

Sepsis: A Molecular Odyssey from Infection to Organ Failure

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Abstract

Background: Sepsis arises when an uncontrolled systemic immune response to infection leads to life-threatening organ dysfunction. Despite available therapies, sepsis remains a major global health challenge with high mortality. Further research into molecular mechanisms, diagnostic and prognostic biomarkers, and novel treatments is critical to improve outcomes.

Main Text: This review explores recent advances in preclinical sepsis research, which provides pivotal insights to guide clinical practice. Studies have revealed intricate molecular pathways underlying dysregulated inflammation, coagulation, mitochondrial dysfunction, and cell death signaling that drive sepsis progression. This has enabled identification of potential therapeutic targets like toll-like receptors, inflammasomes, and endothelial dysfunction. Innovative pharmacological agents, immunomodulatory therapies, and cell-based treatments have shown promise in preclinical evaluations. Precision medicine approaches leveraging genomics, biomarkers, and AI may further enable personalized care. To study sepsis, researchers utilize animal models and *in vitro* systems, which continue to improve in replicating human pathophysiology. However, enhanced translation of preclinical findings to patients remains a barrier.

Short conclusions: Preclinical research has uncovered novel strategies to combat sepsis, but ongoing efforts are vital to translate these scientific innovations into clinical impact. A multifaceted approach can help overcome current management limitations and save lives. Further unraveling molecular mechanisms, developing new therapies, and bridging preclinical-clinical gaps.

Keywords: Pharmacological interventions, Post-sepsis syndrome, Molecular mechanisms, Animal models, Extracorporeal therapies, Immunomodulators, Cell-based therapies

Background

Sepsis, a life-threatening condition resulting from a dysregulated immune response to infection, continues to be a major global health challenge. It is characterized by a systemic inflammatory response that can progress to multiple organ dysfunction and failure. With a high mortality rate and substantial healthcare burden, sepsis demands continuous research efforts to improve its diagnosis, treatment, and outcomes [1]. Sepsis is defined as a complex syndrome

caused by an infection that triggers a systemic inflammatory response. It is characterized by the presence of clinical signs and symptoms of infection along with evidence of organ dysfunction. The prevalence of sepsis is alarmingly high, with millions of cases reported worldwide each year. It affects individuals across all age groups, from neonates to the elderly, and is a leading cause of mortality in hospitals [2]. Preclinical sepsis research plays a pivotal role in understanding the underlying mechanisms and pathophysiology of sepsis. By utilizing experimental models and *in vitro* systems, researchers

can investigate the intricate interplay between the immune system, pathogens, and host responses during sepsis [3]. Preclinical studies enable the exploration of novel therapeutic targets, the evaluation of potential interventions, and the identification of prognostic biomarkers. The insights gained from preclinical research are instrumental in guiding clinical studies and developing effective strategies to combat sepsis [4]. Sepsis is a complex disorder involving intricate molecular pathways that orchestrate the immune response, inflammation, coagulation, endothelial function, and cellular homeostasis. Unraveling these molecular pathways is crucial for gaining a comprehensive understanding of sepsis pathogenesis. Such knowledge not only sheds light on the initial infection phase but also provides insights into the development of post-sepsis syndrome and long-term complications. Understanding the molecular mechanisms underlying sepsis enables the identification of potential therapeutic targets and the development of novel interventions aimed at modulating the immune response, mitigating organ dysfunction, and improving patient outcomes [5]. In this review, we aim to explore the latest advances in preclinical sepsis research, focusing on the molecular pathways involved in sepsis from infection to post-sepsis syndrome. By examining the current understanding of sepsis pathophysiology and potential therapeutic avenues, we strive to contribute to the ongoing efforts in combating this devastating condition.

Molecular Pathways in Sepsis

Sepsis arises when pathogen molecules directly activate immune and endothelial cells, triggering a massive inflammatory response that impacts every bodily system. The central nervous system modulates inflammation through neural signals while also altering neuroendocrine responses to promote survival. Cardiovascular dysfunction is central to sepsis pathogenesis via mechanisms like vasodilation, hypovolemia, microcirculatory disruption, and myocardial depression. Inflamed endothelium and immune cells instigate acute respiratory distress syndrome in the lungs. Kidney injury results from cytokine toxicity and reduced blood flow. Intestinal permeability increases, enabling bacterial product translocation. Bone marrow progenitor cells ramp up emergency myelopoiesis, but at the cost of aberrant cell functioning. Multiple organ failure frequently occurs as crosstalk between damaged organs creates feedback loops that worsen dysfunction. Thus, sepsis elicits an intricate systemic inflammation with pathogenic effects across tissues and processes. Elucidating these interconnected pathways is key to developing targeted therapies as depicted in **Figure 1** [6]. The molecular pathways involved in sepsis play a critical role in orchestrating the cascade of events from the initial infection phase to the development of organ dysfunction and failure.

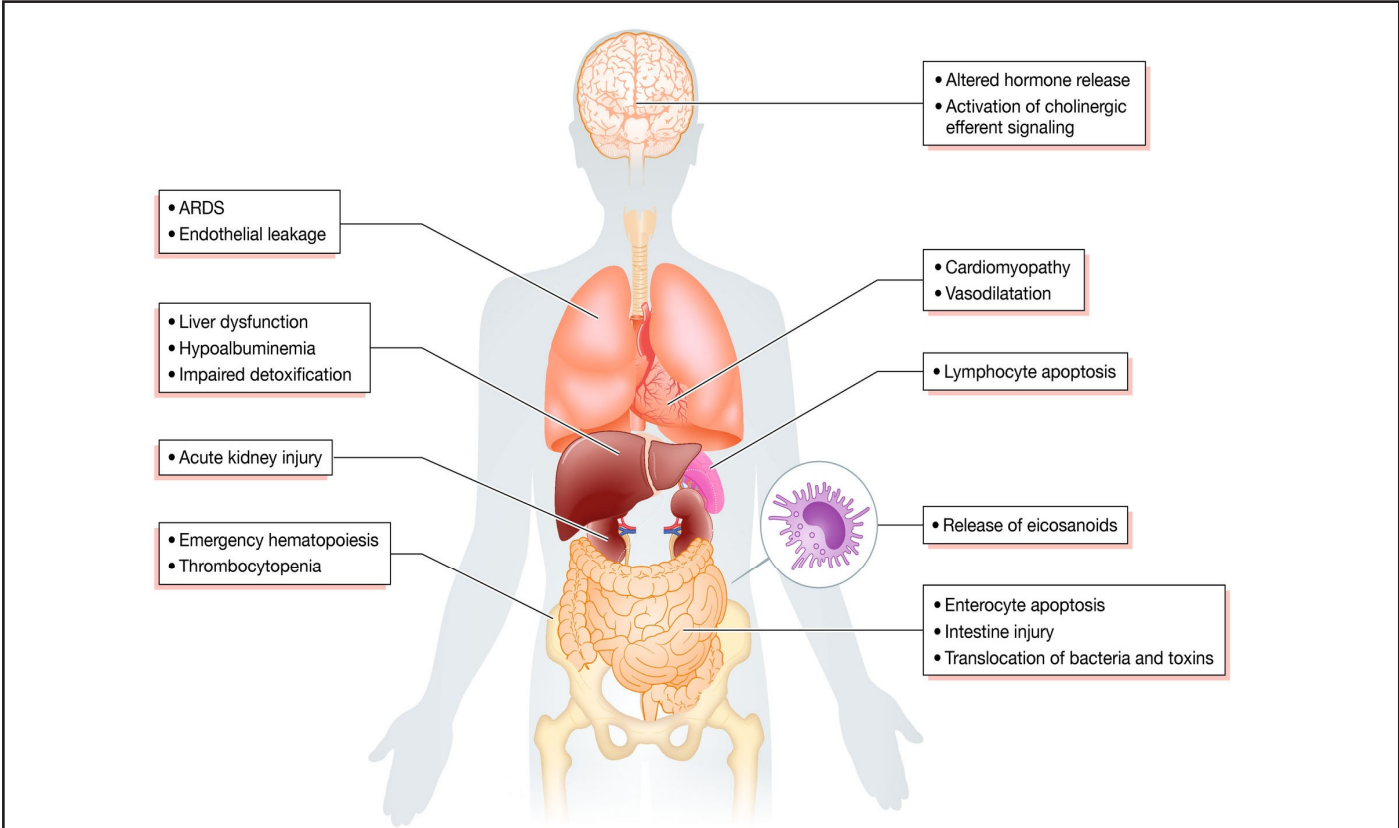


Figure 1. Systemic Inflammation in Sepsis Pathogenesis [6].

Infection phase

During the infection phase of sepsis, the immune system recognizes the presence of pathogens through pattern recognition receptors (PRRs). These receptors, such as Toll-like receptors (TLRs), detect specific molecular patterns associated with pathogens. Upon recognition, PRRs initiate the activation of the innate immune response, triggering a series of immune signaling pathways. This activation leads to the release of pro-inflammatory cytokines and chemokines, which are essential for recruiting immune cells to the site of infection and promoting an effective immune response [7].

Dysregulated immune response

In sepsis, the immune response becomes dysregulated, leading to systemic inflammatory response syndrome (SIRS). SIRS is characterized by an excessive and uncontrolled release of pro-inflammatory molecules, resulting in widespread inflammation throughout the body. This uncontrolled inflammation can contribute to tissue damage and organ dysfunction. Additionally, sepsis triggers the activation of the coagulation cascade, leading to a pro-thrombotic state and the formation of microvascular clots. The dysregulated immune response also disrupts endothelial function and compromises the integrity of the vascular barrier, allowing for the leakage of fluid and cells into surrounding tissues [8].

Organ dysfunction and failure

The dysregulated immune response, along with compromised vascular function, contributes to the development of organ dysfunction and failure in sepsis. Impaired tissue perfusion is a hallmark of sepsis-induced organ dysfunction, resulting from altered blood flow distribution and microcirculatory abnormalities. The inadequate oxygen and nutrient supply to vital organs further exacerbate cellular injury and dysfunction. Mitochondrial dysfunction, a consequence of the dysregulated immune response and impaired tissue perfusion, leads to energy depletion and cellular dysfunction. Additionally, sepsis induces oxidative stress and the generation of reactive oxygen species, which can cause widespread cellular damage and organ dysfunction [9]. Understanding the molecular pathways involved in sepsis is crucial for developing targeted therapeutic interventions. By elucidating the key molecular events in the infection phase, dysregulated immune response, and organ dysfunction, researchers can identify potential therapeutic targets and develop strategies to modulate these pathways. Advancements in our understanding of these molecular mechanisms hold promise for the development of novel therapeutic approaches aimed at improving outcomes in sepsis patients [10].

Preclinical Models for Sepsis Research

To study sepsis and investigate potential therapeutic

interventions, researchers rely on preclinical models that simulate the complex pathophysiology of the condition. These models provide valuable insights into the molecular mechanisms, host responses, and potential therapeutic avenues for sepsis. Preclinical models encompass both animal-based approaches and *in vitro* systems, each offering unique advantages and limitations [11].

Animal models

Rodent models (Mice, Rats): Rodent models, particularly mice and rats, have been extensively used in sepsis research due to their genetic similarity to humans and their relatively low cost. These models allow for the study of various aspects of sepsis, including the immune response, organ dysfunction, and therapeutic interventions [12]. Transgenic and knockout models further enable the investigation of specific genes and pathways involved in sepsis pathogenesis. However, the translation of findings from rodent models to humans can be challenging due to species differences and the complexity of sepsis in human patients [13].

Large animal models (Pigs, Primates): Large animal models, such as pigs and non-human primates, offer several advantages in sepsis research. Their physiological and anatomical similarities to humans make them valuable models for studying complex aspects of sepsis, including hemodynamics, organ interactions, and immune responses. Large animal models also allow for invasive procedures and the evaluation of potential therapies in a more clinically relevant context. However, the cost, ethical considerations, and availability of these models pose challenges in their widespread use [14].

In vitro models

Cell culture systems: *In vitro* cell culture systems provide a controlled environment to investigate specific cellular responses and molecular mechanisms in sepsis. Primary cells, cell lines, and co-culture systems can be utilized to study the interactions between immune cells, endothelial cells, and pathogens. These models are valuable for elucidating signaling pathways, assessing drug efficacy, and conducting high-throughput screening. However, they lack the complexity of whole organisms and may not fully recapitulate the systemic effects and organ crosstalk observed in sepsis [15].

Organ-on-a-chip technologies: Organ-on-a-chip technologies represent a promising advancement in preclinical sepsis research. These microfluidic systems mimic the structure and function of human organs, allowing for the study of organ-specific responses to sepsis. Organ-on-a-chip platforms enable the integration of multiple cell types and physiological parameters, providing a more physiologically relevant context compared to traditional cell culture systems. They offer the potential to investigate organ interactions, drug

metabolism, and personalized medicine approaches. However, the complexity and cost of developing and maintaining these systems remain challenges [16].

Recapitulating sepsis pathophysiology *in vitro*: Researchers aim to develop *in vitro* models that replicate the key pathophysiological features of sepsis, including immune dysregulation, endothelial dysfunction, and organ dysfunction. By incorporating multiple cell types, biomimetic scaffolds, and fluid flow systems, efforts are being made to create more comprehensive and dynamic *in vitro* models [17]. These models allow for the investigation of specific molecular pathways and the assessment of potential therapeutic interventions in a controlled environment [18]. By utilizing a combination of animal models and *in vitro* systems, preclinical sepsis research offers a range of tools to deepen our understanding of sepsis pathophysiology and evaluate potential therapeutic avenues. The choice of model depends on the specific research question, the desired level of complexity, feasibility, and ethical considerations. Integrating findings from diverse preclinical models can enhance the translatability of research findings to clinical practice, ultimately improving outcomes for sepsis patients.

Latest Advances in Preclinical Sepsis Research

Preclinical sepsis research continues to make remarkable strides in identifying novel therapeutic targets and developing innovative approaches to combat this life-threatening condition. These advancements hold the potential to revolutionize sepsis management and improve patient outcomes. In this section, we highlight some of the latest breakthroughs in preclinical sepsis research [19].

Identification of novel therapeutic targets

Toll-like receptors (TLRs) and pattern recognition receptors (PRRs): TLRs and other PRRs play a crucial role in recognizing pathogens and initiating the immune response in sepsis. Recent research has focused on targeting specific TLRs and PRRs to modulate the immune response and prevent excessive inflammation. By developing selective agonists or antagonists, researchers aim to fine-tune immune signaling pathways and restore immune homeostasis [20].

Inflammasome signaling pathways: Inflammasomes are protein complexes involved in the activation of inflammatory responses. Emerging evidence suggests that dysregulated inflammasome signaling contributes to the pathogenesis of sepsis. Researchers are exploring various strategies to modulate inflammasome activation and downstream cytokine release, with the goal of attenuating the inflammatory cascade and mitigating organ dysfunction [21].

Mitochondrial-targeted therapies: Mitochondrial dysfunction is a hallmark of sepsis and contributes to cellular damage and organ dysfunction. Novel therapeutic approaches are being investigated to target mitochondrial dysfunction in sepsis. These approaches include the use of mitochondrial-targeted antioxidants, modulators of mitochondrial biogenesis, and agents that improve mitochondrial bioenergetics. By preserving mitochondrial function, these therapies hold promise in mitigating cellular damage and improving overall organ function [22]. As depicted in **Figure 2**, proinflammatory cytokines spur excessive production of reactive nitrogen species (RNS) and nitric oxide (NO) by upregulating inducible nitric oxide synthase (iNOS) activity during sepsis. NO can

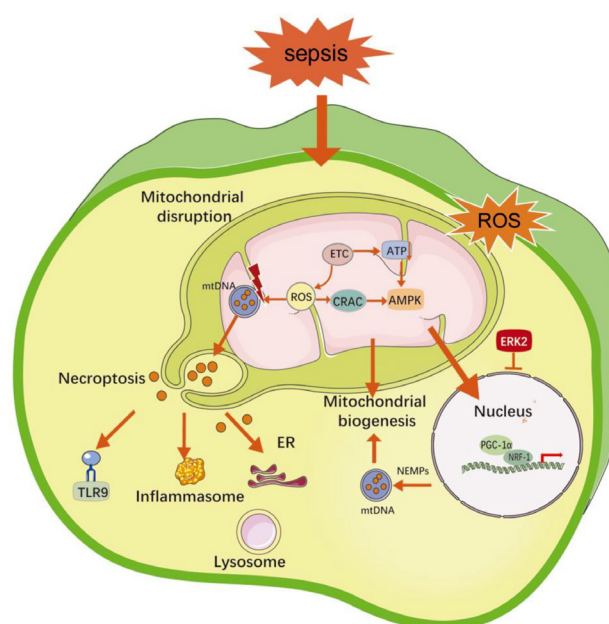


Figure 2. Cytokine-Driven Mitochondrial Dysfunction in Sepsis [23].

bind reactive oxygen species (ROS) peroxides to generate RNS, irreversibly inhibiting the mitochondrial electron transport chain (ETC). Dysfunctional ETC further escalates ROS release from mitochondria, inciting additional mitochondrial damage including inner membrane disruption, impaired ETC activity, and mitochondrial DNA destruction. Ultimately, the mitochondrial matrix swells, the outer membrane ruptures, and apoptosis is triggered. Apoptosis occurs at high rates among immune cells like splenic lymphocytes and across organs in sepsis. Inhibiting apoptosis via caspase inhibitors has been shown to improve sepsis survival. Overall, cytokines elicit a feed-forward cycle of nitrosative and oxidative stress that cripples mitochondrial functioning, fuels further ROS generation, and drives apoptotic cell death – critical factors underlying sepsis pathogenesis and mortality [23].

Immunomodulatory approaches

Immune checkpoint inhibitors: Immune checkpoint inhibitors, which have revolutionized cancer immunotherapy, are now being explored in sepsis research. These inhibitors target immune checkpoints, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), to enhance immune responses and restore immune cell function in sepsis. Early preclinical studies have shown promising results in modulating the immune response and improving survival in septic animal models [24].

Cytokine modulation: Cytokines play a pivotal role in the immune response during sepsis, but excessive or dysregulated cytokine release can contribute to organ dysfunction. Preclinical research is focused on identifying strategies to modulate cytokine production and signaling [25]. This includes the development of cytokine inhibitors, neutralizing antibodies, and immunomodulatory agents that restore the balance of pro-inflammatory and anti-inflammatory cytokines [26].

Targeting neutrophil dysfunction: Neutrophils are key effector cells in the immune response against infections. However, in sepsis, neutrophil dysfunction can lead to tissue damage and exacerbate organ dysfunction. Novel approaches are being explored to restore neutrophil function and prevent excessive neutrophil activation. This includes targeting neutrophil chemotaxis, oxidative burst, and phagocytosis, as well as modulating neutrophil extracellular trap (NET) formation [27].

Targeting coagulation abnormalities

Anticoagulant therapies: Sepsis is associated with a pro-thrombotic state and coagulation abnormalities. Researchers are investigating the use of anticoagulant therapies, such as activated protein C (APC) and direct thrombin inhibitors, to prevent clot formation, improve microvascular perfusion, and reduce organ dysfunction. The development of targeted

anticoagulants with improved safety profiles is a focus of ongoing preclinical studies [28].

Fibrinolytic agents: In sepsis, excessive fibrin formation and impaired fibrinolysis can contribute to microvascular thrombosis and organ dysfunction. Novel fibrinolytic agents are being explored to enhance clot breakdown and restore microvascular perfusion. These agents aim to improve the resolution of coagulopathy and prevent disseminated intravascular coagulation (DIC) associated with severe sepsis [29].

Endothelial protection strategies: Endothelial dysfunction is a critical feature of sepsis and contributes to barrier disruption, vascular leakage, and organ dysfunction. Preclinical research is focused on developing strategies to protect and restore endothelial function. This includes targeting endothelial cell activation, stabilizing the endothelial barrier, and promoting endothelial repair mechanisms [30]. The latest advances in preclinical sepsis research offer promising avenues for therapeutic interventions. By targeting novel pathways, modulating immune responses, and addressing coagulation abnormalities, researchers are working towards effective treatments that can improve outcomes for septic patients. Continued progress in translating these preclinical findings into clinical practice holds the potential to revolutionize sepsis management and save countless lives.

Potential Therapeutic Avenues for Sepsis

Sepsis remains a global healthcare challenge, necessitating the continuous exploration of potential therapeutic avenues to improve patient outcomes. In recent years, significant progress has been made in identifying novel pharmacological interventions, cell-based therapies, and adjunctive approaches to tackle the complex pathophysiology of sepsis [31]. In this section, we delve into the promising therapeutic avenues that hold the potential to revolutionize sepsis management.

Pharmacological interventions

Small molecule inhibitors: Small molecule inhibitors offer a targeted approach to modulate specific molecular pathways implicated in sepsis pathogenesis. By selectively inhibiting key enzymes, receptors, or signaling molecules, these inhibitors aim to attenuate the dysregulated immune response, reduce inflammation, and restore immune homeostasis. Promising targets for small molecule inhibitors in sepsis include pro-inflammatory cytokines, coagulation factors, and intracellular signaling pathways [32].

Immunomodulatory drugs: Immunomodulatory drugs have shown considerable promise in sepsis research. These drugs aim to modulate the immune response, either by enhancing host defense mechanisms or dampening excessive

inflammation. Examples include immune checkpoint inhibitors, which unleash the immune system's ability to recognize and eliminate pathogens, and immunosuppressive agents that target hyperinflammation. Immunomodulatory drugs have the potential to restore immune balance and improve patient outcomes [33].

Targeted therapies: Advancements in molecular understanding have paved the way for targeted therapies in sepsis. These therapies focus on specific molecular targets, such as Toll-like receptors (TLRs), pro-inflammatory cytokines, or coagulation factors. Targeted therapies can range from monoclonal antibodies that neutralize specific molecules to RNA-based therapies that disrupt gene expression. By directly addressing the underlying mechanisms driving sepsis, targeted therapies hold promise in mitigating organ dysfunction and improving survival rates [34].

Cell-based therapies

Mesenchymal stem cells (MSCs): MSCs have emerged as a potential cell-based therapy for sepsis due to their immunomodulatory and regenerative properties. These multipotent cells possess the ability to modulate immune responses, reduce inflammation, and promote tissue repair. MSCs can be administered systemically or targeted to specific organs to mitigate sepsis-induced organ dysfunction. Preclinical studies have shown promising results, highlighting the potential of MSCs as a therapeutic tool in sepsis management [35].

Immune cell therapies: Immune cell therapies involve the administration of immune cells, such as natural killer (NK) cells or dendritic cells, to enhance host defense mechanisms in sepsis. These therapies aim to boost immune cell function, improve pathogen clearance, and restore immune homeostasis. Additionally, adoptive transfer of specific immune cell subsets, such as regulatory T cells (Tregs), holds promise in modulating the immune response and preventing excessive inflammation [36].

Engineering immune cells for sepsis treatment: Recent advancements in genetic engineering techniques have opened up possibilities for modifying immune cells to enhance their therapeutic potential in sepsis [37]. This includes engineering T cells to express chimeric antigen receptors (CAR-T cells) targeting sepsis-associated antigens or equipping immune cells with synthetic gene circuits to fine-tune their responses. These approaches aim to create personalized and precisely controlled immune cell therapies for septic patients [38].

Adjunctive therapies and supportive care

Fluid resuscitation strategies: Early and aggressive fluid resuscitation is a cornerstone of sepsis management. Ongoing research focuses on optimizing fluid resuscitation strategies,

including the type, timing, and volume of fluids administered [39]. Additionally, personalized fluid management guided by advanced monitoring techniques holds promise in tailoring resuscitation to individual patient needs and reducing the risk of fluid-related complications [40].

Nutritional support: Adequate nutritional support is crucial in sepsis to meet the increased metabolic demands and mitigate the risk of malnutrition and organ dysfunction [41]. Research is dedicated to optimizing enteral and parenteral nutrition strategies, considering the timing, composition, and delivery methods to support immune function, maintain gut integrity, and improve patient outcomes [42-47].

Organ support and replacement therapies: Severe sepsis can lead to multi-organ dysfunction, necessitating organ support and replacement therapies. Extracorporeal therapies, such as hemodialysis, hemofiltration, and extracorporeal membrane oxygenation (ECMO), offer vital support to failing organs and help stabilize the patient's condition. Ongoing research focuses on refining these techniques and developing innovative approaches for organ support in sepsis [48]. The potential therapeutic avenues for sepsis encompass a diverse range of approaches, from pharmacological interventions targeting specific molecular pathways to cell-based therapies harnessing the regenerative potential of immune cells. Additionally, adjunctive therapies and supportive care strategies continue to evolve, aiming to optimize fluid resuscitation, nutritional support, and organ support. By combining these innovative therapeutic approaches, we have the potential to transform sepsis management and improve patient outcomes. Continued research and translation of these promising avenues into clinical practice hold the key to combating sepsis and saving lives.

Post-Sepsis Syndrome

Sepsis, a life-threatening condition resulting from a dysregulated immune response to infection, not only poses immediate risks but can also have long-lasting consequences for survivors. Post-Sepsis Syndrome (PSS) has emerged as a significant concern, encompassing a range of physical, cognitive, and psychological impairments that persist beyond the acute phase of sepsis [49]. In this section, we delve into the multifaceted aspects of PSS, exploring its clinical manifestations, underlying mechanisms, and potential interventions and rehabilitation strategies.

Definition and clinical manifestations

Post-Sepsis Syndrome refers to a collection of persistent symptoms and impairments experienced by individuals who have survived sepsis. While the exact definition varies, PSS typically involves a combination of physical, cognitive, and psychological sequelae. Physical manifestations may

include generalized weakness, fatigue, muscle and joint pain, and functional limitations. Cognitive impairments can manifest as difficulties with memory, attention, concentration, and executive functions. Additionally, PSS may give rise to psychological symptoms like anxiety, depression, post-traumatic stress disorder (PTSD), and reduced overall quality of life. The wide-ranging impact of PSS underscores the need for a comprehensive approach to address these long-term consequences [50].

Underlying mechanisms

The underlying mechanisms contributing to PSS are complex and multifactorial. Sepsis-induced systemic inflammation and the subsequent dysregulation of the immune system play a central role. The excessive release of pro-inflammatory cytokines during sepsis can lead to prolonged immune activation, oxidative stress, and tissue damage, which may persist even after the infection has been cleared [51]. Additionally, sepsis-associated changes in the gut microbiome, neuroinflammation, and alterations in the hypothalamic-pituitary-adrenal (HPA) axis functioning have been implicated in PSS. The interplay of these mechanisms highlights the systemic nature of PSS and the need for a holistic understanding of its pathophysiology [52].

Potential interventions and rehabilitation strategies

Efforts to mitigate the impact of PSS focus on two primary aspects: management of the physical and cognitive impairments and addressing the psychological well-being of the survivors. Rehabilitation programs, tailored to individual needs, play a crucial role in improving physical functioning and restoring strength and mobility. These programs often involve physical therapy, occupational therapy, and exercise interventions to enhance muscle strength, endurance, and functional capacity. Cognitive rehabilitation strategies, such as cognitive training and compensatory techniques, aim to address cognitive impairments and improve cognitive functioning [53]. Psychological support is vital in managing the psychological sequelae of PSS. This may include interventions such as counseling, cognitive-behavioral therapy (CBT), and trauma-focused therapies to address anxiety, depression, and PTSD symptoms. Support groups and peer-to-peer networks can also provide a valuable source of emotional support and shared experiences [54]. Furthermore, a comprehensive approach to PSS management involves addressing underlying comorbidities, optimizing nutrition, and promoting a healthy lifestyle. Regular follow-up visits, post-sepsis clinics, and survivorship programs can facilitate ongoing monitoring, early intervention, and continuity of care for sepsis survivors [55]. Research efforts are ongoing to identify novel interventions and rehabilitation strategies specific to PSS. These include exploring the potential benefits of pharmacological agents, such as anti-inflammatory

drugs, antioxidants, and neuroprotective agents, in ameliorating PSS-related symptoms. Additionally, advances in neurorehabilitation techniques, such as brain stimulation, virtual reality, and tele-rehabilitation, hold promise in enhancing recovery and addressing cognitive impairments [56]. By recognizing the multifaceted nature of PSS and implementing a multidisciplinary approach, we can improve the outcomes and quality of life for sepsis survivors. Continued research, early identification, and tailored interventions are crucial in addressing the long-term consequences of sepsis and promoting the recovery and well-being of those affected by Post-Sepsis Syndrome.

Conclusions

Sepsis continues to be a major healthcare challenge worldwide, with high morbidity and mortality. However, significant progress has been made in understanding the intricate molecular mechanisms underlying sepsis pathogenesis through robust preclinical research efforts. Studies have uncovered dysregulated inflammatory and coagulation pathways, endothelial dysfunction, metabolic derangements, and cell death signaling that drive sepsis progression. This has facilitated the identification of potential therapeutic targets, ranging from cytokine inhibitors to stem cell-based immunomodulatory therapies. Ongoing research is focused on refining diagnostic and prognostic biomarkers, developing precision medicine approaches, and optimizing supportive care strategies. While translating these preclinical findings to clinical practice remains challenging, collaborative efforts between researchers, clinicians, and regulators are critical. Continued research aimed at bridging knowledge gaps, fostering innovation, and promoting evidence-based care is essential. By building on the foundation of preclinical discoveries, addressing translational barriers, and maintaining a culture of scientific inquiry, we can envision improved outcomes for sepsis patients in the future through optimized management protocols. Sepsis research remains a high priority in order to alleviate the burden of this deadly syndrome.

Recommendations

To address the complex challenges of sepsis and improve patient outcomes, several key recommendations emerge from the synthesis of existing knowledge and research findings. Firstly, there is a pressing need for enhanced sepsis awareness and early recognition among healthcare professionals. Implementing standardized protocols and guidelines for sepsis identification and management, along with educational initiatives, can help ensure timely intervention and reduce the risk of progression to severe sepsis or septic shock. Furthermore, efforts should be directed towards improving access to adequate resources, including diagnostic tools and effective therapeutics, particularly in resource-limited settings where sepsis burden is often high. Secondly,

a multidisciplinary approach is essential in the comprehensive management of sepsis. Collaboration between healthcare providers, researchers, and policymakers is crucial to foster knowledge exchange, implement evidence-based interventions, and drive innovation in sepsis care. Establishing specialized post-sepsis clinics and survivorship programs can facilitate long-term follow-up and address the unique needs of sepsis survivors, including the management of Post-Sepsis Syndrome. Moreover, investing in research infrastructure and funding is paramount to support further investigations into sepsis pathophysiology, novel therapeutic targets, and innovative treatment modalities. By prioritizing research and fostering a culture of continuous learning, we can advance our understanding of sepsis, optimize treatment strategies, and ultimately improve outcomes for sepsis patients worldwide.

List of Abbreviations

SIRS: Systemic Inflammatory Response Syndrome; PRRs: Pattern Recognition Receptors; TLRs: Toll-Like Receptors; PSS: Post-Sepsis Syndrome; PTSD: Post-Traumatic Stress Disorder; RNS: Reactive Nitrogen Species; NO: Nitric Oxide, Inos: Inducible Nitric Oxide Synthase; ROS: Reactive Oxygen Species; ETC: Electron Transport Chain; DIC: Disseminated Intravascular Coagulation; APC: Activated Protein C; MSCs: Mesenchymal Stem Cells; NK: Natural Killer; Tregs: Regulatory T cells; CAR-T: Chimeric Antigen Receptor T Cells; ECMO: Extracorporeal Membrane Oxygenation; CBT: Cognitive Behavioral Therapy; HPA: Hypothalamic-Pituitary-Adrenal.

Declarations

Ethical approval and consent to participate

Not applicable.

Clinical trial number

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

All data are available and sharing is available as well as publication.

Competing interests

The author hereby declare that they have no competing interests.

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Authors' contributions

The Corresponding author completed the study protocol and was the primary organizer of data collection and the manuscript's draft and revision process. The corresponding author wrote the article and ensured its accuracy.

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