**Journal of Pioneering Medical Sciences**
Received: January 22, 2024 | Accepted: April 27, 2025 | Published: May 5, 2025
Volume 14, Issue 04, Pages 89-97

*DOI https://doi.org/10.47310/jpms2025140412*


# The Impact of Cytokine Storms on Severe Infectious Diseases Progression: A Narrative Review

**Roksolana Yaremkevych[1*], Nataliia Bodnarchuk-Sokhatska[2], Serhii Sydorov[3], Yuliia Kyivska[4] and He GangKui[5]**

[1]Department of Surgery and Transplantology, Faculty of Postgraduate Education, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine
[2]Department of Pediatric, Faculty of Foreign Students, Horbachevsky Ternopil National Medical University, Ternopil, Ukraine
[3]DVM, Department of Forest Biology, Hunting Science and Ichthyology, Zaporizhzhia National University, Zaporizhzhia, Ukarine
[4]Private Entrepreneur, Kharkiv, Ukraine
[5]Dazhou Second People's Hospital, Sichuan, China

Author Designation: [1]Candidate of Medical Sciences, [2,3]Student, [4]Candidate of Biological Sciences, [5]MBBS, Physician

*Corresponding author: Roksolana Yaremkevych (e-mail: roksa1607@gmail.com).



**Abstract** **Background:** Cytokine storm is a life-threatening immune reaction contributing to the severity of various infectious diseases such as COVID-19, sepsis, Ebola, and Dengue. Understanding its pathophysiology is critical for timely diagnosis and effective treatment. **Methods:** A narrative review was conducted using PubMed, Scopus, and Web of Science (September 2024 – January 2025). Keywords included "cytokine storm," "pro-inflammatory cytokines," "COVID-19," "sepsis," "targeted therapy," and "personalised medicine." Studies were analysed thematically. As a narrative review, the findings are limited by the heterogeneity and potential bias of included studies, and no quantitative synthesis was performed. **Results:** The review outlines key mechanisms of cytokine storm, such as IL-6, IL-10, and TNF-α overproduction, and presents clinical cutoff values (e.g., IL-6 > 19.5 pg/mL) associated with disease severity. Targeted therapies (e.g., tocilizumab, anakinra), immunomodulators (e.g., JAK inhibitors), stem cell therapy, and plasmapheresis were reviewed. A personalised approach to treatment based on biomarkers and comorbidities was emphasised. **Conclusions:** Cytokine storm remains a major challenge in infectious disease management. While therapeutic strategies are evolving, individualised, biomarker-driven treatment offers the greatest potential for improving outcomes.

**Key Words** Stress, eustress, distress, stress management, mental health, relaxation techniques, cognitive restructuring, mindfulness meditation, Sudarshan Kriya, Pranayama

## INTRODUCTION

A *cytokine* storm or *cytokine release syndrome* is a serious and life-threatening response to inflammation that can occur in infectious and non-infectious diseases [1,2]. This phenomenon is characterised by the uncontrolled and excessive release of pro-inflammatory cytokines, which leads to organ failure and associated high mortality.

Advances in health care, widespread vaccination programmes and improved sanitation and hygiene have shifted infectious diseases from being the leading cause of morbidity and mortality in many countries. However, they still threaten the health and lives of millions of people [3]. During wars or other crises, when the healthcare system is overwhelmed, and there is significant population displacement, the risk of infectious disease outbreaks increases dramatically [4-6]. In this regard, studying the factors that complicate the course of infectious diseases is becoming increasingly important.

At the same time, chronic non-communicable diseases and lifestyle-related diseases, which currently account for a greater proportion of morbidity and mortality [7], are often accompanied by immune system dysfunction [8]. This dysfunction simultaneously reduces resistance to infectious agents and is a risk factor for severe infectious diseases, including due to excessive cytokine release.

Therefore, understanding the mechanisms of the cytokine storm as a leading risk factor is important for the development of effective treatments for severe infections, which can improve prognosis in conditions such as sepsis, COVID-19, and other viral or bacterial infections.

Although initially described in transplant medicine in the 1990s, the term "cytokine storm" became widely recognised in infectious disease contexts after the SARS outbreak in 2003 [1]. It has since been linked to complications during cancer immunotherapy, and is also prominent in autoimmune diseases

such as systemic lupus erythematosus and hemophagocytic lymphohistiocytosis [9-11]. There are several theories and practical solutions for the emergence, development, and treatment of cytokine storms, although they still lead to deaths and severe disease [9-13]. These diverse origins suggest that the mechanisms underlying cytokine storms transcend individual disease categories and require a broader, cross-disciplinary understanding.

The development of a cytokine storm in infectious diseases under the influence of viral and bacterial pathogens can lead to severe disease [14-16,9,17]. Given the pathophysiological features of excessive cytokine release, the risk of severe disease increases in patients with chronic non-communicable diseases such as diabetes mellitus, cardiovascular, rheumatological and oncological diseases, as well as some congenital malformations [18].

Recent studies (2022–2024) have explored immune checkpoint pathways and longitudinal biomarker profiles to improve cytokine storm management [17,19]. These insights offer new directions for risk stratification and therapeutic interventions. In light of recent advances in clinical research, particularly in the fields of immunomodulation and biomarker-based prediction [2,17,19], an updated synthesis of cytokine storm mechanisms and treatment options is warranted.

Despite extensive research, including during the COVID-19 pandemic, when cytokine storms were implicated in many fatal cases due to ARDS and multiple organ failure [15-17,19], there is still no consensus on optimal management strategies. Most studies focus on specific diseases or isolated molecular pathways, without integrating findings across different clinical contexts. Therefore, a critical research gap exists in synthesising current knowledge about the cytokine storm as a unifying pathophysiological mechanism in severe infectious diseases.

This narrative review aims to synthesize and critically evaluate existing literature on the role of cytokine storms in the progression of severe infectious diseases, identify shared pathophysiological mechanisms, and highlight implications for clinical management.

## METHODS

### General Background

This narrative review aims to synthesise current knowledge on the clinical manifestations, pathophysiological features, and therapeutic strategies related to Cytokine Storm Syndrome (CSS) in infectious diseases. Cytokine storm is a hyperinflammatory response implicated in organ failure and increased mortality in infections such as sepsis, COVID-19, and influenza, especially in patients with underlying chronic diseases.

### Inclusion Criteria

We included peer-reviewed original research articles, systematic and narrative reviews, meta-analyses, and clinical guidelines published in English between 2022 and 2024, focusing on pathophysiology of cytokine storm, biomarkers and clinical presentation, therapeutic and management strategies in infectious diseases.

### Exclusion Criteria

- Articles not related to infectious causes of cytokine storm
- Non-peer-reviewed material such as letters, editorials, commentaries
- Studies focusing exclusively on non-infectious causes (e.g., cancer or autoimmune disorders) unless mechanisms overlapped with infectious cases

### Data Collection

We searched PubMed, Scopus, and Web of Science for literature published from September 2024 to January 2025. The following keywords were used in various Boolean combinations:

- [cytokine storm] OR [cytokine release syndrome] AND ([COVID-19] OR [sepsis] OR [bacterial infection] OR [viral infection]) AND ([pro-inflammatory cytokines] OR [targeted therapy] OR [biomarkers] OR [personalised medicine] OR [surgical intervention])

We also manually screened reference lists of selected articles for additional sources.

### Study Selection and Data Extraction

The selection process involved three reviewers who independently screened the titles and abstracts of retrieved articles. Full texts were then reviewed, and inclusion decisions were made by consensus to reduce individual bias. For each included article, the following data were extracted using a standardised Excel template:

- Study type (e.g., review, clinical trial, meta-analysis),
- population or disease focus,
- Cytokine storm-related findings (e.g., biomarkers, immune pathways),
- Therapeutic approaches discussed,
- Year and source of publication

Articles were thematically categorised under key headings: (1) clinical manifestations, (2) pathophysiology, (3) biomarkers and diagnostics, (4) treatment and management. This thematic structure ensured consistency and reduced subjective interpretation during analysis.

### Statistical Analysis

As this is a narrative review, no quantitative synthesis was performed. The review is qualitative in nature, aiming to compare and contextualise findings across different infectious diseases to draw integrative conclusions on CSS pathophysiology and treatment.

### Article Quality Assessment

Although no formal risk-of-bias assessment was conducted due to the narrative nature of this review, we ensured the reliability of included sources by prioritising publications from high-impact, peer-reviewed journals. Preference was given to articles with a high citation count, publications in Q1–Q2 journals (based on Scopus and Web of Science rankings), and papers published by recognised research institutions or global health organisations (e.g., WHO). Preprints and non-peer-reviewed materials were excluded.

This review followed general principles of narrative review methodology. While it does not strictly adhere to systematic review frameworks such as PRISMA or MOOSE, we ensured transparency by describing our search strategy, eligibility criteria, and thematic approach to data analysis.

## RESULTS

### Theoretical Basis of Pathophysiological Mechanisms of Cytokine Storm Formation

Please ensure that the results and data are consistent and accurate throughout the manuscript. Statistical requirements are shown in the author instruction-"4. STATISTICAL REQUIREMENTS".

According to the current understanding of the peculiarities of cytokine storm development, several theories (Figure 1) explain this phenomenon in terms of excessive activation of various pathways regulating cytokine synthesis.

For example (Table 1), one of the leading concepts is the theory of uncontrolled activation of innate immunity [12,13], which is based on evidence that a cytokine storm occurs due to the overactivation of macrophages, neutrophils, and dendritic cells, which contribute to the release of large amounts of pro-inflammatory cytokines. This theory explains the rapid and systemic pro-inflammatory response in infectious diseases such as sepsis or COVID-19, as well as the rapid progression of ARDS and multiple organ failure. The triggering mechanisms are pathogens that activate Toll-like receptors (TLRs) and overactivate the complement system [11]. Hyperreactivity of the complement system (especially C3a and C5a) leads to excessive recruitment of immune cells to the site of inflammation.

The adaptive immunity activation theory is observed in autoimmune conditions and certain infections, such as Ebola [12,13]. The theory is that T lymphocytes (especially CD8+ cells) hyperactivated in response to antigenic stimulation and excessive interferon-gamma production contribute to the recruitment of other immune cells and the launch of a cytokine cascade. In some cases, B lymphocytes with excessive antibody synthesis are also involved.

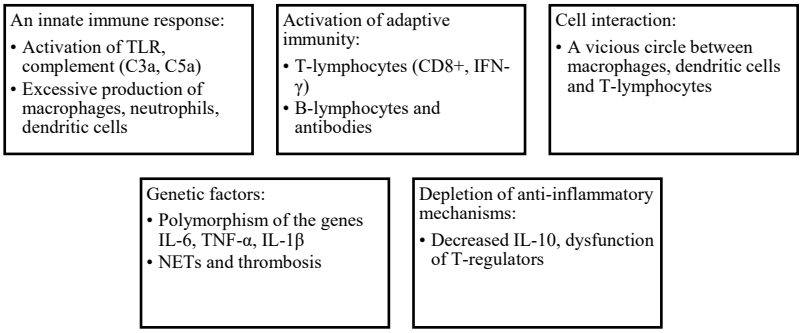


Figure 1: Leading theories of cytokine storm development in infectious diseases

Source: developed by the authors

Table 1: A comparative table of cytokine storm theories

| Theory | Key mechanism | Main immune cells | Key cytokines/molecules | Related conditions |
|---|---|---|---|---|
| Innate immunity overactivation | Excessive TLR stimulation, complement activation | Macrophages, neutrophils, dendritic cells | IL-6, IL-1β, TNF-α | Sepsis, COVID-19 |
| Adaptive immunity hyperactivation | Antigen-driven T cell activation and IFN-γ release | CD8+ T cells, B cells | IFN-γ, IL-2 | Ebola, autoimmune diseases |
| Mixed innate-adaptive interaction | Mutual stimulation loop between macrophages and lymphocytes | Macrophages, dendritic cells, T cells | IL-6, IL-1β, TNF-β | SARS, COVID-19 |
| NETs overproduction | Neutrophil extracellular traps trigger thrombosis and inflammation | Neutrophils | NETs, IL-8 | COVID-19, bacterial infections |
| Anti-inflammatory system depletion | Deficiency of IL-10, Tregs fail to control inflammation | Treg cells | ↓ IL-10, ↑ IL-6, TNF-α | Severe infections, sepsis |
| Genetic predisposition | Polymorphisms in immune-regulating genes | — | PRF1, STXBP2, NLRC4 mutations | Severe COVID-19, HLH |

Another theory suggests that the development of a cytokine storm is influenced by the fact that due to the interaction of innate and adaptive immune cells, the production of IL-6, IL-1, and TNF-b1 increases and mutual stimulation between immune cells creates a vicious circle that is difficult to break [12,13]. That is, the activation of macrophages, dendritic cells, and T lymphocytes leads to increased production of pro-inflammatory mediators.

Recent genetic studies on samples of patients with severe COVID-19 and sepsis have demonstrated a link between polymorphisms in genes that regulate cytokine production (e.g. IL-6, TNF-b1, IL-1\) and the development of a cytokine storm [9]. For example, those at risk include individuals with homozygous PRF1 deficiency, dominant harmful STXBP2 mutation, NLRC4 activating mutation, and SLC7A7 mutation.

Another theory suggests that excessive neutrophil activation leads to the formation of extracellular neutrophil traps [20], which trap pathogens and cause massive local inflammation. As this phenomenon is accompanied by thrombosis, this theory explains the development of complications such as thromboembolism and multiple organ failure.

The theory of "depletion" of anti-inflammatory mechanisms [20,21] occupies a special place. The theory states that anti-inflammatory mechanisms normally regulate the immune response, but in the case of a cytokine storm, these mechanisms do not have time to compensate for excessive inflammation. Patients with severe infections often have low levels of IL-10 and dysfunctional regulatory T cells.

Key questions currently under active discussion include the underlying causes of cytokine storm initiation and the role of genetic factors [12,2].

## Features of the Cytokine Storm in Severe Infections

The cytokine storm in various infectious diseases has its own characteristics, which depend on the type of pathogen, the body's immune response, and the involvement of various target organs (Table 2). The standard features of the cytokine storm (Figure 2) are the hyperproduction of pro-inflammatory mediators and the development of systemic inflammation, accompanied by fever and multiple organ failure [10].

Thus, the cytokine storm is one of the leading causes of severe infectious diseases caused by pathogens from the coronavirus family. In particular, the SARS-CoV virus, which causes severe acute respiratory syndrome SARS, is characterised by lung damage and causes a massive pro-inflammatory response and, due to excessive production of IL-6, IL-8, TNF-α, leads to the development of a cytokine storm [14,15].

In cases of severe COVID-19, the cytokine storm is accompanied by the massive release of interleukins IL-6, IL-1β, IL-8, TNF-α and other pro-inflammatory mediators, such as sCD163, CCL20, HGF, CHintinase3like1 and Pentraxin3 [17]. According to a meta-analysis by Mulchandani *et al.* [15], levels of cytokines such as IL-6 were significantly higher in severe COVID-19: MD, 19.55 pg/ml; CI, 14.80, 24.30; IL-8: MD, 19.18 pg/ml; CI, 2.94, 35.43; IL-10: MD, 3.66 pg/ml; 2.41, 4.92; IL-2R: 521.36 U/ml; 87.15, 955.57 and TNF-alpha: 1.11 pg/ml, and the level of T-lymphocytes was significantly lower. According to Melo et al. [16], elevated IL-6 levels should be considered a red flag for severe COVID-19. Table 3 presents the key biomarkers with clinical cutoff points [15,16]. These data from meta-analyses by Mulchandani *et al.* [15] and Melo *et al.* [16] may vary depending on the research method.

The initiation of the cytokine storm in influenza patients occurs through the hyperproduction of cytokines IL-6, IL-10, and TNF-α. As a result, the course of the disease is complicated by critical conditions such as the development and rapid progression of viral pneumonia and ARDS.

Table 2: Features of the cytokine storm in various infectious diseases

| Diseases | Pathogen | Target organs | Dominant parts of the immune system |
|---|---|---|---|
| Severe acute respiratory syndrome (SARS) | SARS-CoV | Lungs, heart | IL-1β, IL-6, TNF-α, IFN-γ |
| Middle East respiratory syndrome (MERS-CoV) | MERS-CoV | Lungs, kidneys | IL-6, IL-8, IL-17, TNF-α |
| COVID-19 | SARS-CoV-2 | Lungs, heart, kidneys, blood vessels | IL-1β, IL-6, IL-8, TNF-α, IFN-γ |
| Ebola haemorrhagic fever | Ebolavirus | Lungs, liver, kidneys | IL-6, TNF-α, IFN-γ |
| Marburg haemorrhagic fever | Marburg virus | Lungs, liver, blood vessels | IL-6, TNF-α, IFN-γ |
| Dengue fever | Dengue virus | Vessels, liver, bone marrow | IL-6, IL-8, TNF-α, IFN-γ |
| Infectious mononucleosis | Epstein-Barr virus (EBV) | Lymph nodes, liver, spleen | IL-6, IFN-γ, TNF-α |
| Leptospirosis | Leptospira spp. | Liver, kidneys, blood vessels | IL-6, IL-8, TNF-α |
| Smallpox | Variola virus | Skin, blood vessels, liver | IL-1β, IL-6, TNF-α |
| Sepsis | Different types of bacteria | Vessels, liver, kidneys | IL-1β, IL-6, IL-8, TNF-α |

Table 3: A summary table of key biomarkers with clinical cutoff points

| Biomarker | Clinical Cutoff / Range | Associated Outcome | Reference |
|---|---|---|---|
| IL-6 | > 19.6 pg/ml | Severe COVID-19, ARDS | [15] |
| IL-8 | > 19.2 pg/ml | Systemic inflammation | [15] |
| IL-10 | > 3.7 pg/ml | Severe infection, poor prognosis | [15] |
| IL-2R | > 521,4 U/ml | Immune activation | [15] |
| TNF-α | > 1.1 pg/ml | Endothelial damage, organ failure | [15] |
| sCD163, PTX3 | ↑ above baseline (not always quantified) | Macrophage activation, tissue injury | [16] |

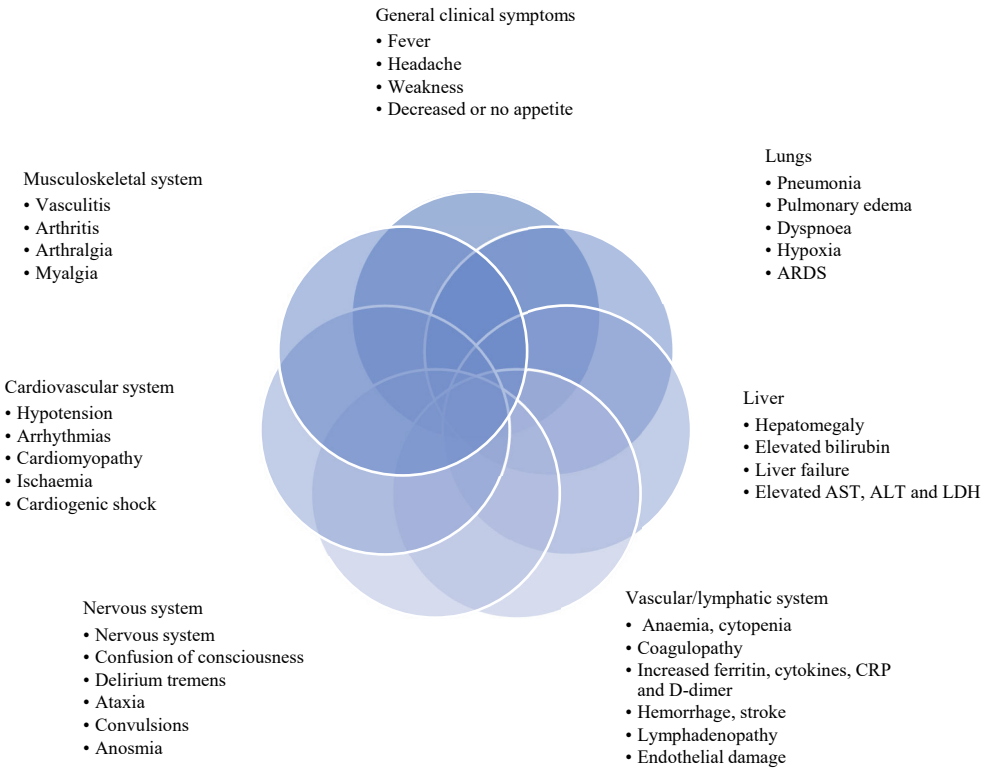


Figure 2: Features of damage to organs and systems during cytokine storm in patients with infectious diseases
Source: translated and adapted from Fajgenbaum and June [10]

Table 4: A comparative table of treatment strategies and their characteristics

| Strategy | Target | Drug examples | Advantages | Disadvantages |
|---|---|---|---|---|
| Targeted therapy | IL-6, IL-1β, TNF-α | Tocilizumab, Anakinra, Etanercept | Selectivity, known safety profile | Limited if target cytokine is misidentified |
| Multifactorial therapy | JAK/STAT pathway, multiple cytokines | Baricitinib, Ruxolitinib | Broad anti-inflammatory effect | Risk of immunosuppression, cost |
| Plasmapheresis/immunoadsorption | Circulating cytokines | — | Direct cytokine removal | Limited availability, procedural risks |

Alongside the hyperreactivity of particular cytokine production, suppression of specific immune system components occurs, increasing the risk of secondary bacterial infections. Differences in cytokine profiles in influenza compared to severe COVID-19, according to Lee *et al.* [22], lie in the fact that the systemic inflammatory response in influenza is less dependent on TNF/IL-1β.

Uncontrolled release of bacterial toxins during sepsis stimulates the immune system to hyperproduce TNF-α, IL-1β, IL-6, and cytokine storm development, resulting in microcirculation disorders, multiorgan failure, hypercoagulation, and septic shock [23].

According to Srikiatkhachorn *et al.* [24], the severe course of fever caused by Dengue virus infection, accompanied by increased vascular permeability and the development of shock syndrome, is attributed to cytokine storm, triggered by elevated levels of IL-2, IL-6, IL-10, and IFN-γ.

Hyperproduction of TNF-α, IL-1β, and IL-6 and the development of a cytokine storm during haemorrhagic fevers like Ebola and Marburg are associated with massive vascular damage, severe hypotension, multiorgan failure, and rapid disease progression. According to Younan *et al.* [25], the primary pathway of cytokine storm activation in this case is the virus binding to T-cells through the Tim-1 pathway.

## Treatment

According to modern concepts, treating patients with infectious diseases in the event of a cytokine storm includes not only traditional approaches aimed at restoring homeostasis and, if possible, pharmacological intervention to eliminate the pathogen but also immunosuppressive therapy (Table 4). Glucocorticoids are drugs that suppress the main components of the inflammation process. Direct inhibitors block one or more cytokines, which can be part of targeted or multifactorial therapy [1,9].

Different approaches to treating patients with cytokine storms have been developed based on specific theories of the onset and development of this pathology. The most studied targets for this therapy are IL-6, TNF-\u03b1 and IL-1\u03b2.

The advantage of this approach is the selectivity of intervention with drugs that block only a specific pathway while keeping the rest of the immune system active. For this purpose, drugs with well-studied pharmacodynamics and known safety profiles previously used in autoimmune diseases are used. These drugs include tocilizumab (IL-6R inhibitor) or anakinra (IL-1 inhibitor). In patients with COVID-19 or sepsis, IL-6 blockade reduced inflammation and improved prognosis. Still, given the genotype polymorphism in the genes that initiate cytokine secretion and the fact that different cytokines may dominate in different patients during the development of a cytokine storm, targeted therapy may be ineffective if the wrong target is chosen.

Another approach takes into account not only the pathophysiological characteristics of the cytokine storm but also the potential consequences of targeted therapies that focus on inhibiting only one cytokine because there is a significant risk that when one cytokine is inhibited, elevated levels of other cytokines may persist and continue to stimulate the inflammatory response. The multifactorial therapy approach involves blocking several pro-inflammatory cytokines or regulating different components of the immune system and the use of drugs that simultaneously block several key cytokines (e.g., JAK inhibitors) and provide better control of inflammation by interrupting the pathophysiological cascade of the cytokine storm. The flexibility of this approach allows for the adaptation of therapy depending on the clinical situation and the level of inflammatory markers individually for each patient. However, this approach has several disadvantages, such as severe immunosuppression, which increases the risk of secondary infections, polypharmacy, and the high cost of combining several targeted drugs.

The choice of therapy is patient-centred and is based on the specific clinical situation, stage of the disease and individual characteristics [9]. In acute conditions, when the speed of response is critical, targeted therapy may be sufficient. However, in complex and chronic forms of disease, a comprehensive approach that considers the multifaceted nature of the immune response is advisable [9].

Some studies have shown the effectiveness of alternative therapies to pharmacotherapy, such as immunoabsorption/plasmapheresis [26,27]. This method is based on the purification of blood from excess pro-inflammatory cytokines using special filters.

In addition to the currently used targeted and multifactorial therapies, recent advancements have introduced promising novel therapeutic strategies for managing cytokine storms. Mesenchymal Stem Cell (MSC) therapy has garnered significant attention for its immunomodulatory properties and tissue repair potential. MSCs have been shown to reduce levels of pro-inflammatory cytokines such as IL-6 and TNF-α, while promoting the secretion of anti-inflammatory mediators [28]. Clinical trials in patients with severe COVID-19 suggest that MSCs can help mitigate the inflammatory response and accelerate recovery.

Monoclonal antibodies targeting cytokines or their receptors such as IL-6R (e.g., tocilizumab), GM-CSF (e.g., lenzilumab, otilimab), and IL-1 (e.g., anakinra) have demonstrated efficacy in clinical trials [29]. These therapies allow for a selective suppression of specific inflammatory pathways, thereby reducing systemic inflammation while preserving the broader immune defense. Several of these agents have been repurposed from autoimmune and oncological indications and are now being evaluated for infectious conditions marked by cytokine storms.

Moreover, gene-based therapies [30], including mRNA technologies and CRISPR/Cas9-mediated gene editing, are being explored to modulate cytokine gene expression. Although still largely in experimental stages, these therapies have the potential to offer highly individualised interventions based on genetic predisposition and cytokine profile, opening new possibilities for precision medicine in infectious disease treatment.

To improve clinical outcomes, future research should focus on identifying patients at highest risk for cytokine storm development using early biomarkers such as IL-6, IL-10, and IL-2R, and applying stratified treatment algorithms. Incorporating such biomarker-driven decision-making into clinical practice could allow for earlier initiation of immunomodulatory therapies, better control of systemic inflammation, and prevention of organ failure.

Taken together, the integration of traditional and emerging therapeutic approaches, informed by molecular and genetic profiling, may lead to more effective and personalised management strategies for patients with severe infectious diseases complicated by cytokine storm syndromes.

## DISCUSSION

The cytokine storm is a key pathophysiological mechanism underlying the severe course of many infectious diseases, including COVID-19, SARS, MERS, sepsis, Dengue fever, Ebola, Marburg haemorrhagic fever, and others [1,2]. According to current knowledge, the primary triggers of this condition are the overactivation of the immune system in response to a pathogen, which leads to the uncontrolled release of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β and others with the involvement of the complement system hyperfunction [2]. Although the overall pathogenesis of the cytokine storm has standard features, its clinical manifestations and target organ damage largely depend on the type of infection, genetic characteristics of the patient, and his or her immune status [9].

Excessive activation of various parts of the immune system causes a cascade of inflammatory reactions, including endothelial activation, microcirculatory disorders, hypercoagulability, and multiple organ failure [9-13]. For example, in COVID-19, the primary mediator is IL-6, which is associated with developing acute respiratory distress syndrome. In the case of Ebola and Marburg haemorrhagic fevers, TNF-α dominates, causing severe vascular damage and hypotension. Dengue fever is characterised by the activation of IL-2, IL-6, IL-10 and IFN-γ, which increase

vascular permeability and contribute to the development of shock syndrome. Sepsis is associated with uncontrolled release of bacterial toxins that stimulate excessive production of TNF-α, IL-1β and IL-6, leading to septic shock and multiple organ failure. These features emphasise the need for an individualised approach to treatment depending on the clinical manifestations and characteristics of the disease.

Current treatment strategies for the cytokine storm include targeted and multifactorial therapies [1,9]. Targeted therapy, which aims to block key cytokines (e.g. IL-6, TNF-α, IL-1β), effectively treats patients with COVID-19, sepsis, and autoimmune conditions. It has the advantage of being selective and preserving the immune response, but limitations include the dependence of effectiveness on the correct choice of target. Multifactorial therapy, which involves inhibiting several pro-inflammatory cytokines or modulating the functioning of different parts of the immune system, allows for better control of the inflammatory process. However, its use increases the risk of severe immunosuppression and the likelihood of secondary infections. Alternative methods, such as immunoadsorption, open up new opportunities to directly reduce the concentration of pro-inflammatory cytokines in the blood of patients with cytokine storm and may be helpful in the treatment of patients with severe infectious diseases [26,27]. In addition to pharmacological interventions, therapeutic plasma exchange (plasmapheresis) has been explored as a method to mitigate cytokine storms by removing circulating pro-inflammatory cytokines and stabilizing the immune response [27]. Recent clinical trials have demonstrated that plasmapheresis can significantly reduce inflammatory markers such as IL-6, CRP, and ferritin, leading to improved oxygenation parameters and reduced mortality in patients with severe COVID-19. Similarly, immunoadsorption techniques, which selectively remove specific cytokines from the plasma, have shown promise in modulating hyperinflammatory states, though further studies are needed to establish their efficacy and safety profiles.

According to Mulchandani *et al.* [15] the gaps in knowledge about the nature of the cytokine storm are mainly due to the heterogeneity of scientific studies, which result from small sample sizes, inconsistent assessment of results, and differences in the definition of the severity of the infectious disease.

In addition to existing treatment strategies, recent advances have introduced new therapeutic approaches that may be applicable in the management of cytokine storms. MSC therapy has shown promise in modulating immune responses and restoring tissue integrity in severe inflammatory conditions, including COVID-19 [28]. MSCs are capable of reducing pro-inflammatory cytokine levels while promoting anti-inflammatory mediators and tissue repair.

Monoclonal antibodies targeting specific cytokines or receptors (e.g., IL-6R, GM-CSF, IL-17) are also under investigation for their ability to selectively suppress the immune overreaction without causing broad immunosuppression [29]. These therapies are already in clinical use for autoimmune diseases and have shown positive outcomes in clinical trials for COVID-19 and sepsis.

Furthermore, gene therapy approaches are being explored to modify cytokine expression or inhibit key inflammatory genes using RNA interference or CRISPR/Cas9 platforms [30]. Although still experimental, such interventions hold potential for highly personalised modulation of immune responses in patients genetically predisposed to severe disease.

The integration of these novel strategies into clinical practice requires further validation but represents a promising direction for future treatment frameworks.

Despite the achievements of modern medicine in studying the pathophysiological features of cytokine storms, the issues of optimal treatment choices for patients remain unresolved. The impossibility of developing a universal approach is due to the high level of immune response polymorphism among patients and the variability of clinical manifestations of severe infectious diseases. Therefore, promising research areas include improving drugs that block multiple inflammatory pathways and keep the immune response effective, studying the role of genetic regulation of cytokines and heredity, and developing personalised medicine strategies. Future research into the predictors and pathogenesis of cytokine storms, as well as the effectiveness of new therapeutic approaches, will significantly improve treatment outcomes and patients' quality of life.

Based on the reviewed data, clinicians may consider stratifying patients by cytokine profiles and inflammatory markers to guide early targeted interventions. Integrating biomarker thresholds (e.g., IL-6>19.5 pg/ml) into decision-making may facilitate the timely initiation of immunomodulatory therapies and improve patient outcomes.

The findings and recommendations presented in this review should be interpreted in light of several limitations. First, the therapeutic strategies discussed are still under investigation, and their effectiveness may vary depending on patient characteristics, disease severity, and timing of intervention. Further research is needed to develop stratified protocols that match cytokine profiles to specific treatments. Second, as a narrative review, this study is inherently limited by the scope and quality of the included literature. Some studies had small sample sizes, lacked randomisation, or focused on specific populations, which may affect the generalisability of findings. In addition, most available data originate from regions with established research infrastructure, leaving potential gaps in representation from low- and middle-income countries.

## CONCLUSIONS

Cytokine storm remains a critical and often life-threatening complication of infectious diseases, particularly in patients with comorbidities and pre-existing immune dysregulation. Despite extensive research, a universal and fully effective treatment approach has not yet been established due to the complexity and heterogeneity of this immunopathological phenomenon. However, current evidence supports several practical recommendations for clinical practice:

Early identification of high-risk patients is essential and should include monitoring of key biomarkers such as IL-6 (>19.5 pg/ml), IL-10, IL-8, and IL-2R, particularly in individuals with diabetes, cardiovascular disease, or immunosuppression.

Prompt initiation of immunomodulatory therapy (e.g., targeted cytokine inhibitors or multifactorial approaches) can reduce the risk of progression to ARDS and multi-organ failure. Regular evaluation of cytokine profiles may help guide therapy selection, especially in settings where access to genetic or molecular diagnostics is available.

In clinical settings, a personalised and dynamic treatment approach—tailored to the patient's immune status, cytokine profile, and disease stage—is likely to yield the best outcomes. Continued research into early predictors, targeted therapies, and immune-genetic interactions will be critical for improving survival and quality of life in patients experiencing cytokine storm syndromes.

## Future Recommendations

To improve outcomes for patients with infectious diseases complicated by cytokine storm syndrome, future research should prioritise the following areas:

Development of personalised medicine approaches that consider the patient's cytokine profile, immune system status, and comorbidities. This may include biomarker-guided treatment algorithms and adaptable therapeutic regimens based on disease stage and severity.

Genetic and epigenetic research aimed at identifying host factors that predispose individuals to hyperinflammatory responses. Understanding these mechanisms will facilitate early risk stratification and targeted prevention strategies.

Investigation of novel therapeutic agents that suppress excessive cytokine release without compromising essential immune functions. This includes studying immunomodulators, next-generation monoclonal antibodies, JAK inhibitors, and combination therapies that preserve host defense while mitigating inflammation.

## Availability of Data and Material

This study is a narrative review based on publicly available literature. No new data were generated or analysed. All data sources are cited within the manuscript. Further information or clarification can be obtained from the corresponding author upon request.

## Ethical Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

## REFERENCES


[1] Karki, Rajendra, and Thirumala-Devi Kanneganti. "The 'cytokine storm': molecular mechanisms and therapeutic prospects." *Trends in immunology,* vol. 42, no. 8, 2021, pp. 681-705. https://www.cell.com/trends/immunology/abstract/S1471-4906(21)00115-0.

[2] Shen, Junyi, *et al.* "Frontiers and hotspots evolution in cytokine storm: A bibliometric analysis from 2004 to 2022." *Heliyon,* vol. 10, no. 10, May 2024. https://www.cell.com/heliyon/fulltext/S2405-8440(24)06986-X.

[3] World Health Organization *Global report on infection prevention and control 2024: executive summary* 2024, https://www.who.int/publications/i/item/B09195.

[4] Biselli, Roberto, *et al.* "A historical review of military medical strategies for fighting infectious diseases: From battlefields to global health." *Biomedicines,* vol. 10, no. 8, August 2022. https://www.mdpi.com/2227-9059/10/8/2050.

[5] Gugushvili, Alexi, and Martin Mckee. "The COVID-19 pandemic and war." *Scandinavian journal of public health,* vol. 50, no. 1, February 2021, pp. 16-18. https://journals.sagepub.com/doi/full/10.1177/1403494821993732.

[6] Gebreyohannes, Eyob Alemayehu, *et al.* "Impacts of armed conflicts on tuberculosis burden and treatment outcomes: a systematic review." *BMJ Open,* vol. 14, no. 3, 2024. https://bmjopen.bmj.com/content/14/3/e080978.abstract.

[7] GBD 2021 Forecasting Collaborators, "Burden of disease scenarios for 204 countries and territories, 2022-2050: a forecasting analysis for the Global Burden of Disease Study 2021." *Lancet,* vol. 403, no. 10440, May 2025, pp. 2204-2256. https://pubmed.ncbi.nlm.nih.gov/38762325/.

[8] Berbudi, Afiat, *et al.* "Type 2 diabetes and its impact on the immune system." *Current Diabetes Reviews,* vol. 16, no. 5, June 2020, pp. 442-449. https://www.benthamdirect. com/content/journals/cdr/10.2174/1573399815666191024085838.

[9] Lee, Pui Y., and Randy Q. Cron. "The multifaceted immunology of cytokine storm syndrome." *The Journal of Immunology,* vol. 210, April 2023, pp. 1015-1024. https://journals.aai.org/jimmunol/article/210/8/1015/263561.

[10] Fajgenbaum, David C. and Carl H. June. "Cytokine storm." *The New England Journal of Medicine,* vol. 383, no. 23, December 2020, pp. 2255-2273. https://pubmed.ncbi.nlm.nih.gov/33264547/.

[11] Rha, Min-Seok, *et al.* "SARS-CoV-2-specific T cell responses in patients with COVID-19 and unexposed individuals." *Immune Network,* vol. 21, no. 1, February 2021. https://pmc.ncbi.nlm.nih.gov/articles/PMC7937509/.

[12] Marcuzzi, Annalisa, *et al.* "Autoinflammatory diseases and cytokine storms—imbalances of innate and adaptative immunity." *International Journal of Molecular Sciences,* vol. 22, no. 20, October 2021. https://www.mdpi.com/1422-0067/22/20/11241.

[13] Jarczak, Dominik, and Axel Nierhaus. "Cytokine storm—definition, causes, and implications." *International Journal of Molecular Sciences,* vol. 23, no. 19, October 2022. https://www.mdpi.com/1422-0067/23/19/11740.

[14] Liu, Tong, *et al.* "Comparison of the characteristics of cytokine storm and immune response induced by SARS-CoV, MERS-CoV, and SARS-CoV-2 infections." *Journal of Inflammation Research,* vol. 14, October 2021, pp. 5475-5487. https://www.tandfonline.com/doi/full/10.2147/JIR.S329697.

[15] Mulchandani, Rubina, *et al.* "Deciphering the COVID-19 cytokine storm: systematic review and meta-analysis." *European journal of clinical investigation,* vol. 51, no. 1, October 2020. https://onlinelibrary.wiley.com/doi/abs/10.1111/eci.13429.

[16] Melo, Ana Karla G., *et al.* "Biomarkers of cytokine storm as red flags for severe and fatal COVID-19 cases: A living systematic review and meta-analysis." *PloS one,* vol. 16, no. 6, June 2021. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0253894.

[17] van Meijgaarden, Krista E., *et al.* "Longitudinal soluble marker profiles reveal strong association between cytokine storms resulting from macrophage activation and disease severity in COVID-19 disease." *Scientific Reports,* vol. 14, no. 1, June 2024. https://www.nature.com/articles/s41598-024-63586-8.

[18] Hanna, John, *et al.* "Risk factors associated with the clinical outcomes of COVID-19 and its variants in the context of cytokine storm and therapeutics/vaccine development challenges." *Vaccines,* vol. 9, no. 8, August 2021. https://www.mdpi.com/2076-393X/9/8/938.

[19] Meggyes, Matyas, *et al.* "Can there be calm during a cytokine storm? Immune checkpoint pathways affecting the severity of COVID-19 disease." *Frontiers in Microbiology,* vol. 15, December 2024. https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2024.1508423/full.

[20] Islam, Md Monirul, and Naoshi Takeyama. "Role of neutrophil extracellular traps in health and disease pathophysiology: recent insights and advances." *International journal of molecular sciences,* vol. 24, no. 21, October 2023. https://www. mdpi.com/1422-0067/24/21/15805.

[21] Wherry, E. John, and Makoto Kurachi. "Molecular and cellular insights into T cell exhaustion." *Nature reviews immunology,* vol. 15, no. 8, July 2015, pp. 486-499. https://www.nature.com/articles/nri3862.

[22] Lee, Jeong Seok, *et al.* "Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19." *Science immunology,* vol. 5, no. 49, July 2020. https://www.science.org/doi/abs/10.1126/sciimmunol.abd1554.

[23] Chousterman, Benjamin G., *et al.* "Cytokine storm and sepsis disease pathogenesis." *Seminars in immunopathology,* vol. 39, May 2017, pp. 517-528. https://link.springer.com/article/10.1007/s00281-017-0639-8.

[24] Srikiatkhachorn, Anon, *et al.* "Immune-mediated cytokine storm and its role in severe dengue." *Seminars in immunopathology,* vol. 39, April 2017, pp. 563-574. https://link.springer.com/article/10.1007/s00281-017-0625-1.

[25] Younan, Patrick, *et al.* "Ebola virus binding to Tim-1 on T lymphocytes induces a cytokine storm." *MBio,* vol. 8, no. 5, September 2017, pp. 1110-1128. https://journals.asm.org/doi/abs/ 10.1128/mbio.00845-17.

[26] Turgutkaya, Atakan, *et al.* "Application of plasmapheresis for Covid-19 patients." *Therapeutic Apheresis and Dialysis,* vol. 25, no. 2, July 2020. https://pmc.ncbi.nlm.nih.gov/articles/PMC7300871/.

[27] Sadeghi, Alireza, *et al.* "Efficacy of plasmapheresis in neutropenic patients suffering from cytokine storm because of severe COVID-19 infection." *Blood research,* vol. 58, no. 2, May 2023, pp. 91-98. https://synapse.koreamed.org/articles/1516083037.

[28] 28. Taufiq, Hannah, *et al.* "Systematic review and meta-analysis of mesenchymal stromal/stem cells as strategical means for the treatment of COVID-19." *Therapeutic Advances in Respiratory Disease,* vol. 17, April 2023. https://journals.sagepub.com/doi/full/10.1177/17534666231158276.

[29] 29. Patel, Jatin, *et al.* "A randomised trial of anti-GM-CSF otilimab in severe COVID-19 pneumonia (OSCAR)." *European Respiratory Journal,* vol. 61, no. 2, 2023.

[30] Shi, Yingying, *et al.* "Progress and prospects of mRNA-based drugs in pre-clinical and clinical applications." *Signal Transduction and Targeted Therapy,* vol. 9, no. 1, November 2024. https://www.nature.com/articles/s41392-024-02002-z.