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Understanding Post-Sepsis Psychiatric Disorder: A Conceptual Approach Based on the Current Research Literature

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ABSTRACT

Sepsis is a serious worldwide health concern, and more survivors are experiencing "post-sepsis syndrome" following their hospitalization. A common consequence that raises long-term mortality is post-sepsis psychiatric disorders, which include delirium, sadness, anxiety, and post-traumatic stress disorder. Clinicians, however, frequently fail to recognize the mental damage linked to sepsis. Neuroinflammation, oxidative stress, neurotransmitter dysfunction, host cell death, poor neuroplasticity, blood-brain barrier dysfunction, and hyperactivation of the hypothalamic-pituitary-adrenal axis are all part of the complicated pathophysiology of post-sepsis psychiatric disease. Although screening scales are frequently employed, no universal diagnostic standards exist for this condition. This condition may be prevented with targeted therapy for modifiable risk factors. Comprehensive nursing care and other non-pharmacological methods may offer a viable treatment option for Psychiatric disorders post-sepsis, while specific medicines are still in short supply.

Keywords: Post-sepsis, Pathophysiology, Neuroinflammation, Blood-brain barrier, Host cell death, Prevention, Treatment

1. INTRODUCTION

A disordered host reaction to infection, sepsis, represents an international health issue. Around eleven million people, or 19.7% of the entire global population, died as a consequence of the 48.9 million cases that occurred worldwide in 2017. Sepsis is a leading cause of death worldwide, according to the WHO, underscoring the urgent need for international health initiatives [1, 2]. Due to improved treatments and a better understanding of the disorder's pathophysiology, the in-hospital mortality rate from sepsis has been gradually decreasing over time [3]. Adequate post-sepsis care is necessary, as evidenced by the growing number of sepsis survivors. After leaving the hospital, around 75% of sepsis survivors receive at least one new diagnosis in medicine, psychology, or cognition [4]. During the two years following hospital release, only half of sepsis survivors in both ICU and non-ICU settings recover totally or almost completely [5]. Sepsis has long-lasting effects that can lead to significant morbidity and mortality, even though it is frequently overlooked [6]. By aggressively researching the pathophysiology and putting prevention measures in place, it is possible to successfully lower the incidence of post-sepsis disorders and improve the health and quality of life of sepsis survivors.

Post-traumatic stress disorder (PTSD), depression, and anxiety are the most common psychiatric disorders among sepsis survivors, and they can all significantly

impact their everyday lives and capacity to resume employment after recovery [5, 7]. Delirium is a neuropsychiatric condition that may appear after sepsis. Complex symptoms include emotional dysregulation, circadian dysrhythmia, cognitive impairments, attention difficulties, and changes in psychomotor function [8]. Numerous investigations of neurocognitive dysfunction and functional disability after sepsis have been conducted in the past ten years [9]. Comparatively, not much research has focused on the potential psychological damage due to sepsis. However, there are not many studies that concentrate on the psychiatric problems that can arise from sepsis. To better understand the causes, prevention, and treatment of psychiatric illnesses after sepsis, the current study aimed to conduct a comprehensive review of the literature.

2. PATHOPHYSIOLOGY OF POST-SEPSIS SYNDROME

One in six individuals, however, suffers from long-lasting problems. In addition to having a worse life expectancy and quality of life, sepsis survivors are more likely to experience chronic disease, recurrent infections, and rehospitalisation [10-15]. Raising awareness of the so-called "post-sepsis syndrome" (PSS), a collection of chronic physical, medical, cognitive, and psychological problems that occur post-sepsis recovery and are linked to a decrease in life expectancy and health, is therefore necessary. Patients with post-sepsis syndrome are more likely to experience cognitive impairment, mental health issues, renal failure, cardiovascular events, and readmission risk for infections than hospitalized patients without the condition [16]. Finding potential treatments by looking at the pathophysiology of post-sepsis disorder.

2.1. Possibility of rehospitalization post-sepsis

Many sepsis survivors are affected by recurrent sepsis, which accounts for up to thirty percent of hospital readmissions within 90 days. Acute renal failure, pneumonia, and heart failure are also common causes for these readmissions. Sepsis survivors experience acute renal failure and sepsis more frequently than individuals with similar comorbidities and ages [10, 12]. Survivors are more likely to develop recurring sepsis than randomly selected individuals, which can lead to anxiety even years after discharge. The recurrent sepsis causes the death of almost one-third of sepsis survivors. For these individuals, rehospitalization, mortality from non-septic causes, and sepsis recurrence are significant concerns [17]. The overlapping nature of sepsis and the associated risk factors, such as age, frailty, cardiovascular and renal illnesses, and cognitive impairment, complicates the prevention of sepsis recurrence [18]. Survivors are also more vulnerable to recurrence due to immunological dysregulation, mitochondrial dysfunction, and chronic inflammation caused by sepsis [19-20]. Active surveillance, immunisation, prophylactic antibiotics, reducing the use of intrusive devices, and staying away from immune-suppressive drugs are measures to prevent recurrence. However, these approaches may not be practical in all situations and could lead to adverse outcomes, such as antibiotic resistance.

2.2. Long-term immunosuppression

Originally considered a hyper-inflammatory syndrome, sepsis has been reframed to include an immunosuppressive phase that happens simultaneously with the hyperinflammatory phase [21]. Innate immune cell reprogramming and lymphocyte death are characteristics of this phase [22]. Long after the patient is discharged from the hospital, the immunosuppression that is visible in the initial stages of sepsis continues. A major factor in post-sepsis disorders is prolonged immunosuppression, which is the cause of the high incidence of fatal infections and sepsis recurrence. One in five survivors of the ICU sepsis had positive blood cultures up to 150 days after the infection, indicating a prolonged inability to

eliminate the bacteria. Patients with COVID-19 also have this immunosuppressive phenotype, and many of them go on to develop sepsis. Sepsis survivors have lower secretion of anti-inflammatory IL-10 and pro-inflammatory IL-6 and TNFα, suggesting a persistent incapacity of immune cells to produce a successful immunological response [23, 24].

2.3. Mechanisms behind post-sepsis-induced immunological dysregulation

Sepsis, an organ malfunction illness that can be fatal, is caused by dysregulated host reactions to infection. It not only presents a significant risk to human health but also places a considerable financial strain on the healthcare system. Today, the cornerstones of treating sepsis remain fluid resuscitation, source control, and timely antibiotic administration. Most clinical trials of potential treatments have not been able to reduce mortality, and no medications have been approved to treat sepsis to date. The complex immune response triggered by pathogens may lead to the dysregulation of both the adaptive and innate immune systems. If left unchecked, this can result in immunosuppression, excessive inflammation, and an inability to restore immune homeostasis. The importance of tailored treatment is highlighted by the compromised immune response in sepsis patients and the potential for immunotherapy to modify the immune response, which may lead to excessive inflammation or enhanced immunity.

2.3.1. Epigenetic modifications

One explanation for the protracted immunosuppressive phase is innate and adaptive immune cells are being reprogrammed by epigenetic processes. The expression of immune-related genes encoding TNFα, IL-1ß, IL-12, and chemokine ligand 2 (CXCL-2/MIP2-α) in macrophages and dendritic cells is suppressed in human patients and murine models resulting from sepsis due to altered DNA methylation and histone modifications [25-27] and interferon-gamma (IFNγ) in CD4+ T-cells [28]. The bone marrow progenitors of rats show repressive epigenetic alteration in inflammatory gene promoters for four weeks after sepsis, producing macrophages that are similar to the impaired macrophages seen in sepsis survivors [29]. This provides a reasonable explanation for the apparent survival of innate immune cells that have been "reprogrammed" after the initial septic event. One of the fundamental processes of epigenetic control, histone post-translational modifications (HPTMs), is attracting more and more attention because of their potential as targeted therapeutic agents and their strong correlation with the development and progression of disorders. Novel HPTMs that have a comparable impact on gene expression, metabolism, and chromatin structure have been discovered due to developments in high-throughput molecular tools and the wealth of bioinformatics data (see Figure 1). Novel histone modifications have also been shown in an increasing number of studies to be important in the onset and progression of many diseases, such as diseases of the psychiatric disorders, reproductive system, heart disease, nervous system, infectious diseases, and several forms of cancer [30].

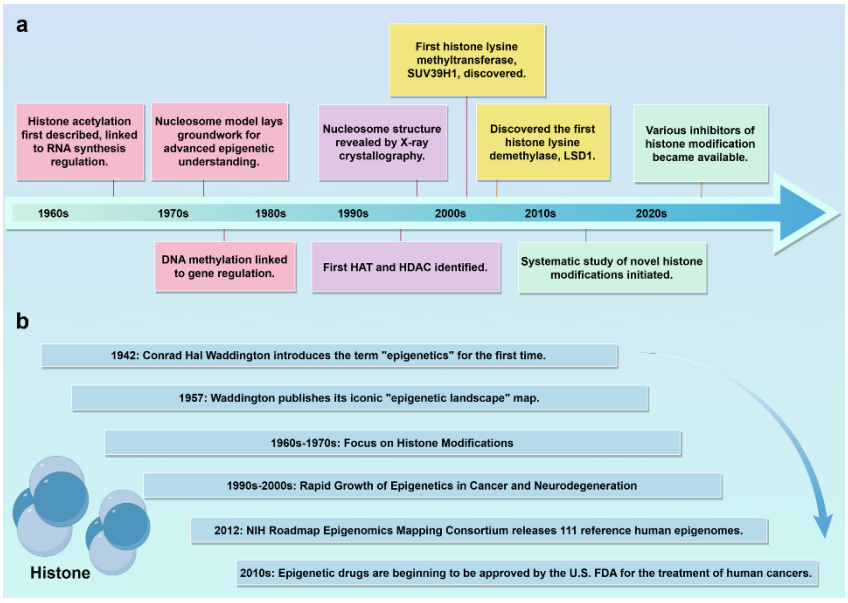

Figure 1. A brief historical synopsis of the evolution of HPTMs and epigenetics. a) Significant results in the 1960s and 2020s about histone changes and chromatin biology. b) A timeline of significant epigenetic events, encompassing theoretical advancements and real-world medical applications [30].

2.3.2. Effects over time on the count of immune cells

Adaptive immunity suffers from sepsis over time. Due to apoptosis, acute sepsis causes a drop in CD4+ and CD8+ T-cell counts [31,32], followed by a return to levels seen in healthy people six months following discharge [23]. Even so, the immune responses of CD4+ T-cells to ex-vivo stimulation by Aspergillus antigen are compromised [34], memory CD8+ T-cells have reduced antigen sensitivity (as shown in post-sepsis mice) [35], and stimulation of whole-blood from sepsis survivors with T-cell activator (α-CD3/28) results in a lower secretion of IFNɣ in comparison to healthy controls [23]. Myeloid-derived suppressor cells (MDSCs), immature neutrophils, and granulocytes that can suppress T-cells may cause these long-term functional deficiencies. During sepsis, circulating MDSCs increase, lasting at least four weeks beyond discharge [36]. Additionally, sepsis is associated with a rise in regulatory T-cells that persists for at least anywhere from five to ten months following the incident. The proliferation of regulatory T-cells may contribute to immunosuppression over time since they are crucial in reducing immunological responses [37].

2.3.3. Therapeutic approaches

Immune cell epigenetic reprogramming and modifications to lymphocyte quantity and function seem to cause long-term immunosuppression, making sepsis survivors more vulnerable to infection. Although these treatments have not been evaluated in clinical settings, epigenetic markers can be altered in vitro to rewire immune cells (for example, by using histone deacetylase inhibitors) [38]. Current human trials are testing treatments including checkpoint inhibitors and IL-7, which may be able to cure chronic T-cell dysfunction in sepsis patients [31, 39]. The best ways to stop recurring sepsis episodes, however, are to actively monitor sepsis survivors and implement infectious disease control measures until such treatments are available. DNA methylation, histone changes, and non-coding RNAs are examples of epigenetic mechanisms becoming increasingly evident in their ability to regulate immunological and inflammatory processes. According to recent data, endothelial dysfunction and immunosuppression are two specific epigenetic processes greatly disrupted as sepsis advances. Although epigenome therapy is still in its infancy, there is strong

evidence from animal models that this strategy may be beneficial (see Figure 2)[40].

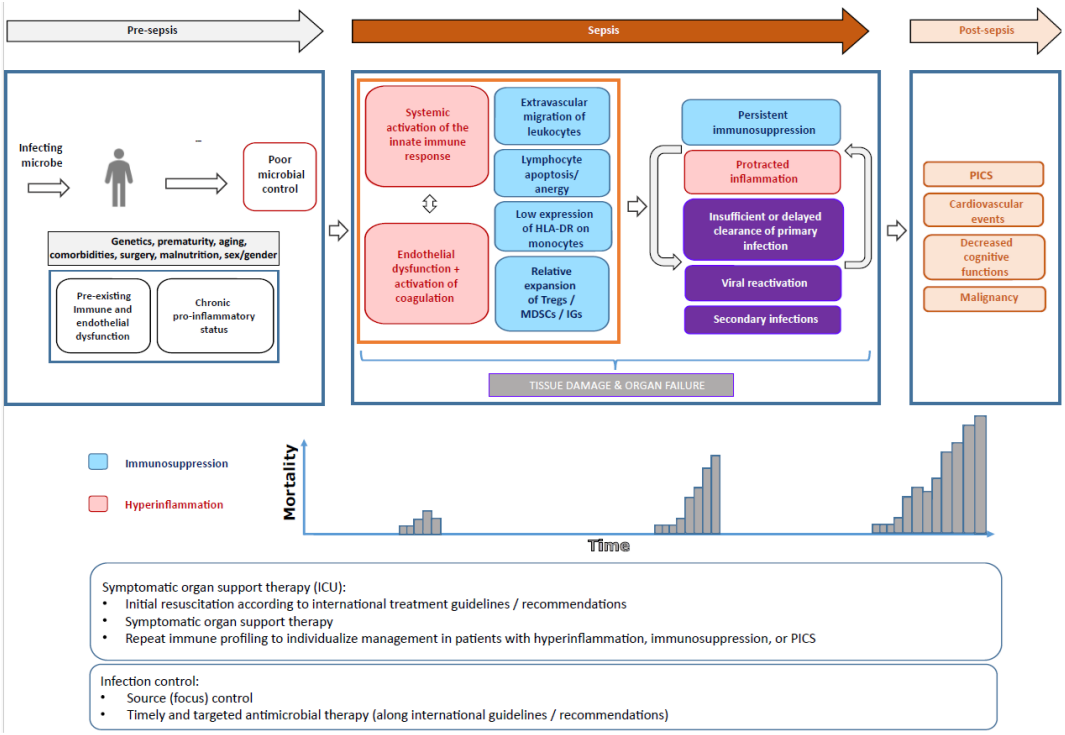

Figure 2. Patients with sepsis frequently have immunological dysregulation due to comorbidities and aging, which hinders their capacity to react appropriately. This results in endothelial dysfunction, increased innate immune response activation, and inadequate microbial control. An immunosuppressive phenotype follows this hyperinflammatory characteristic, leading to organ damage and malfunction. Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS), which can result in cardiovascular, neurological, and cancer issues, is one of the long-term clinical outcomes that sepsis survivors frequently experience [40].

2.4. Blood-brain barrier dysfunction

The blood-brain barrier (BBB) controls the flow of immune cells and nutrients into the brain while keeping harmful things out. The central nervous system's homeostasis is preserved by this vital function [41]. The BBB is composed of specialised endothelial cells, glycocalyx, and a basement membrane that contains astrocyte end foot and pericytes [42]. Tight junctions allow cerebrovascular endothelial cells, which are essential parts of the BBB, to control the permeability of the barrier [41]. Research suggests that psychiatric disorders after sepsis may be linked to disruptions in the BBB. Anxiety and depression symptoms are observed one day after cecal ligation and puncture (CLP) surgery in mice, according to one study. These symptoms resemble human sepsis and are accompanied by a noticeable accumulation of endothelial cell nuclear chromatin at the nuclear membrane's border. Furthermore, a notable rise in the BBB's permeability to Evans blue was noted in the mouse brain, which is suggestive of BBB disruption [43]. The precise reason for this impact is unclear, however it might have to do with astrocyte activation. According to studies, astrocytes are activated during sepsis and release inflammatory mediators including IL-6 and interleukin-1 beta (IL-1β), which damage the blood-brain barrier in the early post-CLP period and worsen mental impairment [44,45].

Acute and chronic brain dysfunction, including sepsis-associated encephalopathy (SAE) and cognitive decline, may arise from sepsis. Changes in consciousness without a definite sign of a central nervous system infection are referred to as SAE. It is quite

prevalent and can significantly affect individuals with sepsis. Neurocognitive decline increases the healthcare burden and has a substantial adverse effect on the quality of life for patients recovering from sepsis. The main pathological mechanisms behind sepsis-induced brain dysfunction involve the interaction of systemic inflammation, BBB dysfunction, neuroinflammation, impaired microcirculation, and brain dysfunction. Currently, altered levels of consciousness and neurological assessments are utilized to identify sepsis-induced brain damage, with the primary therapeutic approach being the management of sepsis itself. Despite the exploration of potential treatments for this condition in animal studies, clinical management of sepsis-induced brain dysfunction continues to be challenging. Therefore, understanding the mechanisms of brain injury resulting from sepsis, which mainly focuses on how systemic inflammation affects the BBB, neuroinflammation, brain microcirculation, and brain functionality, seeks to pave the way for future basic and clinical research aimed at preventing or alleviating brain dysfunction [46].

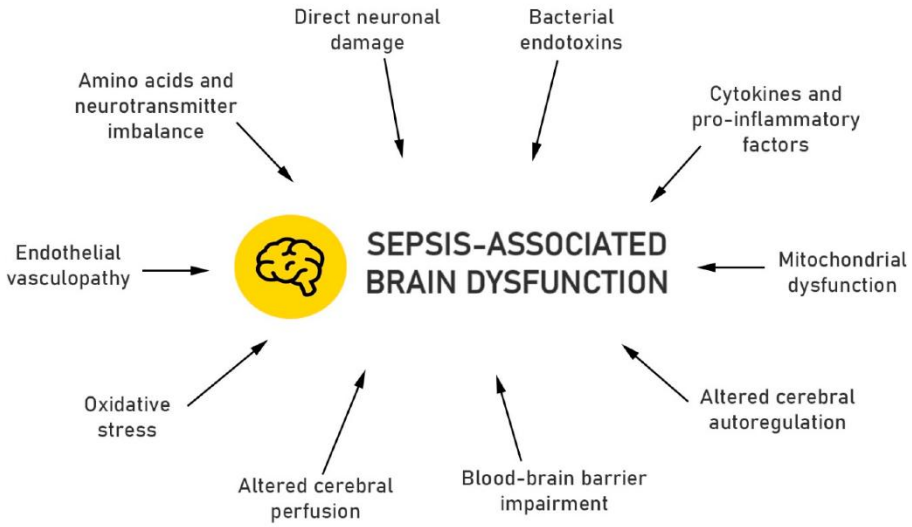

Figure 3. Hypothesized pathophysiologic alterations in brain dysfunction linked to sepsis [47].

Among patients who are very sick, sepsis-associated brain dysfunction (SABD) is an encephalopathy that may be very common. The most common organ deficiency linked to sepsis, SABD, can occur in as many as 70% of septic patients. It can have several severe long-term psychological effects in addition to a wide range of acute neurological symptoms. Through a variety of pathways, SABD may result in different pathological alterations in the brain (see Figure 3). The fundamental screening tool for SABD is a clinical neurological examination, albeit it can be difficult in people using sedatives and opioids. Electroencephalography (EEG) screening may be helpful because 20% of septic patients may have seizures and periodic discharges. For non-invasive evaluation of the structure and function of the brain in SABD patients, several imaging modalities have been proposed; however, their applicability is quite restricted. Although several experimental medicines have been proposed, no specific treatment is currently available. Physicians should concentrate on sepsis prevention and management [47].

Due to a lack of understanding of its pathophysiology, bacterial meningitis continues to be the most dangerous infection of the central nervous system (CNS). The BBB controls how the body and central nervous system communicate. Bacterial meningitis is characterised by enhanced BBB permeability (see Figure 4). Inflammatory pathways, host-specific proteins, and bacterial virulence factors are some of the elements that disrupt the BBB. When treating

bacterial meningitis, focusing on pathogenic causes is a useful therapeutic adjunct to antimicrobial therapy. Gaining insight into how bacteria that cause meningitis impact BBB permeability will open up new paths for research into the illness's etiology, prevention, and treatment [48]. Bacterial meningitis, an important factor in infection-related mortality globally, is most commonly caused by Escherichia coli. According to a study, the integrity of the BBB depends on the transcriptional activator Egr-1. During a meningitic E. coli infection, Egr-1 causes cytoskeletal alterations, suppresses the production of tight junction proteins, and starts neuroinflammatory reactions. Egr-1 may be a potential treatment target for bacterial meningitis, as this suggests a BBB collapse mechanism that depends on it [49].

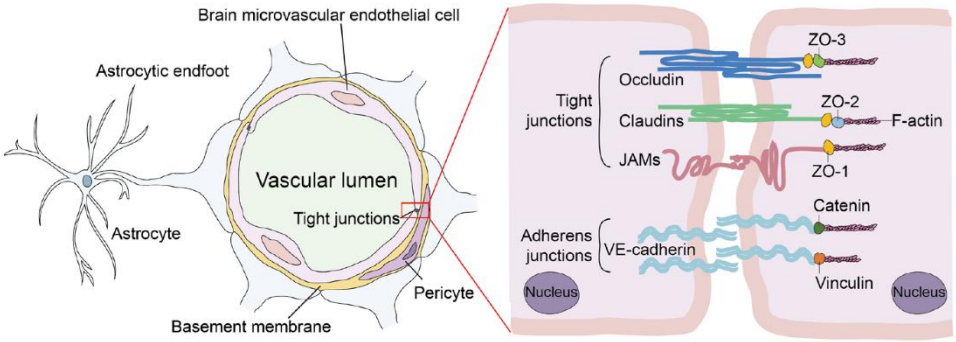

Figure 4. Diagram showing the chemicals and biological components that control the integrity of the blood-brain barrier [48].

2.5. Neuroinflammation

Proinflammatory cytokines are produced as a result of systemic inflammation during sepsis. By attaching to receptors on brain endothelial cells, peripheral proinflammatory cytokines like IL-1β and tumor necrosis factor-alpha (TNF-α) are capable of entering the brain tissue. Once inside, they stimulate glial cells and lead to neuroinflammation, perpetuating a harmful cycle [50-52]. Evidence suggests a connection between neuroinflammation and psychiatric disorders post-sepsis. Increased amounts of TNF-α, IL-6, IL-1β and interferon-gamma (IFN-γ), were detected in brain tissue of mice exhibiting anxiety-like behaviours 10 days after CLP [53]. In mice with sepsis, behavioural symptoms can also be reduced by blocking the nuclear factor-kappa B (NF-κB) pathways to decrease microglial activation [54]. Psychiatric disorders post-sepsis arise due to neuroinflammatory processes, although the precise mechanisms remain unclear. Previous studies have indicated that the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome leads to a notable rise in the levels of IL-1β, IL-18, and TNF-α in the hippocampal regions of septic mice. It also promotes the activation of microglial cells [55], which can subsequently trigger the NLRP3 inflammasome [56]. Furthermore, a wide range of inflammatory mediators is generated and released by activated microglia, contributing to the production of indoleamine 2,3-dioxygenase (IDO), an essential enzyme associated with endotoxin-induced depression [57].

Research indicates that inflammation negatively impacts mental health, particularly following the COVID-19 pandemic. It examines the immune responses activated by inflammation that contribute to mental health challenges. Chronic low-grade inflammation may result from physiological processes such as organ damage and hormonal changes due to infections, potentially leading to psychological alterations in susceptible individuals. A multidisciplinary approach is crucial for recognizing and addressing the mental health effects, as well as for preventing

complications and debilitating health issues (see Figure 5) [58].

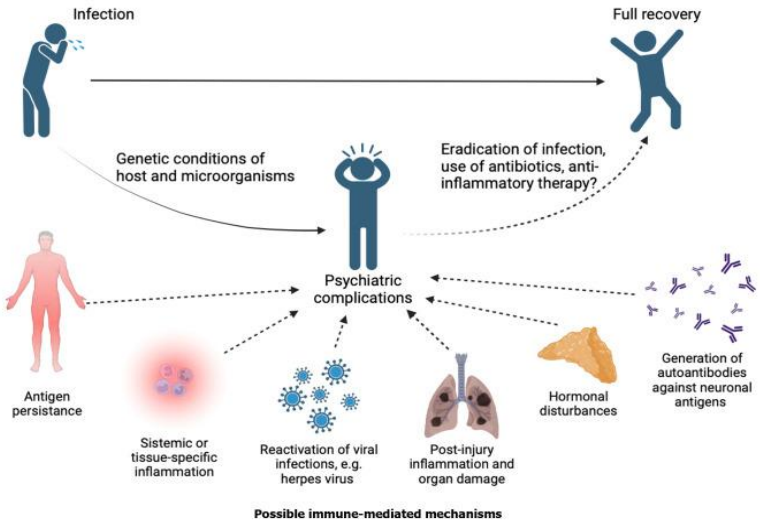

Figure 5. Potential processes by which infections lead to mental health issues [58].

Neuroinflammation and brain damage brought on by sepsis can result in neurological conditions. Known for its anti-inflammatory qualities, minocycline has been investigated for its ability to prevent brain damage brought on by sepsis. Minocycline pre-treatment dramatically sped up sepsis recovery in mice, reducing oxidative stress and inflammation in the brain caused by sepsis. This implied that minocycline might be a viable treatment option to guard against neurological issues brought on by sepsis [59]. Lung and brain inflammation were linked in a study on pulmonary sepsis in mice. After exposure to either pulmonary sepsis or a control group, the mice were infected with Klebsiella pneumonia. According to the study, sepsis weakened the BBB, generated peripheral inflammation, and raised vascular permeability, all facilitating the spread of bacteria. Proinflammatory cytokines, depression-like behaviors, and elevated myeloperoxidase activity were also observed in the animals, indicating a connection between the inflammatory responses in the brain and lungs [60].

2.6. Oxidative stress

The medical disorders oxidative stress and neuroinflammation have similarities and can exacerbate each other. Oxidative stress occurs when there is an overproduction of reactive oxygen species (ROS) combined with a diminished capacity of the antioxidant system to eliminate these molecules [61]. Studies have shown that proinflammatory mediators are released in response to neuroinflammation, which activates microglia and stimulates the production of reactive oxygen species (ROS), ultimately leading to neuronal injury. Oxidative stress also aids in propagating inflammatory signaling pathways [62]. According to recent studies, oxidative stress may contribute to the emergence of psychiatric disorders post-sepsis. While oxidative stress is known to influence post-sepsis psychiatric conditions, the specific mechanisms remain unclear. However, the occurrence of post-sepsis psychiatric disorders is thought to be closely tied to both neuroinflammation and oxidative stress due to their strong association. Investigators have examined how oxidative stress affects nucleic acids (DNA and RNA) and their potential to accelerate aging in individuals with mental disorders. Urinary 8-oxoGuo, a helpful indicator of mortality risk in people with mental illness, is known to be influenced by systemic oxidative stress-induced RNA degradation. The biochemical

processes underlying this phenomenon are not yet fully understood [63].

Ghrelin is a peptide hormone produced in the gastrointestinal tract that plays a key role in regulating energy balance, muscle growth, eating habits, heart cell function, and bone metabolism. Through its interaction with the hippocampus's development hormone secretagogue receptor 1a subtype, it stimulates the anterior pituitary gland to release growth hormone. Areas involved in the control of emotional behaviour and the stress reflex are where ghrelin is expressed. A study indicated that stress can have both antidepressant effects and increased levels of ghrelin (see Figure 6) [64].

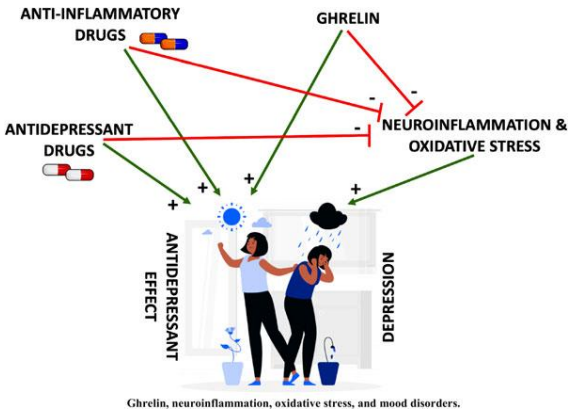

Figure 6. In a graphical depiction of the processes by which ghrelin affects mood, its anti-inflammatory and anti-oxidative qualities might play a significant role [64].

2.7. Host cell death

Necroptosis, pyroptosisapoptosis, autophagy , ferroptosis, and cuproptosis are the various forms of host cell death (HCD) [65]. More and more research indicates that HCD may play a role in the development of sepsis-related psychological impairment. Increased hippocampal neuronal apoptosis and necroptosis are observed in mice exhibiting depressed behavior 14 days following cecal ligation and puncture (CLP) surgery [66]. Hippocampal neurons exhibit a substantial rise in myelocyte differentiation factor 2 (MD2) expression 24 hours following CLP. Both necroptosis and apoptosis are mediated by MD2. Transgenic mice with MD2 deletion exhibit less depression-like behaviour two weeks after CLP, there are fewer dead neurons in the hippocampus, and the production of proteins linked to apoptosis and necroptosis is reduced. This implies that MD2-mediated necroptosis and apoptosis are linked to depression after sepsis. Psychiatric symptoms during sepsis are related to pyroptosis [67].

Early life stress raises the probability of depression later in life (ELS). An apoptosis-related protein called programmed cell death factor 4 (PDCD4) plays a role in inflammation and carcinogenesis. According to a recent study that used a "two-hit" stress mouse paradigm, teenage mice exposed to either LPS or IFS had more severe symptoms of anxiety and sadness. By inhibiting PDCD4, synaptic plasticity damage can be lessened and microglia alterations brought on by ELS can be avoided. PDCD4 may be a therapeutic target for depressive illnesses and may contribute to the sensitivity to depression caused by ELS [68].

2.8. Neuroplasticity

Post-sepsis psychiatric disorders are associated with impaired neuroplasticity, including neurogenesis, axon sprouting, axon regeneration, and synaptic plasticity [69]. Mice show signs of anxiety and depression one month after LPS injection, and their expression of activity-regulated cytoskeletal-associated protein (ARC) and early growth response 1 (EGR1) declines. In the dentate gyrus's subgranular zone, neural stem cell growth has also decreased [54]. The loss of synapses and decreased synaptic protein expression are signs of compromised synaptic plasticity. Using a caspase-1

inhibitor can help restore these protein levels. Translocator protein (Tspo)-knockout mice show more severe mental symptoms 17 days after CLP, suggesting that the C1q complement pathway mediates synaptic clearance. The signalling pathways linked to brain-derived neurotrophic factor (BDNF) are crucial for neuroplasticity. After ten days following CLP, mice exhibited sad behaviour and a decrease in BDNF levels in the hippocampus, which may suggest that neuroplasticity is associated with psychiatric impairment caused by sepsis [70].

Major depressive disorder frequently manifests as neurocognitive dysfunction, which also increases the risk of chronic and recurrent illness. Although the precise relationship between depression and disruption of hypocretin control is still unclear, it is known to exist. In chronic unexpected mild stress (CUMS) model mice, the increase in hypocretin-1 levels in the plasma causing hypothalamus hinders hippocampal remodelling and neurocognitive impairment. These alterations can be undone by HCRTR1 antagonists. The direct effect of hypocretin-1 on hippocampal lactate production and cognitive behavior is confirmed by intraventricular injection and microPET-CT in mice [71]. The brain's capacity to adapt both physically and functionally to internal and external stimuli is known as neuroplasticity. It provides the basis for managing thoughts and feelings, and mental illnesses like Major Depressive Disorder (MDD) can arise from its dysfunction. Impaired neuroplasticity may result in chronic depressed symptoms that impact daily life and work performance. The pathogenesis, pathology, and physiological aspects of MDD have all been studied recently. It has been looked at how monoamine modulation and ketamine absorption contribute to MDD's antidepressant effects [72].

2.9. Neurotransmitters dysfunction

Neuropsychiatric disorders are intimately associated with anomalies in neurotransmitters. According to reports, neurotransmitters like glutamate, gamma amino butyric acid (GABA), dopamine, norepinephrine, acetylcholine, and dopamine are inappropriately expressed during sepsis [73], which may indicate their involvement in post-sepsis behavioral disorders. According to one study, rats' anxiety-like behaviour after CLP was correlated with the hippocampus's IL-1β/GABA form A receptor (GABAAR) network being activated. Post-sepsis anxiety, on the other hand, has been linked in another study to a decrease in 5-hydroxytryptamine 1A receptor (5-HT1AR) expression and an increase in 5-HT2AR expression [74]. An excitatory neurotransmitter is glutamate. Glutamate is released by activated microglia as a result of increased intracellular system xc- activity, and this helps explain why septic mice exhibit depression-like behavior following an intraperitoneal injection of LPS. Curiously, these depressive symptoms were reduced by the use of the glutamate receptor antagonists MK801 and DNQX [75], suggesting that glutamate and the development of depression after sepsis may be related. Tryptophan, the precursor of serotonin, is changed by IDO during neuroinflammation into quinolinic acid, which can attach to the N-methyl-D-aspartate (NMDA) receptor and cause excitatory neurotoxic consequences [76]. Psychiatric disorders after an LPS injection have been linked to increased expression of IDO in the prefrontal cortex and hippocampal regions [78]. The neurotransmitter system disruption during sepsis promotes psychological disorders.

Although the neurochemical causes underlying anxiety are still unknown, it is a serious medical and societal problem. Neurochemicals that affect anxiety reactions include hydrogen sulfide (H2S) and nitric oxide (NO). Animal models of NO signaling's anxiogenic or anxiolytic effects depend on the composition, dosage, treatment plan, and gas release rate of NO donors. H2S and CO are regarded as anxiolytic neurotransmitters, but NO

synthase inhibitors are strong axiolytic drugs. To fully comprehend the potential significance of these neuromediators in anxiety disorders (see Figure 7), more investigation is required [79].

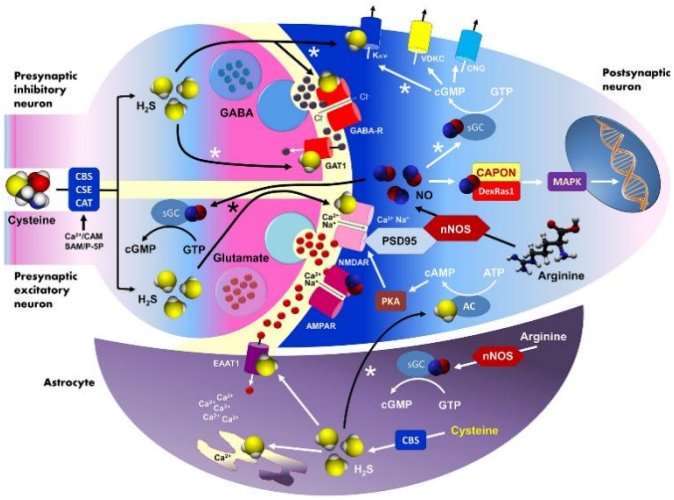

Figure 7. Diagram showing how brain gaseous neurotransmitters contribute to anxiety [79].

2.10. Cardiovascular and kidney disease

Heart failure, myocardial infarction, stroke, ventricular arrhythmia, and chronic kidney disease (CKD) are among the deadly cardiovascular and kidney conditions that survivors of sepsis are more likely to experience. The development of CKD and cardiovascular disease are intimately associated, and they may have the same etiology or develop as a result of cardiovascular disease. Patients who already have CKD are twice as likely to die within 90 days, and acute kidney injury (AKI) is linked to higher mortality during sepsis. Sepsis-AKI is linked to an increased risk of developing chronic kidney disease (CKD) and recurrent sepsis [13, 80-83].

Mitochondrial dysfunction is linked to sepsis, a critical condition that can lead to alterations in mitochondrial structure, damage to DNA, and a decrease in mitochondrial mass. Treatments such as antioxidants aimed at the mitochondria can help prevent AKI and improve organ performance, as this dysfunction is a significant factor in the onset of sepsis-related AKI. Additionally, while impaired mitochondrial function in the kidneys is associated with kidney disease, inadequate mitochondrial performance in the heart can lead to breakdowns in sarcomere structure, reduced contractile ability, and heart failure. By preserving mitochondrial function during sepsis, the potential for improved long-term outcomes and reduced organ damage can be achieved [84-90]. CKD is more prevalent among individuals with serious psychiatric disorders, including bipolar disorder and schizophrenia. The increased rates may be influenced by elements such as cardiovascular issues and the use of lithium; however, the actual prevalence of CKD in this demographic remains uncertain. Although there is a lack of extensive published research on this topic, mental health conditions like anxiety and depression frequently affect CKD patients (refer to Figure 8). Significant health complications, such as higher rates of hospitalization and mortality, are associated with severe mental illness. Training healthcare professionals and promoting collaboration with psychiatric services could enhance the treatment experience for CKD patients [91].

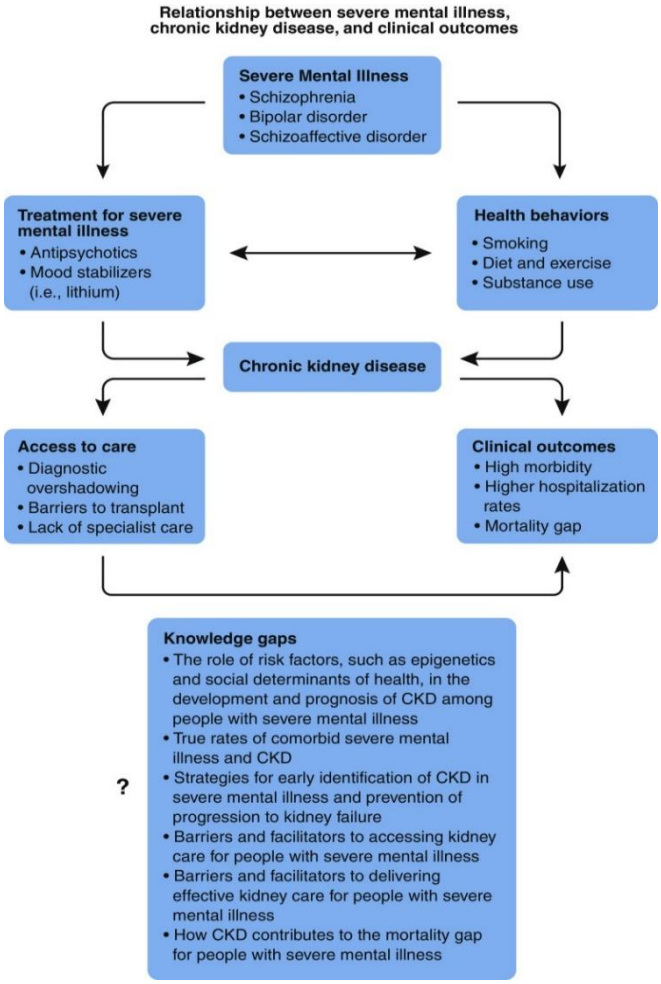

Figure 8. Severe mental conditions, chronic renal failure, and clinical outcomes are connected. [91].

3. NEUROPSYCHIATRIC CONSEQUENCES POST-SEPSIS

3.1. Post-sepsis mental disorders

According to certain research, surviving sepsis is linked to long-term consequences on one's mental health [92, 93]. The psychological effects of sepsis and how they similarly impact both sexes may be explained by the neuroinflammation and cerebrovascular damage that post-sepsis. More investigation is required in this area of post-sepsis syndrome studies because there aren't many studies that explicitly look at mental health problems post-sepsis. The neuropsychiatric aftereffects that fall under the umbrella of post-ICU syndrome have been described in several studies, however. Since a significant portion of intensive care unit survivors have sepsis, the condition is frequently grouped with post-ICU syndrome. Post-ICU syndrome, to put it briefly, is a collection of problems that survivors of critical illness often have. These problems include mental health disorders, cognitive impairment, neuromuscular weakness, cachexia, persistent pain, and dysphagia [94]. Although there is substantial overlap among patient populations in each category, we do not claim that the two disorders are interchangeable. The rest of this section will address the neuropsychiatric effects of surviving critical illness for this article.

Patients frequently experience persistent psychiatric difficulties after a severe illness [95]. Anxiety, depression, and PTSD are some examples of these detrimental emotional effects. Due to gaps in their recollection of events that occurred during their sickness and uncertainty about their future, these individuals may be more susceptible to anxiety and sadness [96]. According to studies, up to 30% of patients claim to experience melancholy, and up to 43% may suffer anxiety [97, 98]. Depression

symptoms can exacerbate functional decline or complicate rehabilitation [99]. Severe sepsis and depression both indicate that survivors' cognitive and functional abilities are likely to deteriorate. It is now known that symptoms of post-traumatic psychiatric disorder can result from critical illness. According to survivors, PTSD-inducing situations are extreme, uncontrollable, and sometimes fatal [100]. Significantly, there was no correlation between psychological results and the Acute Physiology and Chronic Health Evaluation (APACHE II) scoring system, which evaluates the severity of the disease. In a Danish survey of 9,912 severely sick patients, 12.7% received new psychoactive medicine prescriptions, even though many survivors had pre-existing illnesses. In comparison, only 5.0% of control patients admitted to the same hospital during that period received similar treatments. Wagensch et al. (2014) found that within three months of being hospitalised, 0.5 percent of survivors obtained a new psychiatric diagnosis, compared to 0.2% for the control and treatment groups [101].

One recent study found a link between psychiatric disorders and sepsis, but the exact cause is unknown. A two-sample bidirectional MR strategy was used to analyze genetic variants linked to mental disorders such as schizophrenia (SCZ), major depressive disorder (MDD), anorexia nervosa (AN), ADHD, obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), bipolar disorder, posttraumatic stress disorder (PTSD), panic disorder (PD), and tourette syndrome (TS). The results showed that AN was related to a larger risk of sepsis, and N-formylmethionine levels, cystatin D levels, ketogluconate metabolism, and N10-formyl-tetrahydrofolate production may function as mediators in the pathogenesis of AN-sepsis [102].

3.2. Generalized anxiety disorder (GAD)

Neither age nor gender was associated with anxiety symptoms during a critical illness, even though the lifetime prevalence of GAD is 60% higher in women and is most common among individuals aged 30 to 44 [103]. There was a consistent absence of correlation between the emergence of anxiety symptoms and the severity of the illness, duration of hospital stay, and the diagnosis at admission. For survivors of critical illness experiencing anxiety, physical rehabilitation, and journaling proved to be beneficial [104]. There is a growing association between various gastrointestinal disorders and gastroparesis, particularly GAD. A retrospective study conducted in 2014 found that 4,196 patients diagnosed with gastroparesis also had GAD. Those with GAD faced a heightened risk of inpatient mortality, myocardial infarction, intestinal obstruction, sepsis, acute deep vein thrombosis, AKI, and acute respiratory failure. Factors such as prerenal azotemia, increased nausea and vomiting related to GAD, and medications used to treat GAD may contribute to this elevated risk. The combined inflammatory responses triggered by both gastroparesis and GAD may additionally increase the likelihood of developing AKI [105].

Adult patients with acute pancreatitis (AP) who also had comorbid GAD were more likely to experience acute renal failure, sepsis, acute deep vein thrombosis, and inpatient death, according to a new study on the subject. The study looked at frequent hospital outcomes of AP patients with and without GAD using the 2014 National Hospital Sample Database and ICD codes. According to the survey, AP patients with concomitant GAD should be identified at admission and closely monitored while in the hospital to help spot problems early and avoid bad outcomes [106].

3.3. Major depressive disorder

The prevalence of major depressive disorders is highest among those aged 40 to 59 [107], and it is twice as common in women [108]. As with GAD, survivors' major depressive symptoms at follow-up did not correlate with risk factors such as age, sex, duration of stay, the severity of disease, or admission

diagnosis [109]. For a large number of individuals, post-traumatic stress disorder frequently coexists with or is related to anxiety and depression.

The "post-acute COVID-19 syndrome," which is typified by symptoms like anxiety, depression, and cognitive deficits, has emerged as a result of the COVID-19 pandemic. Sleep, quality of life, neurocognitive function, and exhaustion are all negatively impacted by these symptoms. The number of people with depressive disorders may rise as a result of the high incidence of these symptoms. Thus, screening for, diagnosing, treating, and tracking the psychopathology of COVID-19 survivors is essential [110].

3.4. Post-traumatic stress disorder (PTSD)

A poor health-related quality of life, worsening of pre-existing illnesses, and problems with the heart, lungs, musculoskeletal system, and gastrointestinal tract are all linked to PTSD following a severe illness. The aforementioned health problems may be exacerbated or caused by behaviors linked to PTSD, such as substance abuse, sleep disorders, and avoidant coping [111]. The morbidity and mortality of survivors are significantly influenced by the long-term psychological repercussions of sepsis, which can be functionally incapacitating.

A study comparing post-traumatic stress symptoms in sepsis survivors found three clusters: steady low symptoms, growing symptoms, and recovery from symptoms. Patients with high symptoms were more likely to decline, while females and those with early painful ICU memories showed an increase in PTSS levels. This highlights the long-term consequences of post-traumatic stress in survivors [112].

4. DIAGNOSIS

Screening techniques are frequently used to assess the existence of anxiety, sadness, delirium, and PTSD in individuals who have survived sepsis because there are no established diagnostic criteria for psychiatric disorders that occur post-sepsis. When it comes to self-evaluating anxiety, the Beck Anxiety Inventory (BAI) and the Self-rating Anxiety Scale (SAS) are commonly used, while the Major Depression Inventory (MDI), Patient Health Questionnaire-9 (PHQ-9), Self-rating Depression Scale (SDS), and Beck Depression Inventory-II (BDI-II) are commonly used for self-evaluating depression. The Hospital Anxiety and Depression Scale (HADS) is commonly used in clinical settings to test patients for anxiety and depression. The Intensive Care Delirium Screening Checklist (ICDSC) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) are widely used evaluation tools for detecting delirium in patients in the ICU. Self-assessment instruments such as the PTSD Checklist for DSM-5 (PCL-5), the Posttraumatic Symptom Scale-10 (PTSS-10), and the Impact of Events Scale-Revised (IES-R) are typically employed to assess PTSD symptoms. Nonetheless, for an official diagnosis, clinicians depend on the more detailed and structured interview known as the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), which is regarded as the gold standard in diagnosing PTSD. A detailed description of these scales is provided in Table 1. A consensus statement on identifying and predicting post-intensive care syndrome was published in 2019 by the American Society of Critical Care Medicine (SCCM) [138]. When assessing anxiety and depression, the HADS was highly recommended because a score of eight or more indicates significant levels of these disorders. Moderately recommended for PTSD assessment were the IES-R and IES-6, with appropriate cut-off points of 1.6 along 1.75, respectively. These recommendations could potentially be used as a guide to recognise psychiatric conditions that occur post-sepsis.

Table 1 Post-sepsis psychiatric disorder screening scales

Scale	No. of objects	Overall Score	Explanation of the score	Intervention	Strength	Limitation	Ref.
Anxiety BAI	21	63	Normal is 0-9, mild to moderate is 10-18, moderate to severe is 19-29, and severe is 30-63	self-assessment	Quick, simple, and reliable psychometric qualities	Limited scope that emphasizes somatic symptoms; not unrestricted	113, 114
HADS-A	7	21	Normal is 0-7, mild is 8-10, moderate is 11-14, and severe is 15-21	self-assessment	Short, frequently used, and readily available	Decreased validity in some groups (older people, for example); incapacity to screen for anxiety disorders especially	114-116
SAS	20	80 (raw score); 100 (index score)	Index scores range from mild to moderate (45-59), moderate to severe (60-74), and severe (75-100)	self-assessment	Highly sensitive and broadly used	The cut-off number for significance rises since it is simple to mistake the index score for the raw score.	117-119
Depression MDI	10	50	A score of ≥ 4 on two of the top three items and at least four of the remaining items indicates moderate depression; Major depression is defined as having a score of at least four on five of the nine items (not including item 4), with one of the five items indicating a low mood or loss of interest	self-assessment	Short, reliable	Depends on patients' cooperation and reading comprehension	120-123
BDI-II	21	63	Minimal to 13; mild to 19; moderate to 20-28; and severe to 29-63	self-assessment	Quick, commonly used, psychometric qualities	Symptoms of depression can readily coexist with other illnesses; they remain free	113, 124
SDS	20	80 (raw score); 100 (index score)	Index scores range from 25 to 49 for normal, 50 to 59 for mild to moderate, 60 to 69 for moderate to severe, and 70 to 100 for severe	self-assessment	Frequently used, extremely sensitive	Index and raw scores might be easily confused	117, 119
HADS-D	7	21	Normal is 0-7, mild is 8-10, moderate is 11-14, and severe is 15-21	self-assessment	Quick, short, and frequently used	Focusses on cognitive and emotional elements of depression within a narrow scope	115, 116, 124

PHQ-9	9	27	Normal is 1-4, mild is 5-9, moderate is 10-14, moderately severe is 15-19, and severe is 20-27	self-assessment	Fast, strong psychometric properties, widely used, free	Limited specificity	124-127
PTSD PCL- 5	20	80	A cut-off score of 33 is used to make a tentative diagnosis of PTSD	self-assessment	Widely used, strong psychometric properties, fast	Examines only symptoms of PTSD; it does not evaluate symptoms connected to trauma	128-131
PTSS-10	10	70	A score above 35 indicates clinically relevant PTSD	self-assessment	Widely used, high specificity and sensitivity	Developed using DSM-III diagnostic criteria instead of DSM-V, and might not be suitable for usage today	125, 131-133
CAPS-5	30	80	PTSD symptoms are more severe when the score is greater	Structured clinical interview	Superior psychometric qualities and gold standard	Slow; more instruction is needed for regular administration	129-131,134
IES-R	22	88	A high risk of PTSD is indicated by a score of ≥33	self-assessment	Brief, simple to use, and available in multiple copies	Not entirely in line with the diagnostic criteria of DSM-V	129, 132, 135, 136
Delirium CAM-ICU	4	-	Delirium-positive items include items 1 and 2, as well as either item 3 or 4	A single point of observation and interaction	High specificity, sensitivity, and widespread use	ICU nurses find it inconvenient to require patients' cooperation	137
ICDSC	8	8	A total score of > 4 shows that delirium is present	Constant monitoring of standard care	Extremely sensitive and simple to use	Limited specificity	137

5. PREVENTION

Post-sepsis psychiatric disorders significantly affect the daily lives and long-term outcomes of survivors. Therefore, it is crucial to implement targeted preventive strategies to reduce the incidence of associated psychiatric disorders. People who have anxiety, despair, and PTSD before to a severe illness, who experience dread memories while in the intensive care unit, and who don't have social support during their treatment are more likely to suffer from long-term mental health problems following a critical illness, according to the SCCM consensus statement. Consequently, it is recommended that these patients undergo mental health evaluations as soon as possible after their discharge and after any major changes in their health or quality of life [138].

Psychiatric issues arising post-sepsis can stem from a variety of factors. In a prospective cohort research involving 135 patients with abdominal sepsis, 28 percent of participants experienced moderate PTSD symptoms one year after laparotomy, and 10 percent reported severe levels of PTSD symptoms. Variables such as age, length of stay in the ICU, and distressing memories during their hospital stay were associated with the development of PTSD [132]. After making multivariate adjustments, it was found that longer ICU stays and recalling more than four distressing memories while hospitalized were independent risk factors for PTSD. Following an episode of sepsis, 28% of individuals in a prospective cohort study involving 439 elderly patients who survived severe sepsis reported experiencing symptoms of depression. Importantly, clinical factors like the length of hospital stay, organ failure score, and mechanical ventilation were not linked to the depression that followed. In contrast, post-sepsis depression was found to be independently connected to functional impairment post-sepsis and pre-existing depression before the occurrence of sepsis [92].

The prevalence of PTSD was observed to positively correlate with serum S100β levels in another single-center study involving 33 patients with severe sepsis or septic shock. Depressive symptoms were also favorably connected with the total amount of dobutamine administered during the intensive care unit stay [113]. A Korean study reported a number of SAD risk factors. Older age (≥65), reliance on activities, high care demands, lack of consciousness, dyspnea, and thrombocytopenia are some of these. However, it was discovered that using vasopressors or inotropes and having a high albumin level may lower the risk of SAD. Furthermore, the degree of organ dysfunction was found to be correlated with an increased likelihood of delirium [139].

According to the studies mentioned above, the number of traumatic memories, length of stay in the ICU, administration of vasopressors or inotropes, albumin levels, regular activity levels post sepsis, and total dobutamine dosage are among the modifiable risk factors for psychological issues post sepsis. Nursing case management by qualified nurses, clinical decision support by consulting physicians, and evidence-based post-sepsis care education for patients and their main carers are all components of effective primary care management. Research has indicated that one year after implementing intervention, primary care management can significantly reduce the rates of PTSD in sepsis survivors compared to standard care [140]. Moreover, completing the entire ABCDEF bundle—which entails: Assessing, preventing, and managing pain; conducting trials for spontaneous awakening and breathing; selecting appropriate Analgesia and Sedation methods; evaluating, preventing, and managing delirium; promoting Early Mobility and Exercise; and engaging and empowering families was associated with a decreased risk of delirium in a prospective multicenter study of sepsis patients[141].

6. TREATMENT

Post-sepsis psychiatric issues do not currently have a validated treatment. The field's research remains in its early stages.

Both pharmaceutical and non-pharmacological therapeutic approaches may be beneficial.

6.1. Non-pharmacological treatment

Internet-based cognitive behavioural therapy (ICBT) is a writing intervention administered online that is physically independent and accessible. Treatment consists of three parts: in-sensu trauma exposure, resource-oriented biographical reconstruction, and cognitive reconstruction. Following every writing session, prompt feedback is given by a qualified psychotherapist. ICBT's therapeutic benefits are unclear, nevertheless. For instance, one study found that ICBT was ineffective in addressing PTSD symptoms after severe sepsis. At the same time, it was found to improve PTSD symptoms in a case report involving a sepsis survivor and his spouse [134]. In the later study, however, the small sample size might have affected the unfavorable outcome [128]. To find out how effective ICBT is, more research with larger sample sizes is needed. A strategy frequently used in the clinical treatment of patients undergoing surgery and those suffering from chronic illnesses is comprehensive nursing care. To guarantee high-quality nursing care, all nursing tasks should be completed thoroughly and according to accepted nursing practices. Patients in sepsis who receive full nursing care had much lower levels of anxiety and depression, improving their prognosis and quality of life [117]. Furthermore, it has been shown that in critically sick patients who need mechanical ventilation, particularly those with sepsis, early physical and occupational therapy can significantly reduce the length of delirium [142].

6.2. Pharmacological treatment

When creating animal models of sepsis for the study of psychiatric disorders related to sepsis, CLP and intraperitoneal injection of LPS are the most widely utilized techniques. In animal models, several medications, including imipramine, dexamethasone, guanosine, and nicotine, are successful treatments. Among the many ways these medications work are enhancing the neuroinflammatory response, lowering oxidative stress, blocking HPA axis activation, and lowering BBB permeability (for further information, see Table 2). Mesenchymal stem cells have been used in cell therapy and have advanced quickly in recent years. Research has indicated that these cells have neuroprotective and anti-inflammatory qualities [143]. The conditioned media combined with mesenchymal stem cells can lessen the anxiety-like behaviour of rats after CLP. These effects are brought about by lowering astrocyte activation and the inflammatory response [44, 144]. Prospects for the treatment of psychiatric disorder post sepsis appear bright based on these initial findings.

Table 2. Several promising medications and their modes of action

Treatment	Model, Strain	Domain	Mechanism	Target	Ref.
VX765 (0.2 mg, intragastric)	CLP, BALB/c mice	Anxiety and depression↓	Pyroptosis↓, BBB disruption↓, inflammatory cytokine levels↓, microglia activation↓, synaptic plasticity↑	Caspase-1	Xu et al. [43]
Mesenchymal stromal cells (1 × 105 cells, iv)	CLP, Swiss Webster mice	Anxiety↓	BBB dysfunction↓, astrocyte activation↓, levels of inflammatory ediators↓	--	Silva et al. [44]
PDTC (200 mg/kg, ip)	LPS, C57BL/6 mice	Anxiety and depression↓	Microglia activation↓, EGR1↑	NF-κB	Anderson et al. [54]

Indole-3-propionic acid (25 mg/kg,	CLP, specific pathogen-Free C57BL/6 mice	Anxiety↓	NLRP3 inflammasome↓	Aryl hydrocarbon receptor	Fang et al. [56]
CMI (1 mg/kg, oral)	LPS, Swiss mice	Anxiety and depression↓	Neutrophil numbers↓, reactive oxygen species↓, BBB dysfunction↓, inflammation-associated genes↓, oxidative stress markers↓	--	Casaril et al. [78]
Tannic acid (20 mg/kg, ip)	CLP, Wistar rats	Anxiety↓	Inflammatory markers↓, oxidative stress↓	IL-1β/GABAAR	Ranjbaran et al. [74]
Tat-CIRP (50 mg/ kg, ip)	CLP, C57/BL6 mice	Depression↓	Neuronal loss↓	MD2	Fan et al. [66]
Imipramine (10 mg/kg, ip)	CLP, Wistar rats	Depression↓	Corticosterone↓, ACTH↓, BDNF↑	HPA axis	Comim et al. [70]
Mesenchymal stem cells and their conditioned medium (1 × 106 cells, ip)	CLP, Wistar rats	Anxiety↓	Inflammation↓, 5-HT2A receptors↓, 5-HT1A receptors↑	Serotonergic pathway	Ranjbaran et al. [144]
Sulfasalazine (100 mg/kg, ip)	LPS, C57BL/6 mice	Depression↓	Glutamate release↓	System xc−	Kitagawa et al. [75]
Dexamethasone (0.2 mg/kg, ip)	CLP, Wistar rats	Depression↓	Corticosterone↓, ACTH↓	HPA axis	Cassol et al. [145]
Guanosine (8 mg/kg, ip)	CLP, Wistar rats	Depression↓	Oxidative stress parameters↓	--	Petronilho et al. [146]
Nicotine (0.1 mg/kg, subcutaneous)	CLP, Wistar rats	Anxiety↓	---	--	Leite et al [147]
IgG (250 mg/kg, iv); IgGAM (250 mg/kg, iv)	CLP, Wistar albino rats	Anxiety and depression↓	----	--	Ozcan et al. [148]
NU9056 (5 mg/kg, ip)	LPS, C57BL/6 J mice	Anxiety and depression↓	BBB disruption↓, microglia activation↓, inflammatory markers↓, gut dysbiosis↓	NLRP3 inflammasome	Chen et al. [149]
(R)- etamine (10 mg/kg, ip)	LPS, C57BL/6 mice	Delirium↓	Levels of inflammatory cytokines↓	--	Zhang et al. [150]

7. CONCLUSION

Sepsis and post-sepsis syndrome have complicated etiologies, making therapy challenging. Because sepsis affects the cardiovascular, neurological, neurocognitive, and immunological systems, it reduces quality of life and raises mortality. This knowledge has led to the development of mechanism-guided medicines. Post-sepsis psychiatric disorder significantly impairs survivors' quality of life due to its participation in Neurocognitive dysfunction, neuroinflammation, oxidative stress, HCD, poor neuroplasticity, neurotransmitter dysfunction, and overactivation of the HPA axis. Reducing the incidence of post-sepsis psychological disturbance can reduce risk factors. More research is needed to identify

potential therapeutic drugs because there are currently no established treatments for psychological problems that develop post-sepsis.

Declaration by Authors

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