International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Cytokine Storm in Autoimmune Diseases: Immunopathogenesis, Clinical Implications, and Targeted Therapeutic Strategies

Aarti Verma[1], Prof. Dr. Vineeta Batra[2], Prof. Dr. Jayanand Jayanand[3]

[1]Researcher, Pathology, G B PANT HOSPITAL
[2]HOD, Pathology, G B PANT HOSPITAL
[3]Professor, Biotechnology, Shobhit Institute of Engineering and Technology

Abstract

Cytokine storm syndromes associated with autoimmune and autoinflammatory diseases represent a heterogeneous group of hyperinflammatory disorders characterized by dysregulated innate and adaptive immune responses, excessive cytokine production, and life-threatening systemic inflammation. From an immunological perspective, these syndromes most commonly manifest as Macrophage Activation Syndrome (MAS), secondary hemophagocytic lymphohistiocytosis (sHLH), cytokine release syndrome–like states, and fulminant hyperferritinemic syndromes. These conditions arise through a complex interplay of genetic susceptibility, immune dysregulation, and disease-specific inflammatory triggers. Key pathogenic pathways involve aberrant activation of macrophages, neutrophils, cytotoxic T lymphocytes, and inflammasome signaling, leading to excessive production of IL-1β, IL-6, IL-18, TNF-α, and IFN-γ.

This review synthesizes current mechanistic insights into cytokine storm syndromes across autoimmune and autoinflammatory diseases, with particular emphasis on immune signaling pathways, disease-specific inflammatory signatures, and emerging precision-targeted therapies. In addition, the review highlights similarities and distinctions between MAS, sHLH, and cytokine release syndromes to improve diagnostic recognition and therapeutic stratification. Although elevated cytokine levels correlate with disease severity, serum cytokine profiling alone may not reliably predict therapeutic response, emphasizing the need for integrated biomarker-based approaches.

Current therapeutic strategies are increasingly shifting from broad immunosuppression to precision-targeted immunomodulation, including IL-1β blockade, IL-6 inhibition, IFN-γ neutralization, Janus kinase (JAK) inhibition with ruxolitinib, and emerging inflammasome-directed therapies. This review also discusses evolving biomarker-driven and mechanism-based treatment paradigms that may improve early diagnosis, risk stratification, and individualized therapy. A deeper understanding of the immunopathogenesis of cytokine storm syndromes may facilitate the development of more effective targeted interventions and improve outcomes in severe autoimmune hyperinflammatory diseases.

Introduction

Cytokine storm syndromes encompass a spectrum of hyperinflammatory conditions that arise from uncontrolled activation of innate and adaptive immune responses.Although infectious diseases, malignancies, and cellular immunotherapies are well-recognized triggers, cytokine storm is increasingly recognized as a severe complication of autoimmune and autoinflammatory diseases [1-3]. Importantly,

the mechanisms initiating hyperinflammation differ among these disorders, even though they converge on a common phenotype characterized by excessive cytokine production, immune-mediated tissue injury, and multiorgan dysfunction [4].

Within rheumatology, macrophage activation syndrome (MAS) represents the prototypical autoimmune-associated cytokine storm syndrome and is generally considered a subtype of secondary hemophagocytic lymphohistiocytosis (sHLH) [5-8,9]. Although these entities share many clinical and immunological features, they are not synonymous. MAS most commonly complicates systemic juvenile idiopathic arthritis and adult-onset Still disease but is increasingly recognized in systemic lupus erythematosus and selected inflammatory myopathies [10-15]. Distinguishing MAS from infection or severe autoimmune flare remains one of the greatest challenges in clinical practice [16].

The progression from chronic autoimmune inflammation to fulminant cytokine storm is not inevitable and reflects the interaction of disease-specific immune mechanisms, environmental triggers, and host susceptibility. Persistent activation of macrophages, cytotoxic T lymphocytes, natural killer cells, and autoreactive lymphocytes generates self-amplifying inflammatory circuits involving IL-1β, IL-6, IL-18, TNF, IFN-γ, and other mediators [5,8,17-19].

This review summarizes current understanding of the immunopathogenesis of cytokine storm syndromes in autoimmune diseases, with particular emphasis on macrophage activation syndrome as the principal rheumatologic manifestation. We discuss disease-specific mechanisms, emerging diagnostic approaches, and evolving therapeutic strategies, while highlighting current challenges and future directions for precision medicine.

Methodological Framework for Evidence Selection and Synthesis

This narrative review was developed through a comprehensive literature search to summarize current evidence on cytokine storm syndromes in autoimmune diseases, with particular emphasis on macrophage activation syndrome (MAS), immunopathogenesis, diagnostic approaches, and emerging therapeutic strategies. The review was designed to provide an integrated overview of mechanistic and clinical advances rather than a formal systematic review or meta-analysis.

Electronic searches were performed using PubMed/MEDLINE, Scopus, and Web of Science. The search strategy combined Medical Subject Headings (MeSH) and free-text terms including *cytokine storm syndrome*, *cytokine storm*, *macrophage activation syndrome*, *secondary hemophagocytic lymphohistiocytosis*, *systemic lupus erythematosus*, *adult-onset Still disease*, *systemic juvenile idiopathic arthritis*, *dermatomyositis*, *ANCA-associated vasculitis*, *rheumatoid arthritis*, *autoimmune diseases*, *inflammasome*, *IL-1*, *IL-6*, *IL-18*, *interferon-γ*, *JAK inhibitors*, *biomarkers*, and *CAR-T cell therapy*.

Priority was given to peer-reviewed original research articles, randomized clinical trials, observational studies, international guidelines, and high-quality review articles published in English. Landmark studies that established the biological basis of cytokine storm syndromes and macrophage activation syndrome were retained irrespective of publication year because of their continuing relevance, whereas recent publications (2023–2026) were preferentially included to capture advances in disease mechanisms, biomarkers, and targeted therapies.

Studies focusing exclusively on infectious cytokine storm syndromes, primary hemophagocytic lymphohistiocytosis without relevance to autoimmune diseases, or non-peer-reviewed literature were included only when they provided essential mechanistic insights applicable to autoimmune cytokine storm. Evidence was critically synthesized to compare shared and disease-specific inflammatory pathways

across autoimmune disorders and to highlight their implications for diagnosis and precision-targeted therapeutic interventions.

3. Conceptual Framework of Cytokine Storm Syndromes

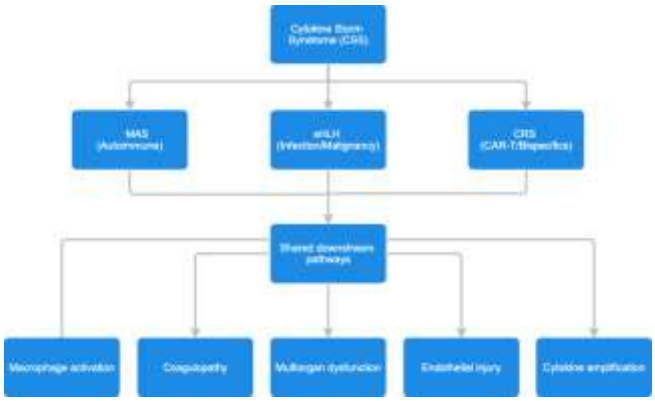
Cytokine storm syndrome (CSS) is an umbrella term describing a spectrum of life-threatening hyperinflammatory disorders characterized by excessive and dysregulated activation of the immune system, resulting in uncontrolled production of pro-inflammatory cytokines, widespread tissue injury, and multiorgan dysfunction. [1-3] Although the initiating triggers vary considerably, the downstream immunopathological cascade is characterized by sustained activation of innate and adaptive immune cells, amplification of inflammatory signaling, endothelial dysfunction, coagulation abnormalities, and progressive organ damage. Consequently, CSS should be regarded as a shared clinical phenotype rather than a single disease entity [4]. Within rheumatology, macrophage activation syndrome (MAS) represents the prototypical autoimmune-associated cytokine storm syndrome and is generally classified as a subtype of secondary hemophagocytic lymphohistiocytosis (sHLH). MAS develops in the setting of autoimmune or autoinflammatory diseases, most commonly systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still disease (AOSD), but is increasingly recognized in systemic lupus erythematosus (SLE) [6,12,14]

Secondary hemophagocytic lymphohistiocytosis (sHLH) comprises a heterogeneous group of acquired hyperinflammatory syndromes triggered by autoimmune diseases, infections, malignancies, or other forms of immune dysregulation. Among these, macrophage activation syndrome (MAS) represents the rheumatologic subtype of sHLH, sharing its core clinical and immunopathological features while differing in the underlying trigger. In autoimmune diseases, persistent immune activation creates a pro-inflammatory environment that predisposes susceptible individuals to uncontrolled macrophage activation and cytokine amplification, distinguishing MAS from infection- or malignancy-associated forms of sHLH as shown in figure 1 [6,9] .

Despite these distinctions, cytokine storm syndrome (CSS), macrophage activation syndrome (MAS), secondary hemophagocytic lymphohistiocytosis (sHLH), and cytokine release syndrome (CRS) share several converging immunological features, including excessive activation of macrophages and monocytes, dysregulated production of pro-inflammatory cytokines such as IL-1β, IL-6, IL-18, TNF-α, IFN-γ, and GM-CSF, endothelial dysfunction, coagulation abnormalities, and progressive tissue injury [1,6]. However, the relative contribution of individual cytokines and immune pathways differs according to the underlying disease. For instance, IL-18 and IFN-γ play central roles in Still disease-associated MAS, whereas the immune response in SLE is characterized by distinct pathogenic mechanisms that shape its hyperinflammatory phenotype [19]. These differences provide the biological rationale for disease-specific targeted therapies and underscore that cytokine storm syndromes represent a heterogeneous group of disorders rather than a single disease entity .

Establishing a clear conceptual distinction between these overlapping hyperinflammatory syndromes provides the framework for understanding the disease-specific mechanisms discussed in subsequent sections. Although they converge on a common phenotype of uncontrolled systemic inflammation, their initiating events, dominant immune pathways, genetic susceptibility, and therapeutic responses differ substantially, emphasizing the need for individualized diagnostic and treatment strategies.

Figure 1. Conceptual Framework of Cytokine Storm Syndromes and Their Shared Downstream Pathophysiological Pathways



Legend

Figure 1. Conceptual Framework of Cytokine Storm Syndromes and Their Shared Downstream Pathophysiological Pathways. Cytokine storm syndrome (CSS) encompasses several clinically distinct hyperinflammatory disorders, including macrophage activation syndrome (MAS) associated with autoimmune diseases, secondary hemophagocytic lymphohistiocytosis (sHLH) triggered by infections or malignancies, and cytokine release syndrome (CRS) following chimeric antigen receptor T-cell (CAR-T) or bispecific antibody therapy. Despite differing initiating triggers, these syndromes converge on common downstream mechanisms characterized by macrophage activation, cytokine amplification, endothelial injury, coagulopathy, multiorgan dysfunction, and systemic hyperinflammation.

4. Shared Immunopathogenesis of Cytokine Storm Syndromes

4.1 Loss of Immune Homeostasis: The Initiating Event

The development of cytokine storm syndrome represents the culmination of progressive immune dysregulation rather than the consequence of a single pathogenic event. Under physiological conditions, innate and adaptive immune responses are tightly regulated by immune tolerance, anti-inflammatory cytokines, regulatory T cells, and efficient cytotoxic clearance of activated immune cells [1]. These mechanisms ensure that inflammatory responses remain proportionate to the initiating stimulus and resolve following pathogen elimination or tissue repair. In autoimmune diseases, however, persistent autoantigen exposure, defective immune tolerance, chronic activation of innate immune pathways, and impaired resolution of inflammation progressively erode these regulatory mechanisms, creating a permissive environment for uncontrolled systemic hyperinflammation [1,2].

The transition from chronic autoimmune inflammation to cytokine storm generally requires multiple converging events. Continuous activation of antigen-presenting cells, macrophages, dendritic cells, neutrophils, and autoreactive T and B lymphocytes establishes self-sustaining inflammatory circuits characterized by excessive production of IL-1β, IL-6, IL-18, TNF-α, IFN-γ, GM-CSF, and multiple chemokines [20]. These mediators amplify immune-cell recruitment and activation through positive feedback mechanisms, resulting in endothelial activation, coagulation abnormalities, metabolic dysregulation, tissue injury, and eventually multiorgan dysfunction [20,21]. Importantly, while the downstream inflammatory phenotype is broadly shared, the initiating immunological pathways differ

substantially among autoimmune diseases, explaining the heterogeneity in clinical presentation and therapeutic responses [20,21].

Increasing evidence suggests that cytokine storm syndrome results from profound dysregulation of immune homeostasis rather than the overproduction of a single cytokine. Under physiological conditions, innate and adaptive immune responses are tightly coordinated to maintain controlled inflammation and facilitate its resolution. However, persistent immune activation can overwhelm these regulatory processes, resulting in self-amplifying inflammatory circuits that drive systemic hyperinflammation. This concept provides the mechanistic rationale for therapeutic strategies targeting multiple inflammatory pathways rather than a single cytokine or signaling mediator **[1,2,22]**

.**4.2 Innate Immune Activation:** The First Driver of Cytokine Storm

Innate immune activation represents an early and central event in the development of cytokine storm syndromes. In autoimmune diseases, persistent exposure to endogenous danger signals activates pattern-recognition receptors (PRRs), particularly Toll-like receptors (TLRs), on innate immune cells, leading to sustained production of pro-inflammatory cytokines [2,20]. Unlike acute inflammatory responses that resolve after elimination of the initiating stimulus, autoimmune diseases provide continuous immune stimulation that perpetuates activation of innate immune pathways and progressively amplifies systemic inflammation [20,23].

Macrophages are the principal effector cells driving cytokine storm syndromes [5,6]. Following activation, they produce large amounts of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, IL-18, and IFN-γ-inducing mediators, thereby amplifying inflammatory signaling and recruiting additional immune cells [18,19]. In macrophage activation syndrome (MAS), persistent macrophage activation results in hemophagocytosis, hyperferritinemia, cytopenias, coagulopathy, and progressive multiorgan dysfunction [24]. Rather than representing an isolated abnormality, macrophage activation reflects profound dysregulation of both innate and adaptive immune responses.

Neutrophils also participate in autoimmune inflammation through the release of inflammatory mediators and formation of neutrophil extracellular traps (NETs), which have been implicated in the pathogenesis of diseases such as systemic lupus erythematosus and ANCA-associated vasculitis [20,25]. Although NETs contribute to sustained immune activation and tissue injury, their precise role in the development of cytokine storm remains incompletely understood and is likely to vary among autoimmune diseases [26].

Inflammasomes provide another critical link between innate immune activation and cytokine storm [10]. Multiprotein complexes such as the NLRP3 and NLRC4 inflammasomes activate caspase-1, promoting the maturation and secretion of IL-1β and IL-18, two cytokines that play central roles in the development of hyperinflammation [18,19]. Inflammasome activation is especially prominent in adult-onset Still disease and systemic juvenile idiopathic arthritis, where excessive IL-18 production contributes to macrophage activation and the development of MAS [12]. Nevertheless increasing evidence indicates that inflammasome activation also contributes to cytokine amplification in several autoimmune diseases, although the relative importance of specific inflammasome pathways varies according to the underlying disease [27].

Endothelial activation contributes to the propagation of cytokine storm by amplifying systemic inflammation and promoting vascular dysfunction [1-3]. Pro-inflammatory cytokines, particularly IL-1β, IL-6, TNF-α, and IFN-γ, increase vascular permeability and facilitate recruitment of inflammatory cells, thereby exacerbating tissue injury and organ dysfunction. Consequently, the interaction between activated

immune cells and the vascular endothelium contributes substantially to disease severity in cytokine storm syndromes [21].

4.3 Adaptive Immune Dysregulation and Cytokine Amplification

Although innate immune activation initiates the inflammatory cascade, sustained cytokine storm in autoimmune diseases is reinforced by extensive involvement of the adaptive immune system. Continuous antigen presentation by activated dendritic cells and macrophages promotes the expansion of autoreactive $CD4^+$ and $CD8^+$ T lymphocytes, while persistent B-cell activation leads to autoantibody production and immune complex formation [28]. Rather than functioning independently, innate and adaptive immune responses establish reciprocal activation loops that perpetuate inflammation and progressively overwhelm physiological immunoregulatory mechanisms [29,30].

Activated $CD4^+$ T-helper cells play a pivotal role in orchestrating cytokine amplification by producing cytokines such as IFN-γ, IL-17, granulocyte–macrophage colony-stimulating factor (GM-CSF), and TNF-α [29,30]. These mediators further activate macrophages, neutrophils, endothelial cells, and antigen-presenting cells, thereby intensifying cytokine production and inflammatory tissue damage [32]. The predominance of specific T-cell subsets varies across autoimmune diseases [29,30]. For example, Th1-mediated IFN-γ responses are particularly important in macrophage activation syndrome (MAS), whereas Th17-associated inflammation contributes significantly to rheumatoid arthritis and selected inflammatory myopathies [5]. These disease-specific immune signatures partly explain differences in clinical manifestations and responses to targeted immunomodulatory therapies [29,30].

B lymphocytes contribute to cytokine storm through mechanisms that extend beyond autoantibody production[28-30]. Activated B cells function as efficient antigen-presenting cells, secrete pro-inflammatory cytokines including IL-6 and TNF-α, and promote sustained activation of autoreactive T cells [29,30]. In systemic lupus erythematosus (SLE), immune complexes generated by pathogenic autoantibodies activate Fc receptors and complement pathways, leading to further stimulation of macrophages, plasmacytoid dendritic cells, and neutrophils [21,28]. This creates a self-amplifying inflammatory circuit characterized by persistent type I interferon production, complement activation, and progressive tissue injury [21,28].

Regulatory T cells (Tregs), which normally suppress excessive immune activation and maintain peripheral tolerance, are functionally impaired in many autoimmune diseases [29,30,33]. Reduced suppressive capacity of Tregs, together with persistent activation of effector T cells and macrophages, facilitates unchecked cytokine production and prolongs inflammatory responses [29,30]. Failure of these regulatory pathways permits inflammatory amplification to become self-sustaining, increasing the likelihood of progression from chronic autoimmune inflammation to systemic hyperinflammation [1,29,30,33].

A central feature of adaptive immune dysregulation is the activation of intracellular signaling pathways that integrate multiple cytokine networks [22,29,30]. Among these, the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway represents a critical signaling hub through which cytokines such as IFN-γ, IL-6, IL-2, IL-10, and GM-CSF exert their biological effects [22]. Persistent activation of JAK–STAT signaling enhances immune-cell proliferation, macrophage activation, and cytokine production, thereby reinforcing inflammatory feedback loops [22,29]. Recognition of the central role of this pathway has provided the biological rationale for the successful use of JAK inhibitors in selected patients with refractory cytokine storm syndromes, highlighting the therapeutic importance of targeting shared signaling pathways rather than individual cytokines alone [22,29,30].

Collectively, these findings demonstrate that adaptive immune dysregulation not only sustains cytokine storm but also determines disease-specific inflammatory phenotypes. The interaction between autoreactive lymphocytes, activated macrophages, and inflammatory cytokine networks establishes self-perpetuating immune circuits that ultimately drive tissue injury and multiorgan dysfunction. Understanding these interactions is essential for identifying therapeutic targets capable of interrupting cytokine amplification before irreversible organ damage occurs.

4.4 Defective Cytotoxic Function, Natural Killer Cells, and the Two-Hit Hypothesis

Although persistent activation of innate and adaptive immune pathways establishes the inflammatory milieu required for cytokine storm, most patients with autoimmune diseases do not develop macrophage activation syndrome (MAS) [6,29,30]. This observation indicates that chronic inflammation alone is insufficient to trigger fulminant hyperinflammation [6,9]. Increasing evidence suggests that progression to MAS results from the interaction between sustained immune activation and impaired mechanisms responsible for terminating immune responses, particularly the cytotoxic functions of natural killer (NK) cells and $CD8^+$ cytotoxic T lymphocytes [5,6,9,17].

Under physiological conditions, NK cells and cytotoxic T lymphocytes eliminate infected, activated, or dysfunctional cells through perforin- and granzyme-mediated cytolysis, thereby limiting antigen presentation and preventing excessive immune activation[6,9,17]. Efficient cytotoxic function is therefore essential for restoring immune homeostasis following an inflammatory response [5,17]. Impaired cytotoxic activity allows activated antigen-presenting cells and macrophages to persist, resulting in prolonged T-cell stimulation, continuous cytokine production, and progressive amplification of inflammatory signaling [5,6,9,17]. Persistent macrophage activation subsequently drives excessive secretion of IL-1β, IL-6, IL-18, IFN-γ, TNF-α, and other inflammatory mediators, ultimately culminating in the clinical manifestations of MAS [6,18,19].

Studies of familial hemophagocytic lymphohistiocytosis (fHLH) have identified pathogenic variants in genes encoding proteins required for cytotoxic granule exocytosis, including **PRF1, UNC13D, STX11, STXBP2**, and **RAB27A [5,9,17]**. While biallelic mutations in these genes cause primary HLH, accumulating evidence indicates that heterozygous or hypomorphic variants may also be present in a subset of patients with autoimmune-associated MAS [6,17]. These variants generally do not produce disease independently but lower the threshold for uncontrolled immune activation when combined with persistent autoimmune inflammation or additional environmental triggers [6,9,17]. Consequently, defective cytotoxicity should be viewed as a predisposing factor rather than the sole cause of autoimmune cytokine storm [6,9,17].

This concept forms the basis of the **two-hit hypothesis** of macrophage activation syndrome [6,9,17]. The first hit consists of chronic immune dysregulation associated with the underlying autoimmune disease, which establishes a sustained pro-inflammatory environment through continuous activation of innate and adaptive immune pathways [6.28-30]. The second hit is provided by additional triggers such as infection, uncontrolled disease activity, certain medications, or inherited defects in cytotoxic function that overwhelm residual immunoregulatory capacity [5,6,9,17]. Together, these factors initiate a self-perpetuating cycle of macrophage activation, cytokine amplification, progressive tissue injury, and multiorgan dysfunction.

Importantly, the contribution of impaired cytotoxic function varies among autoimmune diseases [6,9,17]. In adult-onset Still disease and systemic juvenile idiopathic arthritis, defects in NK-cell function and excessive IL-18 production are strongly associated with MAS susceptibility [6,12,18,19,34]. In contrast,

systemic lupus erythematosus, and ANCA-associated vasculitis appear to progress to cytokine storm through more heterogeneous mechanisms involving immune complexes, complement activation, interferon signaling, NET formation, and macrophage activation [20,25,35]. These observations emphasize that defective cytotoxicity represents one component of a broader network of pathogenic mechanisms rather than a universal explanation for autoimmune cytokine storm [6,9,17,35].

Recognition of impaired cytotoxic function has important therapeutic implications [6,9,17]. Early identification of patients with reduced NK-cell activity, persistent hyperferritinemia, rapidly rising inflammatory markers, or suspected genetic susceptibility may facilitate prompt initiation of targeted immunomodulatory therapy before irreversible organ damage develops [6,17,24,36]. Furthermore, understanding the interaction between genetic susceptibility and inflammatory triggers provides a mechanistic framework for individualized risk stratification and precision medicine in autoimmune-associated cytokine storm syndromes.

5.1 Systemic Lupus Erythematosus: Immune Complex–Driven Hyperinflammation

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by loss of immune tolerance, autoantibody production, immune-complex deposition, complement activation, and chronic inflammation [20,28]. Although most patients experience a relapsing–remitting disease course, a subset develops severe hyperinflammatory complications, including macrophage activation syndrome (MAS), which is associated with substantial morbidity and mortality [6,20,28]. Unlike adult-onset Still disease, where inflammasome activation predominates, cytokine storm in SLE results from the convergence of immune-complex–mediated inflammation, type I interferon signaling, complement dysregulation, neutrophil extracellular trap (NET) formation, and macrophage activation [6,18,19,20,37].

A defining feature of SLE is the formation of circulating immune complexes composed of autoantibodies directed against nuclear antigens [20,28]. These immune complexes activate Fcγ receptors on macrophages and dendritic cells while simultaneously triggering the classical complement pathway, generating the anaphylatoxins C3a and C5a that amplify leukocyte recruitment and inflammatory activation [20,28]. Plasmacytoid dendritic cells exposed to nucleic acid-containing immune complexes produce large quantities of type I interferons, particularly interferon-α, which promote dendritic-cell maturation, autoreactive lymphocyte activation, and sustained cytokine production [20,28]. This interferon-driven inflammatory environment represents a central pathogenic mechanism distinguishing SLE from many other autoimmune diseases [20,28].

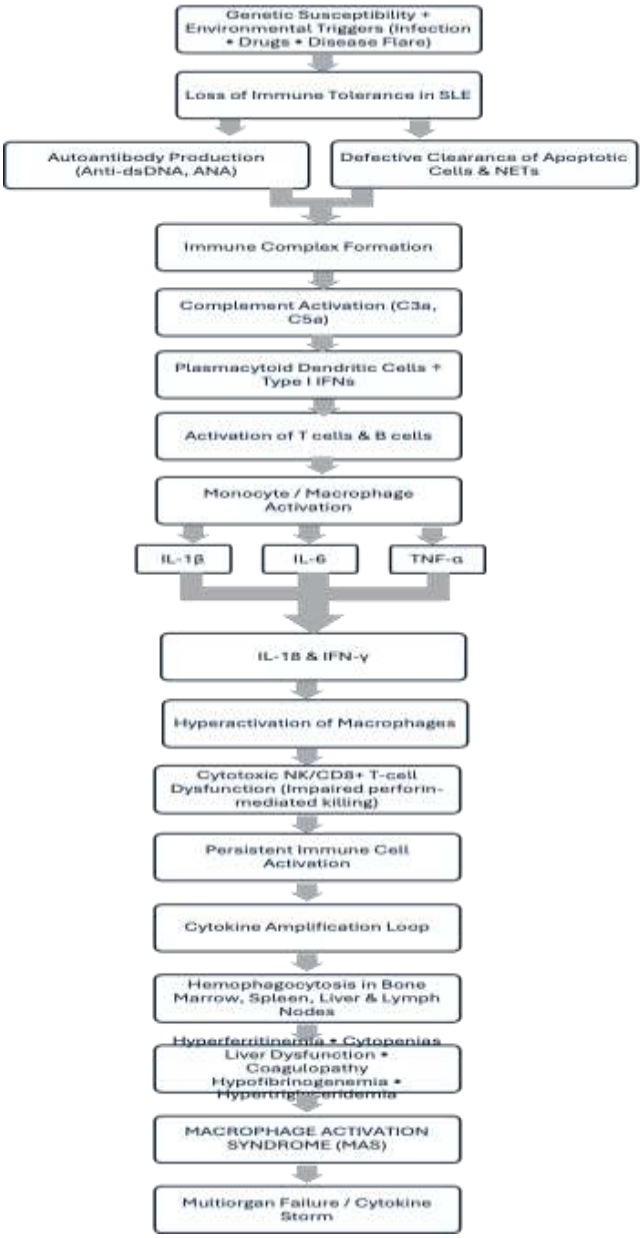
Neutrophils further amplify inflammation through dysregulated formation of neutrophil extracellular traps (NETs) [20,28,34]. Persistent NETosis exposes nuclear autoantigens, activates complement pathways, stimulates plasmacytoid dendritic cells, and perpetuates interferon signaling, thereby establishing a self-reinforcing inflammatory circuit [34]. In addition, activated macrophages release IL-1β, IL-6, TNF-α, IL-18, and other inflammatory mediators that further recruit immune cells and promote endothelial dysfunction [6,20,28]. In susceptible patients, these interacting pathways overwhelm physiological immunoregulatory mechanisms, resulting in uncontrolled macrophage activation and progression to cytokine storm [6,20,28].

Although MAS remains relatively uncommon in SLE compared with Still disease, several factors increase susceptibility, including uncontrolled disease activity, severe infection, complement consumption, persistent hyperferritinemia, impaired NK-cell function, and inherited variants affecting cytotoxic lymphocyte function [6,17,20,24,28]. The clinical distinction between lupus flare, severe infection, and

MAS remains particularly challenging because these conditions share overlapping clinical features, including fever, cytopenias, hepatic dysfunction, and elevated inflammatory markers [6,20,28]. Consequently, early recognition requires careful integration of clinical findings with laboratory parameters such as ferritin, triglycerides, fibrinogen, soluble IL-2 receptor, complement levels, and disease-specific autoantibodies [6,17,20,24,35,38].

Recognition of the distinct immunopathology of SLE-associated cytokine storm has important therapeutic implications. While corticosteroids remain the cornerstone of treatment, increasing understanding of type I interferon signaling, complement activation, IL-1, IL-6, IFN-γ, and JAK–STAT pathways has expanded opportunities for targeted immunomodulation in refractory disease. Emerging biologic agents and precision-based therapeutic approaches are expected to improve outcomes by interrupting disease-specific inflammatory pathways before irreversible organ damage occurs.

Figure 2. Proposed immunopathogenic pathway leading to macrophage activation syndrome (MAS) in systemic lupus erythematosus (SLE)



Legend: Genetic susceptibility and environmental triggers (e.g., infections, drugs, or disease flares) lead to the loss of immune tolerance in SLE, resulting in autoantibody production and defective clearance of apoptotic cells and neutrophil extracellular traps (NETs). The formation of immune complexes activates the complement cascade (C3a and C5a), which promotes plasmacytoid dendritic cell activation and excessive type I interferon production. Subsequent activation of T and B lymphocytes and monocytes/macrophages drives the release of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, IL-18, and IFN-γ. Elevated IL-18 and IFN-γ further amplify macrophage activation, while impaired cytotoxic function of natural killer (NK) cells and $CD8^+$ T cells prevents effective termination of immune activation. This establishes a self-perpetuating cytokine amplification loop that leads to hemophagocytosis in the bone marrow, spleen, liver, and lymph nodes, resulting in hyperferritinemia, cytopenias, liver dysfunction, coagulopathy, hypofibrinogenemia, and hypertriglyceridemia. Collectively, these events culminate in macrophage activation syndrome (MAS) and, if uncontrolled, progress to cytokine storm and multiorgan failure.

Abbreviations: ANA, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA antibodies; NETs, neutrophil extracellular traps; IFN, interferon; NK, natural killer; IL, interleukin; TNF-α, tumor necrosis factor-α; MAS, macrophage activation syndrome; SLE, systemic lupus erythematosus.

5.2 Adult-Onset Still Disease and Systemic Juvenile Idiopathic Arthritis: Inflammasome-Driven Hyperinflammation

Adult-onset Still disease (AOSD) and systemic juvenile idiopathic arthritis (sJIA) represent the autoimmune/autoinflammatory disorders most strongly associated with macrophage activation syndrome (MAS) [6,10,12]. Unlike systemic lupus erythematosus, where adaptive immune dysregulation and immune-complex formation predominate, AOSD and sJIA are characterized primarily by dysregulated innate immune activation [10,12]. Excessive activation of macrophages, neutrophils, and monocytes results in profound production of pro-inflammatory cytokines, placing these diseases at particularly high risk for the development of cytokine storm [6,10,12,18,19].

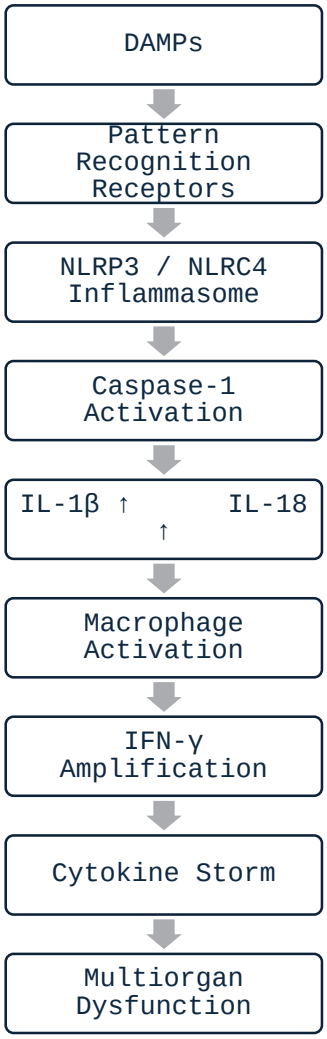
Activation of the innate immune system is initiated through recognition of endogenous danger-associated molecular patterns (DAMPs) by pattern-recognition receptors, leading to assembly of inflammasome complexes, particularly NLRP3 and, in selected patients, NLRC4 [6,10,12]. Inflammasome activation promotes caspase-1-mediated processing of pro-IL-1β and pro-IL-18 into their biologically active forms, generating a powerful inflammatory cascade that amplifies macrophage activation and systemic cytokine production [18,19]. Among these mediators, IL-18 has emerged as one of the most important biomarkers and pathogenic drivers of MAS, with circulating concentrations correlating closely with disease severity and the risk of hyperinflammatory complications [6,10,12,18,19].

The cytokine network in AOSD/sJIA is dominated by IL-1β, IL-6, IL-18, TNF-α, IFN-γ, and granulocyte–macrophage colony-stimulating factor (GM-CSF) [10,12,18,19,34] . IL-18 enhances natural killer (NK) cell and T-cell activation under physiological conditions; however, persistent elevation of IL-18 in susceptible individuals is accompanied by impaired NK-cell cytotoxicity, resulting in ineffective elimination of activated macrophages and antigen-presenting cells [12,18,19,34]. This failure of immune regulation perpetuates macrophage activation and creates a self-amplifying inflammatory loop that culminates in cytokine storm. Consequently, defective cytotoxic function and inflammasome activation should be regarded as complementary rather than independent mechanisms in the pathogenesis of MAS as shown in *Figure 3* [6,12,18,1934].

Several clinical and laboratory findings identify patients at increased risk of MAS [6,12,34]. Persistent fever, rapidly rising serum ferritin concentrations, thrombocytopenia, hypofibrinogenemia, elevated liver enzymes, hypertriglyceridemia, cytopenias, and declining erythrocyte sedimentation rate despite ongoing systemic inflammation should prompt immediate evaluation for evolving MAS [6,12,24, 32]. Hyperferritinemia is particularly informative in AOSD and sJIA, reflecting widespread macrophage activation and serving as both a disease activity marker and an indicator of poor prognosis [24]. Nevertheless, no single biomarker is sufficient for diagnosis, and interpretation should always be integrated with clinical findings and validated classification criteria.

The central role of IL-1β and IL-6 in disease pathogenesis has transformed the therapeutic landscape of AOSD and sJIA [10,12,34]. Biologic agents targeting IL-1 (anakinra, canakinumab), IL-6 (tocilizumab), and, in selected refractory cases, IFN-γ and JAK–STAT signaling have provided the biological rationale for the use of biologic therapies targeting IL-1, IL-6 and, in selected refractory cases, IFN-γ and JAK–STAT signaling [10,12,18,22,34]. IL-18 has also emerged as a potential therapeutic target because of its central role in the pathogenesis of MAS [19]. These advances illustrate how understanding disease-specific immunopathology can directly guide precision-based therapeutic strategies.

Figure 3. Pathogenesis of MAS in AOSD/sJIA



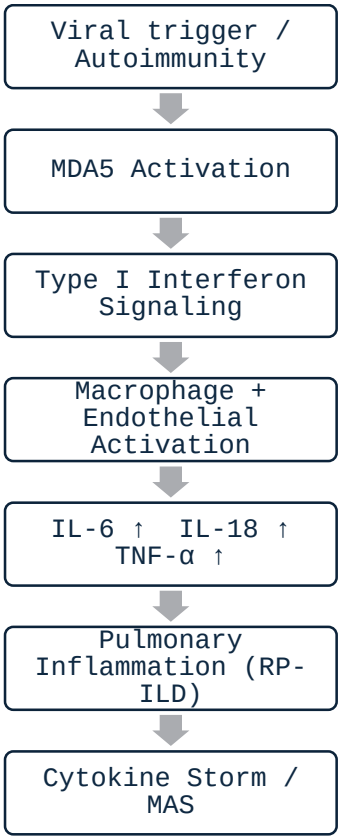
Legend: Damage-associated molecular patterns (DAMPs), released from injured or dying cells during tissue inflammation, are recognized by pattern recognition receptors (PRRs), leading to activation of the NLRP3 and NLRC4 inflammasomes. Inflammasome assembly promotes caspase-1 activation, which cleaves the inactive precursors of interleukin (IL)-1β and IL-18 into their biologically active forms. Elevated IL-1β and IL-18 initiate and sustain macrophage activation, while IL-18 further enhances interferon-γ (IFN-γ) production by natural killer (NK) cells and T lymphocytes. This establishes a feed-forward inflammatory loop characterized by excessive cytokine production, culminating in a cytokine storm that drives widespread tissue injury and multiorgan dysfunction. Dysregulated inflammasome signaling represents a central mechanism underlying hyperinflammation and macrophage activation syndrome (MAS) in several autoimmune and autoinflammatory disorders.
Abbreviations: DAMPs, damage-associated molecular patterns; PRRs, pattern recognition receptors; NLRP3, NOD-like receptor family pyrin domain-containing 3; NLRC4, NOD-like receptor family CARD domain-containing protein 4; IL, interleukin; IFN-γ, interferon-gamma; NK, natural killer.

5.3 Dermatomyositis: Interferon-Mediated Vascular Injury and Hyperinflammation

Dermatomyositis (DM) is a heterogeneous autoimmune inflammatory myopathy characterized by immune-mediated muscle inflammation, characteristic cutaneous manifestations, and variable involvement of multiple organ systems [40]. Among its clinical subtypes, anti-melanoma differentiation-associated gene 5 (anti-MDA5)-positive dermatomyositis is associated with the highest risk of cytokine storm, macrophage activation syndrome (MAS), and rapidly progressive interstitial lung disease (RP-ILD), all of which contribute significantly to morbidity and mortality [41]. Unlike adult-onset Still disease, where inflammasome activation predominates, hyperinflammation in dermatomyositis is driven primarily by dysregulated type I interferon responses, endothelial injury, and macrophage activation [5].Type I interferons play a central role in dermatomyositis pathogenesis [42]. Activation of cytosolic nucleic acid sensors and innate immune pathways induces sustained production of interferon-α and interferon-β, leading to enhanced expression of interferon-stimulated genes, activation of dendritic cells, macrophages, and autoreactive lymphocytes, and amplification of inflammatory cytokine networks. Persistent interferon signaling also promotes endothelial dysfunction, microvascular injury, and tissue ischemia, which are characteristic pathological features of dermatomyositis as shown in *Figure 4* [42].
Macrophages and activated monocytes further amplify inflammation through production of IL-1β, IL-6, IL-18, TNF-α, and other pro-inflammatory mediators [40]. Increasing evidence indicates that elevated serum ferritin, IL-18, CXCL9, CXCL10, and soluble CD163 correlate with disease severity and identify patients at increased risk of hyperinflammatory complications [42]. In anti-MDA5-positive disease, activated macrophages infiltrate pulmonary tissue and contribute to diffuse alveolar damage, explaining the strong association between cytokine storm and rapidly progressive interstitial lung disease[41].
Although macrophage activation syndrome is less common in dermatomyositis than in adult-onset Still disease, the mechanisms responsible for cytokine storm exhibit substantial overlap [12,40]. Persistent activation of innate immune pathways, defective immune regulation, excessive interferon signaling, and sustained macrophage activation establish self-perpetuating inflammatory circuits that can culminate in multiorgan dysfunction[40-42]. Environmental triggers, viral infections, and uncontrolled disease activity may further accelerate progression to fulminant hyperinflammation in susceptible individuals [12,34,40-42].

Recognition of these disease-specific pathogenic mechanisms has important therapeutic implications [40,41]. High-dose glucocorticoids remain the cornerstone of initial treatment; however, early combination therapy with calcineurin inhibitors, cyclophosphamide, rituximab, intravenous immunoglobulin, and Janus kinase (JAK) inhibitors has has become an important treatment strategy for patients with severe anti-MDA5-positive dermatomyositis and rapidly progressive interstitial lung disease [40,41]. Growing evidence also supports targeting interferon signaling pathways, reflecting the central role of type I interferons in disease pathogenesis [40,42]. Future therapeutic strategies are expected to benefit from improved understanding of disease-specific biomarkers and inflammatory pathways, which may facilitate earlier identification of high-risk patients and more individualized therapeutic approaches.

Figure 4. Immunopathogenesis of Cytokine Storm in Anti-MDA5-Positive Dermatomyositis



Legend: Viral infection or autoimmune activation stimulates melanoma differentiation-associated protein 5 (MDA5), a cytosolic pattern recognition receptor that recognizes viral double-stranded RNA. MDA5 activation initiates type I interferon (IFN-α/β) signaling, resulting in robust activation of macrophages and endothelial cells. These activated immune cells release high levels of pro-inflammatory cytokines, including interleukin (IL)-6, IL-18, and tumor necrosis factor-α (TNF-α), leading to amplification of the inflammatory response. In patients with anti-MDA5-associated disease, excessive cytokine production contributes to rapidly progressive interstitial lung disease (RP-ILD), characterized by severe pulmonary inflammation and diffuse alveolar damage. Persistent immune activation may culminate in cytokine storm and, in severe cases, macrophage activation syndrome (MAS), resulting in life-threatening systemic hyperinflammation.

Abbreviations: MDA5, melanoma differentiation-associated protein 5; IFN, interferon; IL, interleukin; TNF-α, tumor necrosis factor-α; RP-ILD, rapidly progressive interstitial lung disease; MAS, macrophage activation syndrome.

5.4 ANCA-Associated Vasculitis: Neutrophil Activation, NETosis, and Complement

ANCA-associated vasculitis (AAV), comprising granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis, is characterized by necrotizing inflammation of small- to medium-sized blood vessels resulting from dysregulated innate and adaptive immune responses [43]. Although cytokine storm and macrophage activation syndrome (MAS) are relatively uncommon complications of AAV, their occurrence is associated with rapidly progressive multiorgan dysfunction and poor clinical outcomes [43,44]. In contrast to systemic lupus erythematosus, where immune-complex deposition is the principal driver of inflammation, hyperinflammation in AAV is initiated by ANCA-mediated neutrophil activation, excessive neutrophil extracellular trap (NET) formation, complement amplification, and endothelial injury [43,44].

The pathogenic process begins when anti-neutrophil cytoplasmic antibodies directed against proteinase-3 (PR3) or myeloperoxidase (MPO) bind to primed neutrophils, inducing their activation and degranulation [43,44]. Activated neutrophils release reactive oxygen species, proteolytic enzymes, inflammatory cytokines, and neutrophil extracellular traps (NETs), which not only contribute directly to vascular injury but also expose autoantigens that sustain autoantibody production and perpetuate inflammation [43,44]. Persistent NETosis creates a self-amplifying inflammatory cycle through activation of macrophages, dendritic cells, and endothelial cells, thereby promoting excessive cytokine production and tissue damage as shown in *Figure 5* [44].

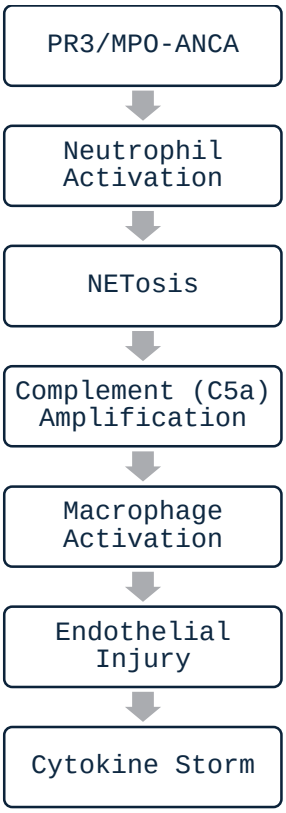
Complement activation, particularly through the alternative pathway, has emerged as a critical amplifier of inflammation in AAV. Generation of the anaphylatoxin C5a establishes a potent positive-feedback loop by priming additional neutrophils for ANCA-mediated activation, enhancing leukocyte recruitment, increasing endothelial permeability, and amplifying cytokine production. The coordinated interaction between activated neutrophils, complement components, macrophages, and endothelial cells results in progressive vascular inflammation, microvascular thrombosis, and multiorgan injury [43,44]. These findings provide the biological rationale for therapeutic strategies targeting complement activation in selected patients with severe AAV.

Although MAS is uncommon in AAV, persistent systemic inflammation, uncontrolled vasculitic activity, severe infection, and impaired immunoregulatory mechanisms may overwhelm physiological immune control, leading to uncontrolled macrophage activation and cytokine storm [5]. Elevated serum ferritin, IL-6, IL-18, TNF-α, soluble IL-2 receptor, and markers of complement activation may provide important clues to evolving hyperinflammation, particularly when accompanied by cytopenias, liver dysfunction, coagulopathy, or rapidly deteriorating organ function [36]. Early recognition remains challenging because these features often overlap with active vasculitis and severe infection.

Understanding the unique immunopathology of AAV has transformed therapeutic approaches [43,44]. High-dose glucocorticoids combined with rituximab or cyclophosphamide remain the foundation of remission induction, while targeted inhibition of the C5a receptor with avacopan provides a biologically rational approach to interrupt complement-mediated neutrophil activation [43]. Emerging evidence also supports investigation of therapies directed against NETosis, inflammatory cytokine signaling, and macrophage activation in patients with refractory hyperinflammatory disease [44]. These advances

illustrate how improved understanding of disease-specific pathogenic mechanisms is guiding the development of more targeted therapeutic strategies for severe AAV.

Figure 5. Proposed mechanism of cytokine storm in ANCA-associated vasculitis (AAV)



Legend: Anti-neutrophil cytoplasmic antibodies (ANCAs) directed against proteinase 3 (PR3) or myeloperoxidase (MPO) activate primed neutrophils, leading to excessive degranulation and the release of neutrophil extracellular traps (NETs) through NETosis. NETs expose autoantigens and amplify inflammation while activating the alternative complement pathway, generating C5a, a potent neutrophil chemoattractant and activator. The C5a–C5a receptor signaling axis establishes a positive feedback loop that further enhances neutrophil activation and promotes macrophage recruitment and activation. Activated macrophages release pro-inflammatory cytokines, contributing to endothelial injury, vascular inflammation, and tissue damage. Persistent immune activation culminates in a cytokine storm, which may result in severe systemic inflammation and multiorgan involvement in patients with ANCA-associated vasculitis.

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; PR3, proteinase 3; MPO, myeloperoxidase; NETs, neutrophil extracellular traps; C5a, complement component 5a.

5.5 Rheumatoid Arthritis: Chronic Cytokine Networks and Systemic Hyperinflammation

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and variable extra-articular manifestations [45]. Although macrophage activation syndrome (MAS) and fulminant cytokine storm are uncommon in RA compared with adult-onset Still disease or systemic lupus erythematosus, chronic activation of inflammatory cytokine networks provides important mechanistic insights into the development of systemic

hyperinflammation [6,45]. Indeed, RA has served as the prototype disease for understanding cytokine-mediated inflammation and the development of targeted biologic therapies [33].

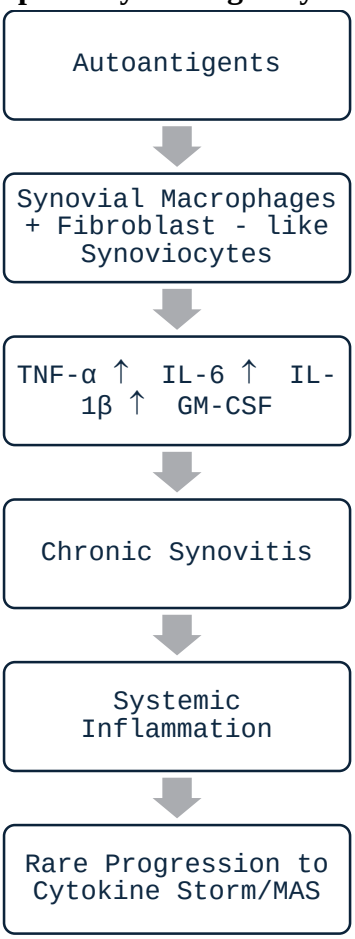
The pathogenesis of RA is driven by a complex interplay between innate and adaptive immune responses within the synovial microenvironment . Activated macrophages, fibroblast-like synoviocytes, dendritic cells, neutrophils, and autoreactive T and B lymphocytes produce a broad array of pro-inflammatory mediators, including TNF-α, IL-6, IL-1β, GM-CSF, IL-17, and multiple chemokines. Rather than acting independently, these cytokines establish interconnected signaling networks that sustain leukocyte recruitment, synovial hyperplasia, angiogenesis, osteoclast activation, and progressive tissue destruction. Persistent activation of these pathways may also contribute to systemic inflammatory manifestations extending beyond the joints as shown in *Figure 6* [33].

Among these cytokines, TNF-α and IL-6 occupy central positions in the inflammatory cascade . TNF-α promotes activation of endothelial cells, macrophages, fibroblast-like synoviocytes, and osteoclasts while stimulating the production of additional cytokines and matrix-degrading enzymes. IL-6 contributes to acute-phase responses, B-cell differentiation, T-cell activation, and systemic inflammation, whereas GM-CSF enhances macrophage and neutrophil activation. Collectively, these cytokine networks establish self-reinforcing inflammatory circuits that explain both chronic disease persistence and the effectiveness of cytokine-targeted therapies in RA [33].

Progression to cytokine storm or MAS in RA is uncommon and is generally associated with exceptional clinical circumstances, including uncontrolled systemic inflammation, severe infection, biologic therapy-related immune dysregulation, or overlap syndromes [6,33,34]. In such patients, sustained activation of macrophages and dysregulated cytokine production may result in fever, cytopenias, hyperferritinemia, liver dysfunction, coagulopathy, and multiorgan involvement. Because these features overlap with severe infection and active autoimmune disease, early recognition requires careful clinical assessment supported by inflammatory biomarkers and exclusion of alternative diagnoses [6,33,34].

The therapeutic evolution of RA has fundamentally transformed the management of immune-mediated inflammatory diseases [33]. The successful introduction of TNF inhibitors, IL-6 receptor antagonists, CTLA4-Ig, B-cell-depleting therapies, JAK inhibitors, and GM-CSF-targeted agents has demonstrated that selective interruption of cytokine signaling can effectively restore immune balance and prevent progressive tissue damage [33]. These therapeutic advances have provided an important conceptual framework for the treatment of cytokine storm syndromes in other autoimmune diseases, supporting the broader application of precision-targeted immunomodulation based on disease-specific inflammatory pathways [46].

Figure 6. Immunopathogenic pathway leading to cytokine storm in rheumatoid arthritis (RA)



Legend: Autoantigens initiate an aberrant immune response in genetically susceptible individuals, resulting in activation of synovial macrophages and fibroblast-like synoviocytes (FLS) within the joint. These activated cells produce high levels of pro-inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1β, and granulocyte–macrophage colony-stimulating factor (GM-CSF), which sustain leukocyte recruitment, synovial hyperplasia, and chronic inflammation. Persistent cytokine production drives chronic synovitis, leading to cartilage destruction, bone erosion, and systemic inflammatory manifestations. Although cytokine production in rheumatoid arthritis is typically localized to the synovium, severe uncontrolled inflammation or precipitating factors such as infection, biologic therapy withdrawal, or macrophage activation can rarely progress to cytokine storm or macrophage activation syndrome (MAS).

Abbreviations: RA, rheumatoid arthritis; FLS, fibroblast-like synoviocytes; TNF-α, tumor necrosis factor-α; IL, interleukin; GM-CSF, granulocyte–macrophage colony-stimulating factor; MAS, macrophage activation syndrome.

5.6 Other Autoimmune Diseases Associated with Cytokine Storm

Although cytokine storm syndrome is most extensively characterized in systemic lupus erythematosus, adult-onset Still disease, systemic juvenile idiopathic arthritis, dermatomyositis, and ANCA-associated vasculitis, similar hyperinflammatory complications have been reported in several other autoimmune and immune-mediated inflammatory disorders [6,34]. In these diseases, progression to cytokine storm remains

uncommon but highlights the convergence of diverse pathogenic pathways toward a shared endpoint of uncontrolled immune activation, excessive cytokine production, and multiorgan dysfunction [6,34].

Systemic sclerosis (SSc) is primarily characterized by immune dysregulation, microvascular injury, and progressive fibrosis [47]. Hyperinflammatory manifestations are uncommon; however, severe disease may be accompanied by macrophage activation, endothelial dysfunction, and elevated circulating concentrations of IL-6, transforming growth factor-β (TGF-β), and other inflammatory mediators [43]. Emerging evidence suggests that innate immune activation and vascular inflammation contribute not only to fibrosis but also to systemic inflammatory complications in selected patients [44].

Primary Sjögren syndrome (pSS) is driven by chronic activation of B lymphocytes, autoreactive T cells, and type I interferon pathways [45]. Persistent interferon signaling, activation of plasmacytoid dendritic cells, and elevated concentrations of IL-6, BAFF, and other cytokines establish a pro-inflammatory environment that may rarely progress to severe systemic hyperinflammation [46]. Although macrophage activation syndrome is uncommon, isolated cases emphasize the importance of recognizing cytokine storm in patients presenting with unexplained fever, cytopenias, and rapidly progressive organ dysfunction [47].

Antiphospholipid syndrome (APS) represents a unique autoimmune disorder in which inflammation and thrombosis are closely interconnected [48]. Antiphospholipid antibodies activate endothelial cells, monocytes, platelets, and complement pathways, promoting tissue factor expression, cytokine production, and immunothrombosis [49]. Catastrophic antiphospholipid syndrome (CAPS) exemplifies how dysregulated inflammatory and coagulation pathways may culminate in a cytokine storm-like clinical syndrome with widespread microvascular thrombosis and multiorgan failure [50].

Behçet disease is characterized by exaggerated activation of neutrophils, macrophages, and T lymphocytes, resulting in increased production of TNF-α, IL-1β, IL-6, IL-17, and other inflammatory mediators. Although fulminant cytokine storm is rare, severe systemic disease involving the central nervous system, gastrointestinal tract, or major blood vessels may exhibit marked cytokine amplification and macrophage activation requiring aggressive immunosuppressive therapy [51].

Mixed connective tissue disease (MCTD) and autoimmune overlap syndromes combine immunological features of several connective tissue diseases and therefore exhibit heterogeneous inflammatory profiles [52]. Patients with severe disease activity may develop excessive cytokine production, complement activation, endothelial dysfunction, and macrophage activation, particularly in the presence of infection or uncontrolled autoimmune inflammation [5]. Although evidence remains limited, these observations reinforce the concept that cytokine storm represents a final common pathway shared across diverse autoimmune diseases rather than a disease-specific phenomenon.

Collectively, these disorders illustrate that autoimmune cytokine storm is not confined to a single disease but represents a spectrum of hyperinflammatory syndromes arising through distinct upstream mechanisms. Appreciating these differences is fundamental for the development of precision medicine approaches in which therapeutic interventions are selected according to the dominant pathogenic pathway rather than the clinical diagnosis alone as shown in *Table 1*.

Table 1. Comparative Immunopathogenesis of Cytokine Storm Across Autoimmune Diseases [6,21,24,35,57,58]

Disease	Dominant immune pathway	Principal pathogenic mechanisms	Predominant cytokines	Characteristic biomarkers	Major targeted therapies
Systemic lupus erythematosus (SLE)	Type I interferon, immune complexes, complement	Immune-complex deposition, plasmacytoid dendritic-cell activation, complement activation, NETosis, macrophage activation	IFN-α, IL-6, TNF-α, IL-18	Anti-dsDNA, C3/C4, ferritin, IFN signature	Corticosteroids, anifrolumab, belimumab, JAK inhibitors
Adult-onset Still disease (AOSD)	Inflammasome activation	NLRP3 activation, IL-18 excess, macrophage activation, impaired NK-cell cytotoxicity	IL-1β, IL-18, IL-6, IFN-γ	Ferritin, IL-18, sCD25	Anakinra, canakinumab, tocilizumab, JAK inhibitors
Systemic juvenile idiopathic arthritis (sJIA)	Inflammasome activation	IL-18 overproduction, macrophage activation, defective cytotoxicity	IL-1β, IL-18, IL-6, IFN-γ	Ferritin, IL-18	Anakinra, canakinumab, tocilizumab
Dermatomyositis (anti-MDA5)	Type I interferon, endothelial injury	IFN signaling, macrophage activation, pulmonary inflammation, endothelial injury	IFN-α, IL-6, IL-18	Ferritin, CXCL9, CXCL10	Glucocorticoids, calcineurin inhibitors, JAK inhibitors, rituximab
ANCA-associated	ANCA-mediated	NETosis, alternative complement	IL-6, TNF-α	MPO-/PR3-ANCA, C5a, ferritin	Rituximab, cyclophosphamide, avacopan

vasculitis (AAV)	neutrophil activation	activation, endothelial injury			
Rheumatoid arthritis (RA)	Synovial cytokine network	Persistent macrophage and fibroblast activation, Th17 responses	TNF-α, IL-6, IL-1β, GM-CSF	CRP, ESR	TNF inhibitors, IL-6 inhibitors, CTLA4-Ig, JAK inhibitors
Antiphospholipid syndrome (APS)	Complement activation, immunothrombosis	Complement-mediated endothelial activation, thrombosis, inflammatory amplification	IL-6, TNF-α	Antiphospholipid antibodies, complement activation markers	Anticoagulation, glucocorticoids, rituximab/eculizumab

Abbreviations: AAV, ANCA-associated vasculitis; AOSD, adult-onset Still disease; APS, antiphospholipid syndrome; HLH, hemophagocytic lymphohistiocytosis; IFN, interferon; IL, interleukin; JAK, Janus kinase; MAS, macrophage activation syndrome; RA, rheumatoid arthritis; sCD25, soluble interleukin-2 receptor; sJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

6. Biomarkers and Diagnostic Challenges in Autoimmune Cytokine Storm

6.1 Challenges in Early Diagnosis

Early recognition of autoimmune-associated cytokine storm remains one of the greatest clinical challenges because its initial manifestations frequently overlap with active autoimmune disease, severe infection, and drug-related inflammatory reactions . Patients commonly present with persistent fever, cytopenias, hepatic dysfunction, coagulopathy, elevated inflammatory markers, and multiorgan involvement, clinical features that lack specificity and often delay diagnosis. As a result, distinguishing macrophage activation syndrome (MAS) from disease flare or sepsis requires careful integration of clinical findings with laboratory biomarkers rather than reliance on any single parameter [6,34].

Current diagnostic criteria, including the HLH-2004 criteria, the HScore, and disease-specific MAS classification criteria, provide useful diagnostic frameworks but have important limitations when applied to autoimmune diseases [53]. These scoring systems were largely developed in pediatric or infection-associated HLH populations and may demonstrate reduced sensitivity in adults with complex autoimmune disorders [53]. Consequently, there remains an unmet need for biomarkers capable of identifying hyperinflammation at an earlier stage, before irreversible organ injury develops.

6.2 Conventional Biomarkers

Several routinely available laboratory parameters remain central to the evaluation of cytokine storm. Serum ferritin is the most widely used biomarker of macrophage activation and correlates with disease severity in macrophage activation syndrome, particularly in adult-onset Still disease and systemic juvenile

idiopathic arthritis. However, ferritin lacks disease specificity because elevated concentrations may also occur in severe infection, liver disease, malignancy, and active autoimmune disease [6,34].

Additional laboratory abnormalities include hypertriglyceridemia, hypofibrinogenemia, elevated liver enzymes, increased lactate dehydrogenase, cytopenias, prolonged coagulation parameters, and elevated soluble IL-2 receptor (sCD25). Dynamic changes in these biomarkers, particularly rapidly rising ferritin combined with declining platelet counts and fibrinogen concentrations, often provide greater diagnostic value than isolated measurements. Therefore, serial monitoring is recommended in patients with suspected evolving cytokine storm [6,34,53].

6.3 Cytokine and Immune Biomarkers

Advances in multiplex immunoassays have enabled detailed characterization of cytokine profiles associated with autoimmune hyperinflammation. Among these biomarkers, IL-18 has emerged as one of the strongest indicators of macrophage activation syndrome in adult-onset Still disease and systemic juvenile idiopathic arthritis, whereas interferon-γ-induced chemokines such as CXCL9 and CXCL10 reflect activation of the IFN-γ signaling pathway. Elevated circulating concentrations of IL-6, IL-1β, TNF-α, granulocyte–macrophage colony-stimulating factor (GM-CSF), and soluble CD163 further indicate activation of macrophages and monocytes [34].

In systemic lupus erythematosus, activation of the type I interferon pathway, complement consumption, and elevated circulating immune complexes provide additional disease-specific biomarkers that complement traditional inflammatory markers. Rather than relying on individual cytokines, integrated cytokine signatures are increasingly recognized as more informative for identifying patients at risk of progression to cytokine storm [6,28].

6.4 Emerging Biomarkers and Multi-Omics Approaches

Recent advances in high-throughput technologies have substantially expanded opportunities for biomarker discovery. Transcriptomic analyses have identified interferon-response signatures, inflammatory gene-expression profiles, and macrophage activation pathways associated with disease severity. Single-cell RNA sequencing has further revealed cellular heterogeneity within inflammatory lesions, allowing identification of pathogenic immune-cell subsets responsible for cytokine amplification [28,34].

Proteomic approaches have enabled comprehensive characterization of circulating inflammatory proteins and signaling networks, providing opportunities to identify biomarkers that reflect both disease activity and therapeutic response. Likewise, metabolomic studies have demonstrated alterations in amino acid, lipid, and energy metabolism associated with systemic inflammation, while epigenetic analyses have identified regulatory mechanisms that influence cytokine production and immune-cell activation [54].

Exosomes have emerged as particularly promising biomarkers because they carry proteins, nucleic acids, lipids, and microRNAs that reflect the physiological state of their parent cells. Their stability in biological fluids and ability to mirror immune-cell activation make them attractive candidates for non-invasive monitoring of disease activity and prediction of hyperinflammatory complications. Integrating exosomal proteomics with transcriptomic and cytokine profiling may improve early diagnosis and facilitate precision medicine approaches for autoimmune cytokine storm [55].

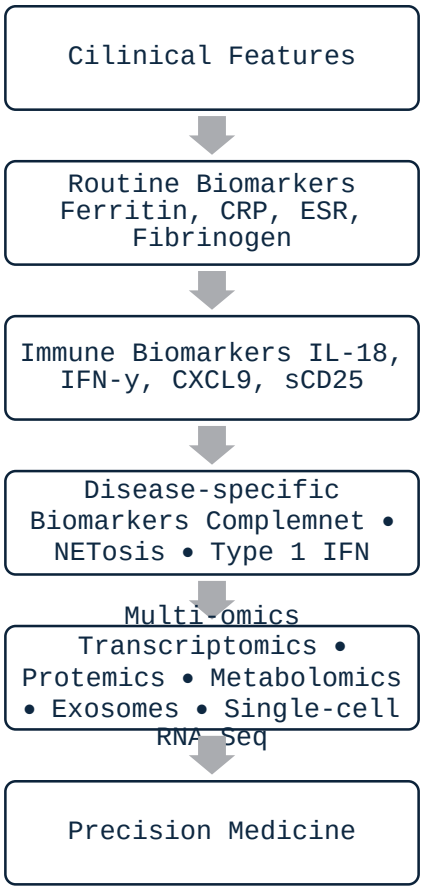
6.5 Future Perspectives in Biomarker-Guided Precision Medicine

The future of autoimmune cytokine storm management is likely to depend on the integration of multidimensional biomarker data rather than reliance on individual laboratory parameters. Combining clinical characteristics with cytokine profiles, complement activation markers, NETosis biomarkers, transcriptomic signatures, proteomic data, and machine learning algorithms may improve risk

stratification, enable earlier diagnosis, and guide individualized therapeutic interventions as shown in *Figure 7*.

Ultimately, the transition from single-marker diagnostics to integrated multi-omics platforms has the potential to transform the management of autoimmune cytokine storm by enabling earlier recognition of high-risk patients, improving therapeutic selection, and facilitating real-time monitoring of treatment response. Large prospective multicenter studies will be essential to validate these emerging biomarkers and establish standardized precision medicine strategies for clinical practice.

Figure 7. Biomarker-based diagnostic and precision medicine approach for cytokine storm in autoimmune diseases



Legend: The diagnostic evaluation of cytokine storm begins with the recognition of clinical features suggestive of systemic hyperinflammation. Initial laboratory assessment includes routine inflammatory biomarkers, such as serum ferritin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fibrinogen, which help identify ongoing inflammation and coagulopathy. Further immune profiling incorporates immune activation biomarkers, including interleukin (IL)-18, interferon-gamma (IFN-γ), C-X-C motif chemokine ligand 9 (CXCL9), and soluble CD25 (sCD25), which reflect macrophage and T-cell activation. Disease-specific biomarkers, including complement activation products, neutrophil extracellular trap (NET) formation markers, and type I interferon signatures, facilitate differentiation among autoimmune disorders and their underlying pathogenic mechanisms. Emerging multi-omics technologies, encompassing transcriptomics, proteomics, metabolomics, exosome profiling, and single-cell RNA sequencing (scRNA-seq), enable comprehensive molecular characterization, biomarker

discovery, patient stratification, and therapeutic response prediction. The integration of conventional and advanced biomarkers supports the implementation of precision medicine, allowing individualized diagnosis, prognostic assessment, and targeted treatment of cytokine storm syndromes.

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; IFN-γ, interferon-gamma; CXCL9, C-X-C motif chemokine ligand 9; sCD25, soluble CD25 (soluble interleukin-2 receptor α); NETs, neutrophil extracellular traps; scRNA-seq, single-cell RNA sequencing.

7. Therapeutic Strategies: From Broad Immunosuppression to Precision Medicine

7.1 Principles of Management

Autoimmune-associated cytokine storm represents a medical emergency requiring prompt recognition and immediate initiation of immunomodulatory therapy. Treatment objectives include rapid suppression of hyperinflammation, stabilization of organ dysfunction, elimination of potential triggering factors, and prevention of irreversible tissue injury. Because cytokine storm may mimic severe infection or autoimmune disease flare, careful clinical evaluation is essential before initiating intensive immunosuppression. Management should ideally involve a multidisciplinary team comprising rheumatologists, immunologists, intensivists, infectious disease specialists, and hematologists [6,34,56].

Current therapeutic strategies are increasingly guided by the dominant immunopathological pathway rather than by disease classification alone. While high-dose glucocorticoids remain the cornerstone of initial treatment, advances in understanding cytokine biology have enabled the development of targeted therapies directed against specific inflammatory mediators and intracellular signaling pathways [6,34,56].

7.2 Conventional Immunosuppressive Therapy

High-dose intravenous methylprednisolone remains the first-line treatment for most patients with macrophage activation syndrome (MAS) and autoimmune-associated cytokine storm because of its rapid anti-inflammatory effects. However, corticosteroid monotherapy is frequently insufficient in severe or refractory disease [6,34].

Conventional immunosuppressive agents, including cyclosporine, cyclophosphamide, tacrolimus, mycophenolate mofetil, and intravenous immunoglobulin (IVIG), are commonly employed according to the underlying autoimmune disease and severity of organ involvement. In selected patients with refractory MAS or secondary hemophagocytic lymphohistiocytosis (sHLH), etoposide-based regimens may be considered, although their use in autoimmune diseases requires careful assessment of potential toxicity [6,34].

7.3 Cytokine-Targeted Biological Therapies

Improved understanding of cytokine networks has transformed the management of autoimmune cytokine storm. Among currently available biologic agents, IL-1 inhibition has demonstrated remarkable efficacy in adult-onset Still disease (AOSD) and systemic juvenile idiopathic arthritis (sJIA), where excessive IL-1β production plays a central pathogenic role. Anakinra and canakinumab have substantially improved clinical outcomes and are associated with improved survival in patients with macrophage activation syndrome complicating these disorders [12,34].

IL-6 inhibition with tocilizumab has shown substantial benefit in AOSD, rheumatoid arthritis, giant cell arteritis, and selected patients with cytokine storm characterized by marked IL-6 elevation. TNF inhibitors remain highly effective for chronic inflammatory diseases such as rheumatoid arthritis and spondyloarthritis but have a more limited role in established macrophage activation syndrome [12,34].

Therapeutic inhibition of IFN-γ with emapalumab has emerged as an important option for refractory HLH and selected patients with severe MAS, illustrating the expanding role of cytokine-specific therapy [34]. Likewise, complement-directed therapies such as avacopan have demonstrated clinical efficacy in ANCA-associated vasculitis by interrupting C5a-mediated neutrophil activation, while agents targeting type I interferon signaling, including anifrolumab, represent important advances in systemic lupus erythematosus [35,57,58].

7.4 Targeting Intracellular Signaling Pathways

The Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway integrates signaling from multiple inflammatory cytokines, making it an attractive therapeutic target across several autoimmune diseases. JAK inhibitors, including baricitinib, ruxolitinib, and tofacitinib, suppress signaling downstream of cytokines such as IFN-γ, IL-6, IL-2, IL-10, and GM-CSF, thereby interrupting multiple inflammatory pathways simultaneously [38].

Growing clinical evidence supports the use of JAK inhibitors in refractory macrophage activation syndrome, dermatomyositis, systemic lupus erythematosus, and other immune-mediated inflammatory disorders. Their ability to modulate multiple cytokine pathways distinguishes them from single-cytokine inhibitors and supports their potential role in personalized treatment strategies.

7.5 Emerging Therapeutic Targets

Rapid advances in immunology continue to identify novel therapeutic targets for autoimmune cytokine storm. IL-18 blockade has emerged as a promising strategy for patients with adult-onset Still disease and recurrent macrophage activation syndrome, while granulocyte–macrophage colony-stimulating factor (GM-CSF) inhibition may reduce macrophage activation in selected inflammatory disorders. Therapies targeting inflammasomes, neutrophil extracellular trap (NET) formation, complement activation, and macrophage polarization are currently under active investigation [59].

Future therapeutic strategies are likely to combine targeted cytokine inhibition with biomarker-guided patient stratification, enabling treatment to be tailored according to the dominant inflammatory pathway rather than the underlying autoimmune diagnosis alone.

7.6 Toward Precision Medicine

The management of autoimmune cytokine storm is evolving from empirical immunosuppression toward precision medicine. Advances in cytokine profiling, transcriptomics, proteomics, single-cell sequencing, and artificial intelligence have created opportunities to identify patients at highest risk for hyperinflammation and predict therapeutic response. Rather than applying identical treatment strategies to all patients, future management will increasingly rely on integrated biomarker signatures that define disease endotypes and guide individualized therapeutic selection [60].

Ultimately, successful management of autoimmune cytokine storm will depend on combining early diagnosis, disease-specific immune profiling, and targeted intervention before irreversible organ damage develops. Continued integration of translational research with clinical practice is expected to improve survival while minimizing treatment-related toxicity.

8. Future Perspectives and Conclusions

Autoimmune-associated cytokine storm syndromes represent one of the most challenging complications in clinical immunology because they arise from the convergence of diverse immunopathological mechanisms on a common phenotype of uncontrolled systemic inflammation. As discussed throughout this review, cytokine storm should not be regarded as a single disease entity but rather as a spectrum of

hyperinflammatory syndromes in which the initiating immune pathways vary substantially across autoimmune disorders. While systemic lupus erythematosus is primarily characterized by immune-complex formation, complement activation, and type I interferon signaling, adult-onset Still disease is driven predominantly by inflammasome activation and IL-18, dermatomyositis by interferon-mediated vascular injury, ANCA-associated vasculitis by neutrophil activation and complement amplification, and rheumatoid arthritis by chronic cytokine network activation. Despite these distinct upstream mechanisms, all ultimately converge on macrophage activation, endothelial dysfunction, cytokine amplification, and multiorgan injury.

Significant advances in immunology have transformed our understanding of cytokine storm from a descriptive clinical syndrome into a mechanistically defined process involving complex interactions between innate immunity, adaptive immunity, genetic susceptibility, environmental triggers, and immune regulatory failure. This evolving understanding has fundamentally changed therapeutic strategies, shifting clinical management from broad immunosuppression toward pathway-specific interventions targeting IL-1, IL-6, IL-18, interferons, complement, and intracellular signaling pathways such as JAK–STAT. Nevertheless, optimal treatment selection remains challenging because reliable biomarkers capable of defining disease endotypes and predicting therapeutic response are still lacking.

One of the most promising developments in the field is the emergence of multi-omics technologies. Transcriptomics, proteomics, metabolomics, epigenomics, and single-cell sequencing are providing unprecedented insights into the molecular heterogeneity of autoimmune diseases and the mechanisms underlying progression to cytokine storm. In particular, exosome-based biomarkers have attracted increasing interest because they reflect the molecular composition of their parent cells and can be detected non-invasively in biological fluids. Their ability to integrate information on immune activation, cellular communication, and tissue injury positions them as promising candidates for early diagnosis, disease monitoring, and prediction of therapeutic response. Future studies integrating exosomal biomarkers with conventional laboratory parameters and cytokine profiling may substantially improve risk stratification and facilitate personalized clinical management.

Artificial intelligence (AI) and machine learning are also expected to play an increasingly important role in autoimmune disease research. By integrating multidimensional clinical, laboratory, imaging, and multi-omics datasets, computational approaches may enable earlier identification of patients at risk of hyperinflammatory complications, improve diagnostic accuracy, predict treatment response, and support individualized therapeutic decision-making. Such approaches have the potential to transform cytokine storm management from a reactive strategy focused on treating established hyperinflammation to a proactive strategy emphasizing early prediction and prevention.

Despite considerable progress, several important challenges remain. Standardized diagnostic criteria for autoimmune-associated cytokine storm are lacking, particularly in adults, and currently available classification systems may not adequately capture the heterogeneity of disease manifestations across different autoimmune disorders. Furthermore, most biomarker studies remain limited by small sample sizes, heterogeneous patient populations, and insufficient prospective validation. Large multicenter collaborative studies integrating standardized clinical phenotyping with longitudinal biomarker assessment will be essential to establish robust diagnostic algorithms and validate precision medicine approaches.

In conclusion, autoimmune-associated cytokine storm should be viewed as a spectrum of mechanistically distinct but biologically interconnected hyperinflammatory syndromes rather than a uniform clinical

entity. Understanding disease-specific immune pathways, identifying reliable biomarkers, and applying targeted therapeutic strategies will be fundamental to improving patient outcomes. Future integration of systems immunology, multi-omics technologies, and biomarker-guided precision medicine is expected to redefine the diagnosis and management of cytokine storm, enabling earlier intervention, individualized therapy, and ultimately improved survival for patients with severe autoimmune disease.

References

1. Fajgenbaum DC, June CH. Cytokine Storm. *N Engl J Med.* 2020;383(23):2255–2273. doi:10.1056/NEJMra2026131
2. Karki R, Kanneganti TD. The 'Cytokine Storm': molecular mechanisms and therapeutic prospects. *Trends Immunol.* 2021;42(8):681–705. doi:10.1016/j.it.2021.06.001
3. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. *J Immunother Cancer.* 2018;6(1):56. doi:10.1186/s40425-018-0343-9
4. Cron RQ, Behrens EM, editors. *Cytokine Storm Syndrome.* 2nd ed. Springer; 2023
5. Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine-directed therapies. *Annu Rev Med.* 2015;66:145–159. doi:10.1146/annurev-med-061813-012806
6. Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, et al. Macrophage Activation Syndrome and Secondary Hemophagocytic Lymphohistiocytosis in Childhood Inflammatory Disorders: Diagnosis and Management. *Pediatr Clin North Am.* 2020;67(4):731–748
7. Eloseily EM, Cron RQ. Macrophage Activation Syndrome. *Microbiol Spectr.* 2018;6(6). doi:10.1128/microbiolspec.GPP3-0015-2018
8. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome. *Front Immunol.* 2019;10:119. doi:10.3389/fimmu.2019.00119
9. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. *Annu Rev Med.* 2012;63:233–246. doi:10.1146/annurev-med-041610-134208
10. Jamilloux Y, Gerfaud-Valentin M, Martinon F, Belot A, Henry T, Sève P. Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart. *Immunol Res.* 2015;61(1–2):53–62. doi:10.1007/s12026-014-8561-3
11. Ombrello MJ, Arthur VL, Remmers EF, et al. Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications. *Ann Rheum Dis.* 2017;76(5):906–913
12. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. *J Autoimmun.* 2018;93:24–36. doi:10.1016/j.jaut.2018.07.018
13. Mellins ED, Macaubas C, Grom AA. Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions. *Nat Rev Rheumatol.* 2011;7(7):416–426. doi:10.1038/nrrheum.2011.68
14. Borgia RE, Gerstein M, Levy DM, Silverman ED, Hiraki LT. Features, treatment, and outcomes of macrophage activation syndrome in childhood-onset systemic lupus erythematosus. *Arthritis Care Res (Hoboken).* 2018;70(4):616–624
15. Zhu, D. X., Qiao, J. J., & Fang, H. (2020). Macrophage activation syndrome as a complication of dermatomyositis: A case report. *World Journal of Clinical Cases*, *8*(11), 2339. https://doi.org/10.12998/wjcc.v8.i11.2339
16. La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood.*

2019;133(23):2465–2477. doi:10.1182/blood.2018894618
17. Kaufman KM, Linghu B, Szustakowski JD, et al. Whole-exome sequencing reveals mutations in genes linked to hemophagocytic lymphohistiocytosis in macrophage activation syndrome. *Arthritis Rheumatol.* 2020
18. Bracaglia C, de Graaf K, Pires Marafon D, et al. Elevated circulating levels of interferon-γ and interferon-γ–induced chemokines characterize macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *Ann Rheum Dis.* 2017;76(1):166–172. doi:10.1136/annrheumdis-2015-209020
19. Weiss ES, Girard-Guyonvarc'h C, Holzinger D, de Jesus AA, Tariq Z, Picarsic J, et al. Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome. *Blood.* 2018;131(13):1442–1455. doi:10.1182/blood-2017-12-820852
20. Tsokos GC, Lo MS, Reis PC, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat Rev Rheumatol.* 2016;12(12):716–730. doi:10.1038/nrrheum.2016.186
21. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol.* 2014;6(10):a016295. doi:10.1101/cshperspect.a016295
22. Villarino AV, Kanno Y, Ferdinand JR, O'Shea JJ. Mechanisms of Jak/STAT signaling in immunity and disease. *J Immunol.* 2017;198(5):1932–1945. doi:10.4049/jimmunol.1602246
23. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol.* 2010;11(5):373–384. doi:10.1038/ni.1863
24. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. *Int Immunol.* 2017;29(9):401–409. doi:10.1093/intimm/dxx031
25. Kronbichler A, Lee KH, Denicolò S, et al. Immunopathogenesis of ANCA-associated vasculitis. *Int J Mol Sci.* 2020;21(19):7319.doi:10.3390/ijms21197319
26. Shahzad, A., Ni, Y., Yang, Y., Liu, W., Teng, Z., Bai, H., Liu, X., Sun, Y., Xia, J., Cui, K., Duan, Q., Xu, Z., Zhang, J., Yang, Z., & Zhang, Q. (2025). Neutrophil Extracellular Traps (NETs) in health and disease. *Molecular Biomedicine*, *6*, 130. https://doi.org/10.1186/s43556-025-00337-9
27. Tartey, S., & Kanneganti, T. D. (2019). Inflammasomes in the Pathophysiology of Autoinflammatory Syndromes. *Journal of Leukocyte Biology*, *107*(3), 379. https://doi.org/10.1002/JLB.3MIR0919-191R
28. Dai X, Fan Y, Zhao X. Systemic lupus erythematosus: updated insights on the pathogenesis, diagnosis, prevention and therapeutics. Signal Transduct Target Ther. 2025 Mar 17;10(1):102. doi: 10.1038/s41392-025-02168-0.
29. Wang R, Lan C, Benlagha K, Camara NOS, Miller H, Kubo M, Heegaard S, Lee P, Yang L, Forsman H, Li X, Zhai Z, Liu C. The interaction of innate immune and adaptive immune system. MedComm (2020). 2024 Sep 15;5(10):e714. doi: 10.1002/mco2.714.
30. Warrick KA, Vallez CN, Meibers H, Pasare C. Bidirectional Communication Between the Innate and Adaptive Immune Systems. Annual Review of Immunology. 2025;43:489–514.
31. Diomedi M, Fattorini F, Aliberti S, Bianchessi LM, Castellucci A, Schmidt J, Cavagna L, Carli L, Barsotti S. Idiopathic inflammatory myopathies: one year in review 2025. Clin Exp Rheumatol. 2026 Feb;44(2):167-177. doi: 10.55563/clinexprheumatol/2z01e0. Epub 2026 Feb 24.
32. Ferrarese R, Boutahar S, Genoni AP, Arcari G, Zambon G, Dolci M, Perego F, D'alessandro S, Delbue S, Mancini N, Signorini L, Novazzi F. Cytokine and Endothelial Activation Patterns Related to Severe and Non-Severe Respiratory Viral Infections. J Med Virol. 2026 Jan;98(1):e70784. doi: 10.1002/jmv.70784.

33. Meng X, Layhadi JA, Keane ST, Cartwright NJK, Durham SR, Shamji MH. Immunological mechanisms of tolerance: Central, peripheral and the role of T and B cells. Asia Pac Allergy. 2023 Dec;13(4):175-186. doi: 10.5415/apallergy.0000000000000128. Epub 2023 Dec 8.
34. Canna SW, de Jesus AA, Gouni S, Brooks SR, Marrero B, Liu Y, et al. An activating mutation in the NLRC4 inflammasome causes autoinflammation with recurrent macrophage activation syndrome. *Nat Genet.* 2014;46(10):1140–1146. doi:10.1038/ng.3089
35. Crow MK. Type I interferon in the pathogenesis of lupus. *J Immunol.* 2014;192(12):5459–5468. doi:10.4049/jimmunol.1002795
36. Taylor, M. L., Hoyt, K. J., Han, J., Benson, L., Case, S., Chandler, M., Chang et al. (2022). An Evidence-Based Guideline Improves Outcomes for Patients with Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome. *The Journal of Rheumatology*, *49*(9), 1042. https://doi.org/10.3899/jrheum.211219
37. Salemme R, Peralta LN, Meka SH, Pushpanathan N, Alexander JJ. The Role of NETosis in Systemic Lupus Erythematosus. J Cell Immunol. 2019;1(2):33-42. doi: 10.33696/immunology.1.008. Epub 2019 Nov 12.
38. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov.* 2017;16(12):843–862. doi:10.1038/nrd.2017.201
39. Sebbag E, Lauper K, Molina-Collada J 2024 EULAR points to consider on the initiation of targeted therapies in patients with inflammatory arthritis and a history of cancer,Annals of the Rheumatic Diseases, 2025; 84, 388-397
40. Parga A, Ratra D, Luu D. An Update on Dermatomyositis and Related Inflammatory Myopathies: Cutaneous Clues, Skeletal Muscle Involvement, and Advances in Pathogenesis and Treatment. Muscles. 2025 Dec 1;4(4):58. doi: 10.3390/muscles4040058.
41. Bhandari, S., Zickuhr, L., Baral, M. R., Bhalla, S., Jones, H., Bucelli, R., & Sen, D. (2024). A Review of MDA-5 Dermatomyositis and Associated Interstitial Lung Disease. *Rheumato*, *4*(1), 33-48. https://doi.org/10.3390/rheumato4010004
42. Greenberg SA. Dermatomyositis and type 1 interferons. Curr Rheumatol Rep. 2010 Jun;12(3):198-203. doi: 10.1007/s11926-010-0101-6.
43. Yaseen K, Mandell BF. ANCA associated vasculitis (AAV): a review for internists. Postgrad Med. 2023 Jan;135(sup1):3-13. doi: 10.1080/00325481.2022.2102368. Epub 2022 Jul 21.
44. Drożdżal, S., Gomółka, A., Opara-Bajerowicz, M., Lisak, M., Sielicka, U., Bąk, K., Przybyciński, J., & Feret-Adrabińska, W. (2025). Neutrophil Extracellular Traps in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: Diagnostic and Clinical Significance—A Review of the Current Literature. *Journal of Clinical Medicine*, *14*(11), 3639. https://doi.org/10.3390/jcm14113639
45. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med.* 2011;365(23):2205–2219. doi:10.1056/NEJMra1004965
46. Radu, A. F., & Bungau, S. G. (2021). Management of Rheumatoid Arthritis: An Overview. *Cells*, *10*(11), 2857. https://doi.org/10.3390/cells10112857
47. Jimenez SA, Mendoza FA, Piera-Velazquez S. A review of recent studies on the pathogenesis of Systemic Sclerosis: focus on fibrosis pathways. Front Immunol. 2025 Apr 16;16:1551911. doi: 10.3389/fimmu.2025.1551911.

48. Ducker, C. B., Preece, M. V., Pericleous, C., Laffan, M., & Arachchillage, D. J. (2026). Revisiting antiphospholipid syndrome: A thrombo-inflammatory disorder beyond clotting. *Blood Reviews*, *76*, 101364. https://doi.org/10.1016/j.blre.2026.101364
49. Allen, K. L., Hamik, A., Jain, M. K., & McCrae, K. R. (2011). Endothelial cell activation by antiphospholipid antibodies is modulated by Krüppel-like transcription factors. *Blood*, *117*(23), 6383. https://doi.org/10.1182/blood-2010-10-313072
50. Rodríguez-Pintó, I., Espinosa, G., & Cervera, R. (2014). The Catastrophic Antiphospholipid Syndrome. *Antiphospholipid Antibody Syndrome*, 249. https://doi.org/10.1007/978-3-319-11044-8_20
51. Lavalle, S., Caruso, S., Foti, R., Gagliano, C., Cocuzza, S., Via, L. L., Parisi, F. M., Calvo-Henriquez, C., & Maniaci, A. (2024). Behçet's Disease, Pathogenesis, Clinical Features, and Treatment Approaches: A Comprehensive Review. *Medicina*, *60*(4), 562. https://doi.org/10.3390/medicina60040562
52. Pepmueller, P. H. (2016). Undifferentiated Connective Tissue Disease, Mixed Connective Tissue Disease, and Overlap Syndromes in Rheumatology. *Missouri Medicine*, *113*(2), 136. https://pmc.ncbi.nlm.nih.gov/articles/PMC6139943
53. Henter, J. I., Sieni, E., Eriksson, J., Bergsten, E., Myrberg, I. H., Canna, S et al (2024). Diagnostic guidelines for familial hemophagocytic lymphohistiocytosis revisited. *Blood*, *144*(22), 2308. https://doi.org/10.1182/blood.2024025077
54. Zhang, Y., Xu, H., Xu, L., Jiang, S., Yu, Y., & Zhao, H. (2025). Multi-omics-driven biomarker discovery in autoimmune diseases: A comprehensive review. *Frontiers in Immunology*, *16*, 1652211. https://doi.org/10.3389/fimmu.2025.1652211
55. Aljohani, M. A. (2025). Exosomes in Clinical Laboratory: From Biomarker Discovery to Diagnostic Implementation. *Medicina*, *61*(11), 1930. https://doi.org/10.3390/medicina61111930
56. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant.* 2019;25(4):625–638. doi:10.1016/j.bbmt.2018.12.758
57. Yokota S, Itoh Y, Morio T, et al. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis under treatment with tocilizumab. *J Rheumatol.* 2015/2016
58. Grom AA, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. *Nat Rev Rheumatol.* 2016
59. Obeagu, E. I. (2026). Taming the Cytokine Storm: Therapeutic Strategies for Post-Acute Sequelae of SARS-CoV-2 Infection. *Health Science Reports*, *9*(3), e72174. https://doi.org/10.1002/hsr2.72174
60. Nie, J., Zhou, L., Tian, W., Liu, X., Yang, L., Yang, X., Zhang, Y., Wei, S., Wang, D. W., & Wei, J. (2025). Deep insight into cytokine storm: From pathogenesis to treatment. *Signal Transduction and Targeted Therapy*, *10*, 112. https://doi.org/10.1038/s41392-025-02178-y