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Sepsis Associated Encephalopathy: Pathology, Diagnosis and Therapeutic Interventions

Dharmanka Bandyopadhyay, Deepak Mishra

Abstract: ***Sepsis, a potentially lethal organ dysfunction caused by dysregulated host response to infection, occurs in more than 30 million patients annually worldwide. Sepsis-associated encephalopathy (SAE) is an early and common complication, manifesting as acute delirium and coma, and often resulting in long-term cognitive dysfunction. This review distils current knowledge of the intricate pathophysiology of sepsis-induced brain dysfunction. The aetiology is multifactorial, resulting from a severe systemic inflammatory response that compromises the blood-brain barrier (BBB) and permits peripheral inflammatory mediators to access the central nervous system. This initiates severe neuroinflammation through microglial and astrocytic activation, accompanied by oxidative stress, resulting in severe mitochondrial dysfunction and a state of "cytopathic hypoxia". In addition, sepsis causes severe dysregulation of key neurotransmitter systems, including excitotoxic glutamate accumulation and dysfunctional cholinergic transmission, and disrupts hormonal homeostasis via the hypothalamic-pituitary-adrenal (HPA) axis. Despite these elaborate descriptions, diagnostic strategies for SAE remain primarily based on clinical examination, and therapeutic interventions are limited to treating the underlying sepsis. This decision is underpinned by controversy regarding adjunctive treatments, such as corticosteroids and sedation. This review identifies the imperative requirement for specific diagnostic biomarkers and neuroprotective interventions to reduce the high morbidity and mortality of SAE and post-sepsis cognitive dysfunction.***

Key words: ***Sepsis, Brain, Neuroinflammation, Cognitive Impairment***

I. INTRODUCTION

Sepsis constitutes a critical and potentially fatal syndrome characterized by organ dysfunction, elicited by the host's dysregulated reactions to pathogenic substances. Annually, there exists a global prevalence of over 30 million individuals afflicted by sepsis. Organ dysfunction represents a significant complication associated with sepsis, with sepsis-induced cerebral dysfunction exhibiting a high incidence and an early onset. The aetiology of brain dysfunction predominantly stems from a variety of factors released during the septic process, and empirical clinical evaluations have failed to identify any direct indication of an infection in the central nervous system (CNS) [1]. Cognitive impairments are correlated with sepsis-associated encephalopathy (SAE), delirium, nausea, cerebral ischemia, and bleeding, which are all signs of sepsis-induced brain dysfunction during the acute phase. The most noticeable aspect of sepsis-induced brain damage throughout the extended period is cognitive impairment. Up to 70% of sepsis patients experience SAE, a primary symptom of the disease that is characterized by changes in consciousness ranging from disorientation to delirium or even coma. The prevalence of SAE often increases the length of stay in the intensive care unit (ICU) and increases the death rate for sepsis patients. Even with considerable improvements in medical technology that have dramatically improved sepsis patient survival, up to 21% of patients still experience long-term consequences including cognitive impairment [2-4]. Effective diagnostic techniques and management options for sepsis-induced brain dysfunction are noticeably lacking in light of these difficulties, especially regarding SAE and cognitive impairment. Currently, the only way to diagnose SAE is through daily neurological examinations along with relevant laboratory testing, and mental tests are used to detect cognitive impairments. Therefore, it is crucial to find effective methods for the early detection, management, and possible reversal of SAE and cognitive impairment. [5]. SAE is a dangerous sepsis-related outcome that appears as a range of altered brain function, from mild delirium to coma [6]. A retrospective investigation of a large sample from a multicenter database revealed that 53% (1341/2351) of the sepsis patients had delirium and coma when they were admitted to the ICU [3]. It is well accepted that cognitive damage is more likely in persons with septic shock. The leading causes of dysfunction in numerous organs, including the brain, are believed to include hypoperfusion, hypoxia, microthrombosis, and abnormalities in the internal environment. Early goal-directed therapy and organ replacement therapy were advocated by guidelines like the Surviving Sepsis Campaign to reverse shock and safeguard organs [7]. Considering the intricate relationship between sepsis-induced cerebral dysfunction, ischemic stroke, and sickness behaviour, improving our understanding of neuroinflammatory processes and developing practical methods for early detection, intervention, and therapy are essential. Confronting these challenges could markedly enhance patient outcomes and mitigate the long-term burden associated with these conditions [5].

The term SAE refers to a systemic infection-induced widespread brain dysfunction that does not directly damage the CNS. SAE has a complex aetiology that involves several key pathways. A key component of this process is the disruption of the blood-

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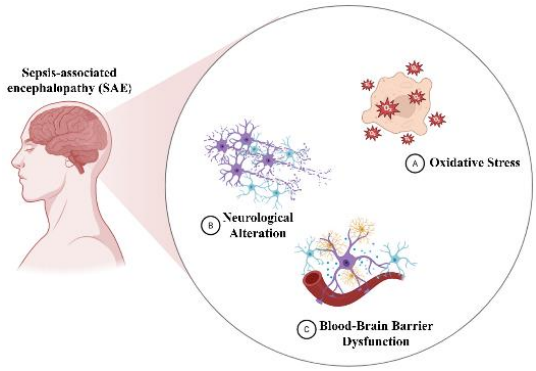
*Correspondence Author(s)
Dharmanka Bandyopadhyay, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Lucknow Campus, Lucknow (U.P.), India. Email ID: dharmankabanerjee@gmail.com
Deepak Mishra*, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Lucknow Campus, Lucknow (U.P.), India. Mail ID: deepak1906mishra@gmail.com, Orcid ID: 0000-0002-3408-9432

brain barrier (BBB), as sepsis-related systemic inflammatory responses stimulate endothelial cells, which increases BBB permeability. This change facilitates the entry of pathogens and peripheral inflammatory mediators into the CNS, resulting in increased neuroinflammation [5]. The activation of microglia and astrocytes facilitates the release of inflammatory cytokines, including IL-1β, TNF-α, and IL-6, which is another fundamental process associated with neuroinflammation. Pro-inflammatory mediators are released as a result of this stimulation, leading to neuronal injury and cognitive impairment [8]. Since oxidative damage is caused by elevated reactive oxygen species (ROS) during sepsis, oxidative stress and mitochondrial dysfunction are also essential factors in this pathogenic process. Cellular damage and apoptosis result from this, which also affects mitochondrial function and neural energy metabolism [9]. An endogenous nitric oxide synthase (NOS) inhibitor, asymmetric dimethylarginine (ADMA), plays a key role in the pathophysiology of sepsis. ADMA has a role in oxidative stress, mitochondrial dysfunction, cytokine release, prothrombotic and proinflammatory disorders, and microvascular dysfunction. Harmful effects such as those generated by L-NAME, a NOS inhibitor related to greater mortality in clinical investigations, have been linked to elevated levels of ADMA in sepsis [10]. Moreover, sepsis exerts detrimental effects on neurotransmission, primarily through the impairment of cholinergic pathways, which may underlie the cognitive dysfunction and altered mental status observed in patients with SAE. The dysregulation of neurotransmitters, marked by variations in dopamine and serotonin levels, is another phenomenon that merits attention in sepsis cases. Such fluctuations may precipitate cognitive deficits, alterations in behaviour, and disruptions in affective states, thereby contributing to the neurological ramifications of sepsis. Additionally, neurological impairment is linked to a disruption of hormonal balance, specifically involving the hypothalamic-pituitary-adrenal (HPA) axis. Sepsis has been shown to induce aberrant levels of cortisol, which may underlie symptoms such as delirium, confusion, and various forms of cognitive dysfunction [11]. Microcirculatory disturbances stemming from endothelial dysfunction and coagulation abnormalities contribute to the formation of microthrombi, leading to reduced brain blood flow. This ischemic condition exacerbates neuronal injury and is implicated in the pathogenesis of brain dysfunction [12].



[Fig.1: Different Neurological Alterations Associated with SAE]

II. PATHOLOGICAL FACTORS OF SEPSIS IN NEUROLOGY

A. Systemic Inflammatory Response

In sepsis, a limited number of inflammatory mediators, such as TNF-α, IL-1, and IL-6, that circulate in the systemic circulation can cross the blood-brain barrier (BBB) and enter the central nervous system. Lipopolysaccharide (LPS), a Gram-negative bacterial component, is potentially able to stimulate glial cells, e.g., microglia and astrocytes, which in turn can compromise the BBB integrity. This compromise of the BBB leads to increased entry of inflammatory cytokines and neurotoxins into the brain parenchyma. Importantly, even without direct infection of the central nervous system, systemic LPS stimulation-induced inflammation leads to neuroinflammation. This is achieved by activating glial cells and recruiting neutrophils to the cerebral compartment, which can lead to neuronal apoptosis and damage. These systemic inflammatory effects may be responsible for the marked cognitive impairment and memory deficits that are the typical presentations of sepsis-associated encephalopathy (SAE) [13]. Changes in mental state, cognition, sleep, agitation, hallucinations, or coma are indicative of sepsis-associated encephalopathy in humans. Glial fibrillary acidic protein (GFAP) and macrophage (CD68/CD45) activation, as well as the increased production of chemokines (CXCL8/10/12, CCL13/22), have been validated by clinical research to create a proinflammatory environment, promote myeloid cell recruitment, and lead to cognitive and functional impairment [14]. Oxidative-nitrosative stress and inflammation caused by sepsis are mutually dependent; ROS/RNS both cause and spread inflammation, while having a shorter half-life than cytokines. Oxidative metabolites can enter the brain parenchyma through disruption of the BBB caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS), which causes localized neuroinflammation and prolongs systemic inflammation [15]. Systemic infection-driven cytokine release further damages the BBB and endothelium, amplifying ROS/RNS generation and lipid peroxidation, worsened by the brain's limited antioxidant capacity. This induces neuroinflammation, inhibits the mitochondrial electron transport chain, and increases the release of free radicals, leading to mitochondrial dysfunction and "cytopathic hypoxia." Combined with predominantly Ca^{2+}-mediated apoptosis, these processes result in brain impairment [16].

B. Blood-Brain Barrier (BBB) Disruption

Brain endothelial cells are essential components of the BBB, and they are distinguished by specific tight junctions (TJs) that form between neighbouring cells, ensuring high electrical resistance and a limited flow of molecules. The junctional complex, which is made up of occludin, claudins, and junctional adhesion molecules (JAM-A, JAM-B, and JAM-C), attaches itself to the actin cytoskeleton by interacting with cytoskeletal scaffolding proteins (ZO-1, ZO-2, ZO-3, CASK, and MAGI-1 to MAGI-3) [17]. Endotoxemia and pro-inflammatory cytokines activate brain endothelial cells during sepsis, increasing permeability and impairing the BBB's ability to function. In vitro investigations demonstrate that plasma derived from septic mice results in the

downregulation of occludin and an increase in endothelial permeability. The integrity of the BBB is further jeopardized by exposure to LPS, which lowers the levels of TJ proteins occludin and ZO-1 [18]. Other effects of LPS-induced endothelial activation include the activation of the pro-inflammatory signalling cascade of nuclear factor kappa beta (NFκB) in cerebral microvascular endothelial cells [19]. This signalling cascade increases the transcription of the inflammatory mediator cyclooxygenase-2, which in turn increases the permeability of the BBB by producing prostaglandin E2, as demonstrated in mouse models of brain endothelial cells [20]. Additionally, leukocyte recruitment and infiltration, increased activation of the coagulation cascade, and microthrombi production are all consequences of brain endothelium activation. When endothelial damage occurs, Factor X cleaves prothrombin, activating thrombin, the primary modulator of the coagulation pathway. The formation of micro-occlusions occurs as thrombin activates platelets and converts soluble fibrinogen into fibrin. The persistent generation of microthrombi exacerbates BBB permeability and intensifies localized ischemia by obstructing the vascular pathways distal to the original sites of occlusion [18]. The BBB's integrity is compromised in patients with SAE, as evidenced by the frequent vasogenic oedema and white matter hyperintensities seen on MRI. Although the precise underlying mechanisms remain enigmatic, the disruption of TJ proteins is recognized as a significant contributing element. Occludin, a predominant TJ protein, encompasses a putative cleavage site for matrix metalloproteinases (MMPs). MMP-2 and MMP-9 were found in cerebral microvessels after cecal ligation and puncture (CLP) in mouse models, and the activation of MMP-2 and MMP-9 was temporally correlated with an increase in BBB permeability. In human subjects, the diminished expression of TJ proteins in cerebral tissue derived from sepsis-related mortalities further substantiates the notion of BBB impairment [12].

C. Neuroinflammation

Both peripheral and localized inflammatory responses stimulate the activation of immune cells found in the CNS, such as astrocytes and microglia, which exacerbates neuroinflammation and increases the severity of septic consequences. Microglia hyperactivation exacerbates neurological impairment by compromising the BBB integrity and increasing the release of ROS. In contrast, in the context of sepsis, microglial activity inhibition improves long-term cognitive performance while reducing inflammation and oxidative damage. Additionally, astrocytes play a crucial role in mediating brain injury associated with inflammation by modulating interactions between the brain and the immune system [21].

D. Mitochondrial Dysfunction

The modified mitochondrial metabolic processes are linked to various inflammatory mediators. TNF-α is a crucial cytokine that can induce mitochondrial dysfunction and is essential for the host's response to septic conditions [22]. Upon its interaction with several TNF receptors, TNF-α facilitates the intracellular liberation of ceramides and the production of ROS, both of which may lead to mitochondrial impairment. In polymorphonuclear leukocytes and monocytes, the activation of TNF receptors incites pro-inflammatory reactions that culminate in ROS generation, mitochondrial DNA (mtDNA) damage, and the suppression of mitochondrial metabolic processes [23]. Electrons undergo deflection when the mitochondrial complexes are subjected to inhibition, which concomitantly enhances the production of ROS. The involvement of manganese superoxide dismutase and glutathione reductase in these biochemical pathways may precipitate a disruption in the equilibrium between ROS generation and the antioxidant capacity inherent to mitochondria. Such a disruption has the potential to induce mitochondrial uncoupling, which is associated with the opening of the transition pores for mitochondrial permeability (PTP) [24]. Initially, the phenomenon of hypoxia was posited as the principal aetiology of mitochondrial dysfunction [25]. However, subsequent investigations have demonstrated that patients suffering from sepsis exhibit either normal or elevated tissue oxygen levels [26]. The underlying concern is not a lack of oxygen, but a decrease in its use [27]. The impairment of oxidative phosphorylation (OXPHOS) leads to a decrease in adenosine triphosphate (ATP) synthesis, consequently resulting in elevated lactate levels and increased glycolytic activity [28]. The resultant ROS and antioxidant imbalance inflict damage on the electron transport chain and mtDNA, thereby initiating a deleterious cycle characterised by ROS production and mitochondrial injury. The augmented permeability of membranes due to ROS and calcium overload culminates in the leakage of mtDNA, thereby acting as a distress signal that exacerbates multiorgan failure and instigates apoptosis, both of which are pivotal factors contributing to tissue injury [29].

E. Neurotransmitter Dysregulation

Neurotransmitters, or chemical messengers, facilitate signal communication between postsynaptic and presynaptic neurons; their disruption appears to contribute significantly to the pathophysiology of SAE. Glutamate, identified as the primary excitatory neurotransmitter of the CNS, tends to accumulate during sepsis, thereby triggering excitotoxic effects on neuronal cells. Experimental models of sepsis in animals have demonstrated the dysregulation of glutamate homeostasis, and interventions for blocking glutamate release have been found to mitigate cognitive dysfunction and improve survival rates [30]. The excitotoxicity caused by elevated levels of glutamate is primarily mediated by the overactivation of the N-methyl-D-aspartate (NMDA) receptor, NR2 subunit. In SAE animal models, the inhibition of NR2-mediated excitotoxicity through ferroptosis blockade has been demonstrated to preserve synaptic and neuronal integrity [31]. Glutamate is crucial in microglial activation, as it regulates the release of cytokines that promote inflammation triggered by LPS stimulation. Pharmacological blockade of NMDA receptors has been shown in empirical studies to diminish neuroinflammatory responses triggered by LPS in microglial populations [32]. Moreover, a pharmacological evaluation revealed that administering glutamate release inhibitors to rats undergoing CLP considerably reduced neurological impairments and increased survival rates [33]. In addition to glutamate, SAE patients and pertinent animal models have been shown to exhibit malfunctioning of several neurotransmitters, including gamma-

aminobutyric acid (GABA), acetylcholine, dopamine, and norepinephrine. One investigation reported a decrease in serum amino acid concentrations requisite for neurotransmitter biosynthesis in SAE patients, which may elucidate the observed dysfunction within neurotransmitter systems [30, 33]. The manifestations SAE and delirium may result from a disruption in cholinergic neurotransmission, particularly involving acetylcholine (Ach). Given that the vagus nerve can transmit inflammatory signals to the CNS, acetylcholine is released from its ends during sepsis to modulate the inflammatory response. Studies conducted on SAE-related murine models have revealed a reduction in hippocampal acetylcholine receptor expression and a weakened vagus nerve cholinergic anti-inflammatory system, which results in an uncontrollable inflammatory response and neurological dysfunction [34]. It has been demonstrated that cholinergic depletion significantly contributes to the cognitive impairment induced by LPS; experimental rat models subjected to LPS administration exhibited behavioural irregularities and deficits in long-term memory, which can be attributed to cholinergic dysfunction within the hippocampus, prefrontal cortex, and cerebral cortex. Notably, pharmacological interventions utilising acetylcholinesterase inhibitors have been shown to improve this cognitive impairment, thereby reinforcing the hypothesis that failures in cholinergic signalling are detrimental in the context of sepsis [35].

F. Metabolic Disturbances

A study conducted in a Japanese hospital discerned that hyperglycaemia within patients diagnosed with sepsis exhibited a prevalence approximately fivefold greater than that of hypoglycaemia. Glycaemic management, primarily aimed at addressing hyperglycaemia, frequently necessitates the implementation of insulin therapy. Glucose Algorithm Regulation's Normoglycemia in Intensive Care Evaluation and Survival study highlighted the importance of hypoglycaemia, revealing that among patients who were not receiving insulin treatment, mortality rates were 36% for instances of moderate hypoglycaemia (41–70 mg/dL) and escalated to 59% for severe hypoglycaemia (≤40 mg/dL). Fatal cases of hypoglycaemia were observed even in the absence of insulin administration. Notably, in patients experiencing distributive shock, the risk of mortality was exacerbated in cases of hypoglycaemia. Given that sepsis is a substantial contributor to the development of distributive shock, the present study conducted a retrospective investigation into the correlation between hypoglycaemia and mortality in individuals suffering from sepsis [36]. The manifestation of stress-induced hyperglycaemia may be correlated with the synthesis of nitric oxide by inflammatory cells, which has the potential to inflict damage upon islet β-cells and diminish insulin secretion during the initial phases, ultimately resulting in the apoptosis of islet β-cells in subsequent stages. In patients experiencing critical illness, hyperglycaemia is linked to significant deleterious consequences, encompassing heightened vulnerability to infectious complications, oxidative stress, and an elevation in mortality rates [37].

G. Endocrine Dysregulation

research involving human subjects experiencing sepsis or hyperinflammatory critical illness, and receiving treatment within intensive care units, has not demonstrated any elevation in plasma concentrations of Adrenocorticotropic hormone (ACTH) from the point of ICU admission onwards [38, 39]. In particular, an increase in plasma ACTH, as determined by modern assays with high specificity for ACTH, has only been noted temporarily, for example, during surgery; after that, and at least during the first week in the intensive care unit, plasma ACTH levels are consistently below the normal range, while plasma cortisol levels are elevated [40]. Research on critically ill patients that have used sophisticated tracer techniques or deconvolution analysis of hormone time series has reported cortisol production rates that are only slightly increased during the day and ACTH-induced pulsatile cortisol secretion rates that are decreased at night [39, 41]. Therefore, ICU patients do not exhibit this activation, save for a brief but fast stimulation of the central HPA axis; yet, there is an apparent increase in the systemic availability of cortisol. Elevated plasma corticosterone levels without increased ACTH were also seen in a clinically relevant, fluid-resuscitated, intensive care-supported mouse model of sepsis-induced critical illness [42, 43].

III. THERAPEUTICS

Septic shock has been linked in post-mortem examinations to a significant frequency of haemorrhagic events and ischemic neuronal damage, especially in areas susceptible to hypotensive and hypoxic circumstances. [44]. A reduction in cerebral blood flow (CBF) has been evidenced in cases of septic shock [45]. Recently, the adverse consequences of microglial activation on the progression of neurological diseases have garnered the attention of scholars, who are investigating pharmacological or genetic strategies to mitigate these deleterious effects. Microglial roles in both normal and diseased CNS states have been more easily studied thanks to the development of pharmacological agents that penetrate the CNS and block the activity of the colony-stimulating factor 1 receptor (CSF-1R), which is necessary for microglial survival [46].

A. Clinical Management

There are presently no particular, evidence-based therapy options for SAE in patients, despite continual improvements in the field. Because SAE arises as a result of sepsis without a direct CNS infection, the goal of treatment is still to cure sepsis and decrease SIRS to prevent SAE from happening. According to data from 1979 to 2000, 90% of sepsis cases in the US are caused by bacterial infections, with Gram-positive bacteria accounting for 52% of cases and Gram-negative bacteria for 38%. Polymicrobial and fungal infections, on the other hand, are responsible for 4.7% and 4.6% of all cases, respectively [47]. Furthermore, the virus has the intrinsic propensity to induce sepsis. Roughly 5% of patients with COVID-19 suffered catastrophic symptoms, which include multiple organ dysfunction, septic shock, and respiratory failure [48]. Antimicrobial drugs that have both broad-spectrum and specific-spectrum are consequently necessary. In addition to therapeutic options, such as glycemia control, fluid resuscitation, vasoactive drug administration, and nutritional support, are additionally suggested for sepsis and septic shocks [49]. The ongoing debate over the use of corticosteroids in sepsis patients must be emphasised [50]. The European Society of Intensive Care Medicine

and the Society of Critical Care Medicine have issued suggestions that suggest the use of prednisolone for adult sepsis patients who have septic shock with a lifelong need to receive vasopressor therapies [8]. This well-designed trial, which had a multicenter, randomized, double-blind, positive drug-parallel control design, included 34 critical care units from German community and university hospitals. A total of 190 cases were collected for every group. The risk of septic shock within 14 days does not diminish when hydrocortisone is used for severe sepsis [51]. These findings are significant because they show that delirium is less common in people taking low-dose hydrocortisone. In general, corticosteroid overdose has long been recognized to alter hippocampal structure and function, aggravating cognitive impairment. Corticosteroid usage usually requires more research, especially when it comes to treating SAE. The use of sedative medications further complicates the diagnosis and management of SAE. Since it often complicates the diagnosis and treatment of SAE, sedation management is also taken into account. Clinical practice guidelines advocate for a protocol-directed approach to prevent this. With short-half-life medications like propofol or dexmedetomidine, mild sedation is preferred. The RASS, an evidence-based instrument, is used to track the level of sedation. Also, guidelines recommend stopping continuous sedatives every day to allow for reawakening and regular assessment of delirium using an evidence-based tool such as the CAM-ICU [49]. About sedation, dexmedetomidine is a standard α2 adrenoceptor agonist. Other clinical studies have verified its neuroprotective properties and positive impact on neurocognitive function in critically ill patients (not only those with SAE), with a decreased risk and shorter duration of delirium and mechanical ventilation [52, 53]. Recent research suggests that the systemic infusion of dexmedetomidine may lower sepsis-associated inflammation and SAE by activating α2A adrenoceptors in astrocytes in a CLP-induced animal model [54]. Propofol, another sedative that is commonly used in clinical settings, is often used in clinical trials to compare with dexmedetomidine because of its short half-life and quick induction of anesthesia. In mechanically ventilated adults with sepsis, a multicenter, double-blind, randomised controlled clinical study with a strict quality control design that included 422 patients found no significant difference between dexmedetomidine and propofol in terms of days alive without delirium or coma, ventilator-free days, death at 90 days, and cognitive status score at 6 months [55]. Dexmedetomidine also increases the incidence of bradycardia, according to a newly published meta-analysis of randomized controlled trials on intensive care unit patients on mechanical breathing [56, 57]. Germany is the source of the more recent figures [58]. Notably, eighteen percent of survivors had recently received a diagnosis of cognitive impairment, and that percentage rose to 28.5% for survivors who were over 80. Functional results, which revealed that 31.5% of survivors without a history of reliance required additional nursing care services, also aroused similar concerns. A three-year total healthcare expenditure of €29,088 (about USD 32,000) for each patient highlights the significant socioeconomic burden. These findings highlight both the ongoing multi-domain effects of sepsis, particularly cognitive impairment (which can be detected with SAE) in older populations, and the need for integrated post-discharge rehabilitation strategies aimed at functional recovery and long-term health management. A cohort study with 15,535 post-sepsis patients found that the 10-year mortality risk is significantly reduced if rehabilitation (including facilitating muscle strengthening and movement, activities of daily living, cardiovascular capacity, functional ability, and occupational and communication therapy) is completed within 90 days after discharge [59]. The guidelines support rehabilitation programs for sepsis survivors, but they do not promote them [8]. It also proposes more research to discover the optimal course of action for patient selection and functional rehabilitation (including timing, dosage, intensity, and duration).

Table 1: Advantages and limitations of Scoring Systems and Models in Identifying Delirium for Sepsis Patients [60]

Tool/Model	Key Indicators/Criteria	Strengths	Drawbacks
CAM-ICU	Evaluates consciousness, attention, thinking, and alertness using a 4-item tool.	Easy to administer, suitable for non-verbal patients, and high specificity.	Requires trained personnel; less effective in detecting hypoactive delirium.
ICDSC	Includes eight indicators: altered consciousness, disorientation, inattention, hallucinations/delusions, psychomotor changes, mood/speech issues, sleep disturbances, and symptom fluctuation. A score of 4 or more suggests delirium.	Very high sensitivity (99%); practical in busy ICU settings; can assess non-verbal patients.	Lower specificity (64%); prone to false positives in patients with psychiatric/neurological disorders.
PRE-DELIRIC	Age, APACHE-II score, kind of admission (medical, surgical, trauma, or neurological), coma status, infection, acidosis, morphine dosage, sedative usage, urea level, and urgent admission are among the ten clinical parameters involved.	Strong predictive accuracy (AUROC = 0.85); validated in multiple international cohorts; allows dynamic risk assessment.	Requires complete patient data; model does not update with changes during ICU stay; variations in external validation.
E-PRE-DELIRIC	Simplified version using five criteria: age, APACHE-II score, admission category, infection status, and urea level.	Quick to apply; requires fewer data inputs.	Tends to underestimate risk (β = 0.58); lower predictive value (~43.7% PPV); not well-suited for surgical cohorts.

IV. CONCLUSION

Sepsis-associated brain dysfunction, manifested as acute sepsis-associated encephalopathy (SAE) and possibly evolving to chronic cognitive impairment, is one of the most significant challenges of contemporary medicine. This review has elucidated the complex and interlinked pathophysiological pathways underlying this syndrome. The pathogenesis begins with a systemic inflammatory response that impairs the integrity of the blood-brain barrier, leading to a noxious cycle of neuroinflammation driven by activated glial cells, severe oxidative stress, and mitochondrial dysfunction. This cellular chaos ultimately deranges neuronal function via neurotransmitter imbalance and metabolic derangements, culminating in clinical features such as delirium, cognitive impairment, and heightened risk of mortality. In the context of an emerging understanding of these foundational pathways, however, a significant gap still exists between molecular understanding and clinical application. To date, there is no targeted therapy for SAE; instead, management focuses on treating the site of infection and providing organ support, with adjunctive therapies such as corticosteroids and certain sedatives remaining topics of ongoing controversy, with no firm evidence to support their use in enhancing long-term neurological outcomes. The absence of effective biomarkers for early detection and prognostic evaluation further compounds the lack of targeted therapies. Thus, future studies should focus on discovering novel biomarkers to facilitate the early identification of SAE and the implementation of targeted neuroprotective approaches. Such interventions should target stabilization of the blood-brain barrier, modulation of the neuroinflammatory process, and preservation of mitochondrial function. Furthermore, given the considerable burden post-sepsis functional and cognitive disability imposes on survivors as well as healthcare systems, more importance should be attached to the implementation of whole-hospital post-discharge rehabilitation programs, shown to reduce long-term mortality significantly. Both the acute neurologic injury and chronic sepsis sequela need to be addressed to enhance patient outcomes and to neutralize the extreme burden of this disabling syndrome.

DECLARATION STATEMENT

After aggregating input from all authors, I must verify the accuracy of the following information as the article's author.

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