Development and Impact of Pathogen on Toxemia

Ankush Pal
Department of Botany, Berhampore Girls' CollegeBerhampore, Murshidabad

Abstract: Sepsis, a severe global healthcare challenge, is characterized by significant morbidity and mortality. The 2016 redefinition by the Third International Consensus Definitions Task Force emphasizes its complexity as a "life-threatening organ dysfunction caused by a dysregulated host response to infection". Bacterial pathogens, historically dominant, exhibit geographic variations, influencing healthcare strategies. The intricate dynamics of bacterial immunity involve recognizing pathogen-associated molecular patterns, triggeringinnate immune responses and inflammatory cascades. Dysregulation leads to immunothrombosis, disseminated intravascular coagulation, and mitochondrial dysfunction, contributing to the septic state. Viral sepsis, historically less prevalent, saw a paradigm shift during the COVID-19 pandemic, underscoring the need to understand the immunological response. Retinoic acid-inducible gene I-like receptors and Toll-like receptors play pivotal roles, and the cytokine storm in COVID-19 differs from bacterial sepsis. Latent viruses like human cytomegalovirus impact sepsis by reactivating during the immunosuppressive phases. Challenges in sepsis management include rapid pathogen identification, antibiotic resistance monitoring, andbalancing therapy beyond antibiotics. This review highlights the evolving sepsis landscape, emphasizing the need for pathogen-specific therapeutic developments in a dynamic and heterogeneous clinical setting.

Keywords: sepsis; bacteria; virus; COVID-19; immunity

INTRODUCTION

Sepsis is a severe medical condition and a critical global healthcare issue. Worldwide, sepsis affects an estimated 48.9 million people annually and is considered to be responsible for 20% of all deaths. The mortality remains high, with 20–30% of patients dying in the acute phase, indicating that sepsis remains one of the leading causesof death worldwide. However, even after surviving the initial phase ofsepsis, patients still face an elevated risk of mortality after being discharged from hospital, with about 30% dying in the first year. Treatment options are still extremely limited, with early antibiotic treatment and surgical or interventional focus control wherever possible still being the only causative therapy. The main problem is the high heterogeneity of sepsis. In fact, it is now widely recognized that sepsis encompasses several phenotypes, which are rooted in the biological and clinical heterogeneity of the affected individuals as wellas the heterogeneity of the infected organs and the pathogens involved. Factors such as age, genetics, underlying comorbidities, concurrent injuries (including surgery), medications, and the source of infection exert significant influence on outcome. Additionally, healthcare crises can also impact the mortality of sepsis. In recent years, preclinical studies have increasingly emphasized the host–pathogen interactions in sepsis leading to this heterogeneity. However, the underlying pathophysiological and molecular mechanisms still remain incompletely understood.

In 2016, the Third International Consensus Definitions Task Force introduced the Sepsis-3 definition, redefining sepsis as a "life- threatening organ dysfunction caused by a dysregulated host response to infection". The new definition underscores the nonlinear pathology of sepsis and focuses on the metabolic changes the immunological syndrome elicits in the host. However, this dysregulated immune reaction must be in response to an infective agent, which distinguishes sepsis from a dysregulated immune response in reaction to trauma or other non-infectious causes (so-called sterile sepsis). Therefore, the impact the pathogen has on the phenotype of sepsis, the immune reaction, and the clinical outcome should not be underestimated. The pathogens causing sepsis can generally be divided into bacteria (Gram-negative, Gram-positive, or mixed), viruses, and fungi. Until 2020, bacterial sepsis was the absolute dominating entity, with viral sepsis being very rare. The COVID-19 pandemic has changed this significantly, as severe cases of COVID-19 can be

defined as viral sepsis. While we see a significant reduction of COVID-19-induced sepsis in the ICUs in post-pandemic times, it is too early to say how this will develop in the future. Therefore, we aim to give the reader an overview of the different bacterial and viral pathogens, their prevalence, and their immunity to guide research and clinical decision-making in the future.

BACTERIAL PATHOGENS AND THEIR EFFECTS ON SEPSIS

Infectious diseases, particularly sepsis, have been recognized as a significant global health challenge, contributing substantially to mortality and hospital expenditures worldwide.

Initially characterized as primarily activated by Gram-negative bacteria, the understanding of sepsis has evolved over the years to encompass a broader spectrum of pathogens, including Gram-positive bacteria, fungi, and viruses.

In their multicentric sepsis study from 2006, Vincent et al. could classify about 45% of identified causal microorganisms as Gram-negative, one of the most common being Escherichia coli in 13% of allidentified cases (Figure 1). They could also identify about 43% of their sepsis cases as caused by a Gram-positive bacterium, with Staphylococcus being the most common. Two years later, Moreno et al. showed a prevalence of about 90% of all identified infective agentsin their 1099 severe sepsis and septic shock patients being bacteria. They identified about 45% as Gram-negative bacteria and about 35% as Gram-positive.

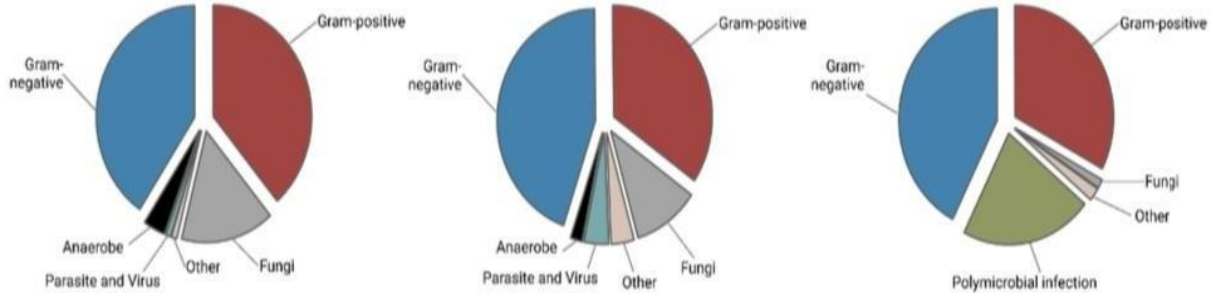

Figure 1. Pathogen prevalence in positive isolates in different cohorts over time, based on the publications of Vincent et al. 2006, Moreno etal. 2008, and Umemura et al. 2020.

Similar levels of Gram-positive (33%) and Gram-negative (42%)sepsis were reported more recently by Umemura et al. in 2021 for a Japanese cohort (Figure 1). This un-derscores that up to 2020, the maininfective agents causing sepsis were bacteria, a fact that is mirrored bythe Surviving Sepsis Campaign guidelines suggesting broad-band antibiotics in patients with sepsis or septic shock in the first hour. This understanding is especially crucial as bacteremic patients have a highermortality rate than patients with culture-negative sepsis.

Geographic variation in sepsis-causing pathogens is a notable aspect ofinfectious disease epidemiology. Sakr et al. conducted a multicentric study, revealing distinct regional differences in the types of organisms responsible for sepsis. Acinetobacter, a Gram-negative bacterium prevalent in sewage water, exhibited significant discrepancies in infection rates across different geographical locations, with a noteworthy correlation observed between prevalence and government healthcare expenditure. This underscores the influence of regional factors on the distribution of sepsis pathogens. Moreover, Umemura et al. emphasized the importance of considering geographical variations in their nationwide cohort study in Japan, noting changes in the spectrum of causative pathogens over the years. These findings highlight the need for a nuanced understanding of sepsis epidemiology, taking into account regional differences in pathogen prevalence and their potential impact on healthcare strategies and resource allocation.

Understanding how the prevalence of different bacteria evolves acrossregions is essential for devising targeted strategies in the face of changing epidemiological landscapes. As pathogens exhibit diverse resistance patterns and geographical disparities, the host's immune system plays a crucial role in determining the outcomes of sepsis. Transitioning from the regional influences on pathogen prevalence, wecan delve into the intricate dynamics of bacterial immunity and the hostresponse.

All pathogens in sepsis share the commonality of entering the host and subsequently infiltrating the bloodstream. Upon entry into the human organism, pathogens are recognized through receptors. Typically, the immune system identifies pathogen-associated molecular patterns (PAMPs) of invading pathogens or damage-associated molecular pat- terns (DAMPs) of dying or damaged cells through pattern-recognitionreceptors. The family of pattern-recognition receptors (PRRs) includes,among others, the Toll-like receptor family (TLR) as well as the leucine-rich repeat (LRR)-containing protein family (NLRP). Gram- positive and Gram-negative bacteria and their specific PAMPs are recognized by different PRRs. For example, while TLR4 recognizes lipopolysaccharides (LPS) from Gram-negative bacteria, TLR2 primarily recognizes the cell wall components of Gram-positive bacteria and peptidoglycan of S. aureus.

The recognition of PAMPs triggers the innate immune system. This isthe quick-reacting but unspecific arm of the immune response. PAMPsprompt monocytes and macrophages to activate the p65:p50 NF-translocation into the nucleus. Crucial cytokines for the pro-inflammatory response include tumor necrosis factor alpha (TNF-α), pro- interleukin (pro-IL)-1β, IL-6, IL-8, IL-12, and pro-IL-18. Furthermore, other important molecules, such as ferritin and C-reactive protein (CRP), are produced. CRP is subsequently used to opsonize extracellular pathogens, activating the complement system. In addition, the complement system is initiated by immunoglobulins in response to invading pathogens or DAMPs, leading to the release of anaphylatoxins, particularly C3a and C5a. While the activation of the complement system is crucial for protective immunity, excessive activation can result in further tissue damage and organ failure due to immunothrombosis or disseminated intravascular coagulation. In addition to PAMPs activating the NF-κB axis, the induction of the inflammasome is also possible. The activation of the inflammasome triggers caspase 1 to work, which results in the cleavage of pro-IL-18 and pro-IL-1β, yielding their active forms. These are secreted, and particularly IL-1β is used to recruit and activate neutrophils. These specialized cells employ a process called “NETosis”, which involves the release of extracellular structures known as neutrophil extracellulartraps (NETs). These NETs can trap and immobilize bacteria, preventing their spread and providing a scaffold for antimicrobial components to exert their effects and further activate the complement system. In addition, neutrophils produce vast amounts of reactive oxygen species (ROS) and nitric oxide (NO) to combat the invading pathogen. In the dysregulated, septic immune response, ROS is thoughtto be generated in excessive amounts, leading to a range of maladaptivechanges in the host. As immune cells shift towards pro-inflammation, their modes of generating energy shift as well. The cells rely mostly onglycolysis, which is increased in the pro-inflammatory phase. Along with glycolysis, the pentose phosphate pathway is increased, which triggers the production of more ROS via NOX (NADPH oxidase) and NO via NOS (nitric oxide synthase). The pyruvate generated during glycolysis is not fed into the citric cycle in the mitochondria but instead converted into lactate and released into the bloodstream. The cell doesthis in order to generate energy fast rather than efficiently. The mitochondria are shut down, probably to protect them from excessive ROS and NO. If the host does not recover from this adaptive process, septic mitochondrial dysfunction can develop. This is one of the main differences between a regulated immune response and the septic state.The mitochondrial dysfunction is also connected to the inflammasome activation and vice versa. Subsequently, the adaptive immune responseis activated by antigen-presenting cells.

In response to the activation of pro-inflammatory networks, the anti- inflammatory response is triggered. Anti-inflammatory cytokines like IL-4, IL-10, and transforming growth factor beta (TGF-ß) are, in turn, released. The number of human leukocyte antigen (HLA) antigen- presenting receptors on monocytes and the cytokine response of monocytes to stimulation are decreased, and the lymphocytes are reduced by means of apoptosis. As stated above, sepsis is characterizedby an imbalance of the immune response, resulting in the activation of both pro- and anti-inflammatory signaling networks at the same time. Hence, the immune system is not able to restore immune homeostasis,resulting in organ dysfunctions and often in a state of immunoparalysis involving innate and adaptive immune responses.

CONCLUSION

While the majority of causative pathogens for sepsis up to2020 were bacteria, virus-induced sepsis has always

been known. The most common virus capable of inducing sepsis in adult patients living in developed countries was the Influenza virus, with incidences ranging between 1% and almost 4%. Especially in tropical countries, outbreaksof zoonotic viruses such as Ebola, Lassa, Marburg, Hanta, or Dengue virus can be much more prevalent. All this, of course, was turned on itshead when the COVID-19 pandemic hit in 2020. Between 2020 and 2023, the incidence of viral sepsis was more than 15%, peaking at 80%of all sepsis cases being COVID-19-induced.

The immunologic response to a viral infection is generally very similarto the bacterial response. For viruses, specific PRRs detecting the invading virus are known. One of the key sensors is the family of the retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs). They can recognize virus-derived RNA mediating the transcriptional induction of type I interferons. As they are also triggered by host-derived RNA, the vicious cycle of reactivating the PRRs upon DAMP production is started as well. The induction of type 1 interferons potentiates both the innate and adaptive immune responses to clear viral infections. The pathogenic virus can also be detected by TLR3, TLR4, and TLR7, leading to the p65:50 NF-kB translocation and the subsequent production of pro-inflammatory cytokines. In the case of COVID-19, this so-called cytokine storm was extensively discussed in the early phases of the pandemic. By now, we know that the levels of IL-6 in COVID-19 sepsis are only moderate in comparison to polymicrobial sepsis. Furthermore, the dynamics of IL-6 seem to be fundamentally different in COVID-19 sepsis, as this cytokine increases in concentration 2-3 weeks after disease onset. The same holds true for the comparison of COVID-19 with other viral sepsis forms, such as Influenza. COVID-19-induced sepsis shows a longer incubation time, delayed onset of symptoms, and a longer inflammatory phase. During viral infection, the immunomodulatory effects of type 1 and type 2 interferons play a pivotal role, acting as tipping point proteins that activate subsequent immune responses. When we compare the interferon (IFN) response between COVID-19- and Influenza-inducedsepsis, we find that IN is released later during the course of severe COVID-19 (following the pro-inflammatory phase) and is less pronounced, leading to longer disease and higher severity.

In addition to viruses such as SARS-CoV-2 and Influenza causing sepsis, there is a significant effort to evaluate the impact virus reactivation has on survival in polymicrobial sepsis patients. The reactivation of human cytomegalovirus (CMV) is especially widely discussed as an independent risk factor for bacterial as well as for viralsepsis.

HCMV belongs to the family of herpes viruses and stays in the body ofthe host after initial infection in a latent form. It can reactivate regularly during the lifetime of the host, which does not cause clinical symptoms and often goes undetected in immunocompetent individuals. In immunocompromised states such as sepsis, the reactivation of HCMVand other herpes viruses can cause severe complications, including death. However, in recent work, we have shown that even the presence of the latent form of the virus, without reactivation, could change the immunity of patients, leaving them more vulnerable to sepsis related death.

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