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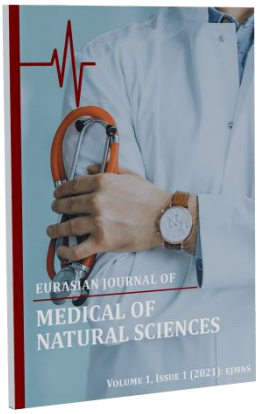

SEPSIS: MECHANISMS OF PATHOPHYSIOLOGY AND EVOLVING THERAPEUTIC APPROACHES

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ABSTRACT

Sepsis is a critical, life-threatening condition and a significant global health burden. It is currently defined as severe organ dysfunction caused by a dysregulated host response to infection, with a renewed focus on the immune system's role in its pathophysiology. Despite extensive experimental and clinical research over the past three decades, effective interventions to alter the progression and outcomes of sepsis remain limited. Current evidence-based treatments are primarily confined to fundamental causal and supportive measures, while adjuvant therapies like blood purification and targeted immunotherapy have yet to demonstrate consistent efficacy. This review aims to provide an updated perspective on the immune pathophysiology of sepsis, explore therapeutic strategies targeting various immunological mechanisms, and advocate for a paradigm shift that prioritizes the host response over the pathogen as a potentially more effective therapeutic focus.

Introduction

Sepsis represents a life-threatening medical condition characterized by profound physiological and biochemical disruptions. According to the Third International Consensus (Sepsis-3), sepsis is defined as "organ dysfunction caused by a dysregulated host response to infection," underscoring the central role of innate and adaptive immunity in its development. Globally, approximately 49 million individuals are affected by sepsis each year, with an estimated 11 million deaths—accounting for nearly 19.7% of all annual deaths worldwide. Although global mortality rates are gradually declining, sepsis remains a major healthcare challenge, with mortality rates as high as 25% in sepsis cases and nearly 60% for septic shock, a severe subset characterized by profound circulatory, cellular, and metabolic abnormalities.

Efforts to define and understand sepsis have undergone continuous evolution over recent decades. While significant progress has been made in elucidating its origins, pathophysiology, and immunological mechanisms, effective therapeutic options remain

limited. Timely fluid resuscitation and early administration of broad-spectrum antibiotics are the only interventions shown to reduce mortality. Prompt diagnosis and initiation of causal, supportive, and adjunctive measures are critical to improving outcomes. Enhancing awareness, implementing quality improvement initiatives, and developing novel diagnostics and therapies are crucial for improving patient survival and advancing the management of sepsis.

Sepsis Pathophysiology

Unlike a localized and uncomplicated infection, sepsis involves a complex disruption of the delicate balance between pro-inflammatory and anti-inflammatory immune responses. This dysregulation triggers the systemic release of cytokines, mediators, and pathogen-associated molecules, which activate the coagulation and complement cascades.

The initiation of sepsis begins with the recognition of pathogen-associated molecular patterns (PAMPs), such as endotoxins, exotoxins, lipids, or DNA sequences, and host-derived danger-associated molecular patterns (DAMPs). These molecules interact with specific receptors, including toll-like receptors (TLRs), on antigen-presenting cells (APCs) and monocytes. This interaction triggers the transcription of genes involved in inflammation, cellular metabolism, and adaptive immunity, thereby driving the clinical manifestations of sepsis.

While both pro-inflammatory and anti-inflammatory pathways are upregulated during sepsis, the resulting systemic inflammation causes progressive tissue injury and ultimately leads to multi-organ dysfunction. Concurrently, many patients develop immunosuppression, marked by the downregulation of activating cell surface molecules, increased immune cell apoptosis, and T-cell exhaustion. This state of "immunoparalysis" renders patients highly susceptible to nosocomial infections, opportunistic pathogens, and viral reactivations.

Upon binding of PAMPs and DAMPs to TLRs on APCs and monocytes, signal transduction pathways are activated, resulting in the nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). This translocation leads to the expression of early activation genes that encode various pro-inflammatory interleukins (e.g., IL-1, IL-12, IL-18), tumor necrosis factor-alpha (TNF-α), and interferons (IFNs). These early mediators further stimulate the production of additional cytokines, such as IL-6 and IL-8, and activate the complement and coagulation pathways. However, through negative feedback mechanisms, these processes also contribute to the suppression of adaptive immune responses.

During the early stages of sepsis, elevated levels of both pro-inflammatory and anti-inflammatory cytokines can be detected. This dynamic and highly individualized immunological response results in significant variability in clinical presentation, oscillating between hyper- and hypo-responsiveness, which complicates diagnosis and treatment strategies.

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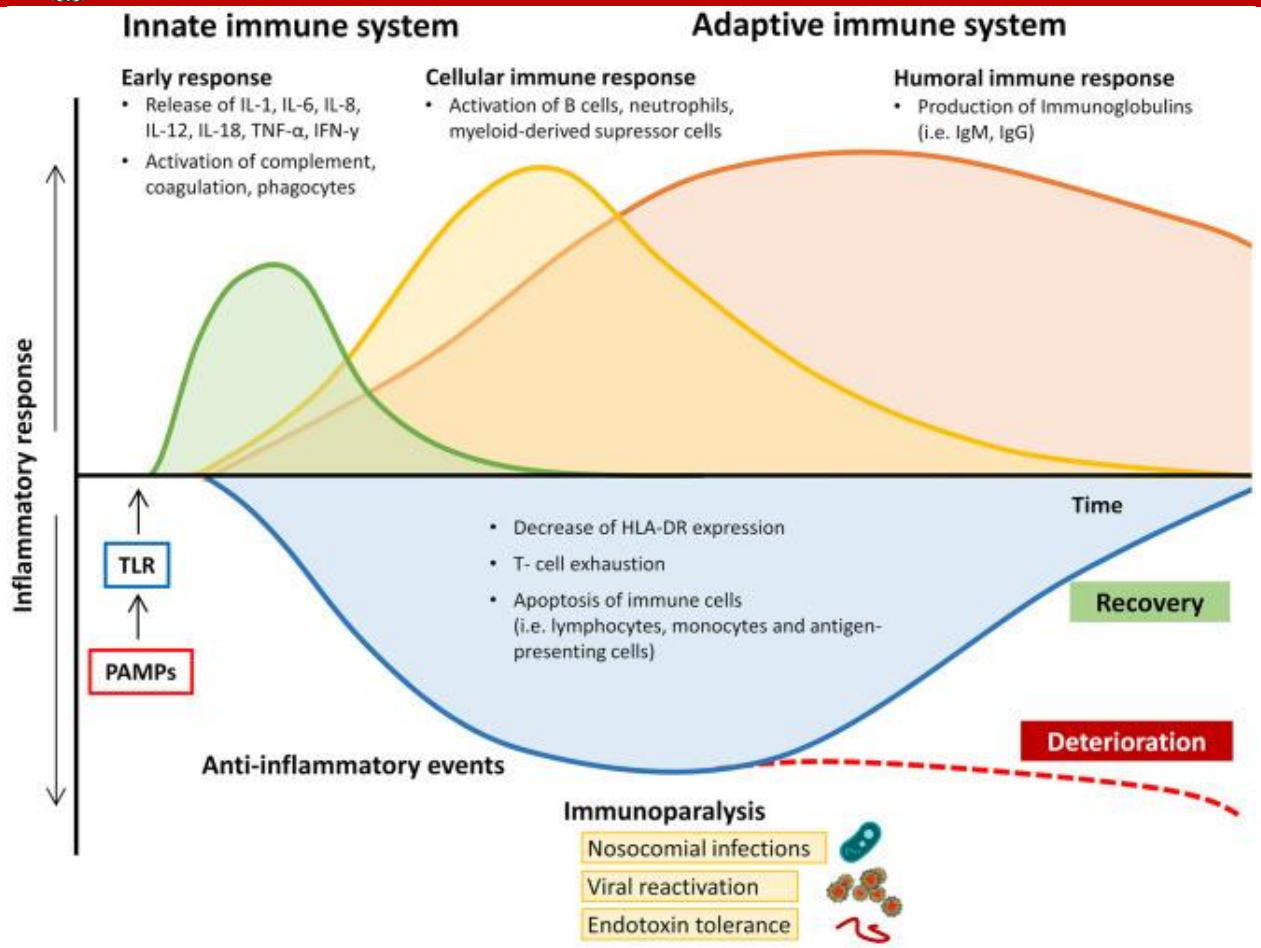

Figure 1. Alterations in the immune system's pro-inflammatory and anti-inflammatory responses during the progression of sepsis and septic shock. Key elements include HLA-DR (human leukocyte antigen-D related), immunoglobulins (IgM/G), interleukins (IL), Interferon-γ (IFN-γ), pathogen-associated molecular patterns (PAMPs), tumor necrosis factor-alpha (TNF-α), and toll-like receptors (TLRs).

The Role of Neutrophils in Sepsis

As a critical component of the innate immune system, neutrophils play a pivotal role in the initial defense against pathogens. During severe bacterial infections, the bone marrow releases both mature and immature neutrophils through a process known as emergency granulocyte maturation. However, when activated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), immature neutrophils exhibit reduced capacity for phagocytosis and oxidative burst. Elevated levels of these immature neutrophils are often associated with clinical deterioration, as well as the spontaneous production and release of neutrophil extracellular traps (NETs).

NETs are diffuse extracellular structures composed of decondensed chromatin and nuclear and granular proteins. They are capable of immobilizing a broad spectrum of pathogens, including Gram-positive and Gram-negative bacteria, viruses, yeasts, protozoa, and parasites that are otherwise too large to be phagocytized. The release of NETs is stimulated by cytokines, chemokines, platelet agonists (e.g., thrombin, ADP, collagen, arachidonic acid), and antibodies. While NETs serve an antimicrobial function, their excessive production or

insufficient degradation is associated with hypercoagulation and endothelial damage, further complicating sepsis.

Sepsis-Induced Coagulopathy and the Role of the Endothelium

Coagulopathy is a frequent and severe complication of sepsis, contributing significantly to organ dysfunction. A study of 1,895 critically ill patients in Japan found that 29% of sepsis patients were diagnosed with sepsis-induced coagulopathy (SIC), a condition synonymous with disseminated intravascular coagulation (DIC). The International Society on Thrombosis and Haemostasis (ISTH) defines DIC as "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization, leading to microvascular damage and organ dysfunction."

In sepsis-associated DIC, systemic activation of coagulation is coupled with suppressed fibrinolysis, resulting in organ dysfunction exacerbated by inflammation. Unlike traditional consumptive coagulopathy, SIC focuses on criteria such as organ dysfunction, decreased platelet count, and elevated prothrombin time-international normalized ratio (PT-INR).

Various pathogens and their products directly and indirectly affect the endothelium through diverse pathomechanisms. In addition to direct activation by pathogens, endothelial cells respond to host-derived DAMPs, amplifying the inflammatory process. In severe cases, such as hemorrhagic fevers or the acute systemic pro-inflammatory response seen in sepsis, endothelial damage becomes a critical determinant of disease progression.

Pro-inflammatory stimulation causes endothelial cells to lose their anticoagulant properties. This is marked by reduced expression of thrombomodulin and heparan sulfate on the cell surface and increased expression of tissue factor (TF), which promotes coagulation. Activated endothelium, tissue factor-loaded monocytes, and leukocytic microparticles drive the coagulation cascade. Additionally, thrombin—a pro-inflammatory serine protease—activates protease-activated receptor-1 (PAR-1) on endothelial cells. This activation exacerbates endothelial dysfunction, inducing hyperpermeability, expression of adhesion molecules, and cytokine production, further contributing to the vicious cycle of inflammation and coagulation.

The Complement System in Sepsis

Complement activation plays a significant role in the early stages of sepsis, with products such as anaphylatoxins C3a, C4a, and C5a showing elevated levels. Among these, C5a is critical for neutrophil chemotaxis to infection sites. Upon binding to its receptor, C5aR, neutrophils acquire migratory capabilities, enabling them to infiltrate inflamed tissues and clear pathogens and cellular debris. At these sites, pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) stimulate the release of neutrophil extracellular traps (NETs), granular enzymes, and reactive oxygen species (ROS) during the oxidative burst. This response shifts the coagulation balance towards a prothrombotic state while simultaneously inhibiting fibrinolysis, triggering disseminated microvascular thrombosis and consumption of clotting factors—hallmarks of overt disseminated intravascular coagulation (DIC).

Excessive activation of C5a in sepsis exacerbates systemic inflammation, promotes lymphocyte apoptosis, and impairs neutrophil function. Elevated levels of C5a can lead to downregulation of C5aR, which worsens disease outcomes by impairing neutrophil migration,

increasing tissue damage, promoting thrombosis, and contributing to multi-organ failure. Experimental studies have shown that blocking C5a or C5aR in mouse models can prevent the progression of sepsis. For instance, mice deficient in C5aR demonstrated significantly improved survival rates in mild to moderate sepsis, along with better pathogen clearance and preserved liver function.

In human sepsis, however, the combination of elevated C5a and reduced C5aR expression correlates with poor prognosis. This highlights the potential of targeting the C5a-C5aR axis for therapeutic intervention. Both C5a and C5aR are pivotal in sepsis-related inflammation, making them attractive pharmacological targets. The development of novel therapeutic agents such as **Vilobelimab** (anti-C5a monoclonal antibody) and **Avdoralimab** (anti-C5aR monoclonal antibody) represents promising advancements. These first-in-class monoclonal antibodies are undergoing clinical trials for sepsis and COVID-19 (e.g., NCT04371367), offering hope for innovative treatment options.

In summary, the C5a-C5aR axis is a central player in acute and chronic inflammatory conditions, and targeting this pathway holds great promise for developing effective therapies for sepsis and other severe inflammatory diseases.

Sepsis-Induced Immunosuppression and Persistent Inflammation, Immunosuppression, and Catabolism Syndrome

While the early systemic inflammatory response is often considered the defining feature of sepsis, immunosuppression plays a significant role in both the early and late stages of the disease. In the initial phase of sepsis, a marked depletion of B and T lymphocytes is observed, accompanied by an increased rate of apoptosis in stromal cells and antigen-presenting cells (APCs). This phenomenon, often referred to as sepsis-induced lymphopenia, is associated with an impaired immune response and heightened susceptibility to secondary infections.

The mechanisms underlying sepsis-induced lymphopenia remain incompletely understood. Potential contributors include increased lymphocyte migration into tissues, enhanced apoptosis, and reduced lymphocyte production. During emergency hematopoiesis, the immune system prioritizes the release of neutrophils and monocytes over lymphocyte production, further exacerbating lymphopenia.

Prolonged lymphopenia and reduced immunoglobulin levels during sepsis are strongly linked to poor outcomes and increased mortality. These factors underscore the importance of addressing the immunosuppressive component of sepsis alongside its inflammatory effects to improve patient survival.

Although much is known about the role of B lymphocytes in sepsis, their function extends beyond producing and secreting immunoglobulins. B lymphocytes also play a key role in immune regulation by producing cytokines, serving as antigen-presenting cells (APCs), and modulating the innate immune response. Through interactions with dendritic cells, macrophages, T cells, and other B lymphocytes, they drive clonal expansion, ultimately resulting in the generation of highly specific antibodies.

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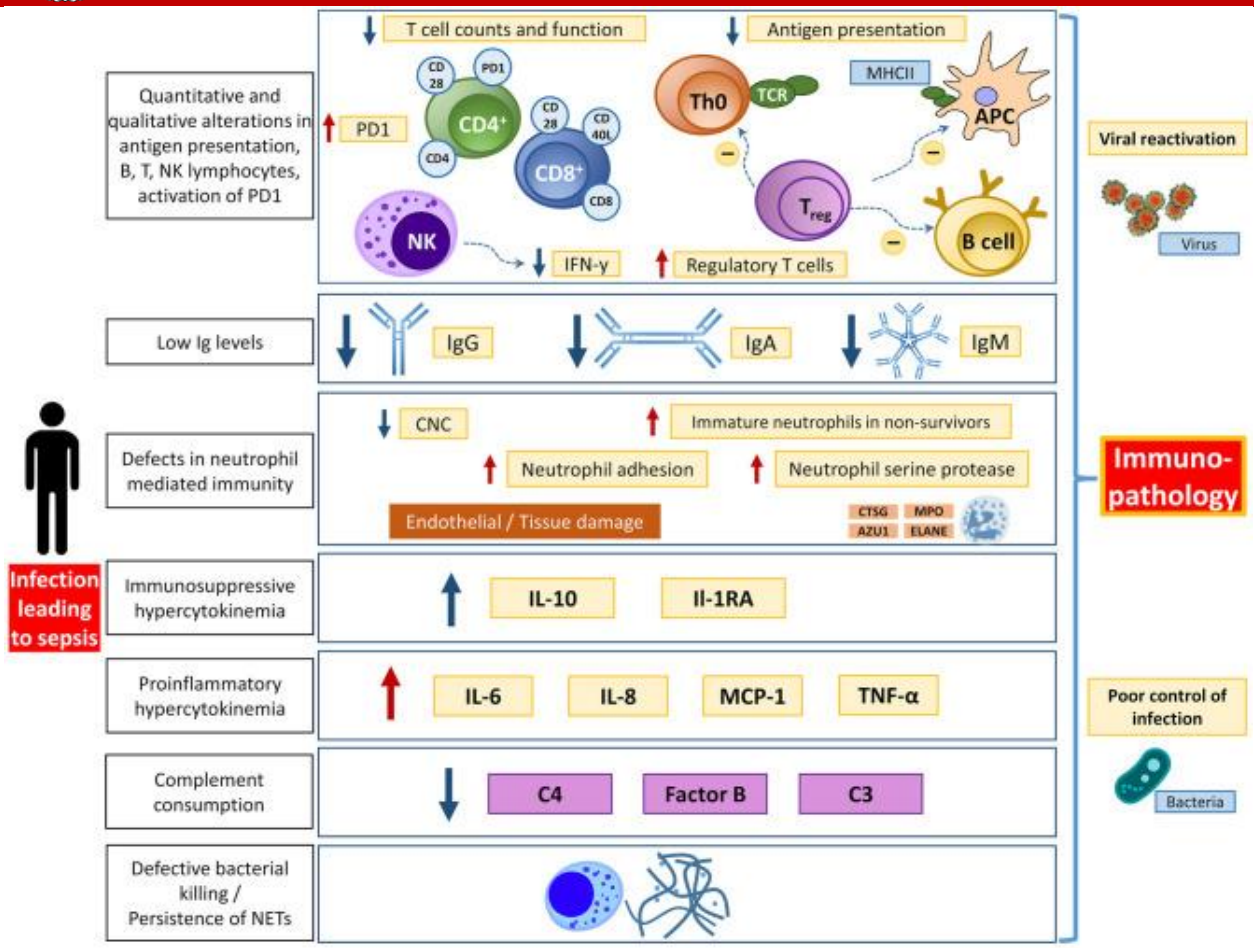

Figure 2. Overview of different aspects of immunological dysfunction with details of the affected entities. APC, antigen presenting cell; AZU1, azurocidine 1; CNC, circulating neutrophils count; CTSG, cathepsin G; ELANE, elastase; IFN-γ, interferon γ; Ig, immunoglobulin; MHCII, major histocompatibility complex II; MPO, myeloperoxidase; PD1, programmed death protein 1; TCR, T cell receptor. Adapted from Bermejo-Martin JF with permission.

After differentiating into high-affinity, antibody-secreting plasma cells, B lymphocytes contribute significantly to host defense by producing antibodies, particularly immunoglobulin M (IgM). At the onset of sepsis, B cells can be directly activated by pathogens through pathogen recognition receptors (PRRs), triggering an early immune response mediated by innate-like B cells. In septic shock, non-survivors exhibit significant functional impairments in B lymphocytes, characterized by decreased IgM production following stimulation and overall lower IgM levels. Additionally, the distribution of peripheral B cell subgroups—such as immature/transitional B cells, naive B cells, tissue-like memory B cells, resting memory B cells, and activated memory B cells—differs markedly between septic patients and healthy controls.

Sepsis survivors demonstrate higher numbers of circulating B lymphocytes, particularly within the first 24 hours of disease onset, suggesting that elevated IgM levels play a critical role in survival. IgM, a natural antibody, is particularly effective against Gram-negative bacteria, supporting the hypothesis that B lymphocyte-mediated IgM secretion provides a protective effect. This observation has been further reinforced by studies detecting elevated

IgM levels in sepsis and septic shock survivors compared to non-survivors during the early stages of the disease. However, the routine use of IgM levels or B lymphocyte counts as prognostic markers remains unsupported due to insufficient data.

Sepsis-induced immunosuppression is also marked by increased apoptosis rates in antigen-presenting cells (APCs) and monocytes, accompanied by decreased expression of human leukocyte antigen-DR (HLA-DR) on their surface. The loss of HLA-DR expression impairs pathogen recognition, reduces opsonization, and disrupts T-helper cell responses, weakening adaptive immunity. Failure to restore HLA-DR expression is associated with poor sepsis outcomes and endotoxin tolerance.

Acute infection also triggers granulopoiesis, resulting in the migration of immature myeloid cells into peripheral blood. These myeloid-derived suppressor cells (MDSCs) release anti-inflammatory cytokines, such as IL-10 and TGF-β, further exacerbating immunosuppression. Emerging research suggests that distinct MDSC subsets may correlate with sepsis outcomes, offering a potential avenue for prognostic tools and therapeutic targets.

During sepsis, immune checkpoint molecules, such as programmed death protein-1 (PD-1) and its receptor (PD-1R), are upregulated on T cells, APCs, and epithelial cells. Binding between PD-1 and PD-1R suppresses leukocyte function, promotes apoptosis, and leads to dysfunction in APCs, depletion of T and B cells, and expansion of regulatory T cells (Tregs). While controlled apoptosis of immune cells can initially benefit the host by limiting excessive inflammation, it also results in significant immune cell loss, impairing the body's ability to fight infections. Inhibiting immune cell apoptosis has shown potential as a therapeutic strategy.

Immunosuppression in sepsis is also driven by epigenetic and metabolic mechanisms. Early activation of pro-inflammatory genes is followed by histone-mediated chromatin remodeling, converting euchromatin to transcriptionally inactive heterochromatin. This process is linked to metabolic pathways, such as glycolysis and oxidative phosphorylation, which generate metabolic products like acetyl-coenzyme A (Acetyl-CoA) and nicotinamide adenine dinucleotide (NAD). These products act as cofactors for epigenetic enzymes, influencing gene expression and further contributing to immune dysregulation.

Post-transcriptional regulation by non-coding RNA, particularly microRNA (miRNA), also plays a significant role in immune modulation. By targeting messenger RNA (mRNA), miRNAs fine-tune protein expression, influencing inflammatory responses and immune cell function. Circulating miRNAs have been detected in various body fluids and may represent a novel biomarker or therapeutic target in sepsis.

The clinical phenotype of **persistent inflammation, immunosuppression, and catabolism syndrome (PICS)** has been identified in patients with prolonged ICU stays following sepsis or other major insults. PICS typically evolves after an initial inflammatory or septic episode and is characterized by ongoing inflammation, acquired immunosuppression, and metabolic derangements. Commonly seen in elderly or trauma patients, PICS is associated with poor outcomes, prolonged ICU stays, and diminished quality of life.

Despite advances in early sepsis diagnosis and organ support, a significant proportion of survivors develop chronic critical illness (CCI), marked by persistent organ dysfunction and systemic debilitation. CCI, particularly in aging populations, poses profound personal and

societal challenges. Early identification of PICS and targeted interventions are essential for improving outcomes and reducing the burden of chronic critical illness.

Acute Respiratory Distress Syndrome in Sepsis

Acute respiratory distress syndrome (ARDS) is a common complication in critically ill patients with pulmonary dysfunction, often associated with underlying conditions such as pneumonia, chronic obstructive pulmonary disease (COPD) exacerbation, aspiration, pulmonary embolism, or pulmonary contusion. Progression of these conditions frequently leads to ARDS, defined by the Berlin criteria, with severe cases occurring in up to 40% of septic shock patients, especially when a pulmonary focus is present. The onset of ARDS can contribute to dysfunction in other organs, such as the kidneys, liver, cardiovascular system, and central nervous system, often persisting throughout the disease course. In cases of sepsis-induced multiple organ dysfunction syndrome (MODS), the lungs are the primary affected organ, even in the absence of an initial pulmonary pathology.

Sepsis-induced ARDS arises from a complex and dysregulated interaction of inflammatory cytokines and cellular mediators, causing damage to the alveolocapillary unit. The condition progresses through three overlapping phases: an initial exudative phase characterized by edema and alveolar hemorrhage, a proliferative phase involving tissue repair, and a fibrotic phase marked by collagenous fibrosis. Damage to the pulmonary epithelium and endothelium increases alveolar capillary permeability, leading to leakage of protein-rich fluid into the alveoli. This fluid inactivates surfactant, and ongoing damage to type II pneumocytes reduces surfactant production, resulting in increased alveolar surface tension and diffuse microatelectasis. Neutrophil entrapment in the pulmonary microcirculation exacerbates the damage by releasing inflammatory mediators, further injuring endothelial cells and destroying type I pneumocytes. Advanced stages result in diffuse alveolar damage (DAD), characterized by fibrosis, honeycombing, bronchiectasis, and enlarged air spaces. While early intervention can often reverse lung injury, persistent exudation, fibrosis, and inflammation lead to irreversible structural damage and respiratory failure.

Sepsis-Induced Acute Kidney Injury

Sepsis-associated acute kidney injury (sa-AKI) is another significant complication, though its pathophysiology remains incompletely understood. Traditionally attributed to decreased renal perfusion and tubular epithelial cell necrosis from hypoperfusion and shock, recent findings suggest that sa-AKI can occur even with stable or increased renal blood flow, indicating additional mechanisms at play. Sepsis induces a combination of inflammation, microcirculatory dysfunction, and metabolic reprogramming. Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) bind to toll-like receptors (TLR-2 and TLR-4) on renal tubular epithelial cells (TECs), triggering oxidative stress, mitochondrial damage, and paracrine signaling. These processes impair renal function by causing endothelial leakage, activation of the coagulation cascade, and glycocalyx damage, leading to microvascular occlusion and medullary hypoperfusion. The resulting edema reduces oxygen delivery to TECs, exacerbating the injury.

Early detection and timely intervention in sa-AKI are critical. Emerging biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-

1), have shown promise in predicting renal replacement therapy (RRT) requirements and in-hospital mortality. NGAL, released by TECs, is an early predictor but lacks specificity due to its elevation in non-renal conditions. KIM-1, released after proximal TEC damage, is a reliable predictor of AKI onset before changes in serum creatinine or glomerular filtration rate (GFR). Additionally, the combination of IGFBP7 and TIMP-2, which quantify cell cycle arrest during cellular stress, has shown robust predictive value for AKI risk, independent of non-renal organ failure. Mid-regional proadrenomedullin (MR-proADM), associated with endothelial dysfunction and capillary leakage, has demonstrated strong predictive capabilities for RRT requirements in severe sepsis, septic shock, and even COVID-19 patients. Despite their potential, these biomarkers require further validation in large-scale clinical trials to confirm their utility in managing sepsis-associated complications.

Cardiac Dysfunction in Sepsis

Sepsis-induced cardiac dysfunction encompasses a range of acute cardiac abnormalities caused by sepsis. Septic cardiomyopathy, a major focus of research in recent decades, is associated with a significantly increased mortality rate of up to 50%. This complex condition affects both ventricles and manifests clinically with symptoms of circulatory failure linked to systemic infection. Unlike decompensated heart failure from non-septic causes, septic cardiomyopathy is characterized by altered global hemodynamic parameters, such as changes in preload, afterload, and microcirculation, requiring a multimodal approach to diagnosis and treatment.

The pathophysiological mechanisms underlying sepsis-induced cardiac dysfunction can be broadly categorized into three main processes: impaired myocardial circulation, direct myocardial depression, and mitochondrial dysfunction.

A balanced intravascular fluid status is critical for maintaining cardiac function. However, arterial vasodilation and loss of vascular tone in sepsis lead to hemodynamic instability. Endothelial dysfunction plays a pivotal role, as microcirculatory maldistribution of blood flow can occur despite adequate coronary blood flow, contributing to myocardial dysfunction.

Direct myocardial depression is partially attributed to a reduced adrenergic response caused by downregulation of β-adrenergic receptors, driven by inflammatory mediators such as IL-1β and TNF-α. These cytokines also promote nitric oxide (NO) synthesis via NO synthase, which impairs myocardial contractility and mitochondrial function. Elevated NO levels suppress the adrenergic response and disrupt oxidative phosphorylation, exacerbating cardiac dysfunction and increasing mortality risk. Similarly, prostanoids like prostacyclin and thromboxane alter coronary endothelial function, although anti-inflammatory therapies targeting these pathways, such as cyclooxygenase inhibitors, have not shown clinical efficacy.

The complement system, particularly complement factor C5a, plays a significant role in sepsis-induced cardiac dysfunction. C5a, a potent pro-inflammatory mediator, promotes the release of granular enzymes, cytokines, and reactive oxygen species (ROS) while enhancing neutrophil chemotaxis. Cardiomyocytes expressing C5a receptors are susceptible to further cardiodepression mediated by C5a, making it a potential therapeutic target for anti-C5a antibodies.

Mitochondrial dysfunction is another key factor in septic cardiomyopathy, as the heart relies heavily on ATP generated by mitochondria. In sepsis, increased ROS and reactive nitrogen species (RNS) inhibit oxidative phosphorylation and mitochondrial respiration, potentially leading to apoptosis and further cellular damage. A depletion of antioxidants such as ascorbic acid, α-tocopherol, and uric acid exacerbates oxidative stress, although clinical trials have not demonstrated meaningful benefits from antioxidant supplementation.

Calcium (Ca^{2+}) imbalance also contributes to mitochondrial damage in sepsis. Disruption of Ca^{2+} storage in the sarcoplasmic reticulum leads to mitochondrial Ca^{2+} overload, opening mitochondrial permeability transition pores (mPTPs) and causing caspase-mediated damage. This process can release mitochondrial DNA (mtDNA), which acts as a damage-associated molecular pattern (DAMP). Elevated mtDNA levels activate immune responses via TLR-9 and are associated with worse outcomes in sepsis, with lower plasma levels observed in survivors compared to non-survivors.

Despite the close relationship between sepsis-induced cardiac dysfunction and prognosis, effective treatment options remain elusive. Ongoing research aims to better understand these mechanisms and develop targeted therapies to improve outcomes in septic cardiomyopathy.

The Role of Immunoglobulins

Immunoglobulins, produced and released by differentiated B cells (plasma cells), play a crucial role in the human humoral immune system. Their variable regions enable non-covalent binding to bacterial and other antigens, while the constant region signals antigen binding. Among the primary immunoglobulin classes—IgA, IgG, and IgM—each serves distinct functions. IgA is key for mucosal immunity, IgG is involved in opsonization, complement activation, and secondary antibody responses, and IgM primarily drives complement activation as part of the primary antibody response. Although IgM antibodies typically have lower binding affinity compared to IgG, their polyvalence allows for high-avidity binding and effective engagement of the complement system to induce complement-dependent cell lysis.

These immunoglobulins work synergistically in sepsis and septic shock, with low plasma levels of IgA, IgG, and IgM correlating with reduced survival. The causes of reduced immunoglobulin levels in sepsis are not entirely understood but likely involve multiple factors, including endothelial dysfunction and vascular leakage, redistribution to inflamed tissues, increased consumption due to complement activation, excessive catabolism, and downregulated production caused by secondary immunosuppression.

Therapeutic Approaches in Sepsis and Septic Shock

The Surviving Sepsis Campaign (SSC), launched in 2004, has advanced the global treatment of sepsis by introducing "sepsis bundles," procedural measures designed to be implemented within specific timeframes. Adherence to these bundles has reduced mortality by up to 25%, though the efficacy of individual measures remains debated.

Causal Therapy

Prompt intervention is critical for effective sepsis treatment. The "Hour-1 Bundle," introduced in 2016, emphasizes immediate action and includes five key clinical interventions: obtaining blood cultures before antibiotics, administering broad-spectrum antibiotics, providing intravenous fluids, applying vasopressors, and measuring lactate levels.

Eliminating the infection source is essential for restoring immune balance and improving survival. Surgical procedures, interventional radiology, and removal of infected devices or catheters are critical components of source control. While blood cultures and other biological samples should be collected, antimicrobial therapy must not be delayed. Simultaneous infection management and hemodynamic stabilization are paramount. Studies such as the MEDUSA trial have shown that delays in antimicrobial therapy and source control increase mortality in sepsis and septic shock patients.

Broad-spectrum antibiotics are recommended for empirical therapy to cover a wide range of pathogens. Knowledge of local pathogen epidemiology and resistance patterns is essential for choosing the appropriate treatment, as these factors vary across regions and hospitals. Once the causative pathogen is identified, de-escalation of therapy is recommended.

The choice between bactericidal and bacteriostatic antibiotics has been debated. Bactericidal antibiotics achieve a 1,000-fold reduction in bacterial density (MBC-to-MIC ratio ≤4), while bacteriostatic antibiotics inhibit bacterial growth (MBC-to-MIC ratio >4). A review of 56 randomized controlled trials found no consistent evidence favoring bactericidal over bacteriostatic agents, as long as treatment was evidence-based and appropriately dosed.

Following an initial loading dose, antimicrobial dosing must be adjusted based on drug properties, pharmacokinetics, and the patient's organ function, which can be significantly altered in sepsis due to factors like fluid resuscitation, capillary leakage, and organ dysfunction.

The SSC's evidence-based approach highlights the importance of timely interventions, appropriate antimicrobial use, and source control, forming the cornerstone of effective sepsis management while allowing for ongoing refinement of treatment strategies.

Use of Lactate as a Marker for Disease Severity and Progression

Lactate levels in critically ill patients are influenced by various factors, including mismatches in oxygen delivery (DO2) and oxygen consumption (VO2), tissue hypoxia, decreased hepatic clearance, and β-adrenergic stimulation of Na/K-ATPase, which increases aerobic glycolysis. Elevated lactate levels are associated with worse outcomes in patients with sepsis, trauma, organ failure, and shock, irrespective of the underlying cause. A serum lactate concentration persistently above 2 mmol/L is an independent predictor of mortality in ICU patients. Severe hyperlactatemia (>10 mmol/L) is linked to significantly increased ICU mortality, particularly when it persists beyond 24 hours, with mortality exceeding 95%. If hyperlactatemia persists for over 48 hours, survival is exceedingly rare. Recent studies confirm that peak arterial lactate levels within the first 24 hours are strong predictors of in-hospital mortality and 90-day survival, with predictive power comparable to APACHE III scores.

Lactate is a vital diagnostic and prognostic marker due to its availability and strong correlation with disease severity. Both absolute values and lactate clearance over time are essential metrics, and monitoring lactate levels (e.g., every 1–2 hours when >2 mmol/L) is recommended to guide volume resuscitation and hemodynamic management, as emphasized in the "sepsis-3" definition.

Supportive Therapy

Fluid Resuscitation

Adequate fluid resuscitation is a cornerstone of the "Hour-1 Bundle" to treat sepsis-induced hypoperfusion and address hypovolemia caused by vasodilation, external fluid loss, and capillary leakage. Early initiation of treatment in patients with hypotension and/or elevated lactate levels has been shown to reduce mortality. The current recommendation is administering 20–40 mL/kg of crystalloid fluids within the first three hours. Non-crystalloid fluids are not advised for initial resuscitation. If hypotension persists despite adequate resuscitation, catecholamines such as norepinephrine should be administered to maintain a mean arterial pressure (MAP) of at least 65 mmHg.

While early aggressive fluid resuscitation is essential, the continuation of fluid administration beyond initial stabilization remains controversial due to concerns about fluid overload and a positive fluid balance negatively impacting prognosis. Emerging evidence suggests that earlier initiation of vasopressors may improve outcomes, although the optimal timing for transitioning from fluid therapy to vasopressors remains uncertain. Prospective studies are needed to evaluate the impact of early vasopressor use on multi-organ dysfunction and total fluid requirements.

Corticosteroids

The use of corticosteroids in sepsis has been debated for decades. Current guidelines recommend hydrocortisone only in patients with vasopressor-dependent refractory septic shock unresponsive to fluid resuscitation. Studies have shown no significant survival benefit from hydrocortisone use, and its long-term use is associated with increased risks of secondary infections, hypernatremia, and hyperglycemia.

The ADRENAL trial in 2018 found no significant reduction in 90-day mortality with glucocorticoid use, though it did report faster hemodynamic stabilization and reduced ventilation duration. Conversely, the APROCCHSS trial demonstrated a significant reduction in 90-day mortality with combined hydrocortisone and fludrocortisone therapy. Other studies suggest that combining hydrocortisone with vitamin C and thiamine may prevent organ dysfunction, but these findings remain unconfirmed in large-scale randomized trials. In cases of toxic shock syndrome caused by exotoxins, steroids are not recommended due to a lack of robust evidence for their efficacy.

Mechanical Ventilation

In sepsis-induced acute respiratory distress syndrome (ARDS), mechanical ventilation aims to improve gas exchange, reduce respiratory effort, and minimize further lung injury. Lung-protective ventilation with tidal volumes of 6 mL/kg and plateau pressures below 30 cm H2O remains the standard approach. Prone positioning in ARDS has been shown to reduce mortality by improving oxygenation and reducing driving pressures, but its use remains underutilized, with only about one-third of severe ARDS patients receiving prone positioning.

The use of corticosteroids in ARDS remains controversial. While prolonged methylprednisolone use has been associated with clinical improvement and reduced mortality in refractory ARDS, the evidence for routine steroid use in ARDS remains insufficient, and more research is needed.

In summary, supportive therapies in sepsis, including fluid resuscitation, corticosteroids, and mechanical ventilation, play critical roles in managing organ dysfunction

and improving outcomes. However, ongoing research is essential to refine these approaches and establish clearer guidelines.

Adjunctive Therapies

In recent decades, significant advancements have been made in understanding the intricate immunological interactions, including pro- and anti-inflammatory pathways, as well as dysfunctions of the complement and coagulation systems. However, translating this knowledge into effective therapeutic strategies for sepsis has proven challenging. Despite numerous efforts, no adjunctive therapy has yet demonstrated consistent efficacy in improving outcomes for sepsis and septic shock. Many commonly used interventions in intensive care lack robust evidence-based support, highlighting the ongoing need for innovation in this area.

Extracorporeal Blood Purification

One promising approach involves controlling excessive immune activation through extracorporeal blood purification techniques (BPTs). These methods aim to mitigate the overactivation of pro- and anti-inflammatory pathways by reducing circulating levels of PAMPs, DAMPs, cytokines, and other inflammatory mediators. Derived primarily from renal replacement therapy (RRT), these techniques include high-volume hemofiltration (HVHF), plasmapheresis, and the use of specialized high cut-off (HCO) membranes.

Other methods target specific mediators, such as endotoxin and cytokines, using adsorption techniques or combining approaches like coupled plasma filtration adsorption (CPFA). While these methods hold theoretical potential to modulate the immune response and improve clinical outcomes, their effectiveness remains under investigation. A detailed overview of various extracorporeal blood purification techniques is illustrated in Figure 3.

Although extracorporeal blood purification therapies can effectively remove inflammatory mediators and bacterial toxins, there is insufficient evidence to support their efficacy in sepsis treatment. High-volume hemofiltration (HVHF), a commonly studied technique, is technically similar to conventional renal replacement therapy (RRT) and requires no additional components in the circuit. However, HVHF employs a significantly higher convective target dose, exceeding 35 mL/kg/h. This procedure is relatively straightforward to implement in settings with experience in continuous renal replacement therapies.

In HVHF, inflammatory mediators are removed from the bloodstream through convection. Numerous studies have examined its effects on sepsis and septic shock outcomes, exploring variables such as different convective target doses and continuous versus intermittent application. A recent meta-analysis demonstrated some benefits, including improved hemodynamic parameters (lower heart rate and higher mean arterial pressure) and reduced mortality in critically ill patients. However, no significant impact was observed on oxygenation indices or disease severity. It is important to note that many of the randomized controlled trials (RCTs) included in the meta-analysis were of low quality, and there was inconsistency in mortality observation periods, limiting the reliability of these findings.

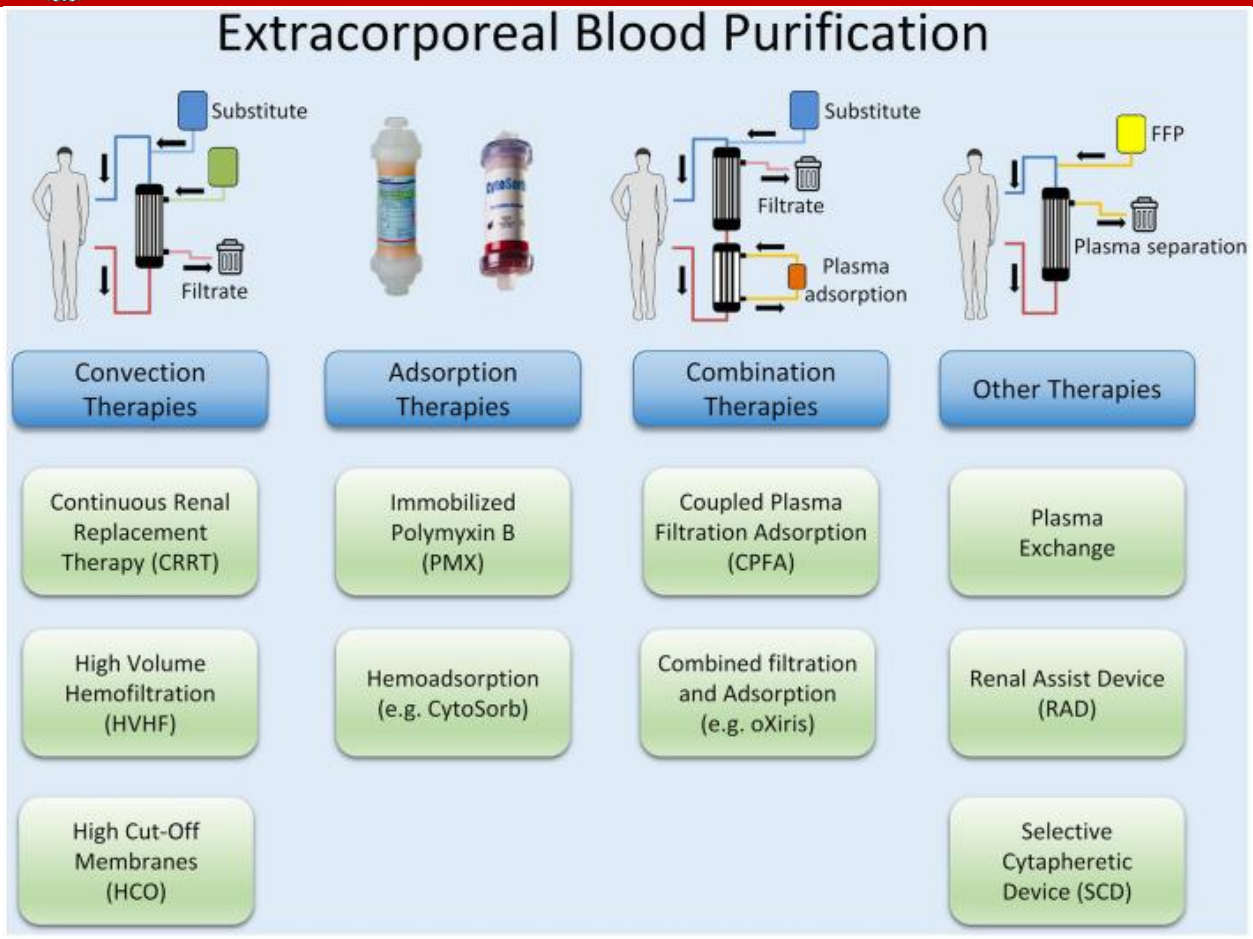

Figure 3: Currently available blood purification methods.

High-cut-off (HCO) membranes, featuring an increased pore size (20 nm compared to the 10 nm standard in high-flux membranes), were developed to enhance the elimination of inflammatory mediators. Clinical trials have demonstrated their ability to effectively remove cytokines such as IL-1, IL-6, and TNF-α in patients with sepsis-induced renal failure. However, these trials also reported significant albumin loss, a major drawback. Additionally, other studies on HCO membranes showed no significant differences in 28-day mortality, vasopressor requirements, ventilation duration, or ICU length of stay compared to conventional membranes, leading to premature termination of some trials.

Plasmapheresis has garnered renewed interest for patients with severe refractory septic shock. Beyond its blood purification effects, it is thought to rapidly replace depleted protective plasmatic factors, supporting microvascular barrier function and improving microcirculation. However, data on therapeutic plasma exchange (TPE) in sepsis remain limited. A recent meta-analysis by Putzu et al. suggested that plasmapheresis might be associated with reduced mortality compared to standard therapy. A pilot randomized controlled trial (RCT) involving 40 patients demonstrated a reduction in catecholamine requirements in septic shock patients treated with TPE. Larger ongoing trials, such as the EXCHANGE trial (NCT03065751) involving 352 participants, aim to further investigate its efficacy.

Key proteins and receptors regulate the interaction between vascular endothelium and circulating cells. Von Willebrand factor (VWF), a critical player in platelet-endothelial

interactions, is controlled by ADAMTS-13, a metalloproteinase that cleaves large VWF multimers. Deficiency of ADAMTS-13, often observed in sepsis due to immune-mediated antibodies, can lead to elevated VWF multimer levels, resulting in thrombotic microangiopathy (TMA). Severe cases manifest as thrombotic thrombocytopenic purpura (TTP) or thrombocytopenia-associated multiple organ failure (TAMOF). The severity of ADAMTS-13 deficiency appears to correlate with sepsis outcomes. Therapeutic strategies include the use of recombinant ADAMTS-13 and TPE, which not only replenishes depleted proteins but may also remove pathogens or autoantibodies.

Coupled plasma filtration adsorption (CPFA), developed in the 1990s for sepsis treatment, combines blood purification methods. Plasma is separated from blood cells using a highly permeable filter, then passed through styrene polymer resin for adsorption before being recombined with cellular components and undergoing conventional hemofiltration. CPFA is thought to offer improved biocompatibility by avoiding direct blood cell contact with the adsorption material. However, the largest RCT on CPFA (192 patients) was prematurely terminated in 2014 due to futility, showing no differences in hospital mortality or ICU-free days. Subsequent studies, including COMPACT 2 (NCT01639664) and ROMPA (NCT02357433), were also terminated early after the COMPACT 2 study reported significantly increased mortality within 72 hours in the therapy group. As a result, further research into CPFA for sepsis has been discontinued, and no new studies on plasmapheresis in sepsis therapy are currently known.

Conclusion

The core principles of sepsis and septic shock management remain early source control, timely administration of anti-infective agents, and hemodynamic stabilization with fluids and vasopressors. In recent decades, a significant paradigm shift has occurred, redirecting focus from the pathogen to the host when studying sepsis pathophysiology. This shift has advanced the understanding of the syndrome, highlighting the intricate interplay of pro- and anti-inflammatory pathways and the dysfunctions of the complement and coagulation systems, revealing the heterogeneity and complexity of sepsis. Unfortunately, translating this knowledge into evidence-based therapeutic strategies has not yet been achieved.

While innovative therapeutic approaches, including targeted immune modulation, novel anti-infective agents, and extracorporeal blood purification methods, show potential, none have yet demonstrated sufficient evidence for consistent efficacy as adjunctive treatments. Given the limited success of drug-based therapies for sepsis in recent years, future research should prioritize methodologically novel and innovative strategies. The disappointing outcomes of exclusively anti-inflammatory treatments emphasize the need to explore approaches that aim to restore immune balance and address the profound immune dysregulation observed in sepsis and septic shock.

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