Open Access

OBM Genetics

LIDSEN Publishing Inc.

Review

The Roles of IL-6, IL-8, and TNF-α in Pediatric Immune Defense and Infection Severity

Monday Uchenna Obaji, Angus Nnamdi Oli *, Malachy C Ugwu

Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Agulu, Nigeria; E-Mails: mobaji@stu.unizik.edu.ng; an.oli@unizik.edu.ng; mc.ugwu@unizik.edu.ng

* **Correspondence:** Angus Nnamdi Oli; E-Mail: an.oli@unizik.edu.ng

Academic Editor: Lunawati L Bennett

OBM Genetics
2025, volume 9, issue 2
doi:10.21926/obm.genet.2502293

Received: December 12, 2024
Accepted: April 13, 2025
Published: April 23, 2025

Abstract

Cytokines are pivotal regulators of immune responses. They are critical in mediating inflammation, recruiting immune cells, and driving pathogen clearance. Among these, interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) stand out as key players in pediatric immunity, as they exhibit unique expression patterns that reflect the dynamic nature of the developing immune system. This review explores the dual roles of these cytokines in orchestrating immune defense and their potential as diagnostic biomarkers for infection severity in children. It highlights how elevated IL-6, IL-8, and TNF-α levels correlate with the severity of bacterial, viral, and fungal infections and discusses their utility in distinguishing between these etiologies. The article pinpoints current technologies for cytokine detection and their impact on early diagnosis and risk stratification. The relevance of cytokine-targeted therapies in managing hyperinflammatory states is highlighted and argued that integrating cytokine profiling with other diagnostics and personalized medicine has transformative potential in pediatric healthcare. These would pave the way for more precise, timely, and effective management of pediatric infections.

Keywords

Cytokines; children; infection; immune responses

1. Introduction

The immune system is a cornerstone of host defense against pathogenic microorganisms. Among the key players in immune regulation are cytokines, which are small signaling proteins that mediate and modulate inflammatory responses. Interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) serve as critical mediators of the immune response to infections [1-3]. These cytokines ar vital for immune defense and hold significant potential as biomarkers for assessing the severity of infections in pediatric populations. IL-6 is a pleiotropic cytokine with pro-inflammatory and anti-inflammatory roles [4]. It is rapidly produced in response to infections and tissue injury, initiating the acute-phase reaction by stimulating the production of C-reactive protein (CRP) and other inflammatory mediators in the liver [5]. In children, IL-6 is particularly crucial in early immune responses because it helps to mobilize leukocytes and enhance pathogen clearance [6]. Elevated IL-6 levels have been observed in severe bacterial infections, sepsis, and inflammatory syndromes.

IL-8 is a chemokine primarily responsible for recruiting neutrophils to sites of infection. This cytokine plays a pivotal role in the first line of defense against bacterial pathogens by directing neutrophils to areas of inflammation where they perform phagocytosis and degranulation [7]. In pediatric infections, elevated IL-8 levels are mostly linked to conditions such as pneumonia, neonatal sepsis, and meningitis. The unique patterns of its expression during various infections in children could serve as a valuable diagnostic tool for distinguishing between bacterial and viral infections and assessing infection severity [8].

TNF-α is a pro-inflammatory cytokine central in mediating immune responses against infections. It promotes the activation of macrophages, the recruitment of immune cells, and the induction of apoptosis in infected cells. In children, it is often a marker of severe infection and systemic inflammation [9]. High levels of TNF-α have been implicated in pediatric sepsis and other hyperinflammatory states, where its dysregulated expression can exacerbate tissue damage and organ dysfunction. This dual role, both as a protector and a potential driver of pathology, forms the basis of its clinical importance in managing and diagnosing severe infections [10-12].

The ability to measure cytokine levels accurately is a potential opportunity for diagnosing infections and measuring their severity. In pediatric patients, where clinical symptoms may overlap between bacterial and viral infections, they provide objective biomarkers that can guide treatment decisions. For instance, elevated IL-6 levels can indicate the need for aggressive treatment in sepsis, while high IL-8 levels may signal bacterial etiology [13-16]. Similarly, TNF-α levels could help identify patients at risk of progressing to severe systemic inflammation or multi-organ dysfunction [17]. Despite their numerous clinical potential, the translation of cytokine data into routine clinical practice faces challenges, including variability in cytokine expression due to age, genetic factors, and comorbidities [18]. There are no standardized protocols for measuring and interpreting cytokine levels in children. This review addresses these gaps by synthesizing current evidence on IL-6, IL-8, and TNF-α in pediatric immune responses and their diagnostic utility.

2. Biological Functions of IL-6, IL-8, and TNF-α

IL-6 is a multifunctional cytokine with critical roles in regulating immune and inflammatory responses. It is produced by various cell types in response to infections, trauma, or tissue injury. It is a primary mediator of the acute-phase response. It stimulates hepatocytes in the liver to produce acute-phase proteins such as C-reactive protein (CRP), fibrinogen, and serum amyloid A. These proteins enhance pathogen clearance and limit tissue damage [19-22]. It acts as both a pro-inflammatory and anti-inflammatory mediator [23]. As a pro-inflammatory mediator, it promotes the activation of T cells and B cells, contributing to adaptive immunity. As an anti-inflammatory mediator, it can inhibit the effects of TNF-α and interleukin-1 (IL-1) by inducing the production of interleukin-10 (IL-10). It is responsible for systemic manifestations of inflammation, including fever and the mobilization of neutrophils from the bone marrow [24, 25]. In pediatric infections, IL-6 levels often correlate with disease severity, making it a critical cytokine in diagnosing and managing severe inflammatory states [26].

IL-8 is primarily involved in the recruitment and activation of neutrophils. It plays a vital role in the innate immune response. It is a potent chemotactic factor that directs neutrophils to sites of infection or injury. This targeted migration ensures a robust and localized response to pathogens [27]. Once at the site, IL-8 activates neutrophils, enhancing their phagocytic activity and degranulation to eliminate pathogens. It also promotes the release of reactive oxygen species (ROS) and neutrophil extracellular traps (NETs) to combat infections [28]. It contributes to tissue repair and healing by promoting the formation of new blood vessels in response to injury or illness. In children, it plays a key role in conditions such as bacterial pneumonia and neonatal sepsis. Elevated IL-8 levels can indicate bacterial infections and help differentiate them from viral infections [29, 30].

TNF-α is a pro-inflammatory cytokine produced by macrophages, dendritic cells, and other immune cells in response to infections and tissue damage. It is a key mediator of inflammation and immune responses. It binds to TNF receptors (TNFR1 and TNFR2) on target cells, initiating apoptotic pathways [31, 32]. This controlled cell death eliminates infected or damaged cells, preventing pathogen replication and aiding tissue repair. It activates the nuclear factor kappa B (NF-κB) pathway that leads to the production of other inflammatory cytokines and chemokines [33]. It enhances the recruitment of immune cells to infection sites and amplifies the inflammatory response. It promotes macrophage activation, increases their ability to phagocytose pathogens, and presents antigens to T cells. It also stimulates endothelial cells to express adhesion molecules and facilitate leukocyte migration [34]. Although essential for host defense, dysregulated TNF-α production can lead to excessive inflammation and tissue damage. In children, elevated TNF-α levels are associated with severe infections like sepsis, severe dengue, and septic shock [35].

Different infections trigger distinct cytokine response patterns due to variations in host-pathogen interactions and immune activation pathways. For instance, bacterial infections are characterized by high IL-6, IL-8, and TNF-α levels, which drive a robust neutrophil-mediated response and promote inflammation and pathogen clearance [36]. In contrast, viral infections typically induce high IFN-γ and IL-10 levels, which reflect antiviral immunity and immune regulation, with IFN-γ enhancing viral clearance and IL-10 helping to prevent excessive immune activation. Meanwhile, fungal infections elicit elevated IL-6, IL-8, and IL-10, which lead to chronic inflammation and immune evasion, as fungi can persist in host tissues by modulating immune responses [37]. To

provide a clearer comparison, Table 1 below presents a comparative overview of cytokine responses in bacterial, viral, and fungal infections.

Table 1 Comparative cytokine profiles in bacterial, viral, and fungal infections.

Cytokine	Bacterial Infections	Viral Infections	Fungal Infections
IL-6	High in bacterial sepsis and pneumonia	Moderate increases in severe viral infections (e.g., COVID-19, influenza)	Elevated, particularly in systemic fungal infections [36, 38]
IL-8	High, attracts neutrophils to infection sites	Low to moderate role in T-cell recruitment	High, promotes neutrophil and macrophage activation [39-41]
TNF-α	Rapid elevation mediates fever and acute inflammation	Moderate, contributes to viral clearance but can worsen inflammation in cytokine storms	Variable, but elevated in invasive fungal infections [42-45]
IL-10	Moderate, balances pro-inflammatory response	Elevated, especially in chronic viral infections (e.g., HIV, hepatitis)	High suppresses immune responses to allow fungal persistence [46-48]
IFN-γ	Low, except in intracellular bacterial infections (e.g., TB)	Very high, essential for antiviral immunity	Moderate, helps activate macrophages in fungal infections [49, 50]

3. Cytokine Expression Patterns in Children

The immune system in children undergoes significant development after birth, adapting to a world filled with diverse antigens. Cytokines, as key mediators of immune responses, play a crucial role in this adaptation process. Their expression patterns in pediatric populations differ markedly from those in adults, influencing both immunity and the ability to regulate inflammation. Newborns have an underdeveloped immune system characterized by limited innate immunity and an immature adaptive immune response. At birth, cytokine production is skewed toward anti-inflammatory pathways to avoid overreaction to environmental antigens. This is partly driven by maternal regulatory factors during gestation [51, 52].

In neonates and infants, the immune system is predominantly Th2-biased, producing cytokines like interleukin-4 (IL-4) and IL-10 [11]. This helps protect against overactive Th1 responses, which could damage tissue. This bias also means lower production of Th1-associated cytokines like TNF-α and interferon-gamma (IFN-γ), potentially reducing the ability to respond robustly to intracellular pathogens. As children grow, their immune system matures, cytokine production shifts toward a balance between pro-inflammatory and anti-inflammatory responses [31]. IL-6 and TNF-α levels become more responsive to infections as the innate immune system matures, while IL-8 production supports neutrophil recruitment, which is critical in bacterial infection defense [53]. In pediatric infections, IL-6, IL-8, and TNF-α are often overproduced in response to pathogens, reflecting the immune system's vigorous attempt to compensate for immaturity. However, this overproduction can lead to excessive inflammation, as seen in conditions like pediatric sepsis or hyperinflammatory syndromes [54-56]. Cytokine production in children is also influenced by genetic factors, epigenetic

modifications, and environmental exposures, which include infections, vaccinations, and nutrition. Regulatory mechanisms, such as the activity of T regulatory (Treg) cells, are still developing, which can contribute to dysregulated cytokine responses in some instances [57].

In adults, innate immune cells like macrophages and neutrophils produce higher baseline levels of pro-inflammatory cytokines (e.g., TNF-α and IL-6) than children. This reflects a more robust first-line defense in adults. Children exhibit delayed and lower IL-6 and TNF-α responses during early life, potentially making them more vulnerable to severe infections. Adults have a well-established adaptive immune response with a balanced Th1/Th2 cytokine profile [58]. In children, the predominance of Th2 cytokines such as IL-4 and IL-10 contributes to weaker cell-mediated immunity but protects against excessive inflammation. In adults, cytokine dysregulation often leads to chronic inflammatory diseases such as rheumatoid arthritis, which are driven by persistent production of cytokines [59]. In children, cytokine dysregulation is more commonly associated with acute inflammatory syndromes, such as MIS-C or pediatric sepsis, where cytokines like IL-6 and IL-8 surge dramatically. Adults are more likely to develop long-lasting immune memory and regulate cytokine expression post-infection [60]. Children may experience prolonged or exaggerated cytokine responses due to the slower resolution of inflammation, which increases the risk of complications like multi-organ dysfunction in severe infections. Studies have shown that cytokine thresholds for diagnostics (e.g., IL-6 levels in sepsis) differ significantly between children and adults. These variations necessitate age-specific reference ranges for cytokine-based diagnostics [61]. Table 2 shows clinical trial data on cytokine-targeted therapies in pediatric patients.

Table 2 Clinical trial data on cytokine-targeted therapies in pediatric patients.

Cytokine Targeted	Therapeutic Approach	Clinical Findings	Reference
IL-6 (Tocilizumab)	IL-6 receptor blockade in pediatric sepsis & COVID-19	Reduced ICU admissions, improved survival in cytokine storm cases	[62]
TNF-α (Infliximab, Etanercept)	TNF-α inhibitors in pediatric inflammatory syndromes	Decreased inflammation, reduced need for mechanical ventilation	[63]
IL-10 (Experimental Therapies)	IL-10 modulation in viral infections (HIV, hepatitis B)	Reduced immune suppression, better viral clearance	[64]

4. Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C is a hyper-inflammatory condition associated with SARS-CoV-2 infection, resembling Kawasaki disease (KD) but with systemic involvement. IL-6 is a key driver of the cytokine storm in MIS-C, contributing to fever, vascular inflammation, and multi-organ involvement [65]. Elevated levels of IL-8 are linked to neutrophil activation and endothelial damage, exacerbating the inflammatory state. TNF-α amplifies inflammation and promotes cardiac dysfunction, a common complication in MIS-C. Cytokine panels, including IL-6 and TNF-α, differentiate MIS-C from other inflammatory conditions and guide treatment. IL-6 receptor inhibitors e.g., tocilizumab and TNF-α blockers are emerging therapeutic options [66-69].

KD is an acute vasculitis of unknown etiology that primarily affects children under 5 years old, with cytokine dysregulation playing a central role. Elevated levels of IL-6 contribute to systemic inflammation and coronary artery involvement. IL-8 is involved in neutrophil activation and vascular

damage, which are hallmark features of KD. TNF-α Plays a role in the progression of coronary artery aneurysms, a severe complication of KD. Monitoring cytokine levels can help identify children at risk for severe cardiac complications. Anti-inflammatory treatments, including IV immunoglobulin (IVIG) and corticosteroids, target cytokine-driven pathways [70, 71]. Acute Respiratory Distress Syndrome (ARDS) in children is characterized by severe lung inflammation and hypoxia, often triggered by infections or trauma. IL-6 **c**ontributes to the acute-phase response and lung inflammation, which leads to fluid accumulation and reduced oxygen exchange. IL-8 drives neutrophil infiltration into the lungs, exacerbating lung damage and inflammation. TNF-α promotes endothelial dysfunction and increases vascular permeability, thereby worsening respiratory distress. Cytokine levels can stratify ARDS severity and inform ventilatory support strategies [72-74].

Cytokine dysregulation is a hallmark of autoimmune conditions such as juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE). IL-6 drives chronic inflammation and contributes to joint damage in JIA and systemic inflammation in SLE. IL-8 promotes neutrophil activation, which leads to tissue damage in autoimmune conditions. TNF-α plays a central role in inflammatory cascades, exacerbating symptoms in autoinflammatory disorders. Cytokine profiling helps tailor immunosuppressive therapies to individual patients [75, 76].

5. Cytokine-Based Diagnostic Tools

Enzyme-linked immunosorbent Assay (ELISA) is widely used for measuring individual cytokines in blood or serum samples. ELISA offers high specificity and sensitivity that makes it suitable for detecting cytokine elevations in infections [77]. Elevated IL-6 levels are reliable biomarkers for bacterial infections, sepsis, and severe inflammation. High IL-6 correlates with organ dysfunction, which makes it an essential marker for stratifying infection severity. IL-8 can differentiate bacterial from viral infections, particularly in febrile infants and children. Elevated levels also predict poor outcomes in conditions like sepsis and pneumonia. High TNF-α levels predict septic shock and mortality in severe bacterial infections. Monitoring TNF-α can aid in the early identification of hyperinflammatory conditions. Combining cytokine data with clinical features, imaging results, and other biomarkers e.g., procalcitonin, can enhance the accuracy of diagnosis. For example, high IL-6 + CRP equals likely bacterial sepsis. Meanwhile, moderate IL-6 + IL-8 + mild CRP elevation equals viral or bacterial infection [78, 79].

Targeting cytokines directly through immunomodulatory agents is a veritable option in treating severe pediatric infections, especially those associated with cytokine storms. For instance, tocilizumab is a monoclonal antibody that blocks the IL-6 receptor and reduces inflammation. It has been approved for conditions like MIS-C and has shown efficacy in severe COVID-19 cases [80]. Sarilumab is another IL-6 receptor antagonist under investigation for pediatric hyperinflammatory conditions. Infliximab is a monoclonal antibody that inhibits TNF-α. These drugs are already used in autoimmune diseases and are being explored for sepsis and severe inflammatory infections [81]. Technologies like Cytosorb are used to physically remove IL-6 and TNF-α from the bloodstream in critically ill children with sepsis or severe inflammatory states. While plasmapheresis removes excess cytokines along with pathogenic components from the blood and helps reduce inflammation. Corticosteroids are used to suppress cytokine production in severe inflammatory states. For instance, dexamethasone is effective in reducing mortality in pediatric sepsis and ARDS. It is also used as an adjunct in conditions like bacterial meningitis to reduce inflammation-induced damage.

IVIG has immunomodulatory effects that can reduce cytokine production. It is widely used in conditions like MIS-C, Kawasaki disease, and severe viral infections in children [82].

Proteomics and transcriptomics have uncovered novel cytokine-related biomarkers, which have improved infection severity stratification. Metabolomics integration has provided insights into how cytokines influence metabolic pathways during infections [83]. Portable cytokine assays (e.g., IL-6 lateral flow devices) are being integrated into mobile health platforms for real-time patient monitoring. Wearable biosensors measuring IL-6 and TNF-α fluctuations could revolutionize early sepsis detection and home-based infection monitoring [84]. Table 3 shows methods for detecting cytokines, their advantages, and challenges.

Table 3 Methods of cytokine detection, their advantages and challenges.

Method	Description	Advantages	Challenges	References
Enzyme-Linked Immunosorbent Assay (ELISA)	Measures individual cytokines using antigen-antibody reactions with a colorimetric or fluorescent readout.	1. High specificity and sensitivity. 2. Cost-effective for single cytokine detection.	1. Time-consuming (several hours). 2. Limited to one cytokine per assay.	[85-87]
Quantitative Polymerase Chain Reaction (qPCR)	Measures cytokine mRNA levels as a proxy for cytokine production.	1. Highly sensitive and quantitative. 2. Useful for studying gene regulation of cytokines.	1. mRNA levels may not correlate directly with protein levels. 2. Time-consuming and requires specialized equipment.	[88, 89]
Western Blot	Detects cytokine proteins via gel electrophoresis and antibody-based visualization.	1. High specificity for target cytokines.	1. Labor-intensive and time-consuming. 2. Semi-quantitative and less suited for high-throughput analysis.	[90, 91]
Flow Cytometry	Measures intracellular or extracellular cytokines at the single-cell level using fluorescence-labeled antibodies.	1. Allows single-cell analysis. 2. Provides detailed cellular context for cytokine expression.	1. Requires expensive equipment and trained personnel. 2. Complex data analysis.	[92, 93]

The detection and quantification of cytokines have historically relied on ELISA and multiplex bead-based immunoassays [85, 90]. Although these methods provide accurate and detailed cytokine profiling, they are also time-consuming and expensive. As a result, their use is often impractical in low-resource areas and emergencies. To address these limitations, recent advancements in point-of-care cytokine assays (POC-CAs) are transforming the field by enabling real-time, bedside cytokine measurement for early infection diagnosis and severity stratification [94]. One of the significant advantages of POC-CAs is their ability to provide faster turnaround times and improved accessibility in low-income settings. For instance, microfluidic immunoassays allow rapid multiplex detection of cytokines such as IL-6, IL-8, and TNF-α using just a single droplet of blood. In addition, electrochemical biosensors offer high sensitivity and specificity in cytokine detection and are being integrated into wearable health monitoring devices. Similarly, lateral flow cytokine assays, which function in the same way as rapid antigen tests, have been developed to detect IL-6 in patients with suspected sepsis, thus enabling early intervention [95, 96].

While these technological advances enhance cytokine detection, it is crucial to recognize that cytokines do not act in isolation. Instead, the immune response is a complex and dynamic network where cytokines interact in highly coordinated ways [97]. For example, IL-6, IL-8, and TNF-α function as part of a broader inflammatory cascade, which can either amplify or suppress immune activity depending on the type and severity of infection. A key example of this interplay is the relationship between IL-6 and TNF-α. Conversely, TNF-α stimulates IL-6 production, contributing to systemic inflammation, as observed in cytokine storm syndromes. On the other hand, IL-8 plays a crucial role as a chemotactic cytokine. Still, when present in excessive amounts alongside high TNF-α levels, it correlates with neutrophil exhaustion and immune paralysis, particularly in severe infections [98, 99]. Furthermore, anti-inflammatory cytokines such as IL-10 are vital in regulating IL-6 and TNF-α activity. However, dysregulation of this balance is a hallmark of sepsis progression. Cytokine interactions are illustrated in Table 4 below.

Table 4 Cytokine interactions in infectious diseases.

Cytokine Pair	Interaction Type	Clinical Impact	Example Disease	References
IL-6 & TNF-α	Synergistic	Exacerbates systemic inflammation & cytokine storm	Sepsis, COVID-19	[87, 99]
IL-8 & TNF-α	Synergistic	Excessive neutrophil recruitment leads to immune paralysis	Bacterial sepsis, pneumonia	[100]
IL-6 & IL-10	Antagonistic	IL-10 suppresses excessive inflammation	Severe viral infections, neonatal sepsis	[101]
IL-8 & IL-6	Synergistic	Enhances the recruitment of immune cells but may worsen inflammation	Acute respiratory infections	[102]

6. Clinical Utility and Challenges of Cytokine-Based Diagnostics

Cytokines play a pivotal role in diagnosing and determining the prognosis of pediatric infections, offering valuable insights into disease type and severity. For example, IL-6 and IL-8 are early markers of infection, often rising before conventional indicators such as CRP. In neonatal sepsis, elevated IL-6 levels can detect infections before symptoms appear, which enables timely antibiotic administration. Similarly, IL-8 can distinguish bacterial from viral infections in febrile children, reducing unnecessary antibiotic use [103]. Beyond bacterial and viral infections, cytokine profiles are crucial in managing fungal infections by guiding treatment choice and duration. Decreasing IL-6 levels in sepsis suggests effective infection control, while persistently high cytokine levels may indicate inadequate response. Additionally, cytokine panels help differentiate between infection types. For instance, bacterial infections typically present with high IL-6, IL-8, and TNF-α, while viral infections exhibit moderate IL-6, low IL-8, and variable TNF-α levels. Fungal infections, on the other hand, are characterized by elevated IL-6 and TNF-α, with moderate IL-8 levels [104].

Cytokines are also key indicators in severe inflammatory conditions, such as MIS-C and Kawasaki disease. Elevated IL-6 and TNF-α levels can predict multi-organ dysfunction risk, while in pediatric ARDS, persistently high cytokines correlate with poor prognosis and prolonged ventilation requirements [105]. Despite their diagnostic potential, several challenges limit the widespread clinical implementation of cytokines. One key limitation is the variability in cytokine levels, which fluctuate throughout the infection course, with different cytokines peaking at various times. Moreover, differences in detection methods (e.g., ELISA vs. multiplex assays) can lead to inconsistent results. At the same time, the lack of standardized cytokine thresholds makes it challenging to generalize findings across patient populations [106].

Another primary concern is the overlap of cytokine elevations with non-infectious conditions. Inflammatory diseases, autoimmune disorders, and even trauma can elevate cytokine levels, complicating diagnosis. For instance, while IL-6 is a known sepsis marker, it is also elevated in autoimmune diseases, reducing specificity. Furthermore, advanced cytokine detection methods are costly and require specialized equipment, limiting their accessibility in resource-constrained settings [107]. Given these challenges, cytokine measurements alone are insufficient for definitive diagnosis. A more reliable approach integrates cytokine data with other biomarkers, such as CRP and procalcitonin (PCT), alongside clinical assessments. This approach enhances diagnostic accuracy and reduces the risk of misclassification. To improve the accuracy and clinical applicability of cytokine-based diagnostics, several strategies must be implemented. Genetic variability is a key factor, as polymorphisms in cytokine genes (e.g., IL-6, TNF-α) can result in individual differences in cytokine levels, making universal reference values unreliable [108]. Developing personalized cytokine reference ranges based on genetic studies could improve precision.

Comorbidities further complicate cytokine interpretation, as chronic conditions such as diabetes, cancer, and autoimmune diseases can alter baseline cytokine levels, potentially leading to misdiagnoses. Combining biomarker panels (e.g., CRP with cytokines) can improve specificity, thereby helping to distinguish infection-related inflammation from pre-existing inflammatory conditions [109]. Additionally, disease severity itself influences cytokine profiles. In severe infections, excessive cytokine elevation may obscure the underlying cause. Introducing severity-adjusted biomarker thresholds can improve diagnostic clarity in critically ill patients. Moreover,

standardizing the timing of cytokine measurement would ensure more consistent and reliable readings, mitigating the impact of fluctuations in cytokine levels.

A multi-biomarker approach significantly enhances diagnostic accuracy by leveraging the complementary strengths of different biomarkers [109]. For instance, combining IL-6 and PCT effectively differentiates bacterial from viral infections by integrating systemic inflammation (IL-6) with bacterial specificity (PCT). Similarly, pairing IL-10 with IFN-γ improves the ability to distinguish viral from bacterial infections, as elevated IL-10 levels indicate viral persistence, whereas IFN-γ plays a critical role in bacterial clearance. Moreover, using IL-8, CRP, and D-Dimer together provides valuable insights into sepsis progression and coagulation abnormalities, since IL-8 acts as a neutrophil chemoattractant, CRP reflects systemic inflammation, and D-Dimer serves as an indicator of coagulopathy risk [110]. While IL-6 and TNF-α inhibitors remain critical immunotherapeutic strategies, emerging approaches offer more precise cytokine modulation in infectious diseases. For instance, next-generation JAK-STAT inhibitors (e.g., Ruxolitinib, Baricitinib) expand the scope of IL-6 signaling modulation. Unlike traditional IL-6 inhibitors, these drugs offer broader immune regulation, which makes them highly effective in treating severe COVID-19 and bacterial sepsis [111].

Beyond pharmacological inhibitors, gene-editing technologies have introduced novel avenues for cytokine modulation. CRISPR interference (CRISPRi) has been successfully used in preclinical models to suppress IL-6 and TNF-α expression, which reduces inflammation without completely shutting down immune function [112]. Similarly, gene-silencing RNA therapies are being actively explored to selectively modulate cytokine expression in acute infections, offering an additional level of precision in cytokine regulation. Dual-cytokine targeting therapies are another promising innovation. For example, simultaneous inhibition of IL-6 and TNF-α has been proposed as a more balanced approach to treating pediatric infections. Additionally, combining cytokine inhibitors with traditional antibiotics is emerging as a synergistic strategy to manage sepsis-associated immune dysregulation [113].

7. Discussion

Cytokines are integral to the immune response in pediatric infections, playing pivotal roles in regulating inflammation, immune cell recruitment, and pathogen clearance. They both orchestrate immune responses and serve as valuable biomarkers for diagnosing and determining the prognosis of infections [114]. Their dynamic expression patterns and unique roles in pediatric immunity provide opportunities for targeted diagnostics and therapies, especially in managing severe infections and hyperinflammatory conditions. IL-6 acts as a central regulator of the acute-phase response and systemic inflammation. It is rapidly produced in response to infections, thereby triggering the release of acute-phase proteins [115, 116]. Its dual role as a pro-inflammatory and anti-inflammatory cytokine makes it crucial for modulating immune responses during infections. Elevated IL-6 levels are consistently associated with severe bacterial infections, sepsis, and hyperinflammatory syndromes. In pediatric sepsis, its levels rise earlier than CRP, making it a reliable early diagnostic marker. However, its role is not limited to diagnosis; IL-6 levels correlate with infection severity and organ dysfunction [117].

IL-8 primarily functions as a chemokine, recruiting and activating neutrophils at infection sites. This activity enhances the innate immune response, facilitating pathogen clearance. Elevated IL-8 levels are most commonly associated with bacterial infections where neutrophil recruitment is

crucial. It also distinguishes bacterial infections from viral ones and serves as a diagnostic marker in febrile children. However, excessive IL-8 activity can contribute to tissue damage and poor outcomes in conditions like severe pneumonia and respiratory syncytial virus (RSV) infection. In addition to its diagnostic utility, its levels provide prognostic information, with persistently high levels indicating severe inflammation and an increased risk of complications [118-120]. TNF-α is a pro-inflammatory cytokine critical in driving systemic inflammation, apoptosis, and macrophage activation. It acts early in infections and enhances pathogen clearance and immune cell recruitment. However, excessive production of TNF-α can lead to immunopathology, including vascular leakage and organ dysfunction. In pediatric sepsis and severe dengue, high TNF-α levels are associated with septic shock and mortality. Its pivotal role in hyperinflammatory states also makes it a target for therapeutic interventions. Anti-TNF-α therapy, infliximab has shown promise in managing severe inflammatory responses in infections and other conditions [121, 122].

Despite their numerous potentials, cytokine-based diagnostics face challenges in clinical application. Current detection methods, such as ELISA and multiplex assays, are highly sensitive and specific but require laboratory facilities and trained personnel, which limit their accessibility in low-income settings. Nevertheless, variability in cytokine responses due to age, genetics, and comorbidities necessitates the development of pediatric-specific thresholds and diagnostic algorithms. Moreover, cytokine elevations are not exclusive to infections, as inflammatory and autoimmune diseases can also increase their levels, which could complicate diagnosis. To address these limitations, integrating cytokine data with other biomarkers enhances specificity and reduces misclassification risks [123-125]. Furthermore, strategies such as developing personalized cytokine reference ranges based on genetic studies, using severity-adjusted thresholds, and standardizing timing protocols can improve diagnostic precision [126]. A multi-biomarker approach enhances accuracy, with combinations like IL-6 + PCT distinguishing bacterial from viral infections, IL-10 + IFN-γ differentiating viral from bacterial infections, and IL-8 + CRP + D-Dimer providing insights into sepsis progression and coagulopathy risk [127-129]. Meanwhile, advancements in cytokine-targeted therapies are expanding treatment options, with next-generation JAK-STAT inhibitors broadening IL-6 signaling modulation. Additionally, gene-editing technologies such as CRISPRi and RNA-silencing therapies offer precise cytokine modulation without compromising immune function. Emerging dual-cytokine targeting strategies and combining cytokine inhibitors with antibiotics present a synergistic approach to managing sepsis-associated immune dysregulation [130-132].

The therapeutic potential of targeting cytokines to manage hyperinflammatory states is another critical area of exploration. IL-6 blockers have demonstrated efficacy in conditions like MIS-C and severe COVID-19 by mitigating inflammation and preventing organ damage. Similarly, TNF-α inhibitors, widely used in autoimmune diseases, are being evaluated for their role in severe bacterial infections and septic shock [133, 134].

8. Conclusion

The cytokines are pivotal biomarkers and therapeutic targets in pediatric infections, which offer significant potential for improving diagnostic precision, risk stratification, and personalized treatment strategies.

Acknowledgments

Acknowledge the people or organization(s) that have technically supported this work, excluding fund provider.

Author Contributions

All the authors contributed equally in conceptualizing the theme of the review and the manuscript's design and structure. While Monday Uchenna Obaji conducted an extensive literature review focusing on IL-6, IL-8, and TNF-α, their biological functions, and diagnostic and therapeutic implications in pediatric infections, Angus Nnamdi Oli contributed to writing the sections on diagnostic innovations and Malachy C Ugwu focused on therapeutic strategies involving cytokine modulation.

Funding

The authors declare that this review was conducted independently and did not receive any specific grant or financial support from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests

The authors declare no competing interest related to this research.

Data Availability Statement

This review is based on data and information sourced from publicly available literature and databases, including PubMed, PubMed Central, Scopus, Elsevier, and other academic repositories. All referenced studies and articles used in this review are cited appropriately within the manuscript. Readers can access these resources through the provided references and links. No primary datasets were generated or analyzed for this study. If specific assistance in accessing any referenced material is required, readers are encouraged to contact the corresponding author.

References

1. Mohd Zawawi Z, Kalyanasundram J, Mohd Zain R, Thayan R, Basri DF, Yap WB. Prospective roles of tumor necrosis factor-alpha (TNF-α) in COVID-19: Prognosis, therapeutic and management. Int J Mol Sci. 2023; 24: 6142.
2. Huang G, Zhou C, Wei CJ, Zhao S, Sun F, Zhou H, et al. Evaluation of in vitro fertilization outcomes using interleukin-8 in culture medium of human preimplantation embryos. Fertil Steril. 2017; 107: 649-656.
3. Zhong H, Sun Q, Chen P, Xiong F, Li G, Wan C, et al. Detection of IL-6, IL-10, and TNF-α level in human single-blastocyst conditioned medium using ultrasensitive Single Molecule Array platform and its relationship with embryo quality and implantation: A pilot study. J Assist Reprod Genet. 2020; 37: 1695-1702.

4. Zhou M, Xu H, Zhang D, Si C, Zhou X, Zhao H, et al. Decreased PIBF1/IL6/p-STAT3 during the mid-secretory phase inhibits human endometrial stromal cell proliferation and decidualization. J Adv Res. 2021; 30: 15-25.
5. Fu Y, Tang L, Hu M, Xiang Z, Hu Y. Changes of serum interleukin-6 in healthy pregnant women and establishment of relevant reference intervals. Clin Chim Acta. 2020; 502: 116-119.
6. Shahshahan Z, Hashemi L, Rasouli O. Maternal serum interleukin 6 and 8 and C-reactive protein in predicting the tocolytic therapy in preterm labor. J Res Med Sci. 2014; 19: 537-541.
7. Matsushima K, Yang D, Oppenheim JJ. Interleukin-8: An evolving chemokine. Cytokine. 2022; 153: 155828.
8. Das MK, Basak S, Ahmed MS, Attramadal H, Duttaroy AK. Connective tissue growth factor induces tube formation and IL-8 production in first trimester human placental trophoblast cells. Eur J Obstet Gynecol Reprod Biol. 2014; 181: 183-188.
9. Yu H, Liu Z, Dong S. Changes in intestinal flora, TNF-α, L-17, and IL-6 levels in patients with gestational diabetes mellitus. Eur J Inflamm. 2018; 16: 2058739218793550.
10. Zhao X, Liu J, Shen L, Wang A, Wang R. Correlation between inflammatory markers (Hs-CRP, TNF-α, IL-1β, IL-6, IL-18), glucose intolerance, and gestational diabetes mellitus in pregnant women. Int J Clin Exp Med. 2018; 11: 8310-8316.
11. Oli AN, Babajide Rowaiye A, Adejumo SA, Anazodo FI, Ahmad R, Sinha S, et al. Classic and current opinions in human organ and tissue transplantation. Cureus. 2022; 14: e30982.
12. Allswede DM, Buka SL, Yolken RH, Torrey EF, Cannon TD. Elevated maternal cytokine levels at birth and risk for psychosis in adult offspring. Schizophr Res. 2016; 172: 41-45.
13. Wang Y, Gu Y, Alexander JS, Lewis DF. Preeclampsia status controls interleukin-6 and soluble IL-6 receptor release from neutrophils and endothelial cells: Relevance to increased inflammatory responses. Pathophysiology. 2021; 28: 202-211.
14. Sun L, Mao D, Cai Y, Tan W, Hao Y, Li L, et al. Association between higher expression of interleukin-8 (IL-8) and haplotype -353A/-251A/+678T of IL-8 gene with preeclampsia: A case–control study. Medicine. 2016; 95: e5537.
15. Heink S, Yogev N, Garbers C, Herwerth M, Aly L, Gasperi C, et al. Trans-presentation of IL-6 by dendritic cells is required for the priming of pathogenic TH17 cells. Nat Immunol. 2017; 18: 74-85.
16. Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J. 2003; 374: 1-20.
17. Chakraborty RK, Burns B. Systemic Inflammatory Response Syndrome. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547669/.
18. Luig M, Kluger MA, Goerke B, Meyer M, Nosko A, Yan I, et al. Inflammation-induced IL-6 functions as a natural brake on macrophages and limits GN. J Am Soc Nephrol. 2015; 26: 1597-1607.
19. Scheller J, Garbers C, Rose-John S. Interleukin-6: From basic biology to selective blockade of pro-inflammatory activities. Semin Immunol. 2014; 26: 2-12.
20. Lacroix M, Rousseau F, Guilhot F, Malinge P, Magistrelli G, Herren S, et al. Novel insights into interleukin 6 (IL-6) cis-and trans-signaling pathways by differentially manipulating the assembly of the IL-6 signaling complex. J Biol Chem. 2015; 290: 26943-26953.

21. Nara H, Watanabe R. Anti-inflammatory effect of muscle-derived interleukin-6 and its involvement in lipid metabolism. Int J Mol Sci. 2021; 22: 9889.
22. Diorio C, Shaw PA, Pequignot E, Orlenko A, Chen F, Aplenc R, et al. Diagnostic biomarkers to differentiate sepsis from cytokine release syndrome in critically ill children. Blood Adv. 2020; 4: 5174-5183.
23. Monsour M, Croci DM, Agazzi S, Borlongan CV. Contemplating IL-6, a double-edged sword cytokine: Which side to use for stroke pathology? CNS Neurosci Ther. 2023; 29: 493-497.
24. Ferreira LC, Regner A, Miotto KD, Moura SD, Ikuta N, Vargas AE, et al. Increased levels of interleukin-6, -8 and -10 are associated with fatal outcome following severe traumatic brain injury. Brain Inj. 2014; 28: 1311-1316.
25. Amirian A, Mahani MB, Abdi F. Role of interleukin-6 (IL-6) in predicting gestational diabetes mellitus. Obstet Gynecol Sci. 2020; 63: 407-416.
26. Pietro L, Bottcher-Luiz F, Velloso LA, Morari J, Nomura M, Lucci De Angelo Andrade LA. Expression of interleukin-6 (IL-6), signal transducer and activator of transcription-3 (STAT-3) and telomerase in choriocarcinomas. Surg Exp Pathol. 2020; 3: 28.
27. Chan LP, Liu C, Chiang FY, Wang LF, Lee KW, Chen WT, et al. IL-8 promotes inflammatory mediators and stimulates activation of p38 MAPK/ERK-NF-κB pathway and reduction of JNK in HNSCC. Oncotarget. 2017; 8: 56375-56388.
28. Kemp B, Menon R, Fortunato SJ, Winkler M, Maul H, Rath W. Quantitation and localization of inflammatory cytokines interleukin-6 and interleukin-8 in the lower uterine segment during cervical dilatation. J Assist Reprod Genet. 2002; 19: 215-219.
29. Bezzerri V, Borgatti M, Finotti A, Tamanini A, Gambari R, Cabrini G. Mapping the transcriptional machinery of the IL-8 gene in human bronchial epithelial cells. J Immunol. 2011; 187: 6069-6081.
30. Corre I, Pineau D, Hermouet S. Interleukin-8: An autocrine/paracrine growth factor for human hematopoietic progenitors acting in synergy with colony stimulating factor-1 to promote monocyte-macrophage growth and differentiation. Exp Hematol. 1999; 27: 28-36.
31. Nist MD, Pickler RH. An integrative review of cytokine/chemokine predictors of neurodevelopment in preterm infants. Biol Res Nurs. 2019; 21: 366-376.
32. Hernández MV, Sanmartí R, Cañete JD. The safety of tumor necrosis factor-alpha inhibitors in the treatment of rheumatoid arthritis. Expert Opin Drug Saf. 2016; 15: 613-624.
33. Van Loo G, Bertrand MJ. Death by TNF: A road to inflammation. Nat Rev Immunol. 2023; 23: 289-303.
34. Zelová H, Hošek J. TNF-α signalling and inflammation: Interactions between old acquaintances. Inflamm Res. 2013; 62: 641-651.
35. Vezzani A, Viviani B. Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. Neuropharmacology. 2015; 96: 70-82.
36. Aliyu M, Zohora FT, Anka AU, Ali K, Maleknia S, Saffarioun M, et al. Interleukin-6 cytokine: An overview of the immune regulation, immune dysregulation, and therapeutic approach. Int Immunopharmacol. 2022; 111: 109130.
37. Najm A, Alunno A, Mariette X, Terrier B, De Marco G, Emmel J, et al. Pathophysiology of acute respiratory syndrome coronavirus 2 infection: A systematic literature review to inform EULAR points to consider. RMD Open. 2021; 7: e001549.

38. Wang X, Tang G, Liu Y, Zhang L, Chen B, Han Y, et al. The role of IL-6 in coronavirus, especially in COVID-19. Front Pharmacol. 2022; 13: 1033674.
39. Gonzalez-Aparicio M, Alfaro C. Influence of interleukin-8 and neutrophil extracellular trap (NET) formation in the tumor microenvironment: Is there a pathogenic role? J Immunol Res. 2019; 2019: 6252138.
40. Amarandi RM, Hjortø GM, Rosenkilde MM, Karlshøj S. Probing biased signaling in chemokine receptors. Methods Enzymol. 2016; 570: 155-186.
41. Cesta MC, Zippoli M, Marsiglia C, Gavioli EM, Mantelli F, Allegretti M, et al. The role of interleukin-8 in lung inflammation and injury: Implications for the management of COVID-19 and hyperinflammatory acute respiratory distress syndrome. Front Pharmacol. 2022; 12: 808797.
42. Sterba G, Sterba Y. Parasitic and fungal triggers of cytokine storm syndrome. Adv Exp Med Biol. 2024; 1448: 293-305.
43. Kombe Kombe AJ, Fotoohabadi L, Gerasimova Y, Nanduri R, Lama Tamang P, Kandala M, et al. The role of inflammation in the pathogenesis of viral respiratory infections. Microorganisms. 2024; 12: 2526.
44. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med. 2020; 383: 2255-2273.
45. Chang D, Dela Cruz C, Sharma L. Beneficial and detrimental effects of cytokines during influenza and COVID-19. Viruses. 2024; 16: 308.
46. Carlini V, Noonan DM, Abdalalem E, Goletti D, Sansone C, Calabrone L, et al. The multifaceted nature of IL-10: Regulation, role in immunological homeostasis and its relevance to cancer, COVID-19 and post-COVID conditions. Front Immunol. 2023; 14: 1161067.
47. Stenken JA, Poschenrieder AJ. Bioanalytical chemistry of cytokines–A review. Anal Chim Acta. 2015; 853: 95-115.
48. Silveira-Nunes G, Speziali E, Teixeira-Carvalho A, Vitelli-Avelar DM, Sathler-Avelar R, Figueiredo-Soares T, et al. Lifewide profile of cytokine production by innate and adaptive immune cells from Brazilian individuals. Immun Ageing. 2017; 14: 2.
49. Van Dis E, Fox DM, Morrison HM, Fines DM, Babirye JP, McCann LH, et al. IFN-γ-independent control of *M. tuberculosis* requires CD4 T cell-derived GM-CSF and activation of HIF-1α. PLoS Pathog. 2022; 18: e1010721.
50. Sakai S, Kauffman KD, Sallin MA, Sharpe AH, Young HA, Ganusov VV, et al. CD4 T cell-derived IFN-γ plays a minimal role in control of pulmonary Mycobacterium tuberculosis infection and must be actively repressed by PD-1 to prevent lethal disease. PLoS Pathog. 2016; 12: e1005667.
51. Ehsani V, Mortazavi M, Ghorban K, Dadmanesh M, Bahramabadi R, Rezayati MT, et al. Role of maternal interleukin-8 (IL-8) in normal-term birth in the human. Reprod Fertil Dev. 2019; 31: 1049-1056.
52. Xu XJ, Tang YM, Song H, Yang SL, Xu WQ, Zhao N, et al. Diagnostic accuracy of a specific cytokine pattern in hemophagocytic lymphohistiocytosis in children. J Pediatr. 2012; 160: 984-990.
53. Green AM, DiFazio R, Flynn JL. IFN-γ from CD4 T cells is essential for host survival and enhances CD8 T cell function during Mycobacterium tuberculosis infection. J Immunol. 2013; 190: 270-277.
54. Stokkeland LM, Giskeødegård GF, Stridsklev S, Ryan L, Steinkjer B, Tangerås LH, et al. Serum cytokine patterns in first half of pregnancy. Cytokine. 2019; 119: 188-196.
55. Kishimoto T. IL-6: From its discovery to clinical applications. Int Immunol. 2010; 22: 347-352.

56. Brown AS, Hooton J, Schaefer CA, Zhang H, Petkova E, Babulas V, et al. Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. Am J Psychiatry. 2004; 161: 889-895.
57. Rose-John S. Interleukin-6 family cytokines. Cold Spring Harb Perspect Biol. 2018; 10: a028415.
58. Yang SL, Xu XJ, Tang YM, Song H, Xu WQ, Zhao FY, et al. Associations between inflammatory cytokines and organ damage in pediatric patients with hemophagocytic lymphohistiocytosis. Cytokine. 2016; 85: 14-17.
59. Al-Qahtani AA, Alhamlan FS, Al-Qahtani AA. Pro-inflammatory and anti-inflammatory interleukins in infectious diseases: A comprehensive review. Trop Med Infect Dis. 2024; 9: 13.
60. Qidwai T. Cytokine storm in COVID-19 and malaria: Annals of pro-inflammatory cytokines. Cytokine. 2024; 173: 156420.
61. Lyra e Silva NM, Gonçalves RA, Pascoal TA, Lima-Filho RA, Resende ED, Vieira EL, et al. Pro-inflammatory interleukin-6 signaling links cognitive impairments and peripheral metabolic alterations in Alzheimer's disease. Transl Psychiatry. 2021; 11: 251.
62. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: Interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020; 55: 105954.
63. Malaviya R, Laskin JD, Laskin DL. Anti-TNFα therapy in inflammatory lung diseases. Pharmacol Ther. 2017; 180: 90-98.
64. Rybicka M, Woziwodzka A, Sznarkowska A, Romanowski T, Stalke P, Dręczewski M, et al. Genetic variation in IL-10 influences the progression of hepatitis B infection. Int J Infect Dis. 2020; 96: 260-265.
65. Udomsinprasert W, Jittikoon J, Sangroongruangsri S, Chaikledkaew U. Circulating levels of interleukin-6 and interleukin-10, but not tumor necrosis factor-alpha, as potential biomarkers of severity and mortality for COVID-19: Systematic review with meta-analysis. J Clin Immunol. 2021; 41: 11-22.
66. Halim C, Mirza AF, Sari MI. The association between TNF-α, IL-6, and vitamin D levels and COVID-19 severity and mortality: A systematic review and meta-analysis. Pathogens. 2022; 11: 195.
67. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol. 2021; 93: 250-256.
68. Yongzhi X. COVID-19-associated cytokine storm syndrome and diagnostic principles: An old and new Issue. Emerg Microbes Infect. 2021; 10: 266-276.
69. Ombrello MJ, Schulert GS. COVID-19 and cytokine storm syndrome: Are there lessons from macrophage activation syndrome? Transl Res. 2021; 232: 1-12.
70. Wolf J, Waetzig GH, Chalaris A, Reinheimer TM, Wege H, Rose-John S, et al. Different soluble forms of the interleukin-6 family signal transducer gp130 fine-tune the blockade of interleukin-6 trans-signaling. J Biol Chem. 2016; 291: 16186-16196.
71. Rose-John S, Jenkins BJ, Garbers C, Moll JM, Scheller J. Targeting IL-6 trans-signalling: Past, present and future prospects. Nat Rev Immunol. 2023; 23: 666-681.
72. Song P, Li W, Xie J, Hou Y, You C. Cytokine storm induced by SARS-CoV-2. Clin Chim Acta. 2020; 509: 280-287.
73. Canna SW, Cron RQ. Highways to hell: Mechanism-based management of cytokine storm syndromes. J Allergy Clin Immunol. 2020; 146: 949-959.

74. Kraft R, Herndon DN, Finnerty CC, Cox RA, Song J, Jeschke MG. Predictive value of IL-8 for sepsis and severe infections after burn injury: A clinical study. Shock. 2015; 43: 222-227.
75. Reikerås O, Borgen P. Activation of markers of inflammation, coagulation and fibrinolysis in musculoskeletal trauma. PLoS One. 2014; 9: e107881.
76. Bonacini M, Soriano A, Cimino L, De Simone L, Bolletta E, Gozzi F, et al. Cytokine profiling in aqueous humor samples from patients with non-infectious uveitis associated with systemic inflammatory diseases. Front Immunol. 2020; 11: 358.
77. Allen TC, Kurdowska A. Interleukin 8 and acute lung injury. Arch Pathol Lab Med. 2014; 138: 266-269.
78. Tsoukas P, Yeung RS. Kawasaki disease-associated cytokine storm syndrome. Adv Exp Med Biol. 2024; 1448: 365-383.
79. Grebenciucova E, VanHaerents S. Interleukin 6: At the interface of human health and disease. Front Immunol. 2023; 14: 1255533.
80. Hennigar SR, McClung JP, Pasiakos SM. Nutritional interventions and the IL-6 response to exercise. FASEB J. 2017; 31: 3719-3728.
81. Chen F, Teachey DT, Pequignot E, Frey N, Porter D, Maude SL, et al. Measuring IL-6 and sIL-6R in serum from patients treated with tocilizumab and/or siltuximab following CAR T cell therapy. J Immunol Methods. 2016; 434: 1-8.
82. Shimizu M, Nakagishi Y, Kasai K, Yamasaki Y, Miyoshi M, Takei S, et al. Tocilizumab masks the clinical symptoms of systemic juvenile idiopathic arthritis-associated macrophage activation syndrome: The diagnostic significance of interleukin-18 and interleukin-6. Cytokine. 2012; 58: 287-294.
83. Rischke S, Gurke R, Zielbauer AS, Ziegler N, Hahnefeld L, Köhm M, et al. Proteomic, metabolomic and lipidomic profiles in community acquired pneumonia for differentiating viral and bacterial infections. Sci Rep. 2025; 15: 1922.
84. Obeagu EI, Okoroiwu GI, Ubosi NI, Obeagu GU, Onohuean H, Muhammad T, et al. Revolution in malaria detection: Unveiling current breakthroughs and tomorrow's possibilities in biomarker innovation. Ann Med Surg. 2024; 86: 5859-5876.
85. Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. Nat Rev Immunol. 2018; 18: 773-789.
86. Wang K, Wadhwa PD, Culhane JF, Nelson EL. Validation and comparison of luminex multiplex cytokine analysis kits with ELISA: Determinations of a panel of nine cytokines in clinical sample culture supernatants. J Reprod Immunol. 2005; 66: 175-191.
87. Rowaiye AB, Onuh OA, Oli AN, Okpalefe OA, Oni S, Nwankwo EJ. The pandemic COVID-19: A tale of viremia, cellular oxidation and immune dysfunction. Pan Afr Med J. 2020; 36: 188.
88. Allen CA, Payne SL, Harville M, Cohen N, Russell KE. Validation of quantitative polymerase chain reaction assays for measuring cytokine expression in equine macrophages. J Immunol Methods. 2007; 328: 59-69.
89. Gallup JM, Ackermann MR. Addressing fluorogenic real-time qPCR inhibition using the novel custom Excel file system 'FocusField2-6GallupqPCRSet-upTool-001'to attain consistently high fidelity qPCR reactions. Biol Proced Online. 2006; 8: 87-153.
90. Kupcova Skalnikova H, Cizkova J, Cervenka J, Vodicka P. Advances in proteomic techniques for cytokine analysis: Focus on melanoma research. Int J Mol Sci. 2017; 18: 2697.

91. Paulitschke V, Kunstfeld R, Mohr T, Slany A, Micksche M, Drach J, et al. Entering a new era of rational biomarker discovery for early detection of melanoma metastases: Secretome analysis of associated stroma cells. J Proteome Res. 2009; 8: 2501-2510.
92. Qiu JG, Mei XL, Chen ZS, Shi Z. Cytokine detection by flow cytometry. Methods Mol Biol. 2014; 1172: 235-242.
93. Bueno C, Almeida J, Alguero MC, Sanchez ML, Vaquero JM, Laso FJ, et al. Flow cytometric analysis of cytokine production by normal human peripheral blood dendritic cells and monocytes: Comparative analysis of different stimuli, secretion-blocking agents and incubation periods. Cytometry. 2001; 46: 33-40.
94. Liu G, Jiang C, Lin X, Yang Y. Point-of-care detection of cytokines in cytokine storm management and beyond: Significance and challenges. View. 2021; 2: 20210003.
95. Bradley Z, Bhalla N. Point-of-care diagnostics for sepsis using clinical biomarkers and microfluidic technology. Biosens Bioelectron. 2023; 227: 115181.
96. Macovei DG, Irimes MB, Hosu O, Cristea C, Tertis M. Point-of-care electrochemical testing of biomarkers involved in inflammatory and inflammatory-associated medical conditions. Anal Bioanal Chem. 2023; 415: 1033-1063.
97. Pavia CS, Plummer MM. The evolution of rapid antigen detection systems and their application for COVID-19 and other serious respiratory infectious diseases. J Microbiol Immunol Infect. 2021; 54: 776-786.
98. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. J Immunother Cancer. 2018; 6: 56.
99. Kara M, Beser OF, Konukoglu D, Cokugras H, Erkan T, Kutlu T, et al. The utility of TNF-α, IL-6 and IL-10 in the diagnosis and/or follow-up food allergy. Allergol Immunopathol (Madr). 2020; 48: 48-55.
100. Rawat K, Shrivastava A. Neutrophils as emerging protagonists and targets in chronic inflammatory diseases. Inflamm Res. 2022; 71: 1477-1488.
101. Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Crit Rev Immunol. 2012; 32: 23-63.
102. Bhol NK, Bhanjadeo MM, Singh AK, Dash UC, Ojha RR, Majhi S, et al. The interplay between cytokines, inflammation, and antioxidants: Mechanistic insights and therapeutic potentials of various antioxidants and anti-cytokine compounds. Biomed Pharmacother. 2024; 178: 117177.
103. Obeng-Aboagye E, Frimpong A, Amponsah JA, Danso SE, Owusu ED, Ofori MF. Inflammatory cytokines as potential biomarkers for early diagnosis of severe malaria in children in Ghana. Malar J. 2023; 22: 220.
104. Aggarwal R, Jain AK, Mittal P, Kohli M, Jawanjal P, Rath G. Association of pro- and anti-inflammatory cytokines in preeclampsia. J Clin Lab Anal. 2019; 33: e22834.
105. Wang J, Yang X, Li Y, Huang JA, Jiang J, Su N. Specific cytokines in the inflammatory cytokine storm of patients with COVID-19-associated acute respiratory distress syndrome and extrapulmonary multiple-organ dysfunction. Virol J. 2021; 18: 117.
106. Matthes T, Manfroi B, Huard B. Revisiting IL-6 antagonism in multiple myeloma. Crit Rev Oncol Hematol. 2016; 105: 1-4.
107. Basnyat P, Peltola M, Raitanen J, Liimatainen S, Rainesalo S, Pesu M, et al. Elevated IL-6 plasma levels are associated with GAD antibodies-associated autoimmune epilepsy. Front Cell Neurosci. 2023; 17: 1129907.

108. Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. Nat Rev Rheumatol. 2020; 16: 335-345.
109. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol. 2015; 16: 448-457.
110. Sukrisman L, Sinto R. Coagulation profile and correlation between D-dimer, inflammatory markers, and COVID-19 severity in an Indonesian national referral hospital. J Int Med Res. 2021; 49: 3000605211059939.
111. Dingle K, Azizieh F. Multivariate comparison of cytokine profiles for normal-and low-bone-density subjects. Diagnostics. 2019; 9: 134.
112. Farhat S, Hemmatabadi M, Ejtahed HS, Shirzad N, Larijani B. Microbiome alterations in women with gestational diabetes mellitus and their offspring: A systematic review. Front Endocrinol. 2022; 13: 1060488.
113. Mun SJ, Cho E, Kim HK, Gil WJ, Yang CS. Enhancing acute inflammatory and sepsis treatment: Superiority of membrane receptor blockade. Front Immunol. 2024; 15: 1424768.
114. Plana-Carmona M, Stik G, Bulteau R, Segura-Morales C, Alcázar N, Wyatt CD, et al. The trophectoderm acts as a niche for the inner cell mass through C/EBPα-regulated IL-6 signaling. Stem Cell Rep. 2022; 17: 1991-2004.
115. Jarmund AH, Giskeødegård GF, Ryssdal M, Steinkjer B, Stokkeland LM, Madssen TS, et al. Cytokine patterns in maternal serum from first trimester to term and beyond. Front Immunol. 2021; 12: 752660.
116. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014; 6: a016295.
117. El-Mikkawy DM, EL-Sadek MA, EL-Badawy MA, Samaha D. Circulating level of interleukin-6 in relation to body mass indices and lipid profile in Egyptian adults with overweight and obesity. Egypt Rheumatol Rehabil. 2020; 47: 7.
118. Rowaiye AB, Asala T, Oli AN, Uzochukwu IC, Akpa A, Esimone CO. The activating receptors of natural killer cells and their inter-switching potentials. Curr Drug Targets. 2020; 21: 1733-1751.
119. Feng Q, Wang YI, Yang Y. Neuroprotective effect of interleukin-6 in a rat model of cerebral ischemia. Exp Ther Med. 2015; 9: 1695-1701.
120. Oli AN, Adejumo SA, Rowaiye AB, Ogidigo JO, Hampton-Marcell J, Ibeanu GC. Tumour immunotherapy and applications of immunological products: A review of literature. J Immunol Res. 2024; 2024: 8481761.
121. Forcina L, Franceschi C, Musarò A. The hormetic and hermetic role of IL-6. Ageing Res Rev. 2022; 80: 101697.
122. Fatima R, Bittar K, Aziz M. Infliximab. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500021/.
123. Kumar V. Toll-like receptors in sepsis-associated cytokine storm and their endogenous negative regulators as future immunomodulatory targets. Int Immunopharmacol. 2020; 89: 107087.
124. Yan L, Hu R, Tu S, Cheng WJ, Zheng Q, Wang JW, et al. Meta-analysis of association between IL-6-634C/G polymorphism and osteoporosis. Genet Mol Res. 2015; 14: 19225-19232.
125. Rose-John S. Interleukin-6 signalling in health and disease. F1000Research. 2020; 9: 1013.
126. Wu D, Dinh TL, Bausk BP, Walt DR. Long-term measurements of human inflammatory cytokines reveal complex baseline variations between individuals. Am J Pathol. 2017; 187: 2620-2626.

127. Paranga TG, Pavel-Tanasa M, Constantinescu D, Plesca CE, Petrovici C, Miftode IL, et al. Comparison of C-reactive protein with distinct hyperinflammatory biomarkers in association with COVID-19 severity, mortality and SARS-CoV-2 variants. Front Immunol. 2023; 14: 1213246.
128. Barabási B, Barna L, Santa-Maria AR, Harazin A, Molnár R, Kincses A, et al. Role of interleukin-6 and interleukin-10 in morphological and functional changes of the blood–brain barrier in hypertriglyceridemia. Fluids Barriers CNS. 2023; 20: 15.
129. Matsuda T, Hirano T. IL-6. In: The Cytokine Reference. San Diego, CA: Academic Press; 2000. pp. 537-563.
130. Sharp M, Donnelly SC, Moller DR. Tocilizumab in sarcoidosis patients failing steroid sparing therapies and anti-TNF agents. Respir Med X. 2019; 1: 100004.
131. Liu C, Chu D, Kalantar-Zadeh K, George J, Young HA, Liu G. Cytokines: From clinical significance to quantification. Adv Sci. 2021; 8: 2004433.
132. Cohen L, Keegan A, Melanson SE, Walt DR. Impact of clinical sample handling and processing on ultra-low level measurements of plasma cytokines. Clin Biochem. 2019; 65: 38-44.
133. Karki R, Kanneganti TD. The 'cytokine storm': Molecular mechanisms and therapeutic prospects. Trends Immunol. 2021; 42: 681-705.
134. Rabiu Abubakar A, Ahmad R, Rowaiye AB, Rahman S, Iskandar K, Dutta S, et al. Targeting specific checkpoints in the management of SARS-CoV-2 induced cytokine storm. Life. 2022; 12: 478.