approaches used in MDS associated with autoimmune diseases. Glucocorticoids are often used first-line, improving autoimmune features in up to 80% of cases, though responses are usually incomplete, and many patients become steroid-dependent. Second-line immunosuppressive therapies may be considered in selected patients to control autoimmunity, although these agents may worsen cytopenias or increase susceptibility to infection [75]. Biologics such as rituximab have demonstrated limited efficacy in treating cytopenias directly attributable to MDS, whereas hypomethylating agents (e.g., azacitidine) may reduce steroid burden and autoimmune activity, though hematologic responses remain uncertain [75]. Hematopoietic stem cell transplantation, although rarely undertaken in this setting, remains the only potentially curative option for both MDS and associated autoimmune manifestations [75].

- **Thrombotic microangiopathy (TMA) and thrombotic thrombocytopenic purpura (TTP)**

Thrombotic microangiopathy (TMA) represents a group of life-threatening syndromes characterized by microangiopathic hemolytic anemia, thrombocyto-

penia, and organ injury resulting from widespread microvascular thrombosis. In patients with SLE, TMA may occur secondary to several mechanisms, including immune-mediated TTP, complement-mediated TMA, APS, or severe systemic inflammation. Among these, TTP represents one of the most severe manifestations [76]. TTP occurs in 1% - 4% of SLE patients, typically during periods of active disease, and is frequently associated with lupus nephritis, neuropsychiatric involvement, and systemic inflammatory activity [77]. Untreated, the condition is almost universally fatal, but plasma exchange has improved survival to 80% - 90% when initiated promptly [77]. Despite these advances, outcomes remain poorer in SLE-associated TTP than in idiopathic cases, with mortality ranging from 34 to 62.5% and relapse rates of 30% - 60% [77].

Diagnosis is often challenging because clinical features overlap with other lupus-related hematologic complications, including autoimmune hemolytic anemia, APS, and bone marrow failure. Consequently, recognition may be delayed, and some studies suggest that SLE-associated TTP may represent a distinct and more aggressive clinical phenotype [77]. Early treatment is therefore essential, and therapy should be initiated based on clinical suspicion without waiting for confirmatory laboratory results [78]. A key pathogenic mechanism in TTP is severe deficiency of a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13). ADAMTS13 is a metalloprotease responsible for cleaving ultra-large von Willebrand factor (vWF) multimers; deficiency of this enzyme results in accumulation of large vWF multimers, promoting platelet aggregation and microvascular thrombosis [78].

Plasma exchange remains the cornerstone of therapy, reducing mortality from more than 90% to approximately 25% [79]. However, patients with SLE-associated TTP may demonstrate partial responses or refractory disease, necessitating additional immunosuppressive therapies. Adjunctive treatments commonly include high-dose corticosteroids, cyclophosphamide, or IVIG. In a study by Majithia *et al.*, all five patients with SLE-associated TTP achieved hematologic recovery following treatment with plasma exchange and corticosteroids, although two patients experienced relapse and three progressed to end-stage renal disease [18]. In contrast, Aleem *et al.* reported remission in all six patients treated with plasma exchange, with faster responses and no progression to renal failure; three of these patients also received cyclophosphamide, suggesting a potential benefit of combination therapy [15]. These findings suggest that adjunctive cyclophosphamide may improve remission durability and renal outcomes in selected cases. Rituximab has also emerged as an effective second-line therapy [38]. In a cohort of 21 patients with SLE-associated TMA, three-month survival was 92.3% in patients treated with rituximab compared with 33.3% in those who did not receive rituximab, although infections occurred in 38.5% of treated patients [38]. More recently, complement inhibition has been explored as a therapeutic option in refractory disease. Park *et al.* reported durable remission in seven of eight patients treated with eculizumab, while Kello *et al.* described sustained hematologic and

renal recovery in all seven cases, with 100% survival at three months [10] [11]. The role of splenectomy in refractory SLE-associated TTP remains uncertain [80]. Further studies are needed to clarify its potential role.

Collectively, current evidence supports a stepwise therapeutic strategy for SLE-associated TMA/TTP: plasma exchange combined with corticosteroids as first-line therapy, cyclophosphamide for severe systemic disease or inadequate response, rituximab for refractory or relapsing cases, and complement inhibition with eculizumab reserved for patients with persistent or complement-mediated TMA unresponsive to conventional therapy.

- **Evans syndrome (ES)**

ES, characterized by the coexistence of AIHA and ITP, represents a rare but serious hematologic complication in patients with SLE. In a retrospective review of 953 patients with SLE, Costallat and colleagues reported 26 cases of ES (2.7%), all occurring in young women with a median age of 27 years. Most patients (92%) developed both AIHA and ITP simultaneously at the time of SLE diagnosis. ES was frequently accompanied by active systemic disease, including arthritis (77%), malar rash (61.5%), photosensitivity (57.6%), oral ulcers (34.6%), nephritis (73%), serositis (54%), neuropsychiatric manifestations (19%), and pulmonary involvement (15%). Recurrence of ES occurred in four patients (15%), while approximately one-third of patients had concomitant autoimmune conditions, most commonly APS [81]. No formal guidelines exist for the management of ES in SLE. Treatment is generally initiated in patients with clinically significant cytopenias, typically when Hb levels fall below 10 g/dL, platelet counts fall below 20 - 30 $\times$ 10^9/L, or when patients present with bleeding or symptomatic anemia [82].

Corticosteroids are the mainstay of first-line therapy. However, relapse and steroid dependence are common. In the cohort described by Costallat *et al*., 73% of patients required second-line therapies, such as azathioprine, cyclophosphamide, or danazol. IVIG was used for acute exacerbations or when immunosuppressive therapy was contraindicated, while rituximab was reserved for refractory disease and splenectomy was performed selectively [81]. Evidence from other cohorts supports this therapeutic hierarchy. In the study by Serris *et al*., rituximab was administered to all 10 patients with ES, achieving complete or partial responses in 60.5% of cases and durable remission lasting more than two years in 62.5% of patients, although 39% subsequently relapsed. The median relapse-free survival was 67 months, and rituximab was generally well tolerated, including in patients who had previously undergone splenectomy [37]. In contrast, Avina-Zubieta *et al.* reported the use of conventional immunosuppressive agents, including prednisone, danazol, azathioprine, cyclophosphamide, and dapsone, with no substantial differences in relapse rates among therapies**,** although treatment-related adverse effects were observed. Danazol was associated with rash, hepatitis, and menstrual abnormalities, while dapsone and cytotoxic agents were linked to gastrointestinal toxicity [43].

Taken together**,** available evidence supports a pragmatic stepwise approach to

the management of ES in SLE**,** with corticosteroids as first-line, conventional immunosuppressants as steroid-sparing second-line agents, rituximab as the preferred option for refractory or relapsing disease, and splenectomy or dapsone reserved for resistant cases or settings where biologics are unavailable.

3.6. Strengths, Limitations and Future Directions

This review synthesizes the current evidence on the management of cytopenias in SLE, organized according to hematologic lineage to reflect real-world clinical decision-making. Key strengths include a systematic and comprehensive multi-database search strategy, the inclusion of diverse observational study designs reflective of routine clinical practice, and a structured synthesis of therapeutic approaches across anemia, leukopenia, thrombocytopenia, and bi-/pancytopenia. By focusing on treatment selection, sequencing of therapies, and reported hematologic outcomes, this review addresses a clinically important area where evidence remains fragmented and randomized controlled trials are scarce.

Several limitations should be acknowledged. First, the available literature is predominantly observational, consisting largely of retrospective cohorts and case series, which introduces potential selection bias and limits the strength of causal inferences regarding treatment efficacy. Across all cytopenia subtypes, the synthesized evidence is further limited by small sample sizes and marked heterogeneity in study design and outcome definitions, resulting in an overall low to very low certainty of evidence. Although efforts were made to distinguish findings derived from included primary studies from those informed by external reviews, guidelines, or expert consensus, this distinction was not consistently feasible across all cytopenia subtypes due to the limited availability of SLE-specific data. Where feasible, the source of evidence was explicitly indicated. Second, substantial heterogeneity across studies in patient populations, definitions of cytopenia severity, treatment regimens, and outcome reporting precluded quantitative synthesis and direct comparison of therapeutic strategies. Third, drug dosing regimens and treatment schedules were inconsistently reported and frequently individualized, making it difficult to derive dose-specific treatment approach. Fourth, the review focused on cytopenias identifiable through routine complete blood count testing because of their direct therapeutic relevance; therefore, other hematologic abnormalities described in SLE, such as basopenia or emerging hematologic biomarkers of disease activity, were not included due to the limited availability of treatment-focused evidence and lack of standardized clinical assessment.

Future research should prioritize prospective and multicenter studies to better define optimal treatment strategies for SLE-associated cytopenias. Standardized definitions of hematologic response, relapse, and treatment thresholds would also facilitate comparison across studies and improve evidence synthesis. In addition, translational research exploring the immunologic and molecular mechanisms underlying lupus-associated cytopenias may help identify biomarkers that predict treatment response and guide personalized therapeutic strategies. Ultimately, the

development of evidence-based clinical guidelines will require coordinated international efforts integrating clinical trials, registry data, and real-world observational cohorts.

4. Conclusions

Cytopenias are common manifestations of SLE and contribute substantially to morbidity and mortality, highlighting the importance of early recognition and appropriate management. Because these abnormalities arise from diverse mechanisms, including immune-mediated destruction, bone marrow dysfunction, and secondary complications, treatment should be tailored to the affected hematologic lineage and the underlying cause.

Management strategies vary according to cytopenia subtype. Anemia requires etiology-specific therapy, whereas leukopenia is often monitored unless associated with infection risk or active disease. Thrombocytopenia typically warrants treatment when platelet counts fall significantly or bleeding occurs, with glucocorticoids as first-line therapy and escalation to immunosuppressive agents, rituximab, or TPO-RAs when necessary. Bi- and pancytopenia often reflect more severe underlying pathology and require prompt diagnostic evaluation and targeted therapy.

Despite advances in SLE management, therapeutic approaches for hematologic cytopenias remain largely based on observational evidence. Future prospective studies and multicenter collaborations are needed to establish evidence-based management strategies. Such efforts will be essential to improve outcomes of hematologic complications in SLE.

Authorship Contributions

All authors contributed equally to the conception and design of the work, the acquisition, analysis, and interpretation of data, as well as drafting and critically revising the manuscript for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the study. The guarantor of the work takes full responsibility for the content, had access to all data, and made the decision to publish.

AI Assistance Disclosure

Artificial intelligence (AI) assisted technologies were not used to generate the content of this manuscript. AI was employed solely to assist with editing for grammar and spelling mistakes in the final version.

Ethical Approval

Ethical approval was not required, as this is a review article.

Patient Consent

Patient consent was not required, as this is a review article.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability Statement

Data underlying this study are available upon reasonable request, subject to institutional policies and ethical guidelines.

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Clinical Trial Registration

Registration was not required because this is a review article.

Conflicts of Interest

The authors declare no potential conflicts of interest concerning the review, authorship, and/or publication of this article, except for Professor Munther Khamashta, who is a full-time employee of GSK.

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Supplementary

Table S1. Electronic Search Strategy.

MEDLINE	1) Lupus Erythematosus, Systemic/ or Systemic lupus erythematosis.mp. 2) Cytopenia.mp. or exp Cytopenia/ 3) anemia.mp. or exp Anemia/ 4) exp Thrombocytopenia/ or thrombocytopenia.mp. 5) leukopenia.mp. or exp Leukopenia/ 6) 2 or 3 or 4 or 5 7) (Corticosteroids or Prednisone or Prednisolone or Methylprednisolone or Hydrocortisone or Dexamethasone or Immunosuppressants or Azathioprine or Mycophenolate mofetil or MMF or Mycophenolic acid or MPA or Methotrexate or Cyclophosphamide or Leflunomide or Chlorambucil or Biologics or B-cell targeted therapy or Belimumab or Rituximab or Obinutuzumab or Dapirolizumab or Blisibimod or Interferon-targeted therapy or Anifrolumab or Sifalimumab or Complement inhibitors or Eculizumab or JAK Inhibitors or Tofacitinib or Baricitinib or Upadacitinib or Antimalarials or Hydroxychloroquine or Chloroquine or Immunomodulators or Tacrolimus or Cyclosporine or Voclosporin or Intravenous Immunoglobulin or IVIG or Hematopoietic Growth Factors or Erythropoietin or EPO or Darbepoetin or Granulocyte colony-stimulating factor or G-CSF or Filgrastim or Pegfilgrastim or Thrombopoietin receptor agonists or Romiplostim or Eltrombopag or Avatrombopag or Plasmapheresis or Plasma Exchange or Lenalidomide or Thalidomide or Bortezomib or Vincristine or Carfilzomib or Decitabine or Azacitidine or CAR-T cell therapy or FasTCAR-T GC012F or CABA-201 or Gotu Kola).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 8) 1 and 6 and 7
EMBASE	1) exp systemic lupus erythematosus/ or Systematic lupus erythematosis.mp. 2) exp cytopenia/ or cytopenia.mp. 3) anemia.mp. or exp anemia/ 4) exp thrombocytopenia/ or Thrombocytopenia.mp. 5) leukopenia.mp. or exp leukopenia/ 6) 2 or 3 or 4 or 5 7) (Corticosteroids or Prednisone or Prednisolone or Methylprednisolone or Hydrocortisone or Dexamethasone or Immunosuppressants or Azathioprine or Mycophenolate mofetil or MMF or Mycophenolic acid or MPA or Methotrexate or Cyclophosphamide or Leflunomide or Chlorambucil or Biologics or B-cell targeted therapy or Belimumab or Rituximab or Obinutuzumab or Dapirolizumab or Blisibimod or Interferon-targeted therapy or Anifrolumab or Sifalimumab or Complement inhibitors or Eculizumab or JAK Inhibitors or Tofacitinib or Baricitinib or Upadacitinib or Antimalarials or Hydroxychloroquine or Chloroquine or Immunomodulators or Tacrolimus or Cyclosporine or Voclosporin or Intravenous Immunoglobulin or IVIG or Hematopoietic Growth Factors or Erythropoietin or EPO or Darbepoetin or Granulocyte colony-stimulating factor or G-CSF or Filgrastim or Pegfilgrastim or Thrombopoietin receptor agonists or Romiplostim or Eltrombopag or Avatrombopag or Plasmapheresis or Plasma Exchange or Lenalidomide or Thalidomide or Bortezomib or Vincristine or Carfilzomib or Decitabine or Azacitidine or CAR-T cell therapy or FasTCAR-T GC012F or CABA-201 or Gotu Kola).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 8) 1 and 6 and 7

Continued

Cochrane Library	1) MeSH descriptor: [Lupus Erythematosus, Systemic] explode all trees 2) Systemic Next lupus Next Erythematosus OR SLE OR Lupus) 3) 1 OR 2 4) MeSH descriptor: [Cytopenia] explode all trees 5) MeSH descriptor: [Anemia] explode all trees 6) MeSH descriptor: [Thrombocytopenia] explode all trees 7) MeSH descriptor: [Leukopenia] explode all trees 8) Anemia OR Leukopenia OR thrombocytopenia 9) 4 OR 5 OR 6 OR 7 OR 8 10) (Corticosteroids or Prednisone or Prednisolone or Methylprednisolone or Hydrocortisone or Dexamethasone or Immunosuppressants or Azathioprine or Mycophenolate mofetil or MMF or Mycophenolic acid or MPA or Methotrexate or Cyclophosphamide or Leflunomide or Chlorambucil or Biologics or B-cell targeted therapy or Belimumab or Rituximab or Obinutuzumab or Dapirolizumab or Blisibimod or Interferon-targeted therapy or Anifrolumab or Sifalimumab or Complement inhibitors or Eculizumab or JAK Inhibitors or Tofacitinib or Baricitinib or Upadacitinib or Antimalarials or Hydroxychloroquine or Chloroquine or Immunomodulators or Tacrolimus or Cyclosporine or Voclosporin or Intravenous Immunoglobulin or IVIG or Hematopoietic Growth Factors or Erythropoietin or EPO or Darbepoetin or Granulocyte colony-stimulating factor or G-CSF or Filgrastim or Pegfilgrastim or Thrombopoietin receptor agonists or Romiplostim or Eltrombopag or Avatrombopag or Plasmapheresis or Plasma Exchange or Lenalidomide or Thalidomide or Bortezomib or Vincristine or Carfilzomib or Decitabine or Azacitidine or CAR-T cell therapy or FasTCAR-T GC012F or CABA-201 or Gotu Kola).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 11) 3 AND 9 AND 10

Table S2. Quality Assessment Using the NIH Tools.

No.	Author (Year)	NIH Tool Used	Total Checklist Items	Score	Overall rating
1	**Toker Dincer *et al.* (2025)** [7]	NIH Case Series Checklist	9	8/9	Good
2	**Li *et al.* (2023)** [8]	NIH Case Series Checklist	9	9/9	Good
3	**Shobha *et al.* (2020)** [9]	NIH Case Series Checklist	9	8/9	Good
4	**Kello *et al.* (2019)** [10]	NIH Case Series Checklist	9	7/9	Good
5	**Park *et al.* (2017)** [11]	NIH Case Series Checklist	9	7/9	Good
6	**Jiang *et al.* (2015)** [12]	NIH Case Series Checklist	9	8/9	Good
7	**Jovancevic *et al.* (2013)** [13]	NIH Case Series Checklist	9	8/9	Good
8	**Calderón Saldierna *et al.* (2009)** [14]	NIH Case Series Checklist	9	7/9	Good
9	**Aleem *et al.* (2006)** [15]	NIH Case Series Checklist	9	7/9	Good
10	**Gomard-Mennesson *et al.* (2006)** [16]	NIH Case Series Checklist	9	9/9	Good
11	**Lambotte *et al.* (2006)** [17]	NIH Case Series Checklist	9	7/9	Good
12	**Majithia *et al.* (2006)** [18]	NIH Case Series Checklist	9	7/9	Good
13	**Quartuccio *et al.* (2006)** [19]	NIH Case Series Checklist	9	8/9	Good
14	**Arnal *et al.* (2002)** [20]	NIH Case Series Checklist	9	9/9	Good
15	**Euler *et al.* (1997)** [21]	NIH Case Series Checklist	9	6/9	Fair

Continued

16	**Wong (1991)** [22]	NIH Case Series Checklist	9	9/9	Good
17	**Boumpas *et al.* (1990)** [23]	NIH Case Series Checklist	9	8/9	Good
18	**Maier *et al.* (1990)** [24]	NIH Case Series Checklist	9	7/9	Good
19	**Raguin *et al.* (1989)** [25]	NIH Case Series Checklist	9	7/9	Good
20	**West *et al.* (1988)** [26]	NIH Case Series Checklist	9	9/9	Good
21	**Hall *et al.* (1985)** [27]	NIH Case Series Checklist	9	9/9	Good
22	**Homan *et al.* (1978)** [28]	NIH Case Series Checklist	9	8/9	Good
23	**Cimé-Aké *et al.* (2024)** [29]	NIH Cohort Checklist	14	914	Fair
24	**Wu *et al.* (2024)** [30]	NIH Cohort Checklist	14	9/14	Fair
25	**Jiang *et al.* (2022)** [31]	NIH Cohort Checklist	14	8/14	Fair
26	**Roussotte, 2022** [32]	NIH Cohort Checklist	14	8/14	Fair
27	**Lobbes *et al.* (2021)** [33]	NIH Cohort Checklist	14	7/14	Fair
28	**Zhang *et al.* (2021)** [34]	NIH Cohort Checklist	14	8/14	Fair
29	**Wu *et al.* (2019)** [35]	NIH Cohort Checklist	14	9/14	Fair
30	**Li *et al.* (2018)** [36]	NIH Cohort Checklist	14	9/14	Fair
31	**Serris *et al.* (2018)** [37]	NIH Cohort Checklist	14	9/14	Fair
32	**Sun *et al.* (2018)** [38]	NIH Cohort Checklist	14	10/14	Good
33	**Barrera-Vargas *et al.* (2017)** [39]	NIH Cohort Checklist	14	7/14	Fair
34	**Subedi *et al.* (2015)** [40]	NIH Cohort Checklist	14	9/14	Fair
35	**Zhou *et al.* (2013)** [41]	NIH Cohort Checklist	14	8/14	Fair
36	**Chen *et al.* (2011)** [42]	NIH Cohort Checklist	14	9/14	Fair
37	**Aviña-Zubieta *et al.* (2003)** [43]	NIH Cohort Checklist	14	9/14	Fair

Abbreviations: NIH, National Institutes of Health.