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CONFRONTING SEPSIS: A CALL FOR URGENT ACTION

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Sepsis, a life-threatening condition triggered by the body's overwhelming response to an infection, continues to wreak havoc on global healthcare systems and claim countless lives.[1] Despite significant medical advancements, sepsis remains a pervasive and urgent public health crisis. In this editorial, we shed light on the gravity of the problem, explore the key challenges faced in addressing sepsis, and advocate for a comprehensive and coordinated approach to combat this silent menace.

A Greek physician named Hippocrates was the first to coin the term "sepsis" in the 5th century BCE, referring to the process of putrefaction or decay. However, in the recent decades the term was redefined in1991 as Systemic inflammatory response syndrome (SIRS), the understanding of sepsis has evolved significantly since then to describe a set of clinical signs associated with sepsis.[2] Later, in 2001, a new consensus conference proposed the term "severe sepsis" to refer to sepsis with evidence of organ dysfunction. The concept of sepsis was further refined in 2016 with the introduction of the "Sepsis-3" definition[3], which emphasized the presence of organ damage and subsequent dysfunction caused by a dysregulated host response to infection.[4]

Sepsis affects millions of people worldwide, with mortality rates that surpass those of many major diseases. Its indiscriminate nature makes it a formidable adversary, striking individuals of all ages and backgrounds.[5] According to the World Health Organization, sepsis claims approximately 11 million lives annually, with low- and middle-income countries bearing an enormous burden. The social and economic impact of sepsis cannot be underestimated, as survivors often face long-term physical, psychological, and financial challenges.[6,7]

Despite its devastating impact, sepsis often remains misunderstood, misdiagnosed, and underreported. Multiple factors contribute to these challenges, including lack or inadequate epidemiology studies[8] inadequate healthcare infrastructure, and fragmented surveillance systems. Additionally, the complexity of sepsis and its variable presentation make early identification and treatment difficult. It is essential to address these challenges head-on to improve sepsis outcomes and save lives. Hence the need to understand the scale of the problem, and to identify the key challenges.[9] Surveys in the ICU units of hospitals found that "approximately 70% to 80% of the cases of severe sepsis in adults occurred in individuals who were already hospitalized for other reasons". There is no singular pathophysiology to sepsis, as sepsis can be manifested by several pathways.

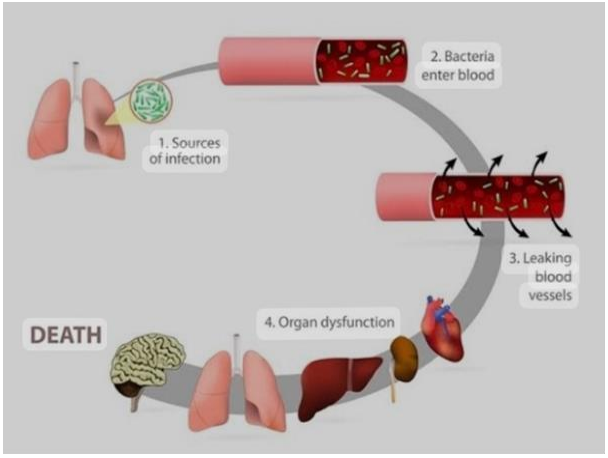

Figure- showing stages of sepsis progression - Source [Google images]

The pathophysiology of sepsis involves multiple pathways and mechanisms.[11,12], including the activation of inflammatory and coagulation cascades, endothelial dysfunction, and impaired cellular function. Some of the known pathways include inflammatory response. Infections, particularly bacterial, release pathogen-

associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These molecules are recognized by pattern recognition receptors (PRRs) on immune cells, such as macrophages, leading to the release of pro-inflammatory cytokines (such as tumor necrosis factor-alpha [TNF-α], interleukin-1 [IL-1], and interleukin-6 [IL-6]). This excessive cytokine release contributes to systemic inflammation. Sepsis can activate the coagulation cascade, leading to disseminated intravascular coagulation (DIC). The release of inflammatory mediators promotes the activation of clotting factors, platelets, and endothelial cells, resulting in microvascular thrombosis. Simultaneously, the coagulation system can be impaired, leading to excessive bleeding in some cases.[13] Further, endothelial cells which line up the blood vessels become activated and dysfunctional. This leads to increased vascular permeability, impaired blood flow regulation, and the release of pro-inflammatory and pro-coagulant molecules. Dysfunction of the endothelium contributes to tissue edema, organ dysfunction, and hypoperfusion.

Further, the involvement of the Immune system is crucial[14,15] as Sepsis can cause a non-functional immune response. This includes both a hyperactive response characterized by excessive inflammation and a hypoactive response characterized by immune suppression. Immune cells may become functionally impaired, compromising their ability to clear the infection effectively. This kind of response may contribute to the persistence and spread of the infection and can lead to secondary nosocomial (hospital-acquired) infections.

Some of the key risk factors of sepsis that can arise from various sources and scenarios in a hospital setting[16] include: Reporting from hospital settings any patient with the following conditions can develop sepsis such as a patient with severe urinary tract infection (UTI) due to bacterial infections spreading to their bloodstream, or an individual admitted to the hospital for pneumonia can develop sepsis as a result of infection in their lungs. Similarly, a postoperative patient can develop sepsis due to a surgical site infection that spreads to their bloodstream. A patient receiving intravenous (IV) therapy can develop sepsis when the IV line becomes contaminated, leading to a bloodstream infection. A person with a compromised immune system, such as an organ transplant recipient, after acquiring a bacterial infection during their hospital stay. An individual with an infected ulcer, when the infection enters their bloodstream or a patient undergoing chemotherapy as a result of a fungal infection that spreads from their mouth to their bloodstream. A premature new-born in the neonatal intensive care unit (NICU) develops sepsis due to a bloodstream infection acquired through an umbilical catheter. In the elderly patients infections often occur with a urinary catheter due to a bacterial infection associated with catheter use. Also, patients with a central venous catheter can develop septicaemia when bacteria enter the bloodstream through the catheter insertion site. Sepsis is a complex medical condition that requires prompt recognition and aggressive treatment to improve patient outcomes.[17] For this reason, the best possible knowledge of the pathogen epidemiology and the presumed anatomical focus are prognostically important for enhancing recovery from sepsis.[18]

These pathways interact and amplify each other, leading to a vicious cycle of inflammation, coagulation, endothelial swelling, and organ failure. Ultimately, the uncontrolled systemic inflammatory response and the resulting organ failure characterize the clinical manifestations of sepsis. The understanding of sepsis pathophysiology is still evolving, hence the intricate mechanisms underlying this complex syndrome is not clearly understood.[19]

To tackle sepsis comprehensively, healthcare systems must be fortified at various levels. This involves enhancing infection prevention and control measures, optimizing antimicrobial stewardship, and implementing robust surveillance systems to track sepsis cases accurately. Investing in research and development of novel diagnostic tools and therapies will also play a pivotal role in improving sepsis management and reducing mortality rates. Sepsis is a multifaceted challenge that demands collaboration across borders, disciplines, and sectors. Governments, healthcare providers, researchers, and advocacy groups must join forces to share best practices, harmonize guidelines, and facilitate knowledge exchange. International collaborations can help foster innovation, resource sharing, and capacity building in countries with limited healthcare resources, ultimately strengthening the global response to sepsis, but we have completely overlooked the complement system in the dysregulated inflammatory response, which also has an important role in sepsis.[20]

In this era the cornerstones for sepsis therapy or septic shock still consist of early focus control, timely administration of broad spectrum antibiotics[21] and hemodynamic stabilization through fluids and vasopressors. Over the last few years, a paradigm shift is happening, that is shifting the focus from the pathogen to the host genome susceptibility when examining sepsis pathophysiology. Clinical understanding of the patients is continuously developing toward an immunological perspective.[22,23] Complex pro- and anti-inflammatory pathways and disorders of the complement and coagulation system have been elucidated, thus revealing the heterogeneity and complexity of the syndrome, even after knowing the difference between- sepsis, severe sepsis and septic shock.[24] Alas, it has not yet been possible to transform knowledge into evidence-based practice for the effective treatment of sepsis.

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