International Journal of Scientific Research and Modern Technology (IJSRMT) ijsrmt.com
Volume 4, Issue 10, 2025
DOI: https://doi.org/10.38124/ijsrmt.v4i10.945

Sepsis: A Comprehensive Review of Etiological Factors, Risk Determinants, Clinical Outcomes and Emerging Therapeutic Paradigms

Hajra Ayaz[1]; Hafsa Ayaz[2]; Abbas Khan[3]; Suhaib Mesbah[4]; Muhammad Rehan Ahmed[5]; Azka Sana[6]; Hifsa[7]

[1]Department of Biotechnology, COMSATS University Islamabad, Abbottabad Campus, Abbottabad-22060, KPK Pakistan.
[2,6,7]Department of Chemistry, COMSATS University Islamabad, Abbottabad Campus, Abbottabad-22060, KPK Pakistan.
[3,4,5]Bachelor of Medicine and Bachelor of Surgery, Northwest School of Medicine, Peshawar-25000, KPK, Pakistan.

Publication Date: 2025/11/12

Abstract

Sepsis is quite a significant health issue all over the world, which is a dysregulated organ dysfunction due to host response to infection that threatens with life. This review will discuss multifactorial etiology of sepsis, major factors such as malnutrition, alcoholism, diabetes mellitus, and malignancies, acute and long-term clinicalization. There is still a high mortality rate in the immediate term and the survivors experience high morbidity such as cognitive impairment, physical disability and permanent immune dysfunction. Existing diagnostic and therapeutic problems are due to heterogeneity of sepsis and the absence of specific biomarkers. New avenues of research are on the horizon: immunosuppression and neuroinflammation as sepsis consequences can be studied mechanostatically to provide targeted treatments; nanotechnology can be used to diagnose sepsis faster and deliver drugs, and personalized treatment strategies can be provided using sepsis endotyping. The required paradigm shift in sepsis management is the abandonment of standardized protocols and the introduction of endotype-specific and individualized intervention and survivorship care models, in which recovery needs require the improvement of long-term rehabilitation and care.

Keywords: *Septic Shock, Immunosuppression, Precision Medicine, Malnutrition, Diagnostic Challenges, Survivorship Care.*

I. INTRODUCTION

Sepsis also called blood poisoning is the resistant of immune system to infection or injury. Our immune system fight with infection but sometime overreaction occur and our immune system attack on own body. Sepsis is a regular and hazardous disorder portrayed by intense organ dysfunction(Napolitano, 2018). Sepsis is a disorder of physiological, pathologic and biochemical variation from the norm incited by infection(Torio & Moore, 2016). The most regular essential contamination bringing about sepsis is the lungs, the stomach area and the urinary tract. Normally half of sepsis cases start as the contamination of lungs, no source can found in 33% cases(*Mandell, Douglas, and Bennett's Principles and Practice of Infectious* , n.d.). Severe sepsis is characterized as sepsis related to organ dysfunction and hypotension. Septic shock in youngsters refers to a condition of acute circulatory failure described by persistent blood vessel hypotension in spite of satisfactory volume resuscitation in the nonappearance of other case of hypotension(Singer et al., 2016).

Sepsis has existed since the light period and has been described for over 2000 years but it clinical definition is more recent. Sepsis has historically been hard to analyze and diagnose until 100BC, Ancient Roman scholar and researcher "Marker Stelentins Baro (116-27BC)", states

Ayaz, H., Ayaz, H., Khan, A., Mesbah, S., Ahmed, M. R., Sana, A., & Hifsa. (2025). Sepsis: A Comprehensive Review of Etiological Factors, Risk Determinants, Clinical Outcomes and Emerging Therapeutic Paradigms. *International Journal of Scientific Research and Modern Technology*, *4*(10), 139–146. https://doi.org/10.38124/ijsrmt.v4i10.945

that microscopic organism fill the climates and inhaled through the nose cause dangerous illness(Martin, 2012). The most perceptive depiction of sepsis is from the history specialist, thinker, humanist and renaissance creator "Niccolo Machiavelli (1469-1527)" as announced in his "dissertation prince" in 1513. From the starting in his book, he very persuasive expressed in his book hechtic fever is hard to recognize but simple to treat. Hechtic fever is not the same name that currently known sepsis. The depiction of in ailment that is hard to recognize in its beginning times, when condition might be amiable to treatment, and increasingly hard to treat in its later progressively evident stages in an away from the more serious type of sepsis(Martin, 2012). It was traditionally described by famous American doctor "William Oster (1849-1919)" in his fundamental perception that person seem to be dying due to body reaction to the infection, not the infection itself. In 1972 this idea was get constrained over clinical survey, taking note of that "it is the overreaction that makes the infection"(Thomas, 1972). The general idea has for some time viewed as a type of poisoning also known as blood poisoning(Martin, 2012).

Sepsis the one of the main cause of death in hospital(LaRosa et al., 2012). It is assessed that more than 31.5 million individual are affected worldwide and about 5.3 million people die due to intermitted organ dysfunction(Fleischmann et al., 2016). Annually more 1.7 million American is determined to have sepsis and in excess of 270,000 individuals die due to sepsis(CDC, 2018). Additionally the most costly clinical condition, in 2013 the United State spent 23.7 billion dollars(Torio & Moore, 2016).

People who endure sepsis may experience long-term side effects, severe and persistent dysfunction and reduce health-related satisfaction of life (Iwashyna et al., 2012; Scherag et al., 2017). The rate of sepsis increments gradually in industrialized nation in the middle of 200-400 cases for each 100,000 individuals per 2-4 years(Álvaro-Meca et al., 2018; Azkárate et al., 2016; Esteban et al., 2007).

Sepsis outcome, therapies and prevalence study is an ongoing universal point prevalence investigation of pediatric serious sepsis or septic shock, and provide rich information source for assessing difference between youngsters with postsurgical verses clinical sepsis (Weiss et al., 2015).

A review of inner information from the human services suggested that 90% of septic patient require hospitalization to emergency department. Early acknowledgment and mediation in the emergency department is fundamental for early objective coordinated treatment and disease of motility (Delawder & Hulton, 2020).

II. CAUSES OF SEPSIS

Sepsis is brought about by different variables, for example, pathogens and hosts. Its pathogenesis is extremely confused. At the point when the pathogenic microorganisms attack the body, they can invigorate the immune function of the body; in the interim, various lymphocytes, for example, T cells and B cells, start to experience apoptosis. Hence, the immune function of the body is harmed, bringing about immunosuppression. The two procedures of hyper immune and immunosuppression may exist at the same time in the event and advancement of sepsis and may change with the movement of the sickness. In such an access, various incendiary variables are produced by the host and associated with the response, which makes certain harms the function of the body when the provocative reaction is unbalanced(Yang et al., 2020).

The rate of sepsis is influenced by different factors. Age is a significant component of somebody hazard for creating sepsis. As well as various co-existing medical conditions, may be most clear condition are HIV, cancer and diabetes, every one of which alter the immune system(Danai et al., 2006) these condition bring about an essentially raised hazard for creating sepsis. It has also been perceived that race, ethnicity and gender also differential the hazard for creating sepsis(Danai et al., 2006; Esper et al., 2006; Mayr, 2010).In general for creating sepsis men are at high risk of sepsis than sepsis in women depending on age(Danai et al., 2006; Dombrovskiy et al., 2007; Esper et al., 2006).

From "1950 to 1980s"; sepsis is a condition that was essentially inferable from gram-negative bacteria(Kreger et al., 1980). Occurrence of sepsis with gram-negative seems to be decreasing from its degree of the "1970 and 1980". A gram-negative bacterium is being the leading cause of nosocomial infection(Richards et al., 1999). "The national nosocomial infection surveillance IS" relaved that from "1992 and 1997" coagulase-negative *Staphylococci* were the most widely recognized blood stream isolate(Richards et al., 1999). *"Enterococci* and *Staphylococcus aureus*" were next common microorganism isolated from blood. After urinary tract infection nosocomial pneumonia is the second common nosocomial infection. These two infections are cause of sepsis, most often gram-negative bacteria *Staphylococci aureus* was also cause of nosocomial pneumonia(Richards et al., 1999).

The occurrence of sepsis, extreme sepsis and septic shock increase continuously, and in spite the fact that gram-positive bacterial infection remain the most widely recognized reason for the sepsis, fungal microorganism are increasing quickly(Martin, 2012).

Infection is a significant reason for mortality among people with "end stage renal disease". Infection is second cause of death after coronary artery disease in ESRD patients registry in United State, with sepsis accounting for over 75% of these infectious death(Collins et al., 2015). This expands sensitivity to bacterial infection(Keane et al., n.d.; Kessler et al., 1993).

Cytokines for example," tumor necrosis factor A and interleukin-1" are secrete in huge amount by monocytes,

macrophages and different leucocytes to counter response to gram-positive and gram-negative bacterial substance that play important role in the pathogenesis of septic shock(BILLIAU & VANDEKERCKHOVE, 1991; Calandra et al., 1990; Gutierrez-Ramos & Bluethmann, 1997; Waage et al., 1987). Both these microorganisms induce sepsis causes apoptosis of thymocytes and TNF-A association is basic to both(Alerts, 2018). Cytokine association in septic shock, there is proof that over activation of macrophages change endothelial penetrability in various organs during septic shock(Deng et al., 1996).

The absence of lymphatic seepage and partition from the blood by blood-brain barrier in the mammalian central nerves system mammals is viewed as an immunologically special site. The BBB assume a significant job in controlling the entrance of inflammatory cell and other macromolecules into mind by micro vascular endothelial cells(Abbott & Romero, 1996; Janzer & Raff, 1987; Perry et al., 1997). Bacterial meningitis is related with harm to BBB(van Furth et al., 1996), clinical proof also proposes that bacterial meningitis result sepsis(Chang et al., 1998).

It is acknowledge supposition that diabetes compounds anticipation of infection, especially sepsis(Bertoni et al., 2001; Falguera et al., 2005; METAN et al., 2005), reduce utilitarian limits of organ system in diabetes and impeded immune systems are likely most significant causes(Gornik et al., 2007).

- *Risk Factor Responsible for Sepsis*

Components that are possibly answerable for the developing occurrence of sepsis and septic shock are:(balk, 2000).

- Expanded recognition and sensitivity to diagnosis
- increase utilization of cytotoxic and immune suppressant operators
- increase number of people with immunodeficiency disorders
- high number of old patients
- There are also some other factor responsible for sepsis:

- *Malnutrition*

Any condition that bargains the host immune system increments the probability of disease and conceivably the improvement of sepsis. Malnutrition has been related with an expanded rate of respiratory contaminations, for example, tuberculosis, viral hepatitis, herpes simplex infections, bacteremia, parasitic contaminations, and contamination from enteric gram-negative microorganisms through the procedure of translocation from the intestine(Weiss et al., 2015). Malnutrition and nutrient lacks can compromise the boundary limit of the skin and mucosal layers. Extreme lack of healthy sustenance can bring about adjustments in leukocyte chemo taxis, adherence, and phagocytic killing. Nutrient and follow component lacks can bring about decay of the lymphoid tissues and changed immune system capacity, production level of antibody, and supplement levels(Weiss et al., 2015).

- *Alcoholism*

Those people who are alcoholic addict are at increase frequency of infection. Furthermore susceptible to tuberculosis, pneumonia particularly with *Klebsiella* and other exemplified organism and unconstrained bacterial peritonitis when they have going with hepatic defeat and ascites(Weiss et al., 2015). Patients with alcoholism much of the time have sustenance deficiencies that intensify the contamination hazard. At the point when serious liver brokenness exists with cirrhosis there might be adjustments in supplement and immune capacity and changes in mental status that may put the patient at expanded danger of infection and septic inconveniences(balk, 2000).

- *Diabetes Mellitus*

Diabetics may have reduced immune function Relevant for few mechanisms(Weiss et al., 2015). Elevated glucose levels decrease circulating "polymorphonuclear leukocyte (PMNL) chemotaxis, adherence, and phagocytosis". There is a reduction in lymphocyte activation, cytokine release, and cellular immunity. Diabetics have certain risks of fungal infections, such as "*mucormycosis*, *aspergillosis*, *cryptococcosis*, and *coccidioidomycosis*". It also increases the risk of infection of the urinary tract, skin and skin structures. Regular bacterial pathogens in patients with diabetes incorporate "*staphylococci, streptococci, Profeus sp., Klebsiella sp., Escherichia coli, Pseudomonas sp., and anaerobes"*(balk, 2000).

- *Malignancies*

The developing field of transplantation is liable for the production of an enormous number of patients who are in danger for disease and sepsis. The sensitive parity that must be kept up to stifle the body's endeavors to dismiss the foreign tissue and still inhibit the improvement of infectious diseases and keep challenge the transplant doctor and transplant beneficiary(balk, 2000).

III. ACUTE AND LONG-TERM EFFECTS OF SEPSIS

- *Short-Term Outcomes of Sepsis:*

The early outcomes of sepsis are often critical in determining survival. Hospital mortality for sepsis ranges from 15–30%, and in cases of septic shock, it can exceed 50% (Barbash et al., 2021). These outcomes are greatly dependent on the severity of illness, promptness of treatment and comorbid conditions present. Patients may need aggressive treatments, such as vasopressors to manage circulatory failure, mechanical ventilation to resolve respiratory distress and renal replacement to treat acute kidney injury. Timely administration of broad-spectrum antibiotics as well as fluid resuscitation has proven to save life to a great extent. In the real world, however, such time-sensitive protocols have been inconsistently applied. An example is the U.S. SEP-1 bundle that did not have a statistically significant positive effect on mortality but did show an improvement in certain process measures such as lactate monitoring (Barbash et al., 2021).

The duration of ICU stay is larger in patients with sepsis because of the complexity of the multi-organ support and the presence of a threat of the hospital-acquired infection. Delirium, nosocomial pneumonia, or venous thromboembolism are some of the complications that many survivors encounter during their stay thus worsening morbidity and recovery time. There are also high rates of readmission with over 30 percent of the survivors going back to the hospital within 3 months of dispensation (Fleischmann-Struzek et al., 2021).

- *Long-Term Effects of Sepsis:*

Outside of the acute phase, sepsis has long-term effects on the physical, cognitive and emotional health of survivors. Persistent physical disability is one of the most significant complications that can be associated with weaknesses in the ICU and critical illness myopathy. A fifth of sepsis survivors indicate that one year later they are still having impaired mobility and are unable to perform activities of daily living independently (Fleischmann-Struzek et al., 2021).

Another severe sepsis sequela is cognitive impairment. Memory loss, attention deficit, and executive dysfunction are common among the survivors. These symptoms can be attributed to sepsis-related encephalopathy and neuroinflammation and lead to structural changes in the brain. Neuroimaging and neuropsychological testing, are supported in longitudinal studies that prove that a significant proportion of survivors have cognitive paths that resemble those of early-stage dementia (Liu et al., 2022).

Psychiatric effects are less frequent but also usually discussed. A significant percentage of survivors experience depression, anxiety and post-traumatic stress disorder (PTSD). According to Prescott et al. (2019), almost a third of survivors of sepsis reported symptoms of PTSD, but mental health assistance was not a part of the usual post-discharge.

Besides these direct effects, sepsis survivors are predisposed to other chronic health problems. The cardiovascular events are especially frequent. In a meta-analysis, survival subjects were found to be 2–3 times more at risk of myocardial infarction and stroke than matched controls. (Kosyakovsky et al., 2021). Other sequelae are chronic kidney disease, insulin resistance and predisposition to infections, presumably caused by the immune dysregulation.

The quality of life in the survivors of sepsis is considerably diminished. Some cannot go back to work or even the old forms of social roles. A Swedish national cohort study of sepsis survivors indicated that long-term mortality and readmission were significantly greater among sepsis survivors where typical cause of death comprised infections, cardiovascular diseases and malignancy (Inghammar et al., 2024).

IV. CHALLENGES IN DIAGNOSIS AND TREATMENT OF SEPSIS

Sepsis diagnosis has been complicated because it is heterogeneous and has similarity to other inflammatory diseases. The early signs such as fever, tachycardia, and confusion are general. The scoring systems such as the SOFA and qSOFA are useful to stratify risk, but they are not sensitive especially in immunocompromised or children. Temperature instability or difficulties in feeding could be the only signs in the first stages of the neonatal phase, which further complicates the early diagnosis (Esposito et al., 2025).

Biomarkers like procalcitonin and C-reactive protein have been useful in providing diagnostic support, although these two biomarkers are not too specific to differentiate sepsis and other systemic inflammatory responses. Moreover, the timely intervention can be curtailed by the delay of lab results. Other potential technologies such as the electrochemical biosensors have demonstrated the capabilities of fast bedside detection of sepsis-related biomarkers; however, their utilization in clinical practice has not been widespread because of its high costs, complexity and lack of standardization (Kumar et al., 2024).

There are also challenges in treatment. Although timely and correct use of antibiotics is fundamental, many cases of antimicrobial resistance have been on the increase, especially in intensive care units due to the indiscriminate use of broad-spectrum agents. It is challenging to maintain the principle of prompt empiric therapy and remain a good steward, particularly in an environment of resource scarcity.

The heterogeneity of immune response in patients is also not considered in the current treatment protocols. Sepsis subphenotyping (classifying patients according to immune, metabolic, or genetic biomarkers) has become an encouraging approach to lead to personalized therapy. According to Zhang et al. (2025), these methods of precision medicine have the potential to transform the sphere of treatment, but they still needed to be validated and become part of clinical practice.

Besides, the majority of healthcare systems do not have a systematized post-acute care channel of sepsis survivors. Rehabilitation, mental health assistance and follow-up screening are not often provided, although evidence shows that these interventions can be of great benefit in the long run.

V. IMPROVING SEPSIS SURVIVORSHIP AND CARE MODELS

With falling acute mortality due to sepsis, the significance of planned survivorship care is becoming more tangible. Tactical interventions such as ENCOMPASS have demonstrated that coordinated follow-up, such as telehealth services and nurse navigator services, can be used to decrease readmissions and

enhance outcomes through medication management, as well as symptom management and continuity of care (Kowalkowski et al., 2021).

Sepsis survivors require a physical rehabilitation process specific to them to regain their functionality and independence. Early mobilization in ICU and outpatient rehabilitation referral have been proved useful in enhancing strength and lowering hospital dependency.

Mental health care should also form part of survivorship models. Depression and PTSD are common but not well-known. Clinics have been established in the UK and Scandinavia, which provide extensive assessment and mental health referral but these types of clinics are not prevalent in most other parts of the world (Prescott et al., 2019).

Another important element is the patient and care giver education. Self-management and less hospitalization can be achieved by teaching a survivor to recognize signs of deterioration and follow the treatment plans, as well as, understand their long-term risks. Learning materials must be provided on a basis of personal literacy and technology availability.

Lastly, policy programs are required to institutionalize sepsis survivorship in health systems. The World Health Organization has also encouraged governments to come up with national sepsis strategies incorporating long-term care. The government should provide incentives to hospitals to adopt post-discharge interventions and follow-up on the long-term outcomes in sepsis registries to make a step toward comprehensive care models.

VI. EMERGING PERSPECTIVES AND RESEARCH DIRECTIONS

- *Sepsis-Induced Immunosuppression*

Although the initial phases of sepsis can be characterized by hyper inflammatory response, emerging data point to a later, in most cases persistent period of immunosuppression, which contributes significantly to morbidity and mortality in sepsis. The change can be defined by the significant changes in both natural and adaptive immune responses, including excessive lymphocyte death, proliferation of myeloid-derived suppressor cells, and elevated expression of immune checkpoint molecules, such as PD-1 and CTLA-4 (Liu et al., 2022).

A study by Liu et al. (2022) shows that the disruption of immune homeostasis via anti-inflammatory cytokine release (e.g., IL-10), immune cell death (effectors T-cells), and tolerogenic dendritic cell persistence are some of the important mechanisms that drive immunosuppression in sepsis. Such alterations reduce the capacity of the host to eliminate primary infections and predispose further secondary infections especially in the ICU.

Immunosuppression reversal therapeutic approaches that include PD-1/PD-L1 inhibitors, IL-7 supplement, and GM-CSF have provisional success in preclinical models. Nonetheless, it is difficult to transfer these results into clinical practice because of the diversity of immune responses in different patients (Liu et al., 2022). Thus, personalized immune profiling and real time tracking of immune condition perhaps is the key to finding immunotherapy candidates.

- *Neuroinflammation and Sepsis-Associated Encephalopathy*

Sepsis-Associated Encephalopathy (SAE) is a common, however, underrecognized form of sepsis and it occurs in 70 percent of critically ill patients who are devoid of direct central nervous system infection. SAE is a continuum of acute cerebral dysfunction, between delirium and coma, which is independently related to augmented mortality and impaired cognitive function in the long term (Pan et al., 2022).

SAE is a multifactorial pathophysiology. Systemic inflammation interferes with the blood-brain barrier (BBB) allowing the entry of cytokines, immune cells, and possibly microbial components into the central nervous system (CNS). This leads to microglial activation, oxidative stress and neuroinflammation. Additionally, changes in the blood flow of the brain and the dysfunction of mitochondria caused by sepsis also cause neuronal damage (Pan et al., 2022).

Recent studies have emphasized on the role of cytokine storms such as IL-6 and TNF-alpha in the promotion of neuronal apoptosis and cognitive defects. SAE may last well beyond a clinical sepsis recovery phase, and survivors have memory losses, poor executive functioning, and evidence of a hastened neurodegeneration process. Though relatively so, SAE is rather clinically diagnosed, and there are no designated biomarkers or focused treatment options.

The current treatment aims at systemic sepsis control and hemodynamic stability. Nevertheless, future treatments could be provided by increasing the current literature on the neuroprotective mechanisms, including the regulation of neuroinflammation and maintaining BBB integrity.

- *Nanotechnology in Sepsis Management*

The nanotechnology presents some new prospects in the diagnosis and treatment of sepsis. Overall, the classic procedures of blood cultures and polymerase chain reaction (PCR) are lengthy and can give false-negative outcomes, especially in culture-negative sepsis. High surface area and tunability of nanomaterials enable increased sensitivity in detecting pathogens as well as host-response biomarkers (Papafilippou et al., 2020; Lim et al., 2021).

Biosensors based on nanoparticles have the capacity to detect sepsis associated molecules such as procalcitonin, C-reactive protein, and interleukins with

great specificity and rapidity enabling an earlier diagnosis than the traditional tests. There is also the development of nanosystems that identify microbial DNA or proteins direct in biofluids, eliminating growth of the pathogens (Lim et al., 2021). Therapeutically, the entire nanoscale drug delivery system enables specific delivery of antibiotics, anti-inflammatory, or immune modulators into the infected tissues reducing the systemic toxicity. Polymeric nanoparticles, dendrimers and liposomes have been proven to be effective at delivering drugs to important locations like lungs and kidneys in septic models. Other systems are even sensitive to sepsis-specific stimuli (e.g., pH or enzyme levels) and can release the drugs under control. Although this study has had promising results in preclinical trials, bio-compatibility, big-scale production and regulatory acceptance of the technology has limited its clinical translation. Nevertheless, the convergence of nanotechnology and point-of-care diagnostics and precision medicine has a transformative potential on sepsis treatment in the near future (Papafilippou et al., 2020).

VII. PRECISION MEDICINE AND SEPSIS ENDOTYPES

The conventional methods of treating sepsis are usually based on generalized treatments, but the response of the patient is quite diverse, as it is a heterogeneous syndrome. Recent genomics, transcriptomics, and single-cell technologies have made the identification of molecular subtypes -or endotypes -of sepsis possible. These endotypes are characterised by unique immune, metabolic and inflammatory phenotypes which determine the course of the disease and response to the treatment (Kwok et al., 2023). Kwok et al. (2023) multi-omic study mapped the immune cells in sepsis patients and found specific neutrophil-dominated signatures related to immune suppression and adverse outcome. Respondents with increased emergency granulopoiesis and inflammation mediated by STAT3 had a hyper-suppressive endotype. Identification of these subtypes may be used to guide specific interventions including immune checkpoint inhibitors or tailored antibiotic therapy. In addition, incorporation of host transcriptomic data into clinical parameters has presented possibilities of enhancing prognostic accuracy and making therapeutic decisions. The use of biomarker panels to identify sepsis phases, organ dysfunction risks and recovery probability are also strategies included in the category of precision medicine (Póvoa et al., 2023).

In spite of the promise, there are challenges of clinical implementation of sepsis endotyping such as cost, data interpretation complexity, and rapid turnaround. However, precision medicine can be discussed as a paradigm shift a one-size-fits-all approach to sepsis to one-on-one care pathways.

VIII. CONCLUSION

Sepsis is one of the most complicated problems in modern medicine that puts significant healthcare pressures across the world. This review has discussed sepsis because of its various etiological causes to major risk factors such as malnutrition, alcoholism, diabetes mellitus, and malignancies which puts vulnerable population at risk of this life-threatening condition. There are acute and long-term outcomes that go well beyond the premoral illness and have survivors who have ongoing physical, cognitive, and immunological disability that require the full survivorship care models. The heterogeneity of sepsis and the lack of specific biomarkers are the current issues in the diagnosis and treatment of the disease, whereas the traditional methods fail to deal with the underlying immunological dysregulation. There is, however, some promising change in the emerging research directions: immunosuppression detection in sepsis allows immunomodulatory treatment; the neuroinflammation knowledge allows neuroprotective treatment; nanotechnology facilitates fast diagnostics and targeted drug delivery, and precision medicine based on sepsis endotyping facilitates individual treatment algorithms. Going ahead, battling sepsis means approaching it as a paradigm shift, considering that sepsis is not a single acute crisis but a heterogeneous syndrome which has specific endotypes and which needs a precision-based intervention and extensive long-term care. The devastating effect of sepsis can only be diminished by means of integrated innovative and patient-centered strategies that would lead to better outcomes of millions of affected people worldwide.

REFERENCES

[1]. Abbott, N. J., & Romero, I. A. (1996). Transporting therapeutics across the blood-brain barrier. *Molecular Medicine Today*, *2*(3), 106–113. https://doi.org/10.1016/1357-4310(96)88720-X

[2]. Alerts, E. (2018). *Sepsis-induced apoptosis of the thymocytes in mice.*

[3]. Álvaro-Meca, A., Jiménez-Sousa, M. A., Micheloud, D., Sánchez-Lopez, A., Heredia-Rodríguez, M., Tamayo, E., & Resino, S. (2018). Epidemiological trends of sepsis in the twenty-first century (2000–2013): an analysis of incidence, mortality, and associated costs in Spain. *Population Health Metrics*, *16*(1), 4. https://doi.org/10.1186/s12963-018-0160-x

[4]. Azkárate, I., Choperena, G., Salas, E., Sebastián, R., Lara, G., Elósegui, I., Barrutia, L., Eguibar, I., & Salaberria, R. (2016). Epidemiology and prognostic factors in severe sepsis/septic shock. Evolution over six years. *Medicina Intensiva (English Edition)*, *40*(1), 18–25. https://doi.org/10.1016/j.medine.2015.01.002

[5]. Balk, A. R. (2000). severe sepsis and septic shock. *Critical Care Clinics*, *16*(2), 1–14.

[6]. Bertoni, G. alain, Saydah, S., & Brancati, fredrick L. (2001). Diabetes and the Risk of Infection related mortality in the u.s. *Diabetes Care*.

[7]. BILLIAU, A., & VANDEKERCKHOVE, F. (1991). Cytokines and their interactions with other inflammatory mediators in the pathogenesis of sepsis and septic shock. *European Journal of*

Clinical Investigation, *21*(6), 559–573. https://doi.org/10.1111/j.1365-2362.1991.tb01410.x

[8]. Calandra, T., Baumgartner, J.-D., Grau, G. E., Wu, M.-M., Lambert, P.-H., Schellekens, J., Verhoef, J., & Glauser, M. P. (1990). Prognostic Values of Tumor Necrosis Factor/Cachectin, Interleukin-l, Interferon- , and Interferon- in the Serum of Patients with Septic Shock. *Journal of Infectious Diseases*, *161*(5), 982–987. https://doi.org/10.1093/infdis/161.5.982

[9]. CDC, C. for D. C. and P. (2018). *Data Reports | Sepsis | CDC*. https://www.cdc.gov/sepsis/datareports/index.html

[10]. Chang, Y.-C., Huang, C.-C., Wang, S.-T., Liu, C.-C., & Tsai, J.-J. (1998). Risk Factors Analysis for Early Fatality in Children With Acute Bacterial Meningitis. *Pediatric Neurology*, *18*(3), 213–217. https://doi.org/10.1016/S0887-8994(97)00184-7

[11]. Collins, A. J., Foley, R. N., Gilbertson, D. T., & Chen, S.-C. (2015). United States Renal Data System public health surveillance of chronic kidney disease and end-stage renal disease. *Kidney International Supplements*, *5*(1), 2–7. https://doi.org/10.1038/kisup.2015.2

[12]. Danai, P. A., Moss, M., Mannino, D. M., & Martin, G. S. (2006). The Epidemiology of Sepsis in Patients With Malignancy. *Chest*, *129*(6), 1432–1440. https://doi.org/10.1378/chest.129.6.1432

[13]. Delawder, J. M., & Hulton, L. (2020). An Interdisciplinary Code Sepsis Team to Improve Sepsis-Bundle Compliance: A Quality Improvement Project. *Journal of Emergency Nursing*, *46*(1), 91–98. https://doi.org/10.1016/j.jen.2019.07.001

[14]. Deng, X., Wang, X., & Andresson, R. (1996). alterations in endothhelial barrier permeability in multiple organ durnig overactivation of macrophages in rata. *Endothelial Barrier Injury*, 1–8.

[15]. Dombrovskiy, V. Y., Martin, A. A., Sunderram, J., & Paz, H. L. (2007). Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003*. *Critical Care Medicine*, *35*(5), 1244–1250. https://doi.org/10.1097/01.CCM.0000261890.41311.E9

[16]. Esper, A. M., Moss, M., Lewis, C. A., Nisbet, R., Mannino, D. M., & Martin, G. S. (2006). The role of infection and comorbidity: Factors that influence disparities in sepsis. *Critical Care Medicine*, *34*(10), 2576–2582. https://doi.org/10.1097/01.CCM.0000239114.50519.0E

[17]. Esteban, A., Frutos-Vivar, F., Ferguson, N. D., Peñuelas, O., Lorente, J. Á., Gordo, F., Honrubia, T., Algora, A., Bustos, A., García, G., Diaz-Regañón, I. R., & de Luna, R. R. (2007). Sepsis incidence and outcome: Contrasting the intensive care unit with the hospital ward*. *Critical Care Medicine*, *35*(5), 1284–1289. https://doi.org/10.1097/01.CCM.0000260960.94300.DE

[18]. Falguera, M., Pifarre, R., Martin, A., Sheikh, A., & Moreno, A. (2005). Etiology and Outcome of Community-Acquired Pneumonia in Patients With Diabetes Mellitus. *Chest*, *128*(5), 3233–3239. https://doi.org/10.1378/chest.128.5.3233

[19]. Fleischmann, C., Scherag, A., Adhikari, N. K. J., Hartog, C. S., Tsaganos, T., Schlattmann, P., Angus, D. C., & Reinhart, K. (2016). Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *American Journal of Respiratory and Critical Care Medicine*, *193*(3), 259–272. https://doi.org/10.1164/rccm.201504-0781OC

[20]. Gornik, I., Gornik, O., & Gašparović, V. (2007). HbA1c is outcome predictor in diabetic patients with sepsis. *Diabetes Research and Clinical Practice*, *77*(1), 120–125. https://doi.org/10.1016/j.diabres.2006.10.017

[21]. Gutierrez-Ramos, J. C., & Bluethmann, H. (1997). Molecules and mechanisms operating in septic shock: lessons from knockout mice. *Immunology Today*, *18*(7), 329–334. https://doi.org/10.1016/S0167-5699(97)01085-2

[22]. Iwashyna, T. J., Cooke, C. R., Wunsch, H., & Kahn, J. M. (2012). Population Burden of Long-Term Survivorship After Severe Sepsis in Older Americans. *Journal of the American Geriatrics Society*, *60*(6), 1070–1077. https://doi.org/10.1111/j.1532-5415.2012.03989.x

[23]. Janzer, R. C., & Raff, M. C. (1987). Astrocytes induce blood–brain barrier properties in endothelial cells. *Nature*, *325*(6101), 253–257. https://doi.org/10.1038/325253a0

[24]. Keane, W. f., Shapiro, F. l., & L.raij. (n.d.). *incidence and type of infections occurance in 445 chronic hemodialisis patients* (pp. 1–6).

[25]. Kessler, M., Hoen, B., Mayeux, D., Hestin, D., & Fontenaille, C. (1993). *bacteremia in patients on chronic hemodialysis*. 1–6.

[26]. Kreger, B. E., Craven, D. E., & McCabe, W. R. (1980). Gram-negative bacteremia. *The American Journal of Medicine*, *68*(3), 344–355. https://doi.org/10.1016/0002-9343(80)90102-3

[27]. LaRosa, J. A., Ahmad, N., Feinberg, M., Shah, M., DiBrienza, R., & Studer, S. (2012). The Use of an Early Alert System to Improve Compliance with Sepsis Bundles and to Assess Impact on Mortality. *Critical Care Research and Practice*, *2012*, 1–8. https://doi.org/10.1155/2012/980369

[28]. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious* . (n.d.).

[29]. Martin, G. S. (2012). Sepsis , severe sepsis and septic shock : changes in incidence , pathogens and outcomes. *Expert Reviews*, *10*(6), 701–706.

[30]. Mayr, F. B. (2010). Infection Rate and Acute Organ Dysfunction Risk as Explanations for Racial Differences in Severe Sepsis. *JAMA*, *303*(24), 2495. https://doi.org/10.1001/jama.2010.851

[31]. METAN, G., ZARAKOLU, P., CAKIR, B., HASCELIK, G., & UZUN, O. (2005). Clinical outcomes and therapeutic options of bloodstream

infections caused by extended-spectrum β-lactamase-producing. *International Journal of Antimicrobial Agents*, *26*(3), 254–257. https://doi.org/10.1016/j.ijantimicag.2005.06.012

[32]. Napolitano, L. M. (2018). Sepsis 2018: Definitions and Guideline Changes. *Surgical Infections*, *19*(2), 117–125. https://doi.org/10.1089/sur.2017.278

[33]. Perry, V. H., Anthony, D. C., Bolton, S. J., & Brown, H. C. (1997). The blood-brain barrier and the inflammatory response. *Molecular Medicine Today*, *3*(8), 335–341. https://doi.org/10.1016/S1357-4310(97)01077-0

[34]. Richards, M. J., Edwards, J. R., Culver, D. H., & Gaynes, R. P. (1999). Nosocomial infections in medical intensive care units in the United States. In *Critical Care Medicine* (Vol. 27, Issue 5, pp. 887–892). https://doi.org/10.1097/00003246-199905000-00020

[35]. Scherag, A., Hartog, C. S., Fleischmann, C., Ouart, D., Hoffmann, F., König, C., Kesselmeier, M., Fiedler, S., Philipp, M., Braune, A., Eichhorn, C., Gampe, C., Romeike, H., & Reinhart, K. (2017). A patient cohort on long-term sequelae of sepsis survivors: study protocol of the Mid-German Sepsis Cohort. *BMJ Open*, *7*(8), e016827. https://doi.org/10.1136/bmjopen-2017-016827

[36]. *Septic Shock_ Current Pathogenetic Concepts, Optimal Management, and Future* . (n.d.).

[37]. Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G. R., Chiche, J.-D., Coopersmith, C. M., Hotchkiss, R. S., Levy, M. M., Marshall, J. C., Martin, G. S., Opal, S. M., Rubenfeld, G. D., van der Poll, T., Vincent, J.-L., & Angus, D. C. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, *315*(8), 801. https://doi.org/10.1001/jama.2016.0287

[38]. Thomas, L. (1972). Germs. *New England Journal of Medicine*, *287*(11), 553–555. https://doi.org/10.1056/NEJM197209142871109

[39]. Torio, C. M., & Moore, B. J. (2016). Statistical brief #204 national inpatient hospital costs: The most expensive conditions by payer, 2013. *Hcup*, *204*, 1–15. https://doi.org/10.1377/hlthaff.2015.1194.3

[40]. van Furth, A. M., Roord, J. J., & van Furth, R. (1996). Roles of proinflammatory and anti-inflammatory cytokines in pathophysiology of bacterial meningitis and effect of adjunctive therapy. *Infection and Immunity*, *64*(12), 4883–4890. https://doi.org/10.1128/IAI.64.12.4883-4890.1996

[41]. Waage, A., Halstensen, A., & Espevik, T. (1987). ASSOCIATION BETWEEN TUMOUR NECROSIS FACTOR IN SERUM AND FATAL OUTCOME IN PATIENTS WITH MENINGOCOCCAL DISEASE. *The Lancet*, *329*(8529), 355–357. https://doi.org/10.1016/S0140-6736(87)91728-4

[42]. Weiss, S. L., Fitzgerald, J. C., Pappachan, J., Wheeler, D., Jaramillo-Bustamante, J. C., Salloo, A., Singhi, S. C., Erickson, S., Roy, J. A., Bush, J. L., Nadkarni, V. M., & Thomas, N. J. (2015). Global Epidemiology of Pediatric Severe Sepsis: The Sepsis Prevalence, Outcomes, and Therapies Study. *American Journal of Respiratory and Critical Care Medicine*, *191*(10), 1147–1157. https://doi.org/10.1164/rccm.201412-2323OC

[43]. Yang, J., Ma, Y., Mao, M., Zhang, P., & Gao, H. (2020). Application of regression model combined with computer technology in the construction of early warning model of sepsis infection in children. *Journal of Infection and Public Health*, *13*(2), 253–259. https://doi.org/10.1016/j.jiph.2019.11.012