Sepsis-associated brain injury: underlying mechanisms and potential therapeutic strategies for acute and long-term cognitive impairments

Nobufumi Sekino¹, Magdy Selim² and Amjad Shehadah²*

Abstract
Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis causes cerebral dysfunction in the short and long term and induces disruption of the blood–brain barrier (BBB), neuroinflammation, hypoperfusion, and accumulation of amyloid β (Aβ) and tau protein in the brain. White matter changes and brain atrophy can be detected using brain imaging, but unfortunately, there is no specific treatment that directly addresses the underlying mechanisms of cognitive impairments in sepsis. Here, we review the underlying mechanisms of sepsis-associated brain injury, with a focus on BBB dysfunction and Aβ and tau protein accumulation in the brain. We also describe the neurological manifestations and imaging findings of sepsis-associated brain injury, and finally, we propose potential therapeutic strategies for acute and long-term cognitive impairments associated with sepsis. In the acute phase of sepsis, we suggest using antibiotics (such as rifampicin), targeting proinflammatory cytokines, and preventing ischemic injuries and hypoperfusion. In the late phase of sepsis, we suggest targeting neuroinflammation, BBB dysfunction, Aβ and tau protein phosphorylation, glycogen synthase kinase-3 beta (GSK3β), and the receptor for advanced glycation end products (RAGE). These proposed strategies are meant to bring new mechanism-based directions for future basic and clinical research aimed at preventing or ameliorating acute and long-term cognitive impairments in patients with sepsis.

Keywords: Sepsis, Cognitive impairment, Neuroinflammation, White matter change, Alzheimer’s disease, Amyloid-beta, Tau protein

Introduction
Sepsis is a systemic inflammatory disease defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Sepsis is a global health problem affecting 49 million people and causing 11 million deaths each year worldwide [2]. The mortality rate of sepsis has been declining, but it is still remarkably high, ranging between 15 and 25%. In-hospital mortality of patients with septic shock could be as high as 30% to 50% [3]. Studies have shown that many patients with sepsis experience acute and long-term cognitive impairments [4–6]. However, no specific treatment that directly addresses the underlying mechanisms of cognitive impairments in sepsis currently exists, and many controversies surround the optimal treatment approach for these patients. Advances in therapy for sepsis are urgently needed to improve clinical outcomes [7]. Here, we review the underlying mechanisms of sepsis-associated brain injury, with a focus on blood–brain barrier dysfunction.
(BBB) dysfunction, neuroinflammation, and amyloid β (Aβ) and tau protein accumulation in the brain. We also describe the neurological manifestations and imaging findings of sepsis-associated brain injury, and finally, we propose potential therapeutic strategies for acute and long-term cognitive impairments associated with sepsis.

**Underlying mechanisms of sepsis-associated brain injury**

Multiple mechanisms contribute to brain damage in sepsis, including systemic inflammation, neuroinflammation, BBB dysfunction, ischemia/hypoxia due to hypoperfusion, Aβ and tau protein accumulation, and direct damage to the brain (Fig. 1 and Table 1). Notably, systemic inflammation in sepsis can exacerbate BBB dysfunction, hypoperfusion, as well as, accumulation of both Aβ and tau protein. On the other hand, BBB disruption induces brain inflammation and may ultimately cause white matter changes and cerebral dysfunction.

**Sepsis modeling in animals**

Although no one model reflects all the clinical complexities of sepsis, animal modeling is a valuable way to study its underlying mechanisms and to develop new therapeutic strategies [8, 9]. The main two animal models used in sepsis research are the cecal ligation and puncture (CLP) and lipopolysaccharide (LPS) models. The CLP model mimics the nature and evolution of severe sepsis in humans [10]. Following a simple procedure to ligate and puncture the cecum, the CLP model induces sepsis as a result of stercoral peritonitis, followed by polymicrobial translocation in the blood circulation [8]. During gram-negative bacterial infection and other acute illnesses, LPS is a major mediator in sepsis [11]. In the LPS model, endotoxins are infused intravascularly, which results in an early and transient peak of cytokines, whereas in the CLP model, the pro-inflammatory response is delayed and persists over a longer period [9]. Due to the effects of the intense inflammatory response on the cardiovascular system, mortality in the LPS model occurs early, whereas in the CLP model, the mortality is delayed and occurs due to multiple organ failure as a complication of the induced peritonitis [8, 12].

**From systemic inflammation to neuroinflammation and BBB dysfunction**

**Systemic inflammation**

Sepsis is fundamentally a systemic inflammatory disease mediated by the activation of the innate immune system [3]. The activation of the innate immune response is mediated by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors, retinoic acid-inducible gene (RIG)-like receptors, mannose-binding lectin, and scavenger receptors [3, 13]. PRRs detect both pathogen-associated molecular patterns (PAMPs)
and damage-associated molecular patterns (DAMPs), which initiate the upregulation of inflammatory-related genes [14] and induce a complex intracellular signaling system [15]. The transcription complex nuclear factor kappa B (NF-κB) is triggered in response to numerous extracellular inflammatory stimuli [16]. The activation of NF-κB induces the expression of early activation genes, including tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-12, IL-18, and type I interferons (IFNs), among others. These cytokines initiate a cascade of other inflammatory cytokines and chemokines, including IL-6, IL-8, IFNγ, CC–chemokine ligand 2 (CCL2), CCL3, and CXC–chemokine ligand 10 (CXCL10), exacerbating the inflammatory response [3, 17]. The activation of these inflammatory networks begins within minutes of PAMP or DAMP recognition [3]. Maciel et al. reported that plasma levels of IL-6 and IL-10 in patients at hospital discharge from the intensive care unit (ICU) correlated with long-term functional and cognitive performance (mean follow-up, 4 years) [18], suggesting that the effects of proinflammatory cytokines are not limited to the acute phase of sepsis.

**Neuroinflammation**

Proinflammatory cytokines enter the brain during sepsis by several mechanisms. LPS can activate TLRs through areas that lack BBB, such as the choroid plexus, circumventricular organ, and leptomeninges [19]. Many cytokines enter the brain through receptor-mediated endocytosis on brain endothelial cells. Receptors for IL-1β, IL-6, and TNF-α are expressed on cerebral endothelium [20–22] and systemic IL-1β and TNF-α cause cerebral endothelial activation [23]. Activation of cytokine receptors such as IL-1 receptor (IL-1R1) and
TNF receptor (TNFR) elevates cytokine levels in the brain [24, 25]. Once these inflammatory mediators enter the brain tissue, microglial cells get activated [26]. Animal [27] and human [28] studies during sepsis consistently show microglial activation without any known cerebral infection [27, 29]. Immunostaining of a marker for microglia (CD68) was higher in brain tissues of patients who died of sepsis, supporting that neuroinflammation occurs after the onset of sepsis [28, 30]. Once microglia are activated, they most likely induce brain damage during sepsis [29, 31]. Sustained microglia activation enhances the production of inflammatory cytokines and reactive oxygen species (ROS), which creates a vicious cycle of increased BBB permeability and increased neuronal apoptosis [32, 33].

**BBB dysfunction**

The BBB is a specialized multicellular structure that selectively separates the brain interstitium from the contents of the blood vessels [34, 35]. The BBB is a dynamic barrier, with active communication between cells of the BBB and the brain parenchymal cells [36]. The innermost layer of the BBB is composed of endothelial cells, and the BBB regulates the paracellular permeability of endothelial cells through junctional proteins, including tight junction (TJ) proteins [37].

Increasing evidence suggests that BBB permeability is increased during sepsis. Using contrast-enhanced MRI of the brain, Towner et al. showed increased BBB leakage at 24 h in LPS-exposed rat brains in the cerebral cortex, hippocampus, thalamus, and perirhinal cortex regions [38]. Patients with sepsis-associated encephalopathy (SAE) frequently have vasogenic edema and white matter hyperintensities on MRI, indicating BBB disruption [39, 40]. How sepsis disrupts BBB is not entirely understood, but several mechanisms have been postulated.

An important pathway that could mediate BBB dysfunction is the disruption of TJ proteins induced by sepsis. TJ-associated proteins, mainly occludin, contain a putative matrix metalloproteinase (MMP) cleavage site [41]. After CLP in rats, MMP-2 and MMP-9 were detected in cerebral microvessels, and the increase in detected BBB permeability was time-related to the increase in MMP-2 and MMP-9 activation [41]. In humans, a reduction in TJ proteins expression was detected in the brain tissue of patients who died due to sepsis, indicating BBB damage [42].

Sepsis may also disrupt the BBB through the endothelial sphingosine 1-phosphate (S1P) receptor pathway, which maintains the BBB integrity by regulating the proper localization of TJ proteins [43]. It has been shown that in patients during sepsis, serum S1P levels were dramatically decreased and inversely associated with disease severity [44]. Additionally, the upregulation of endothelial caveolin-1 causes S1P to interact with intercellular adhesion molecule 1 (ICAM-1) and increases its binding affinity for peripheral immune cells [45]. Wu et al. found that caveolin-1 facilitates T-cell trafficking into the CNS via ICAM-1-mediated signaling [46].

Research suggests that TNF-α is another important mediator of BBB dysfunction in sepsis. TNF-α induces depolymerization of actin and the generation of intercellular gaps in the endothelial cytoskeleton [47]. In cultured brain endothelial cells, both TNF-α and IL-1β increased the expression of leukocyte adhesion molecules, such as ICAM-1, resulting in increased barrier permeability as measured by transendothelial electrical resistance [48]. TNF-α also increases barrier permeability through activating protein-kinase-6 and the internalization of VE-cadherin [49]. TNF-α has been reported to play a crucial role in the development of brain edema in acute liver failure, and increased BBB permeability was associated with loss of the TJ-associated protein occludin [50].

**Ischemia/hypoperfusion**

Hypoxic or ischemic changes are the most common abnormalities found on brain autopsies of patients with sepsis [51]. Decreased cerebral flow and hypercoagulability are the main factors behind the development of cerebral ischemia in patients with sepsis [52]. Not surprisingly, impairment of cerebral blood flow autoregulation is also common in patients with septic shock, especially in the presence of hypercapnia [53].

The acute dysregulated inflammatory response that is meant to eradicate the infectious agent in patients with sepsis may cause hypercoagulability and vasculopathy of cerebral blood vessels leading to cerebral ischemia. Acute vascular endothelial dysfunction is a central event in the pathogenesis of sepsis, contributing to vascular permeability and impaired autoregulation of cerebral blood flow [52, 54]. Infiltration of immune cells into the brain tissue and increased proinflammatory cytokines release activate endothelial cells, resulting in the activation of the coagulation cascade. Microthrombi may then form in blood vessels and can cause cerebral ischemia [5].

Available studies suggest that hypoperfusion and ischemia can induce white matter (WM) changes and may contribute to long-term cognitive impairments in patients with ischemic stroke. For example, microstructural changes to the WM have been reported in patients with hyperacute ischemic stroke (less than 6 h) [55]. It has also been proposed that hypoperfusion may also cause long-term cognitive impairments in stroke through the accumulation of tau pathology [56, 57]. Studies investigating the role of ischemia/hypoperfusion in sepsis-associated cognitive impairments are warranted.
Amyloid β and tau protein accumulation

Available preclinical and clinical data indicate that sepsis-associated brain injury is associated with molecular alterations that are shared with those seen in patients with Alzheimer’s disease (AD). It is well established that neuroinflammation in age-related brain diseases, such as AD, induces accumulation of Aβ and phosphorylated tau (p-tau) [58–62]. Data from animal models show that Aβ plaques and p-tau also accumulate acutely after experimental sepsis [59, 61]. It has also been shown that 30 days after the induction of sepsis, the brains of survivor animals have increased accumulation of Aβ and p-tau and this was associated with cognitive impairment [63]. In an animal sepsis model, LPS exposure in the rat resulted in hippocampal accumulation of Aβ plaques and intracellular p-tau, accompanied by behavioral deficits attributable to the dorsal dentate gyrus [61]. In another study, it was shown that both sepsis and aging induce brain inflammation, oxidative damage, and accumulation of Aβ, as well as impaired behavioral learning and memory function [62].

Although most of the data that show that sepsis triggers the accumulation of Aβ and p-tau in the brain come from animal research, there are several pieces of evidence that support the hypothesis that sepsis also triggers Aβ and p-tau accumulation in the brain of patients. In patients with sepsis, serum levels of tau protein are higher in those who had SAE than those who did not, and tau levels are independently associated with SAE [64]. In a prospective observational study, Orhun et al. investigated the association between neuroimaging features of sepsis-induced brain dysfunction and neuroinflammation and neurodegeneration factors [65]. The authors found that brain atrophy on MRI was associated with an increased serum level of p-tau. Regression analysis also identified an association between C5a levels and the presence of lesions on MRI and p-tau levels and the presence of atrophy on MRI [65].

Ehler et al. showed that in postmortem brain tissue from 5 patients who died as a result of sepsis there was diffuse staining of axons for Aβ precursor protein (β-APP). The authors also found amyloid plaque in a 79-year-old patient whose medical history did not suggest cognitive impairment [40]. Rogne et al. used 18F-flutemetamol positron emission tomography to visualize Aβ accumulation in patients with brain abscess and found that in 3 patients out of 17 there was an accumulation of Aβ [66]. Kramer et al. also showed that periodontal infection was associated with higher Aβ load in the brain of normal elderly as measured by PIB–PET scan [67]. Kantonen et al. detected strong APP immunoreactivity in autopsies of patients with COVID-19 [68]. In a more recent study, published as a preprint, Rhodes et al. found numerous Aβ deposits in the neocortex of patients under the age of 60 who died with COVID-19 [69].

Excessive phosphorylation of tau protein is the main cause of tauopathy in AD, and glycogen synthase kinase-3β (GSK3β) is one of the most important kinases of the tau protein [70]. In addition, GSK3β is a powerful regulator of inflammation. The NF-kB pathway is a key player for the proinflammatory actions of GSK3β [71–75]. GSK3β is necessary for full stimulation of the production of several pro-inflammatory cytokines, including IL-6, IL-1β, and TNFα, and inhibition of GSK3β greatly reduces the production of pro-inflammatory cytokines [73, 75]. GSK3β regulates the inflammatory response by differentially affecting the nuclear amounts of transcription factors NF-kB subunit p65 and cAMP response element-binding protein (CREB) interacting with the coactivator CREB-binding protein (CBP) [73]. Signaling of rapamycin complex 1 (mTORC1) and GSK3β converge, and the capacity of mTORC1 to regulate the inflammatory response is related to the inactivation of GSK3β [76]. In addition, GSK3 participates in modulating the downstream signaling induced by IFNγ and the JAK/STAT pathway [77].

The receptor for advanced glycation end products (RAGE) has been identified as an important link between inflammation, amyloidogenesis, and apoptosis during AD progression [78, 79]. RAGE binds to several DAMPs, including advanced glycation end products (AGES) [80], S100 [81, 82], and DNA [83]. In patients with AD, the plasma levels of soluble RAGE (sRAGE) are lower than in normal elderly and associated with cognitive deterioration [84]. Analysis of brain tissue from patients with AD compared to individuals without dementia showed upregulation of RAGE expression in microglia and neurons in the hippocampus, entorhinal cortex, and suprerior frontal gyrus [85]. By employing transgenics with targeted neuronal overexpression of RAGE and mutant APP, Arancio et al. showed that RAGE is a cofactor for Aβ-induced neuronal perturbation in a model of AD-type pathology [86]. Fang et al. showed that transgenic mice expressing human mutant APP in neurons and RAGE in microglia displayed enhanced IL-1β and TNF-α production, increased infiltration of microglia and astrocytes, accumulation of Aβ, reduced acetylcholine esterase activity, and accelerated deterioration of spatial learning/memory [87].

Available data indicate that RAGE is also involved in the pathogenesis of sepsis-associated brain injury. In the CLP animal model of sepsis, the levels of RAGE and p-tau are increased in the brain [63]. In addition, injection of RAGE antibodies into the hippocampus reduces Aβ and p-tau accumulation [60]. It has also been shown that RAGE-dependent signaling pathway regulates β-
γ-secretase cleavage of APP to generate Aβ, at least in part through activation of GSK3β and p38 MAP kinase [88].

Direct brain damage
Patients with sepsis may have focal lesions that cause direct damage to the brain. Sharshar et al. reported various focal lesions in 23 patients who died in the ICU from septic shock: ischemia (100%), hemorrhages (26%), hypercoagulability syndrome (9%), micro-abscesses (9%), and multifocal necrotizing leukoencephalopathy (9%) [89]. Severe sepsis can induce life-threatening coagulopathy, including disseminated intravascular coagulation (DIC) and intracerebral hemorrhage [90]. Focal brain lesions should be considered in patients with sepsis who show signs of cognitive impairment.

Other mechanisms, such as mitochondrial and neurotransmitter dysfunction, age-related changes, and iatrogenic factors may also be involved in the pathogenesis of brain damage in sepsis. For a thorough discussion of these mechanisms, please refer to previous publications by Mazeraud et al. [29], Annane et al. [91], and Manabe et al. [92].

Neurological manifestations of sepsis-associated brain injury
The spectrum of acute cognitive impairments in sepsis
In the acute phase, sepsis causes several clinical syndromes that are associated with cognitive impairments, including SAE, delirium, sickness behavior, and cerebral ischemia and hemorrhage [93]. For unclear reasons, acute cognitive impairments may sometimes persist for a long time even after sepsis has improved. Currently, the management of acute sepsis-associated brain injury is still focused on treating sepsis as the underlying disease, with no specific treatments to address brain dysfunction. While this is the case, it is encouraging that appropriate management of sepsis can help prevent cognitive impairments [91, 94].

Sepsis-associated encephalopathy
SAE is a key manifestation of sepsis, ranging from delirium to coma [29]. SAE is defined as cognitive dysfunction associated with sepsis, in the absence of infection in the central nervous system, structural brain injury, or other metabolic abnormalities [94]. Clinically, SAE is manifested by confusion, anxiety, irritability, depression, anhedonia, decreased social communication and environmental interest, and other cognitive changes, including decreased concentration and learning capacity and impaired memory [94]. SAE is a relatively common cause of altered mental status in critically ill patients admitted to the ICU, and its prevalence varies from 8 to 70% depending on the inclusion and exclusion criteria [95]. Sonnevile et al. reported that 53% of 2513 patients with sepsis admitted to the ICU had SAE, which was associated with a higher mortality rate, higher use of ICU resources, and a longer hospital stay [96]. The pathophysiology of SAE is diverse, and the mechanisms by which sepsis induces cognitive dysfunction in patients with SAE are complex and may include cerebrovascular damage, BBB disruption, neuroinflammation, neurotransmitter, and mitochondrial dysfunction, oxidative stress, and severe glial (microglia and astrocytes) activation [29, 91]. For a thorough discussion of the roles of systemic inflammation, neuroinflammation, BBB dysfunction, ischemia/hypoperfusion, and Aβ and tau accumulation in sepsis-associated cognitive dysfunction, please refer to “Underlying mechanisms of sepsis-associated brain injury” section of this manuscript. For additional information on other mechanisms, such as mitochondrial and neurotransmitter dysfunction and iatrogenic factors, please refer to published reviews by Mazeraud et al. [29] and Annane et al. [91].

Delirium
Delirium has many shared characteristics and symptoms with the acute phase of SAE: agitation, hallucinations, reduced concentration, and alteration of the sleep-wake cycle [97]. Delirium is commonly seen in critically ill patients and is clinically diagnosed using screening tools, such as the Confusion Assessment Method for the ICU (CAM–ICU) or the Intensive Care Delirium Screening Checklist (ISDSC). Zhang et al. reported sepsis as a risk factor for delirium in ICU patients; others reported risk factors include a history of hypertension, hypoxemia, use of benzodiazepines, deep sedation, and mechanical ventilation [98].

There is still much to learn about the mechanisms underlying sepsis-associated delirium; however, the current understanding is that its pathophysiology involves a combination of neuroinflammation and disturbances in cerebral perfusion, BBB, and neurotransmission [99]. Girard et al. identified four clinical delirium phenotypes: hypoxic, septic, sedative-associated, and metabolic delirium, which were defined a priori based on clinical judgment as well as common risk factors and hypothesized mechanisms for delirium during critical illness [100]. The authors found that longer durations of each one of these phenotypes predicted worse long-term cognitive impairment. Sedative-associated delirium was the most common phenotype and predicted more profound long-term cognitive impairment [100].
Patients who experience infection show common symptoms of sickness, such as loss of appetite, sleepiness, withdrawal from normal social activities, fever, aching joints, and fatigue. Collectively, this clinical syndrome is described as sickness behavior, and it has been shown that physiological concentrations of proinflammatory cytokines that occur after infection affect the brain and induce these symptoms. Sickness behavior is now recognized as part of a motivational system that reorganizes the organism’s priorities to promote recovery from infection [101, 102]. Among proinflammatory cytokines, IL-6 and IL-1β have significant relationships with sickness behavior [103]. In the CLP animal model, the severity of sickness behavior correlated with sepsis severity, mortality, increased permeability of the BBB, high level of IL-6 and oxidative stress, as well as cognitive and memory impairments [104].

Long-term cognitive impairments in sepsis

Sepsis has various long-term effects on brain function and neurological outcomes, including alteration in mood, motor function, and cognitive impairments [4–6]. More than half of sepsis survivors have long-term cognitive impairments [91], which are still inadequately characterized, but may include loss of verbal fluency, memory, and attention deficits [4–6, 91]. Although their prevalence and temporal trajectory differ depending on the cognitive instruments used [105], cognitive impairments among ICU survivors appear to be common, severe, and persistent [105]. Furthermore, sepsis is associated with an accelerated long-term decline in global cognitive function. Compared with pre-sepsis slopes, the long-term rates of cognitive decline are faster after sepsis [106]. SAE has long been considered a reversible syndrome; however, many patients with SAE experience long-term cognitive impairments [5]. Mild to moderate neurological symptoms, including memory changes, depression, anxiety, or cognitive disorders persist in 20% to 40% of these patients 1 year after hospital discharge [94]. Acute delirium in patients with critical illness is also associated with cognitive impairments that persist long after hospital discharge [6, 107].

Imaging findings in sepsis-associated brain injury

WM changes have a direct effect on brain dysfunction and cognitive impairments [108, 109]. Patients with sepsis-associated brain injury tend to have decreased volumes of cerebral and cerebellar WM [110]. Global WM changes on CT head imaging have been reported in adult cases of SAE [111], with no specific locations or patterns for these changes [39]. WM changes tend to worsen with a longer duration of septic shock and worse Glasgow Coma Scale scores [112].

Atrophy has also often been described in long-term observational studies of brain function after recovery from sepsis [113], and early brain atrophy may have long-term effects on the cognitive function of sepsis survivors [113]. Gunther et al. reported that a longer duration of sepsis-related delirium in ICU patients was independently associated with increased global brain atrophy and smaller hippocampal volume [114]. Furthermore, greater brain atrophy at 3 months was associated with worse cognitive performance at 12 months [114].

Apart from WM changes and atrophy, other types of pathological intracranial findings may also be present in patients with sepsis, including hemorrhages, microabscess formation, central pontine myelinolysis, multifocal necrotizing leukoencephalopathy, and ischemic changes [115].

Although it appears that sepsis can cause widespread damage to the brain, specific anatomical locations such as the medial temporal and frontal cortex may correlate with a specific cognitive domain that has been affected in patients with sepsis [92]. Neuroimaging studies show reduced volumes of the hippocampus, amygdala, and cortex during hospitalization due to sepsis [110]. In post-mortem brain tissues from patients who died from sepsis, Sharshar et al. found that apoptotic neurons were found in the amygdala, as well as in the hypothalamus and medulla [89, 116].

New imaging modalities, such as magnetic resonance spectroscopy, diffusion tensor imaging, and positron emission tomography are promising options for early detection of sepsis-associated brain changes [39, 112, 117].

Potential therapeutic strategies for acute and long-term cognitive impairments associated with sepsis

Based on the underlying mechanisms of sepsis-associated brain injury, we propose the following brain-directed therapeutic strategies in the acute and late phases of sepsis to help prevent or ameliorate cognitive impairments (Table 1).

Acute phase therapeutic strategies

**Antibiotics**

Appropriate use of antimicrobial drugs is critical for the treatment of bacterial sepsis. Fluoroquinolones (e.g., ciprofloxacin, moxifloxacin), sulfonamide, rifampicin (i.e., rifampin), metronidazole, and chloramphenicol readily enter the brain, regardless of the BBB state. In contrast, more hydrophilic and larger drugs, such as vancomycin
and members of the β-lactam class of antibiotics, cannot enter the brain, unless the meninges are inflamed [5]. Rifampicin should be noted in particular, because it inhibits Aβ1–40 protein aggregation and neurotoxicity in vitro [118], attenuates the inhibition of autophagosome formation and suppresses the accumulation of Aβ1–42 in vivo [119]. Furthermore, in a mouse model of LPS-induced sepsis, rifampicin protected hippocampal neurons and ameliorated cognitive impairments [119]. Iizuka et al. retrospectively reviewed FDG–PET findings of elderly patients with mycobacterium infection who were treated with rifampicin and did not have dementia at the start of treatment to examine the preventive effects of rifampicin on the progression to AD [120]. The authors found that rifampicin therapy (450 mg/day for at least 12 months) before the onset of dementia improved or stabilized AD-type hypometabolism and made metabolic decline milder in long-term follow-up after completion of therapy. Multiple regression analysis revealed that rifampicin dose and treatment duration significantly influenced FDG uptake in the posterior cingulate cortex [120].

Thus, we propose that the use of rifampicin for the acute treatment of sepsis may have the potential to prevent long-term cognitive dysfunction. However, further research is needed to test this hypothesis. Rifampicin was initially approved for the treatment of tuberculosis. Because of its low toxicity, broad-spectrum activity, and good bioavailability, rifampicin is now commonly used as part of a combination antimicrobial therapy for various infections caused by bacterial infections other than mycobacteriosis (such as acute bacterial meningitis, infective endocarditis and bacteremia, pneumonia, and biofilm-related infections) [121]. Further studies to explore the effects of rifampicin on cognitive function in sepsis should be considered. Any benefits will need to be balanced against the known complications of rifampicin use and its toxicity, including the risk for adverse drug–drug interactions and the emergence of rifampicin resistance during treatment [121].

**Targeting proinflammatory cytokines**

Proinflammatory cytokines, such as IL-6 and IL-1, are important in the early phase of systemic inflammation [4] and have been associated with cognitive impairments in sepsis [103]. Another type of brain injury caused by severe inflammation is chimeric antigen receptor (CAR)-T cell-related encephalopathy syndrome (CRES), a treatment-related complication that may occur in patients with cancer after receiving genetically modified T cells. Cytokine release syndrome (CRS) and its associated CRES neurotoxicity are caused by the release of IL-1 and IL-6, among other cytokines [122]. To suppress this inflammation, both IL-6 and IL-1 are considered viable therapeutic targets, and monoclonal antibodies (mAbs) are already established for this purpose (anakinra against IL-1R, siltuximab against IL-6, and tocilizumab and sarilumab against IL-6R). Targeting IL-1 abolished both CRS and neurotoxicity, whereas targeting IL-6 has failed to suppress delayed lethal neurotoxicity in humanized mice models [123]. In a clinical trial, anakinra was associated with significant improvement in the survival of patients with sepsis [124]. However, cognitive impairments were not assessed in this trial. Given the known role of IL-1 in sepsis, the use of mAbs against IL-1 may represent a new promising approach to suppress neuroinflammation in patients with sepsis and prevent long-term cognitive impairments, but further studies are required.

TNF-α is another promising target in sepsis. In a clinical trial, TNF-α blockade therapy in patients with sepsis significantly reduced mortality 3 days after infusion, and at 28 days following treatment, a trend toward reduced mortality continued, but the difference in mortality was not significant. Neurologic outcomes were not included as part of this trial [125].

**Prevention of hypovolemia and cerebral ischemia**

Fluid replacement in sepsis is necessary to treat hypotension and hypovolemia and to prevent ischemic changes that may occur. Several studies have been conducted to determine what is the best fluid replacement strategy for sepsis. As of today, fluid replacement with crystalloid solutions is recommended [126, 127], whereas the use of colloid solutions is discouraged [128–130]. Further studies are needed to determine the efficacy of albumin-containing fluid replacement therapy [127]. Adequate fluid replacement could help prevent ischemia/hypoxia, subsequently preventing future cognitive impairments in patients with sepsis.

As noted earlier, sepsis induces hypoperfusion in the brain in a similar fashion to ischemic stroke. MRI and CT imaging studies showed that patients with SAE have similar imaging characteristics to those found in patients with stroke [39]. If neuroprotective agents (e.g., PSD-95 inhibitors [131, 132]) currently being investigated in acute ischemic stroke are proven to be beneficial, their use for early ischemic changes in patients with sepsis may help prevent long-term cognitive sequelae.

**Long-term therapeutic strategies**

**Targeting neuroinflammation**

Neuroinflammation starts acutely after sepsis and persists for months [133]. Olivieri et al. showed that brain inflammation persists up to 3 months after sepsis in rats and is associated with increased Aβ level, activated microglia, and long-term cognitive impairment [133].
Microglia is the main inflammatory cell that gets activated in sepsis [26] in animals [27] and humans [28]. Thus, modulating activated microglia may be a promising approach to prevent chronic neuroinflammation and long-term cognitive impairment associated with sepsis. Recent research revealed that IL-17A/IL-17R might serve as a checkpoint in microglia-mediated neuroinflammation [134, 135]. In the CLP animal model, neutralizing anti-IL-17A or anti-IL-17R antibodies mitigated neuroinflammation and microglia activation, and alleviated cognitive dysfunction [136]. In another research using a traditional medicinal herb that is widely used for treating inflammatory conditions in South-East Asia [137], it was shown that attractylone treatment attenuates sepsis-associated encephalopathy and cognitive dysfunction by inhibiting microglial activation and neuroinflammation [138]. Despite these encouraging data, targeting microglial activation might have drawbacks, as microglia also have neuroprotective effects [139], and inhibiting their function might have deleterious effects. More research is needed to examine targeting microglia as a therapeutic approach to help alleviate cognitive impairments associated with sepsis.

**Targeting BBB dysfunction**

BBB breakdown is an early biomarker of cognitive dysfunction in humans [140]. In patients with sepsis and SAE, vasogenic edema and WM hyperintensities on MRI are found frequently, indicating BBB disruption [39, 40]. Brain tissues of patients who died due to sepsis show a reduction of TJ proteins, indicating BBB damage [42]. Sepsis may disrupt the BBB through the S1P pathway, which maintains BBB integrity [43, 41]. Serum-S1P levels are dramatically decreased and inversely associated with disease severity in patients with sepsis [44] and in LPS-induced SAE in mice [142]. Fingolimod (FTY720) is an S1P modulator that is approved for the treatment of relapsing–remitting multiple sclerosis [143]. Fingolimod was also shown to modulate multiple neuroinflammatory markers and to decrease Aβ plaque density in a mouse model of AD [144]. Fingolimod and other S1P modulators have also shown promising results in modulating neuroinflammation [145] and BBB integrity [146] after ischemic stroke. Thus, targeting BBB disruption through modulation of the S1P pathway may be a promising direction to alleviate sepsis-induced BBB disruption and cognitive impairment, but more research is needed to test this approach.

**Targeting amyloid β and tau phosphorylation**

Growing evidence suggests that targeting Aβ oligomers (soluble aggregates of Aβ) and plaques (insoluble extracellular aggregates of fibrillar Aβ) with selective mAbs (e.g., aducanumab) can slow disease progression in patients with AD [58, 147]. Available data from animal [59, 61–63] and human research [64–69] suggest that similar to AD, Aβ and p-tau accumulation may be involved in long-term cognitive dysfunction associated with sepsis. Thus, targeting Aβ and p-tau with mAbs may also be a promising new approach to prevent or treat long-term cognitive impairments in patients with sepsis, but more research to test this hypothesis is warranted.

**Targeting GSK3β**

Excessive phosphorylation of tau is the main cause of tauopathy. GSK3β is one of the most important kinases of the tau protein [70] and a powerful regulator of inflammation [71]. This makes GSK3β another potential target for sepsis-associated brain injury. Lithium is a known inhibitor of GSK3β that has been mainly used to treat bipolar disorders and major depression. In a meta-analysis of randomized placebo-controlled trials investigating lithium as a treatment for mild cognitive impairment and AD dementia, it was suggested that lithium might have beneficial effects on cognitive performance [148, 149]. Taken together, these data and the known underlying mechanisms of sepsis-related cognitive impairments suggest that lithium might have the potential to ameliorate long-term cognitive impairments in sepsis survivors.

**Targeting RAGE**

RAGE is upregulated in microglia and neurons in the brains of patients with AD [85], and it has been identified as an important link between inflammation, amyloidogenesis, and apoptosis during AD progression [78, 79]. In animal models of sepsis, the levels of RAGE and p-tau are increased in the rat brain [63], and the injection of RAGE antibodies into the hippocampus reduces Aβ and p-tau accumulation [60]. High mobility group box 1 (HMGB1) plays an important role in inflammation and operates mainly through RAGE and TLR4 receptors [150]. In sepsis survivors, serum HMGB1 levels remain elevated at the time of hospital discharge [151], and administration of neutralizing anti-HMGB1 antibody beginning at 1 week [152] after the onset of sepsis in animals provided significant protection against cognitive impairment [152]. These data suggest that targeting RAGE directly or through HMGB1 might be a promising approach to regulate inflammation and decrease cognitive impairment in sepsis; however, more research is needed to further confirm the findings of these preliminary studies.

For discussion of other therapeutic strategies that were not mentioned in this article, please refer to Barichello et al. [4], Jarczak et al. [153], and Slikke et al. [154].
Conclusions
In this review, we have described the spectrum of cognitive brain injuries associated with sepsis. Although the diverse molecular mechanisms underlying brain damage in sepsis are intertwined and have not been fully characterized, it is evident that local and systemic inflammation plays an important role in both the short and long term. Our proposed strategies here are meant to bring new mechanism-based directions for future basic and clinical research aimed at preventing or ameliorating acute and long-term cognitive impairments in patients with sepsis. New imaging modalities are also needed for clinical detection and characterization of sepsis-associated brain injuries.

Abbreviations
Aβ: Amyloid-beta; AD: Alzheimer’s disease; BBB: Blood–brain barrier; CRES: CAR-T-related encephalopathy syndrome; CRS: Cytokine release syndrome; GSK3β: Glycogen synthase kinase-3 beta; ICU: Intensive care unit; IL: Interleukin; LPS: Lipopolysaccharide; MRI: Magnetic resonance imaging; SAE: Sepsis-associated encephalopathy; TJ: Tight junction; WM: White matter.

Acknowledgements
We thank Haifa Kassis, MD, for her editorial assistance.

Author contributions
Conceived and designed the manuscript: NS and AS; Wrote the main manuscript: NS and AS; Revised the manuscript: AS, NS and MS; All authors reviewed the manuscript. All authors read and approved the final manuscript.

Funding
The work was supported by NIH grant R01AG055559.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors consented for publication.

Competing interests
The authors have no competing interests.

Author details
1 Department of Medicine, Translational Therapeutics Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.

2 Department of Neurology, Stroke and Cerebrovascular Diseases Division, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, CLS-641, Boston, MA 02215, USA.

Received: 3 January 2022 Accepted: 14 April 2022
Published online: 29 April 2022

References
1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10.

2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kvielian DR, Colombara DV, Ikuwa KS, Kissoon N, Finder S, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200–11.

3. Hotchkiss RS, Moldawer LL, Opal SM, Reinharth K, Tumblir JR, Vincent JL. Sepsis and septic shock. Nat Rev Dis Primers. 2016;2:16045.

4. Barichello T, Sayana P, Girdharan VV, Arunanayagam AS, Narendran B, Della Giustina A, Petroniho F, Quevedo J, Dal-Pizzolo F. Long-term cognitive outcomes after sepsis: a transnational systematic review. Med Biol. 2019;56(1):186–251.

5. Nwofor DC, Brichacek AL, Mohammad AS, Griffith J, Lucke-Wold BP, Benkovic SA, Geldenhuyns WJ, Lockman PR, Brown CM. Targeting the blood–brain barrier to prevent sepsis-associated cognitive impairment. J Cent Nerv Syst Dis. 2019;11:179573519840652.

6. Pandharpande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306–16.

7. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Furrer R, Krumar A, Sevransky JE, Sprung C, Nunnally ME, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock. 2016. Crit Care Med. 2017;45(3):486–552.

8. Ruiz S, Vardon-Bounes F, Merlet-Dupuy V, Cornil JM, Buleon M, Fourcade O, Tack I, Minville V. Sepsis modeling in mice: Ligation length is a major severity factor in cecal ligation and puncture. Intensive Care Med Exp. 2016;4(1):22.

9. Buras JA, Holzmann B, Siktovskiy M. Animal models of sepsis: setting the stage. Nat Rev Drug Discov. 2005;4(10):854–65.

10. Raven K. Rodent models of sepsis found shockingly lacking. Nat Med. 2012;18(7):998.

11. Gabarin RS, Li M, Zimmel PA, Marshall JC, Li Y, Zhang H. Intracellular and extracellular lipopolysaccharide signaling in sepsis: avenues for novel therapeutic strategies. J Innate Immun. 2021;13(6):323–32.

12. Remick DG, Newcomb DE, Bolgos GL, Call DR. Comparison of the mortality and inflammatory response of two models of sepsis: lipopolysaccharide vs. cecal ligation and puncture. Shock. 2000;13(2):110–6.

13. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol. 2010;11(5):373–84.

14. Raymond SL, Holden DC, Mira JC, Stortz JA, Mohr AM, Moldawer LL, Moore FA, Larson SD, Efron PA. Microbial recognition and danger signals in sepsis and trauma. Biochim Biophys Acta Mol Basis Dis. 2017;1863(10 Pt B):2564–73.

15. Tang D, Kang R, Coyne CB, Zeh HJ, Lotze MT. PAMPs and DAMPs: signal 0s that spur autophagy and immunity. Immunol Rev. 2012;249(1):158–75.

16. Pahl HL. Activators and target genes of Rel/NF-κappaB transcription factors. Oncogene. 1999;18(49):6653–66.

17. Nedeveda C, Menassa J, Puthalakath H. Sepsis: inflammation is a necessary evil. Front Cell Dev Biol. 2019;7:108.

18. Maciel M, Benedict SR, Lunardelli EB, Delzotto H, Domingues RL, Vuolo F, Tomasi CD, Walz R, Ritter C, Dal-Pizzolo F. Predicting long-term cognitive dysfunction in survivors of critical illness with plasma inflammatory markers: a retrospective cohort study. Mol Neurobiol. 2019;56(1):763–7.

19. Laflamme N, Echchannaoui H, Landmann R, Rivest S. Cooperation between toll-like receptor 2 and 4 in the brain of mice challenged with cell wall components derived from gram-negative and gram-positive bacteria. Eur J Immunol. 2003;33(4):1127–38.

20. Tomasi CD, Walz R, Ritter C, Dal-Pizzolo F. Type 1 interleukin-1 receptor in the rat brain: distribution, regulation, and relationship to sites of IL-1-induced cellular activation. J Comp Neurol. 1995;361(4):681–98.

21. Valleriès L, Rivest S. Regulation of the genes encoding interleukin-6, its receptor, and gp130 in the rat brain in response to the immune activator lipopolysaccharide and the proinflammatory cytokine interleukin-1beta. J Neurochem. 1997;69(4):1688–83.

22. Nadefu S, Rivest S. Regulation of the gene encoding tumor necrosis factor alpha (TNF-alpha) in the rat brain and putatory in response in different models of systemic immune challenge. J Neuro reflect Exp Neurol. 1999;58(1):61–77.

23. Skelly DT, Hennessy E, Dansereau MA, Cunningham CA. A systematic analysis of the peripheral and CNS effects of systemic LPS, IL-1beta,
Sekino et al. Journal of Neuroinflammation  (2022) 19:101

Page 11 of 14

24. Liu X, Nemeth DP, McMickin DB, Zhu L, DiGibato DJ, Berdysz O, Gorantla G, Oliver B, Witcher KG, Wang Y, et al. Cell-type-specific interleukin 1 receptor 1 signaling in the brain regulates distinct neuroimmune activities. Immunity. 2019;50(3):764–6.

25. Gutierrez EG, Banks WA, Kastin AJ. Murine tumor necrosis factor alpha is transported from blood to brain in the mouse. J Neuroimmunol. 1993;47(2):169–76.

26. van Goor WA, van de Beek D, Eikelenboom P.Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet. 2010;375(9716):773–5.

27. Hoogland IC, Houbolt CJ, van Westerloo DJ, van Gool WA, van de Beek D, Rauschka H, Butovsky O, Weiner H, Mazeraud A, Righy C, Bouchereau E, Benghanem S, Bozza FA, Sharshar T. Septic-associated encephalopathy: a comprehensive review. Neurotherapeutics. 2020;17(2):392–403.

28. Zrzavy T, Hoftberger R, Berger T, Rauschka H, Butovsky O, Weiner H, Laisermann H. Pro-inflammatory activation of microglia in the brain of patients with sepsis. Neuropathol Appl Neurobiol. 2019;45(3):278–90.

29. Mzaourad A, Rigby C, Benghanem S, Bozza FA, Sharshar T. Septic-associated encephalopathy: a comprehensive review. Neurotherapeutics. 2020;17(2):392–403.

30. Lemstra AW, Grooten t/m Woud JC, Hoozemans JJ, van Haastert ES, Rozeboom AW, Moraes CA, Santos G, de Sampaio e Spohr TC, D'Avila JC, Lima FR, Akrout N, Sharshar T, Annane D. Mechanisms of brain signaling during acute inflammation and microglial activation: systematic review of animal experiments. J Neuroinflamm. 2015;12:114.

31. Hughes CG, Patel MB, Pandharipande PP. Pathophysiology of acute brain dysfunction. Crit Care. 2012;16(Suppl 3):P185–6.

32. Halley MJ, Lawrence CB. The blood-brain barrier after stroke: structural changes in the cerebral endothelium. J Cereb Blood Flow Metab. 2017;37(2):456–70.

33. Bernardo-Castro S, Sousa JA, Bras A, Cecilia C, Rodrigues B, Almendra L, Colasante-Zapatero D, Peres-Bota D, Vincent JL, Berre J, Melot C. Cerebral autoregulation is influenced by carbon dioxide levels in patients with septic shock. Neurocrit Care. 2010;12(3):35–42.

34. Melot C. Cerebral autoregulation is influenced by carbon dioxide levels in patients with septic shock. Neurocrit Care. 2010;12(3):35–42.

35. Alonso-Becerra T, Cepeda-Fernandez L, Mendieta-Valenzuela A, Ritter C, Dal-Pizzol F. The impact of age on long-term behavioral and neurochemical parameters in an animal model of severe sepsis. J Neuroinflamm. 2018;15(1):49–60.

36. Stubbs DJ, Yamamoto AK, Menon DK. Imaging in sepsis-associated encephalopathy—insights and opportunities. Nat Rev Neurol. 2013;10(10):551–61.

37. Eftier J, Barrett LK, Taylor M, Groves M, Scaravilli F, Witsworth M, Kidbaske S, Grossmann A, Herschel J, Gloger M, et al. Translational evidence for two distinct patterns of neuroaxonal injury in sepsis: a longitudinal, prospective translational study. Crit Care. 2017;21(1):262.

38. Dal-Pizzol F, Rosas HA, dos Santos EM, Vieira F, Constantino J, Leite R, et al. Matrix metalloproteinase-2 and metalloproteinase-9 activities are associated with brain-blood barrier dysfunction in an animal model of severe sepsis. Mol Neurobiol. 2013;48(3):513–38.

39. Paris L, Tonutti L, Vannini C, Bazzoni G. Structural organization of the tight junctions. Biochim Biophys Acta. 2008;178(3):646–59.

40. Towner RA, Saunders D, Smith KA, Towler W, Cruz M, Do S, Maher J, Whitaker K, Lerner M, Morton KA. Assessing long-term neuroinflammatory responses to encephalopathy using MRI approaches in a rat endotoxemia model. Geroscience. 2018;40(1):49–60.

41. Kirk RA, Kesner RP, Wang LM, Wu Q, Towner RA, Hoffman JM, Morton KA. Lipopolysaccharide exposure in a rat sepsis model results in hippocampal amyloid-β plaque and phosphorylated tau deposition and corresponding behavioral deficits. Geroscience. 2019;41(4):467–81.

42. Gasparrato J, Girardi CS, Somensi N, Ribeiro CT, Moreira JCF, Michels M, Soni B, Rocha M, Steckert AV, Barichello T, et al. Receptor for advanced glycation end products mediates sepsis-triggered amyloid-β accumulation, Tau phosphorylation, and cognitive impairment. J Biol Chem. 2018;293(1):226–44.

43. Gasparrato J, Girardi CS, Somensi N, Ribeiro CT, Moreira JCF, Michels M, Soni B, Rocha M, Steckert AV, Barichello T, et al. Receptor for advanced glycation end products mediates sepsis-triggered amyloid-β accumulation, Tau phosphorylation, and cognitive impairment. J Biol Chem. 2018;293(1):226–44.

44. Zhao T, Xia Y, Wang D, Pang L. Association between elevated serum tau protein level and sepsis-associated encephalopathy.
in patients with severe sepsis. Can J Infect Dis Med Microbiol. 2019;2019:1876174.

65. Orhun G, Esen F, Ozcan PE, Sencer S, Bilgic B, Ulusoy C, Noyan H, Kucukkerden M, Ali A, Barbuglu M, et al. Neuroimaging findings in sepsis-induced brain dysfunction: association with clinical and laboratory findings. Neurocrit Care. 2019;30(1):106–17.

66. Rogne AG, Muller EG, Udnaes E, Sigurdardottir S, Raudeberg R, Kamer AR, Pirraglia E, Tsui W, Rusinek H, Vallabhajosula S, Mosconi L, Yi JZ, Xia YY, Grundke-Iqbal I, Iqbal K. Abnormal hyperphosphorylation of tau in sepsis-induced brain dysfunction: association with clinical and laboratory findings. Neurocrit Care. 2019;30(1):106–17.

67. Kamer AR, Pirraglia E, Tsui W, Rusinek H, Vallabhajosula S, Mosconi L, Yi JZ, Xia YY, Grundke-Iqbal I, Iqbal K. Abnormal hyperphosphorylation of tau in sepsis-induced brain dysfunction: association with clinical and laboratory findings. Neurocrit Care. 2019;30(1):106–17.

68. Martin M, Rehani K, Jope RS, Michalek SM. Toll-like receptor-mediated cytokine production is differentially regulated by glycogen synthase kinase-3. J Biol Chem. 2008;283(32):21934–44.

69. Gompich A, Mimirn E, Hemmati F, Ibrahim NM, Rahman B, Mohamed Z, Raymond AA, Dargahi L, Ghasem R, Ahmadnia A. Glycogen synthase kinase-3 beta (GSK-3β) signaling: Implications for Parkinson’s disease. Pharmacol Res. 2015;97:16–26.

70. Dong G, Ge Y, Chen S, Liang E, Esparza A, Sabo E, Yango A, Gohh R, Rifi A, Dworkin LD. Glycogen synthase kinase 3beta: a novel marker and modulator of inflammatory injury in chronic renal allograft disease. Am J Transplant. 2008;8(9):1852–63.

71. Martin J, Maharani S, Manypapa MI, Tynnenen O, Paetau A, Andersson N, Sajantila A, Vapalahti O, Carpen O, Kekalainen E, et al. Neuro-pathologic features of four autopsied COVID-19 patients. Brain Pathol. 2020;30(6):1012–6.

72. Rhodes CH, Prierer DS, Eska K, Perl DP, James G. B-Amyloid deposits in young COVID patients. Preprints with THE LANCET. 2022.

73. Wang JZ, Xia YY, Grundke-Iqbal L, Iqbal K. Abnormal hyperphosphoryla-
tion of tau: sites, regulation, and molecular mechanism of neurofi-
lbrogeneic degeneration. J Alzheimers Dis. 2013;33(Suppl 1):S123-139.

74. Oliven C, Zhai J, Xiong Y, Zhang W, Liu Y, Chen J, Wang L, Wang X, He K, et al. Involvement of microglial receptor for advanced glycation end products (RAGE) in Alzheimer’s disease: identification of a cellular activation mechanism. Exp Neurol. 2001;171(1):29–45.

75. Beurel E. Regulation by glycogen synthase kinase-3 of inflammation during ageing. Nat Rev Immunol. 2021. https://doi.org/10.1038/s41590-021-02303-2.

76. Beurel E, Jope RS. Differential regulation of STAT family members by glycogen synthase kinase-3. J Neuroinflammation. 2022;19:101.

77. Beurel E, Jope RS. Differential regulation of STAT family members by glycogen synthase kinase-3. J Neuroinflammation. 2022;19:101.

78. Yu Y, Ye RD. Microglial Abeta receptors in Alzheimer’s disease. Cell Mol Neurobiol. 2016;36(4):483–95.

79. Wautier MP, Tessier FJ, Wautier JL. Advanced glycation end products: a contributor to neuroinflammation, Abeta accumulation, and impaired learning/memory in a mouse model of Alzheimer’s disease. FASEB J. 2010;24(4):1043–55.

80. Fang F, Yu Q, Arancio O, Chen D, Gore SS, Yan SS, SF. RAGE mediates Abeta accumulation in a mouse model of Alzheimer’s disease via modulation of beta- and gamma-secretase activity. Hum Mol Genet. 2018;27(6):1002–14.

81. Sharshar T, Annane D, de la Grandmaison GL, Broussaud JP, Hopkinson NS, Francoise G. The neuropathology of septic shock. Brain Pathol. 2004;14(1):21–33.

82. Valderrama EV, Humbert K, Lord A, Frontera J, Yaghj S. Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke. Stroke. 2020;51(7):1247–49.

83. Czermak PF, Pluta MP, Krzech LJ. Sepsis-associated brain dysfunction: a review of current literature. Int J Environ Res Public Health. 2020;17(16):5852.

84. Catarina AV, Branchini G, Bettioni L, De Oliveira JR, Nunes FB. Sepsis-associated encephalopathy: from pathophysiology to progress in experimental studies. Mol Neurobiol. 2021. https://doi.org/10.1007/s12035-021-02303-2.

85. Chaudhry N, Duggal AK. Sepsis-associated encephalopathy. Adv Med. 2014;2014:762320.

86. Sonnerrville R, de Montomillon E, Paujade J, Garrouste-Orgues M, Souweine B, Darmon M, Manioite E, Arguel G, Barbier F, Goldgran-Toledano D, et al. Potentially modifiable factors contributing to sepsis-associated encephalopathy. Intensive Care Med. 2017;43(8):1075–84.

87. Chung HY, Widell J, Brunskhorst FM, Geis C. Sepsis-associated encephalo-
pathy: from delirium to dementia? J Clin Med. 2020;9(3):703.

88. Zhang H, Yuan J, Chen Q, Gao Y, Wang Z, Lu W, Bao J. Development and validation of a predictive score for ICU delirium in critically ill patients. BMC Anesthesiol. 2021;21(1):57.

89. Atterton B, Paulino MC, Pooa P, Martin-Loeches I. Sepsis associated delirium. Medicina (Kaunas). 2020;56(5):240.

90. Giral TD, Thompson JL, Pandharipande PP, Jackson J, Patel MB, Hughes CG, Chandrasekhar R, Pun BT, Boehm LM, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. Lancet Respir Med. 2018;6(3):213–22.

91. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun. 2007;21(2):153–60.

92. Kelley KW, Bluthé RM, Dantzer R, Zhou JH, Shen WH, Johnson RW, Brossard SS. Cytokine-induced sickness behavior. Brain Behav Immun. 2003;17(Suppl 1):S112-118.

93. Shattuck EC, Muehlenbein MP. Towards an integrative picture of human sickness behavior. Brain Behav Immun. 2003;17(Suppl 1):S112-118.

94. Pereira de Souza Goldim M, Delia Giustina A, Mathias K, de Oliveira Junior A, Fileti ME, De Carlì R, Zarbato G, Garbossa L, da Rosa N, Oliveira J, et al. Sickness behavior score is associated with neuroinflammation and late behavioral changes in polymicrobial sepsis animal model. Inflammation. 2020;43(3):1019–34.

95. Honarmand K, Lalli RS, Priestap F, Chen JL, McIntyre CW, Owen AM, Slessarev M. Natural history of cognitive impairment in criti-
cal illness survivors: A systematic review. Am J Respir Crit Care Med. 2021;202(2):193–201.

96. Wang HE, Kabeto MM, Gray M, Wadley VG, Muntner P, Judd SE, Safford MM, Kemperk J, Levine DA. Trajectory of cognitive decline after sepsis. Crit Care Med. 2021. https://doi.org/10.1097/CCM.0000000000004897.

97. Mart M, Williams Roberson S, Salas B, Pandharipande PP, By EW. Pre-
vention and management of delirium in the intensive care unit. Semin Resper Crit Care Med. 2021;42(1):112–26.
108. Bennett LJ, Madden DJ. Disconnected aging: cerebral white matter integrity and age-related changes in cognition. Neuroscience. 2014;276:187–205.

109. Hase Y, Horsburgh K, Ihara M, Kalaria RN. White matter degeneration in vascular and other age-related dementias. J Neurochem. 2018;144(5):617–33.

111. Luitse MJ, van Asch CJ, Klijn CJ. Deep coma and diffuse white matter abnormalities caused by sepsis-associated encephalopathy. Lancet. 2013;381(9884):2222.

112. Shashar T, Carlier R, Bernard F, Guidoux C, Brouland JP, Nardi O, de la Grandmaison GL, Aboab J, Gray F, Menon D, et al. Brain lesions in septic shock: a magnetic resonance imaging study. Intensive Care Med. 2007;33(5):798–806.

113. Seidel G, Gaser C, Götz T, Günther A, Hamzei F. Accelerated brain ageing in sepsis survivors with cognitive long-term impairment. Eur J Neurosci. 2020;52(10):4395–402.

114. Gunther ML, Morandi A, Krauskopf E, Pandharipande P, Girard TD, Jack JP, et al. Brain volume changes in patients with acute brain dysfunction due to sepsis. Neurocrit Care. 2020;32(2):459–68.

115. Norelli M, Camisa B, Barbiera G, Falcone L, Purevdorj A, Genua M, Sanvito F, Ponzoni M, Doglioni C, Cristofori P, et al. Monocyte-derived IL-17A/IL-17R pathway protected mice from sepsis-associated encephalopathy by inhibition of microglia activation. Mediators Inflam. 2019;2019:8461725.

116. Avila AA, Kinberg EC, Sherwin NK, Taylor RD. The use of fluids in sepsis. Cureus. 2016;8(3):e528.

117. Sevigny J, Choi P, Bussière T, Weirenb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer’s disease. Nature. 2016;533(7618):50–6.

118. Nitzschke A, Poittevin M, Benarab A, Bonnin P, Faraco G, Uchida H, Favre J, Garcia-Bonilla L, Garcia MCL, Leger PL, et al. Endothelial S1P1 signaling counteracts infects injury in ischemic stroke. Circ Res. 2021;128(3):363–82.

119. Willis MA, Cohen JA. Fingolimod therapy for multiple sclerosis. Semin Neurol. 2013;33(1):37–44.

120. Aytan N, Choi JK, Carreras I, Brinkmann V, Kowall NW, Jenkins BG, Dedeoglu A, Fingolimod modulates multiple neuroinflammatory markers in a mouse model of Alzheimer’s disease. Sci Rep. 2016;6:24939.

121. Gaire BP, Lee CH, Sapkota A, Lee SY, Chun J, Cho HJ, Nam TG, Choi JW. Identification of sphingosine-1-phosphate receptor subtype 1 (S1P1) as a putative mechanism underlying LPS-induced BBB disruption. J Neurochem. 2018;144(2):172–85.

122. Willis MA, Cohen JA. Fingolimod therapy for multiple sclerosis. Semin Neurol. 2016;36(Suppl 1):10–7.

123. Nitzschke A, Poittevin M, Benarab A, Bonnin P, Faraco G, Uchida H, Favre J, Garcia-Bonilla L, Garcia MCL, Leger PL, et al. Endothelial S1P1 signaling counteracts infects injury in ischemic stroke. Circ Res. 2021;128(3):363–82.

124. Sevigny J, Choi P, Bussière T, Weirenb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer’s disease. Nature. 2016;533(7618):50–6.
148. Hampel H, Lista S, Mango D, Nisticò R, Perry G, Avila J, Hernández F, Geerts H, Vergallo A. Lithium as a treatment for Alzheimer’s disease: the systems pharmacology perspective. J Alzheimers Dis. 2019;69(3):615–29.

149. Matsunaga S, Kishi T, Annas P, Basun H, Hampel H, Iwata N. Lithium as a treatment for Alzheimer’s disease: a systematic review and meta-analysis. J Alzheimers Dis. 2015;48(2):403–10.

150. Yang H, Wang H, Andersson U. Targeting inflammation driven by HMGB1. Front Immunol. 2020;11:484.

151. Angus DC, Yang L, Kong L, Kellum JA, Delude RL, Tracey KJ, Weissfeld L, Gen IMSI. Circulating high-mobility group box 1 (HMGB1) concentrations are elevated in both uncomplicated pneumonia and pneumonia with severe sepsis. Crit Care Med. 2007;35(4):1061–7.

152. Chavan SS, Huerta PT, Robbini S, Valdes-Ferrer SI, Ochani M, Dancho M, Frankfurt M, Volpe BT, Tracey KJ, Diamond B. HMGB1 mediates cognitive impairment in sepsis survivors. Mol Med. 2012;18:930–7.

153. Jarczak D, Kluge S, Nierhaus A. Sepsis-pathophysiology and therapeutic concepts. Front Med (Lausanne). 2021;8:628302.

154. van der Slikke EC, An AY, Hancock REW, Bouma HR. Exploring the pathophysiology of post-sepsis syndrome to identify therapeutic opportunities. ElBioMedicine. 2020;61:103044.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.