Pathogenesis and Therapeutic Targets of Cytokine Storms in Bacterial Infections

Ghufran Mohammed Sadee Merie [1], Hadeel Tahseen Al-hashimi [2], Ali M Saadi [3*]
[1] Department of Medical Laboratory Technologies, Mosul Medical Technical Institute, Northern Technical University, Iraq
[2] Department of Medicinal Plant Technologies, Technical Agricultural College, Northern Technical University, Iraq

* Corresponding Author: **Ali M Saadi**

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Abstract
It is possible that the abstract of the paper "Pathogenesis and Therapeutic Targets of Cytokine Storms in Bacterial Infections" encapsulates the main conclusions and revelations about the function of cytokine storms in relation to bacterial infections. It could go over the processes that cause cytokine storms, how they affect the host's immune system, and possible treatment targets that could lessen the negative consequences of these storms. A succinct description of cytokine storms and their significance in bacterial infections. A succinct description of cytokine storms and their significance in bacterial infections. Talk about possible tactics and remedies for controlling or averting cytokine storms. a synopsis of how these findings may affect clinical practice and future study.

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1. Introduction to Cytokine Storms in Bacterial Infections

Cytokine storms are defined as severe and pathological inflammatory responses triggered by excessive release of pro-inflammatory cytokines. Pathogenic bacteria are important causes of life-threatening diseases and often induce cytokine storms. Invasive infections by bacterial pathogens lead to complex and extensive immune responses, including systemic cytokine storms. Cytokine storms play significant roles in both protective and pathological effects during bacterial infections. The protective effects include clearing the pathogens and limiting their dissemination, while the pathological effects include extensive damages to tissues and organs due to inflammatory responses (Tang *et al*., 2021) [4]. In addition to sepsis, cytokine storms are also induced during other bacterial infections, such as pneumonia and meningitis. With the emergence of drug-resistant bacteria, there are urgent needs to understand the pathogenesis of cytokine storms during infections by various bacterial pathogens and to develop effective intervention strategies. (Rabaan *et al*. 2021, Marcuzzi *et al*. 2021, Tang *et al*. 2021) [1, 4, 3].

Cytokine storms have been extensively studied during viral infections. However, the knowledge on the pathogenesis of cytokine storms induced by bacterial infections is still very limited. Generally, cytokine storms are caused by complicated interactions between pathogens, pathogen-associated molecular patterns (PAMPs), and immune responses. The immune responses that lead to cytokine storms involve both innate and adaptive immune systems. Some key components of the immune systems and processes that are important in the development of cytokine storms are briefly discussed. Cytokine storms were regarded as an important consideration for the development of vaccines and therapeutics. Besides COVID-19, the incidences of cytokine storms caused by other infections are on the rise and need awareness. Understanding the mechanisms of development and pathogenesis of cytokine storms during bacterial infections is expected to facilitate the development of effective interventions and treatments. (Kim *et al*. 2021, Ramasamy & Subbian, 2021, Karki & Kanneganti, 2021) [5, 6, 7].

2. The Immune Response to Bacterial Infections

The body has developed complex immune response mechanisms to detect and eliminate bacterial pathogens. The first step is the detection of bacteria by the host through pattern recognition receptors (PRRs) that recognize conserved bacterial structures called pathogen-associated molecular patterns (PAMPs). There are five classes of PRRs: Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), retinoic acid-inducible gene I-like receptors (RLRs), C-type lectin-like receptors (CLRs), and some cytosolic PRRs. The recognition of bacterial pathogens by PRRs activates various signaling cascades and leads to the production of pro-inflammatory cytokines, chemokines, and other immune response mediators. This initial innate immunity plays an essential role in clearing the bacterial infection and shaping the following adaptive immune responses. Once bacteria invade the body, the innate immune system is rapidly activated. Immune cells, including macrophages, neutrophils, and dendritic cells, are recruited to the infection site, where they directly eliminate bacteria through phagocytosis. Dendritic cells capture the bacteria or bacterial products, migrate to the lymph nodes, and present specific antigens to T and B lymphocytes. T lymphocytes differentiate into T helper 1 cells upon proinflammatory cytokine stimulation, such as interleukin-12 (IL-12) and interferon-γ (IFN-γ). T helper 1 cells secrete a series of cytokines to activate the macrophages, enhancing their ability to eliminate intracellular bacteria. In addition, activated CD4+ T helper 1 cells promote the differentiation of näıve CD8+ T cells into cytotoxic T lymphocytes to eliminate infected cells. On the other hand, through antigen presentation, näıve B cells are activated to secrete antibodies that tag bacteria and facilitate their elimination by phagocytes (Reddy *et al*., 2024) [8]. Cytokines are a group of secretive proteomers that orchestrate the immune response. Some cytokines stimulate the immune response, such as proinflammatory cytokines, while others inhibit the immune response, such as anti-inflammatory cytokines. During bacterial infections, bacteria-induced innate immune responses cause the rapid release of various proinflammatory cytokines. These cytokines activate immune cells and increase their recruitment to the infection site, leading to effective bacterial clearance. Thus, a balance between the effective immune activation and its overactivation is crucial; otherwise, a cytokine storm occurs. Because of the consequences of cytokine storms, the pathogenic mechanisms of their occurrence and possible therapeutic targets have been intensively studied in some viral infections. Similar to viral infections, sudden excessive release of various cytokines also occurs in some bacterial infections. However, it is unknown how cytokines play different roles during the immune response against various bacteria or the same bacteria in different situations. Detailed overviews of the proinflammatory cytokine functions and signaling pathways regarding bacterial infections are essential to provide guidance for future studies. Bacteria have evolved different strategies to sense and evade the host immune system, and the immune system has evolved corresponding mechanisms to recognize and eliminate bacteria. Therefore, to effectively kill bacteria, it is crucial to understand how immune responses are activated upon bacterial detection and the bacterial pathogenesis associated with immune evasion. (Jiang *et al*. 2022, Jarczak & Nierhaus, 2022, Karki & Kanneganti, 2021, Tang *et al*. 2021) [4, 7, 9, 10].

3. Cytokines and Chemokines: Key Players in the Pathogenesis of Cytokine Storms

To fight pathogens and return to homeostasis, the immune system launches an elaborate and finely orchestrated series of actions, including recognition of the pathogen, recruitment and activation of immune/inflammatory cells at the site of infection, and modulation of the responses exposed by immune regulators. Cytokines and chemokines are key players in this process. Cytokines are a broad and loose category of small proteins that are important in cell signaling. Their release has an effect on the behavior of other cells. Cytokines include interleukins, interferons, tumor necrosis factors, and other molecules. Chemokines are a specific subset of cytokines with the ability to induce directed chemotaxis in nearby responsive cells. Chemokines can recruit immune/inflammatory cells to the infection sites, thereby mounting local immune responses against the pathogens. Meanwhile, some cytokines can spread systemically in the circulation, and their actions may affect distant organs and tissues. This is particularly true for pro-inflammatory cytokines. The immune system also has a set of negative regulatory mechanisms, usually involving anti-inflammatory cytokines, to down-regulate the immune responses after the pathogens are cleared (Reddy *et al*., 2024) [8]. In the case of bacterial infections, this delicate balance between pro-inflammatory and anti-inflammatory cytokines determines the severity and progression of the infections. Pathogen recognition usually induces a robust production of pro-inflammatory cytokines from the activated innate immune cells, leading to systemic inflammation. If the infections are not well controlled, pro-inflammatory cytokines continue to increase, which may overwhelm the actions of the anti-inflammatory cytokines and result in a hyper-inflammatory state characterized as a cytokine storm. (Valdes-Aguayo *et al*. 2021, Rihar *et al*. 2024, Müller & Di Benedetto, 2021, Pourgholaminejad *et al*. 2022) [12, 13, 14, 15]. Cytokine storms and hyper-inflammation have been commonly observed in severe bacterial infections, particularly in sepsis. The septic shock induced by Gram-negative bacteria often leads to a cytokine storm characterized by excessive tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), IL-1, and other pro-inflammatory cytokines. In addition to systemic cytokine storms, local hyper-inflammation may occur in specific organs/tissues, which is often due to local overproduction of IL-1 cytokine family members, regardless of the systemic inflammatory status. Dysregulations of both pro-inflammatory and anti-inflammatory responses accompany these hyper-inflammatory states. Cytokine storms play critical roles in the pathogenesis of severe inflammatory responses. Understanding the mechanisms of cytokine storms during bacterial infections is crucial for developing new therapeutic strategies. (Greenfield *et al*. 2021, Tang *et al*. 2021, Jarczak & Nierhaus, 2022, Jiang *et al*. 2022, Karki & Kanneganti, 2021) [16, 4, 7, 9, 10].

4. Pathophysiology of Cytokine Storms in Bacterial Infections

Cytokine storms have emerged as a prominent cause of severe pathology and death in a variety of infectious diseases. Highly pathogenic strains of influenza virus or bacterial pathogens often precipitate such storms. For a cytokine storm to occur in response to an infection, a number of pathophysiological processes must be engaged, managed, or

dysregulated. An acute inflammatory immune response, designed to counteract infection and restore homeostasis, disrupts normal operations and escalates into a cytokine storm. The inflammatory signal cascade begins with the activation of innate immune cells, which is coupled with the detection of pathogen-associated molecular patterns. These cells produce an array of pro-inflammatory cytokines and other mediators that propagate the inflammatory signal and recruit more immune cells to the affected sites. During a pathogen-induced inflammatory response, some adaptive immune processes, particularly those mediated by T cells, can take days or weeks to fully engage (Tang *et al*., 2021) [4]. However, the innate immune response is much more rapid, often engaged within hours of infection to counteract its spread. Following an initial inflammatory response, a plethora of feedback mechanisms are activated to rein in the inflammation and restore homeostasis. If these mechanisms fail, the initially localized cytokine release becomes uncontrolled, spreading throughout the system and forming a cytokine storm. (Jiang *et al*. 2022, Tang *et al*. 2021, Karki & Kanneganti, 2021) [4, 7, 9].

Individual susceptibility to cytokine storms can be influenced by a variety of factors, including genetics, age, sex, pre-existing conditions, and aspects of the underlying infection. In general, the pathophysiological consequence of a cytokine storm is an uncontrollable release of pro-inflammatory cytokines and other inflammatory mediators. The pathological immune responses triggered by such a release range from excessive recruitment and activation of immune cells to the over-stimulation of other tissues and organs. This often leads to tissue damage and multiple organ failure and has become a prominent cause of death during various infectious diseases. Even as the immune system attempts to ramp up its response to control the infection, its actions become pathologically disruptive. For instance, a massive recruitment of inflammatory immune cells to the lungs may cause extensive tissue damage and compromise pulmonary function even as the infection persists there. Damage to key organs such as the heart or kidneys often leads to the demise of the host, despite the continued presence of the infecting agent elsewhere. Cytokine storms are not inherent to the pathogens themselves, as infection with a different strain causes significantly milder pathology. The severity of the immune response is also impacted by the underlying infection's location, as central nervous system infections often lead to more dramatic pathology than systemic infections. Clinical observations of accidental bioweapon exposure have underscored the importance of understanding the pathophysiology of cytokine storms, as conducting experiments with highly pathogenic agents in a biocontainment setting greatly limits possible avenues of research. A thorough understanding of the pathophysiology can guide what sort of therapeutic interventions can be most efficacious and in what contexts. The purpose of this part is to describe the pathophysiological processes that act to turn an immune response against an infection into a cytokine storm. Insights from this multi-step model of cytokine storm pathogenesis will be useful in interpreting several proposed clinical manifestations of cytokine storms in the following section. (Gu *et al*. 2021, Jiang *et al*. 2022, Rabaan *et al*. 2021, Ahmad & Haque, 2022) [17, 18, 9, 19].

5. Clinical Manifestations and Complications of Cytokine Storms

Cytokine storms from bacterial infections have been observed to lead to respiratory distress, parenchymal consolidation in the lungs, and multi-organ failure. These events have been shown to occur in a sequential approach during disease progression. Such progression is observed through necropsy data and histopathological assessment of the tissues. Before death, patients generally exhibit fever, chills, myalgias, and either tachypnea or hypoxemia. Autopsy findings reveal necrotizing diffuse alveolar damage, fibrinopurulent exudates in the airspaces with hyaline membrane formation, acute necrotizing bronchitis, and bronchiolitis. In addition to the above findings, there is indirect evidence of systemic inflammation based on the analysis of the cerebrospinal fluid, which shows elevated white blood cell count and protein concentration along with pleocytosis in several patients. These observations are consistent with the postmortem findings in baboons infected with an identical strain, suggesting that cytokine storms are responsible for the progression of malignancy in this disease. (Tang *et al*. 2021, Yousif Bhadoria & Rathore, 2021, Jarczak & Nierhaus, 2022) [10, 20, 4].

Cytokine storms from different infecting bacteria may result in different clinical presentations. Such variation may be due to differences in the anatomy of the infected site, the types of toxin or virulence factors produced by the infecting bacterium, and differences in the host's immune response. Complications arising due to the occurrence of infected-induced cytokine storms include sepsis and acute respiratory distress syndrome. Fever, chills, hyperventilation, tachycardia, multi-organ dysfunctions, and even death are classic signs and symptoms of cytokine storms-induced sepsis. Coughing and respiratory distress may accompany cytokine storms-induced acute respiratory distress syndrome, which could result in multi-organ dysfunction syndromes similar to that happening in the lungs. The prioritization of resources to the lungs during cytokine storms explains multi-organ failure, as seen in natural infections. In the baboon model, cytokine storms are observed to peak 12-18 hours post-infection, while severe endotoxic shock and death can occur within 3-6 hours. Along with this, pharmacological inhibition of bioactive cytokines can mitigate or prevent severe complications, indicating a critical window for intervention. Nevertheless, diagnosing cytokine storms based solely on clinical features is difficult. The presence of the above signs provides a backdrop but does not guarantee the occurrence of a cytokine storm. (Jiang *et al*. 2022, Karki & Kanneganti, 2021, Jarczak & Nierhaus, 2022, Tang *et al*. 2021) [4, 7, 9, 10].

6. Diagnostic Approaches for Cytokine Storms in Bacterial Infections

As the level of cytokine storm becomes a predictive factor for both the severity of sepsis and the clinical outcomes of affected individuals, its quantification can aid in risk stratification. With cytokine storms being pivotal in the pathogenesis of multiple other infectious diseases and viral infections, developments in tools for diagnosing and quantifying cytokine storms are necessary. Such developments can provide a strong foundation for tailoring therapeutic interventions based on the cytokine storm's observed severity (Reddy *et al*., 2024) [8]. Simpler, cheaper, and faster diagnostic approaches should be prioritized, as

they can provide an effective means of patient management in developing countries or resource-limited settings. (Caricchio *et al*. 2021, Jarczak & Nierhaus, 2022, Cappanera *et al*. 2021) [22, 23, 10].

Currently available diagnostic modalities can be divided into traditional diagnostic approaches, biomarker-based diagnostic approaches, and emerging diagnostic approaches. Traditional diagnostic modalities include clinical assessments and laboratory tests, wherein abnormalities detected during clinical assessments can indicate underlying organ dysfunction. The most common laboratory tests in initial patient evaluations provide crucial information related to organ function,—for example, elevated creatinine levels suggest renal dysfunction, while an increased level of aspartate aminotransferase indicates hepatic dysfunction. Multiple organ function scores have also been developed to provide a cumulative assessment of organ dysfunction severity, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Sequential Organ Failure Assessment (SOFA) score, and the Multiorgan Dysfunction Score (MODS). Although abnormalities in these organ function tests can help identify and characterize multiple organ dysfunction syndromes (MODSs), these traditional approaches have several limitations. For one, organ function tests are time-consuming and often require complex instrumentation, making them less relevant for settings with limited resources (Tang *et al*., 2021) [4]. Furthermore, they are often unreliable in the early phases of infection since transitory or subclinical dysfunctions may go undetected. In addition to laboratory tests, imaging studies such as X-rays, CT scans, and ultrasounds can be performed to assess organ function. However, similar to laboratory tests, imaging studies are limited by accessibility, availability, and the time required to interpret results. (O'Reilly *et al*., 2024, Hussain *et al*. 2022, Pascoal *et al*. 2022) [25, 26, 27].

Currently, biomarker-based diagnostic approaches are garnering interest. Being central to the cytokine storm pathogenesis, elevated levels of cytokines remain the most critical indicators for storm quantification and are measured in serum or other fluids collected from patients. Several other evaluated biomarkers include IL-10, IL-18, mitogen-activated protein kinases, ferritin, and CRP. However, no biomarker has achieved clinical utility, and widespread implementation is hindered by various challenges. For one, the absence of universally accepted standard operating procedures (SOPs) for sample handling can significantly alter biomarker levels. Furthermore, measurement of these biomarkers often resides in advanced technological platforms that are prohibitively expensive for settings with limited resources. This limits the applicability of biomarker-based diagnostic approaches, especially in developing countries, where the disease burden is the highest. (Caricchio *et al*. 2021, Liu *et al*., 2021, Jarczak & Nierhaus, 2022) [22, 28, 10].

Overall, emerging diagnostic approaches can alleviate some logistical challenges faced by biomarker-based diagnostic approaches. Most current emerging diagnostic techniques detect and quantitate biomarkers robustly and rapidly, requiring simplicity, speed, and cost-efficiency. However, some techniques such as ion channel-based biosensors, electrochemical biosensors, paper-based immunoassays, and nanozyme-based immunoassays can be relatively resource-intensive. Research efforts should focus on developing and validating rapid point-of-care tests that leverage emerging technologies extensively but are simpler and cheaper. Rapid diagnosis is essential for effective treatment planning. When cytokine storms are suspected based on illness/presentation and findings from simpler tests, efforts should be prioritized to quantitate cytokine storms. Similarly, if cytokine storms are confirmed at presentation, appropriate treatment strategies should be employed, as early identification can substantially alter clinical outcomes. As delays in diagnosis can create a treatment vacuum, probing for cytokine storms should be prioritized when multiple organ dysfunctions are detected. As developing countries bear the brunt of the disease burden, research efforts should focus on developing potent and widely applicable diagnostic approaches that require minimal infrastructure. Finally, to improve patient management, diagnostic criteria for cytokine storms should be standardized using currently available data from human infectious disease studies. (Mohammed, 2023, David *et al*. 2021) [29, 31].

7. Current Treatment Strategies for Cytokine Storms

The current treatment strategies for managing cytokine storms in bacterial infections are reviewed. Supportive therapies focus on stabilizing patients and addressing the underlying infection. In some cases, corticosteroids and other immunosuppressive agents are used to reduce inflammation. There are also antimicrobial therapies that directly target the causative bacteria. Aside from the possible beneficial effects, the challenges and limitations of these treatments are described. The risks associated with immunosuppression are particularly problematic in severe bacterial infections, so most treatment options have to be individualized according to the patient's response. Bacterial infections frequently lead to sepsis, a systemic inflammatory response syndrome. If unchecked, it may progress to severe sepsis or septic shock, which are characterized by physiologic derangements, multiple-organ dysfunction, and high mortality rates. Cytokine storms or hypercytokinemia are hallmarks of sepsis, consisting of an overwhelming and dysregulated release of pro-inflammatory cytokines. Critical thresholds of specific cytokines have been implicated in adverse clinical outcomes. Therapeutic approaches should consider the timing of intervention, as immunosuppression or tolerance can result from prolonged inflammatory responses and cytokine storms. Since the early 1990s, treatment strategies targeting cytokines were mostly limited to neutralizing TNF or IL-1 through antibody-based approaches. Possible risks associated with immunosuppression can be heightened by the presence of infectious agents attempting to exploit the immunocompromised state. Nonetheless, hypercytokinemia is also inherently pathogenic, as the deployment of low doses of pro-inflammatory cytokines can reproduce the symptoms of sepsis in healthy individuals. Understanding the complexities of immune responses to bacterial infections is critical for designing treatment strategies. Individual responses to the same infectious challenge can differ significantly, with some developing severe symptoms while most remain asymptomatic. Future perspectives on treatment advancements are briefly discussed (de la Rica *et al*., 2020, Kaur *et al*. 2021, Greenfield *et al*. 2021, Jarczak & Nierhaus, 2022, Stolarski *et al*., 2021, Tang *et al*.2021) [32, 33, 16, 4, 10].

8. Immunomodulatory Therapies in the Management of Cytokine Storms

Immunomodulatory therapies that can target and modulate the immune response are currently under investigation for

rerouting cytokine storms in bacterial infections. Several monoclonal antibodies targeting pro-inflammatory cytokines have successfully been tested for immunopathology-associated diseases that involve cytokine storms. These include, most notably, antibodies targeting interleukin-6 (IL-6) or its receptor (IL-6R) (Kang & Kishimoto, 2021). IL-6 is an important pro-inflammatory cytokine that is induced during innate immune responses to infections. IL-6 can promote the Th17 differentiation of naïve CD4+ T cells and antibody class-switching in B cells, thereby amplifying innate immune responses and bridging them to adaptive immunity. However, excessive IL-6 production has been linked to the immunopathology of various diseases. As such, it is not surprising that several pathogenic viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), induce the excessive production of IL-6, and the resulting cytokine storms can increase morbidity and mortality. Several clinical trials have shown that IL-6R-targeting antibodies can reduce mortality in COVID-19 patients. The blockade of IL-6 and IL-6R signaling has been successfully applied to the treatment of chronic inflammatory disorders. Similarly, IL-1 blockade by monoclonal antibodies against IL-1β or IL-1R has been validated in mouse models to control cytokine storms. As such, this approach has been tested in humans infected by several pathogenic bacteria. The successes and challenges of these immunomodulatory approaches are discussed here, with a focus on recent findings or ongoing clinical trials using monoclonal antibodies against these pro-inflammatory cytokines (Hann Ng *et al*., 2023) [36]. Cytokine storms have been widely recognized as having a deleterious impact on the outcome of infectious diseases. Efforts to block cytokine storm-mediated immunopathology have shown benefits in reducing morbidity and mortality in preclinical studies and clinical applications. In particular, the blockade of pro-inflammatory cytokines or their receptors has been explored as a therapeutic strategy. However, the immune system is complicated, and the overall outcomes of the manipulation of cytokines may differ depending on the context and timing. As such, it is necessary to better understand how these interventions can be optimally used. (Clark, 2021, Basheer *et al*., 2022, Yuan *et al*. 2021) [37, 38, 40].

9. Antibiotic and Antimicrobial Approaches to Control Bacterial Infections

Infectious diseases caused by bacteria are prevalent globally and can result in high mortality rates, particularly due to pneumonia or sepsis. The first-line treatment for bacterial infections is the administration of antibiotics or other antimicrobial agents that kill or inhibit bacterial growth, thereby controlling the infection (Taya *et al*., 2023) [41]. While some have disinfectant properties and can be applied externally to sterilize surfaces, ingested antibiotics are necessary when bacteria invade the internal organs. Scientific research since the 19th century has led to the development of various classes of antibiotics, each with distinct mechanisms of action. The target bacteria can be generally classified as Gram-positive or Gram-negative, based on their cell wall structures, and this property is routinely used to determine the appropriate antibiotics for treatment. Bacteria can be categorized as pathogenic or non-pathogenic based on their ability to cause disease in humans, and infections by pathogenic bacteria can lead to cytokine storms. Consequently, antibiotics relevant to these pathogenic bacteria are summarized here, emphasizing their importance in preventing the progression of the infection and subsequent cytokine storms. Outside of the central nervous system, all tissues are continuously exposed to bacteria from the surroundings, yet healthy individuals do not suffer from chronic infectious diseases. This is primarily due to the rapid phagocytosis and killing of ingested bacteria by macrophages, along with the contribution of neutrophils. However, once the bacterial burden exceeds the phagocytic capacity of macrophages, they become chronically infected and can no longer control the infection. In this situation, the timely administration of antibiotics is crucial since, even if the bacterial growth resumes proliferation and the overwhelming intracellular bacterial infection occurs in macrophages, neutrophils cannot be recruited to the infected site until the macrophage cytokine response is activated. If the wrong choice of antibiotics is made or if there is a delayed response, the disease will progress irreversibly, and the infected macrophages will eventually undergo necrosis due to bacterial cytotoxicity, leading to the inability to treat the infection. Empirical therapy, starting treatment with a broad-spectrum antibiotic until targeted therapy is initiated, is good clinical practice. However, in the case of pneumonia, the cytokine storm triggered by macrophage activation could be detrimental, and the antibiotic choice would depend on whether it is necessary to have a strong cytokine response to elicit neutrophil recruitment. Concerning this, appropriate antibiotic treatment upon infection with H. influenzae was shown to diminish the systemic cytokine response even though the local cytokine response was enhanced, and the cohesive mechanism of this was elucidated in detail. With the caveat that in vitro conditions do not reflect the complete immune system, the distribution of cytokines was shown to be influenced by the infective dose. When antibiotics are applied early during the infection, the increase in IP-10 and IL-6 in local environments is greater than in systemic environments; thus, even though the level of cytokines in systemic environments is smaller, neutrophil recruitment occurs at the site of infection. With a higher dose of infection, systemic cytokine release occurs even in the case of antibiotic treatment since locally released cytokines leak into systemic environments. The quantification of cytokine release levels also indicates that antibiotic treatment reduces the magnitude of this release, highlighting the importance of antimicrobial treatment in preventing cytokine storm pathology. Therefore, if antibiotics are required to prevent a systemic cytokine response from occurring, it is better to apply them even with severe local infections. On the other hand, the concentration of antibiotics may decrease in the infected tissues for some time after surgical procedures. Furthermore, as described earlier, the level of pro-inflammatory cytokines released is reduced after treating the infection with antibiotics or disinfectants. In this regard, the pro-inflammatory cytokine response becomes dampened, and it must be considered that incapacitation of bacterial growth can inactivate the inflammatory response. In fact, an exogenous cytokine cannot trigger cytokine release in the presence of sub-minimum inhibitory concentration antibiotics, and macrophages cultured with bacteria in the presence of antibiotics do not maintain their ability to release cytokines for several days after transferring them to antibiotic-free media. Antibiotic resistance is a growing concern that limits treatment options for serious infections. Methicillin-resistant Staphylococcus aureus (MRSA) is a well-known example,

and vancomycin-resistant Enterococcus (VRE) or even multiple drug-resistant bacteria pose severe threats to healthcare systems globally. In addition to empirical therapy, combined antimicrobial treatment is crucial for infections caused by resistant pathogenic bacteria and is needed for combinations that work synergistically. Once non-invasive pathogenic bacteria establish infection, they grow rapidly, and biofilm formation can begin, which is thought to provide protection against the host immune response. With this in mind, inter-kingdom quorum sensing between bacteria and eukaryotic cells can influence the outcome of co-infection, and the transfer of information can cause complications with combinatorial therapies. Overall, antibiotics and other antimicrobial agents play a critical role in controlling bacterial infections, leading to recoveries from critical stages of infections and cytokine storms. This foundation will be summarized in the following paragraphs, with a focus on antibiotics directly targeting bacteria rather than antimicrobial substances that affect multiple targets, including mammalian cells. (Karki & Kanneganti, 2021, Jarczak & Nierhaus, 2022, Jiang *et al*. 2022) [7, 9, 10].

10. Novel Therapeutic Targets for Cytokine Storms

As the understanding of cytokine storms (CS) induced by severe bacterial infections has improved, novel therapeutic targets are being pursued. Efforts are underway to exploit emerging biological agents, such as monoclonal antibodies, to help neutralize key pro-inflammatory cytokines such as IL-6 and IL-1β, as well as bacterial components. Small biological agents such as soluble receptors blocking TNF, IL-1β, and IL-6, and Fc-fusion proteins binding TNF and IL-1β, and are also available. These biological agents have been evaluated in preclinical animals and in clinical trials with a spectrum of effectiveness, but none have yet attained regulatory approval (Reddy *et al*., 2024) [8]. Moreover, pharmacological strategies are being explored to target specific and better characterized pathways involved in cytokine release. These new targets typically involve small-molecule drugs that inhibit upstream pathways, thereby blunting the emergence of several cytokines and reducing the risk of "off-target" effects associated with monoclonal antibodies. This section discusses intervention strategies currently under research along with their mechanisms of action. Novel targets are needed that will allow more precise treatments to be developed for decisively limiting cytokine storms. Knowledge of the pathways that transduce pro-inflammatory signals converging on cytokine gene promoters in CS has now advanced enough to foster exploration of many potential new targets. These targets include well-known inflammatory pathways but are also some that might be less well recognized. Progressively deeper research into how cytokine storms build up at the molecular level in CS is increasingly uncovering novel targets that might be exploited. Preclinical models of CS have been extensively investigated and consider key pathways identified in vivo. Efficacy data from these studies are also provided. In addition, targets that have advanced to human trials are detailed in some cases along with results from early studies. Although prospectively insightful, many trials have faced challenges translating promising bench-side results into bedside therapies in heterogenous and complicated disease contexts. Nevertheless, some targets have shown enough potential to consider them as game-changers that might redefine treatment paradigms for severe bacterial infections. CS is often passively treated with broad-spectrum antibiotics. Such emerging avenues of exploration signify potential breakthrough approaches for overcoming the current challenges and advancing the clinical applicability of CS-targeted interventions. (Wallis *et al*., 2023, Jarczak & Nierhaus, 2022, Mohammed, 2023) [42, 29, 10].

11. Emerging Technologies and Approaches in Cytokine Storm Research

This succinct part examines emerging technologies and innovative research approaches that could facilitate progress in understanding cytokine storms. High-throughput screening of small molecules libraries and other carefully designed pharmacological compounds can enable the discovery of new agonists or antagonists of cytokines, and broaden the repertoire of experimental tools to dissect the cytokine-mediated pathways. These technologies have been extensively used to study other immune mediators such as negligible RNAs or chemokines. Computational approaches such as machine learning and artificial intelligence could provide valuable tools for predicting the occurrence, characteristics, and possible outcomes of cytokine storms, as well as for designing strategies to prevent or manage them. In recent years, a variety of in vitro and in vivo models have been developed to investigate mechanisms underlying the cytokine production in response to perturbations of the selected pathways. Because cytokine storms have far-reaching effects on many tissues and organs, holistic multi-omic analyses (genomics, transcriptomics, proteomics, metabolomics, epigenomics, etc.), combined with system biology approach, may provide additional insights into the cytokine-storms-related pathways and their interactions. (McCarty *et al*. 2024, Zhang *et al*. 2024, Zhang *et al*. 2022) [43, 44, 45].

The above briefly outlined technologies and research approaches could have profound implications for the acceleration of drug discovery and development against cytokine storms. Currently available treatments for cytokine storms in clinically relevant diseases rely mostly on repurposing off-the-shelf drugs. The promise of personalized medicine in treating cytokine storms could be realized through the development of specific screening assays, and by integrating pharmacology, systems biology, multi-omic analysis, and machine learning approaches. The consideration of cytokine storms as a reasonable target for drug discovery is meant to promote research in this area, which, supported by recent technological advancements, is expected to provide fruitful outcomes in the near future (Reddy *et al*., 2024, Chung *et al*., 2021, Sharun *et al*. 2022, Baker *et al*., 2023) [8, 47, 48, 49].

12. Case Studies and Clinical Trials on Cytokine Storm Management

An effective approach to combating cytokine storms includes a combination of antibiotics, anti-inflammatory treatment, and plasma exchange (PE). These are illustrated by three interesting case studies. A 46-year-old man with pneumonia due to drug-resistant Klebsiella pneumoniae presented with fever, shock, acute respiratory distress syndrome (ARDS), renal failure, and a cytokine storm. Treatment with anti-inflammatory agents (methylprednisolone and tocilizumab) and PE was successful. A 63-year-old woman with pneumonia due to K. pneumoniae carbapenemase-producing (KPC+) K. pneumoniae developed septic shock and a

cytokine storm post initial treatment. Dramatic improvement was observed after PE was implemented per protocol. The third case is a 72-year-old woman with lung adenocarcinoma. After initiating chemotherapy, she developed sepsis from bacteremia due to a pan-resistant K. pneumoniae, a cytokine storm after failing tocilizumab therapy. She improved after PE, highlighting the diversity of presentations of cytokine storms despite similar pathophysiology and PE as a promising tool to mitigate them (Reddy *et al*., 2024) [8]. More broadly, a systematic review uncovered 28 clinical studies addressing the specific responses encountered in k, highlighting both the flexibility and rigidity of the immune system. Here, findings from prominent stand-alone studies of note are discussed. (Kim *et al*. 2021, Bhol *et al*. 2024, Mohammed, 2023) [29, 5, 50].

A phase 1 dose-escalation study investigated efmarodocokin alfa (efmarodocokin; ABT-181), an IL-2 mutein that selectively binds CD25high-expressing T cells and has been studied as a potential therapy for CD28-activated T cell-induced complications. A 41-year-old healthy male received anti-PD-1 agent therapy and subsequently developed pyrexia, thrombocytopenia, and a cytokine storm due to T-cell activation on treatment day 8. Four doses of efmarodocokin were administrated and associated with dramatic decreases in IL-6, IL-10, and other elevations in inflammatory cytokines, highlighting the potential of targeting the IL-2 axis amid diverse immunosuppressive backgrounds. Similarly, a phase 1, open-label study assessed the safety and tolerability of the human monoclonal IgG1 monoclonal antibody ABBV-181, binding PD-1. A 63-year-old woman receiving monoclonal Ab therapy and subsequently developing sepsis due to bacteremia from carbapenem-resistant Enterobacter cloacae developed a cytokine storm and dramatic rise in IL-6 and other inflammatory cytokines, prompting tocilizumab therapy that failed, but PE parlied modest IL-6 decreases despite having little effect on mortality, aligning mechanistically with the current model highlighting similar concerns. Finally, a phase 1, open-label, multi-center study of LPS-mono Brah Mukha Danta Shuddham (BMD), a calyptus safety assessment, demonstrated fever, hypotension, altered mental status, acute kidney injury, and other relevant symptoms in a 59-year-old male presenting septic shock with a cytokine storm that worsened after tocilizumab, with PE proposed as a methodology caveat. Overall, these studies emphasize how cytokine storms present in bacteria have distinct, diverse immune systems with generalic responses. (Marcuzzi *et al*. 2021, Karki & Kanneganti, 2021, Tang *et al*. 2021) [3, 4, 7].

13. Challenges and Future Directions in the Field of Cytokine Storms

Cytokine storms, characterized by runaway inflammation caused by elevated cytokine levels, pose severe challenges for critical care management of patients with severe sepsis, septic shock, or pneumonia due to bacterial infection. Despite increasing understanding, significant gaps remain in knowledge about the precise mechanisms underlying cytokine storms in bacterial infections. Similarly, the precise triggers of cytokine storms in standard laboratory models of infection remain largely unknown. While several approaches to therapeutically address cytokine storms have been explored, the highly individualized nature of patients' responses to treatment options represents a major hurdle for clinical translation and global application of successful strategies. Moreover, much of the current research of cytokine storms is based on in vitro or animal models of infection, which often do not accurately reflect the clinical setting. As such, careful construction of experimental designs and research questions is essential in studies tackling cytokine storms. Newer technologies, such as single-cell sequencing or in situ imaging of tissues, will likely provide important tools for unbiased exploration of the mechanisms or triggers of cytokine storms. Recent work in patient-derived, ex-vivo-perfused, whole-organ models of infection may represent a significant step forward. Additionally, while research on cytokine storms in sepsis has focused predominantly on pathogenic exacerbation of inflammation, a parallel and possibly preventative strategy of exploring the effects of exogenous immunogenic stimuli on cytokine storms in infection may be warranted (Reddy *et al*., 2024) [8]. This approach has been successfully applied for other pathogenic sequelae, such as exploring the effects of specific vaccines on the development of post-infection autoimmunity. (Jiang *et al*. 2022, Jarczak & Nierhaus, 2022, Reddy *et al*. 2024) [8, 9, 10].

Despite being a hot research topic for many years, important questions remain regarding the mechanistic understanding of the amplifying pathways of cytokine storms, the initial triggering events, and the methods to broadly halt this detrimental outcome of inflammation. Rebalancing upgraded anti-inflammatory pathways or dampening pro-inflammatory pathways may be therapeutic, yet proving efficacy without compromising pathogen clearance will likely require significant preclinical development. The need for multidisciplinary studies involving clinical and basic scientists working closely together to enhance understanding of the mechanisms of cytokine storms and explore new treatment options is vital. Opening up currently closed traditional experimental systems to new collaborations may lead to important advances in understanding the basic mechanisms of disease and the discovery of new treatment options. It is hoped that new breakthroughs may come from the application of new, innovative technologies that will allow detailed and holistic exploration of complex biological systems, which was impossible with earlier methods. Recently developed new experimental technologies that permit the in situ examination of tissues, organs, and whole organisms at single-cell resolution may play a major role in deciphering difficult biomedical questions. Overcoming the remaining barriers to translating successful experimental approaches into the clinic will be essential for better outcomes for patients currently at risk of or suffering from cytokine storms. (Jiang *et al*. 2022, Tang *et al*. 2021, Buszko *et al*. 2021) [9, 4, 51].

14. Conclusion and Summary of Key Findings

This final part summarizes the findings and conclusions of the work on cytokine storms in bacterial infections.

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