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Long-Term Cognitive Outcomes After Sepsis: a Translational Systematic Review

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Abstract

Sepsis is systemic inflammatory response syndrome with a life-threatening organ dysfunction that is caused by an unbalanced host immune response in an attempt to eliminate invasive microorganisms. We posed questions, "Does sepsis survivor patients have increased risk of neuropsychiatric manifestations?" and "What is the mechanism by which sepsis induces long-term neurological sequelae, particularly substantial cognitive function decline in survivor patients and in pre-clinical sepsis models?" The studies were identified by searching PubMed/MEDLINE (National Library of Medicine), PsycINFO, EMBASE (Ovid), LILACS (Latin American and Caribbean Health Sciences Literature), IBECS (Bibliographical Index in Spanish in Health Sciences), and Web of Science databases for peer-reviewed journals that were published until January 2018. A total of 3555 papers were included in the primary screening. After that, 130 articles were selected for the study. A number of pre-clinical studies have shown an auto amplification of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6 in the first few hours after sepsis induction, also increased blood-brain barrier permeability, elevated levels of matrix metalloproteinases, increased levels of damage-associated molecular patterns were demonstrated. In addition, the rodents presented long-term cognitive impairment in different behavioral tasks that were prevented by blocking the mechanism of action of these inflammatory mediators. Clinical studies have showed that sepsis survivors presented increased bodily symptoms such as fatigue, pain, visual disturbances, gastrointestinal problems, and neuropsychiatric problems compared to before sepsis. Sepsis leaves the survivors with an aftermath of physiological, neuropsychiatric, and functional impairment. Systematic review registration: CRD42017071755.

Keywords Sepsis · Neurocognitive impairment · Neuropsychiatric outcome · Inflammation

Introduction

Sepsis is a systemic response to infection with severe organ dysfunction caused by an unbalanced host immune response, in an attempt to eliminate invasive microorganisms [1]. After the infection, pathogens and their compounds, pathogen-associated molecular patterns (PAMPs), are identified by antigen-presenting cells via pattern recognition receptors

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(PRRs). The interaction between PAMPs and PRRs promotes the activation of pro-inflammatory pathways releasing cytokines, chemokines, and acute-phase proteins such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-6, and pentraxin-3 (PTX-3) PMID [2–4]. Additionally, endogenous constituents from damaged tissue or those actively released from cells during inflammatory processes can bind and activate PRRs. These endogenous products, named damage-associated molecular patterns (DAMPs), are sterile inductors of the immune system, and the most studied are heat shock protein (HSP), high mobility group box-1 protein (HMGB-1), S-100 proteins, advanced glycation end products (AGEs), and mitochondrial sub products [5, 6]. In clinical studies, patients diagnosed with severe sepsis and septic shock presented an overlapping network of PAMPs and DAMPs with elevated levels of HMGB-1, HSP, and the S100 calcium-binding protein B (S100B) family in their bloodstream [7, 8]. This exacerbated host immune response increases the blood-brain barrier (BBB) permeability, facilitating the infiltration of immune cells from the bloodstream into the brain, which together with the brain immune response causes cell damage. Additionally, evidence suggests that sepsis survivors present long-term neurological sequelae with decline in cognitive function [9]. The pathway by which sepsis triggers cognitive dysfunction probably includes systemic metabolic disorders, increased host immune response, oxidative and nitrosative stress, and BBB disruption, followed by immune cells infiltrating the brain and severe microglial activation [9]. Thus, based on the high incidence of sepsis in the world and post-sepsis cognitive impairment, this systematic review aims to (i) identify mechanisms by which sepsis induces long-term neurological sequelae, particularly substantial decline in cognitive function in sepsis survivor patients and in pre-clinical sepsis models; (ii) provide evidence of biomarkers involved in brain neuroinflammation that can predict cognitive impairment in sepsis patients and in pre-clinical sepsis models; and (iii) draw attention to adjuvant treatment as a new avenue to prevent cognitive impairment post-sepsis.

Methods

We accomplished this systematic review as stated in a prospective protocol using PRISMA statement guidelines [10]. The review protocol is registered at PROSPERO (registration number: CRD42017071755; http://www.crd.york.ac.uk/prospero).

Literature Search Strategy

A systematic review of pre-clinical and clinical studies was conducted to evaluate mechanisms by which sepsis induces long-term neurological sequelae. The studies were identified by searching the PubMed/MEDLINE (National Library of Medicine), PsycINFO, and EMBASE (Ovid) databases for peer-reviewed journals that were published until January 2018. To identify additional relevant citations, we conducted forward searches in LILACS (Latin American and Caribbean Health Sciences Literature), IBECS (Bibliographical Index in Spanish in Health Sciences), and Web of Science. The abovementioned databases were searched with the following combinations of keywords: ("sepsis" OR "septic shock" OR "septicemia" OR "lipopolysaccharide" OR "LPS" OR "cecal ligation and puncture" OR "cecal ligation and perforation" OR "CLP") AND ("cognitive impairment" OR "encephalopathy" OR "delirium" OR "dementia" OR "psychiatric disorder" OR "sickness behavior" OR "neurocognitive impairment" OR "Alzheimer's disease" OR "schizophrenia" OR "mental disorder" OR "depressive disorder" OR "memory" OR "functional deficits" OR "functional impairment" OR "stress disorder" OR "post-traumatic stress disorder").

Review of Interventions for Health, Patient, Intervention, Comparators, Outcome Measures, and Study Design (PICO)

We posed the questions "Do sepsis survivor patients have increased risk of neuropsychiatric manifestations?" and "What is the mechanism by which sepsis induces long-term neurological sequelae, particularly substantial cognitive function decline in survivor patients and in pre-clinical sepsis models?"

Eligibility Criteria

We included the original peer-reviewed articles with no language restriction and with pre-clinical and clinical studies to study the mechanisms by which sepsis induces long-term neurological sequelae and cognitive impairment. We omitted review articles, in vitro studies, and studies that included patients with previous disease as a risk factor for sepsis.

Screening

A total of 3555 articles were included in the primary screening. Reference management software (EndNote X7 for Windows from Thomson Reuters, 2013) was used for screening purposes. After the omission of 562 duplicates, a total of 2993 articles were selected for the study. The retrieved studies were first screened on the basis of their title and abstract and 2819 articles were further omitted on the basis of the exclusion criteria (reviews, in vitro studies, previous disease as a risk factor to acquire sepsis). The full-text articles of the remaining 174 articles were obtained and thoroughly evaluated for a second screening. At the end of the second screening, 130 articles were

ultimately included after 44 articles were discarded on the basis of the exclusion criteria (Fig. 1).

Article Selection

Primarily, two authors screened the titles and abstracts for eligibility (PS and ACSA). Any controversies regarding the studies were resolved through unison checking. Upon agreement from the two authors, valid references on the basis of the selection criteria were selected for final inclusion, and full-text PDFs were obtained and analyzed for their data. The third and fourth authors, TB and VVG, settled issues whenever a consensus could not be reached between the first two authors.

Data Extraction

The data were extracted from the comprehensively reviewed journal articles in a methodical manner. The extracted variables included in our review are as follows: sample size (*n*), sepsis model, inflammatory biomarkers, intervention, and behavioral task in pre-clinical studies. For clinical studies, we extracted the following: the study design, sample size (*n*), sepsis assessment, inflammatory biomarkers, intervention, and how the inflammatory marker profile was associated with cognitive impairment in sepsis survivor patients.

Results and Discussion

Pre-Clinical Sepsis Studies

Sepsis Pre-Clinical Models

There are different models to induce sepsis, including the cecum ligation and puncture or perforation (CLP), colon ascendens stent peritonitis (CASP), lipopolysaccharide (LPS) induced, bacterial infusion, bacterial sepsis, and fibrin experimental peritonitis models; however, a translational model to mimic the clinical symptoms is crucial [11]. The CLP is considered the gold standard model to study sepsis [12]. The CLP model includes ligation of the cecum distal to the ileocecal valve and puncture of the cecum to permit leakage of fecal substances into the peritoneum, triggering peritonitis that ultimately causes sepsis [13]. The CASP model was first described by Zantl and colleagues in 1998 [14]. In this model, a stent is inserted into the ascending colon by puncture and immobilized with a suture to the colonic wall. Stent insertion allows transmigration of colonic flora from the gut into the peritoneal cavity. The LPS sepsis model mimics an infection triggered by Gram-negative bacteria. LPS is the major component of the bacterial outer membrane localized in the outer layer of the membrane in non-capsulated bacterial strains. LPS may be administered intraperitoneally (i.p.) or intravenously (i.v.) in rodents, and it can increase pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6 in the plasma and in the peritoneal cavity, which attain peak

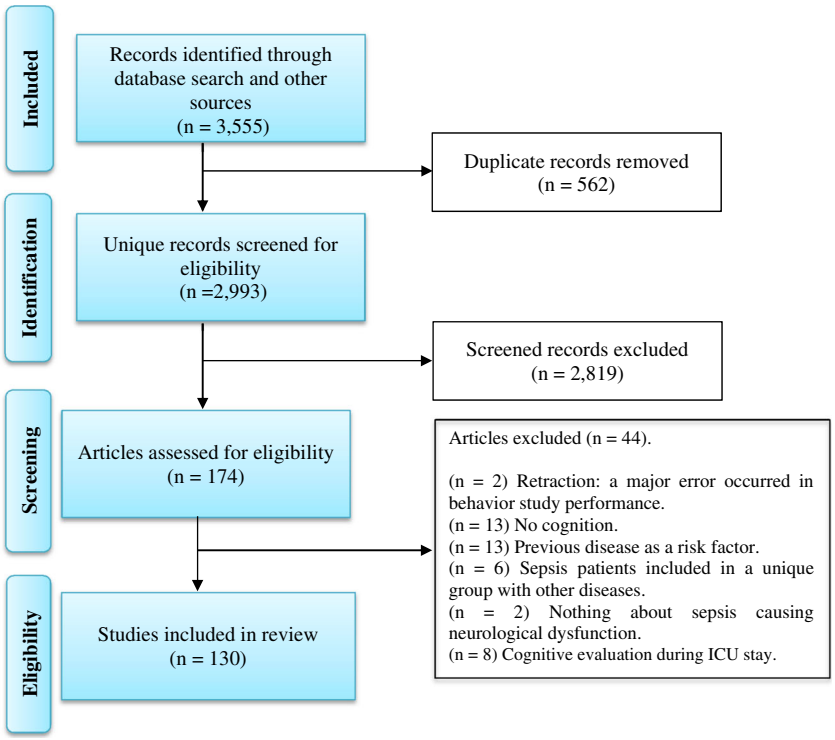

Fig. 1 Flowchart study design

levels between 1.5 and 4 h and decline after 8 h of LPS administration. However, the mortality rates are comparable to those in the CLP sepsis model [15]. In the bacteria infusion model, the rodents receive an i.p. infusion of *Escherichia coli* at a concentration of 6.5×10^8 colony forming units (CFU) over 12 h. In this model of peritonitis, the rodents reproduce several clinical features observed in human sepsis [16]. In the bacterial sepsis model, rodent feces are macerated in 0.5 mL sterile saline to produce a 5 mg/mL (*w*:*v*) suspension. The suspension is centrifuged, and the supernatant is recovered and injected via i.p. into the rodent [17]. In the fibrin experimental peritonitis model, 0.5% bovine fibrin clots containing 2×10^8*E. coli* are implanted into the rodent peritoneal cavity. Mortality was reduced to 0% in 24 h; however, on day 10 after fibrin implantation, the mortality rate was between 90 and 100% [18].

Cognitive Impairment in Pre-Clinical Sepsis Model

In pre-clinical sepsis models, cognitive impairment and neuropsychiatric-like behavior have been identified from early hours after sepsis until several months after recovery.

The most common forms of cognitive impairment found in different sepsis models were impairment of aversive memory, learning, locomotor and exploratory activities, short-term and long-term memories, depressive-like behavior, anxiety-like behavior, anhedonia-like behavior, and fear memory. A study by Bozza et al. demonstrated that rodents inoculated with intraperitoneal feces presented with avoidance memory impairment 24 h after inoculation [19]. The CLP sepsis model also presented with memory impairment evaluated by novel object recognition (novel recognition memory) 24 h after the surgery [20]. In an endotoxin sepsis model, at 24 h after LPS-challenge, sepsis animals presented cognitive impairment evaluated by habituation to T-maze (memory and spatial learning), rota rod (motor coordination and balance), and activity cage tests [21]. A high dose of LPS (60 mg/kg) caused hypothermia as well as impaired spontaneous locomotor activity at 24 h after injection in BALB/c mice [22]. Four days after LPS-induced sepsis, the rodents presented depressive-like behavior assessed by the sucrose preference test [23]. Rodents showed similar behavior on the same test even with CLP-induced sepsis [23]. The Morris water maze task (spatial memory) was evaluated from the 4th to the 7th day after CLP. The rodents presented spatial and working memory (Y-maze task) impairment on day 7 after CLP surgery [24, 25]. Rodents subjected to CLP presented cognitive impairment evaluated by novel object recognition task at 9 days after surgery [26]. At 10 days after CLP surgery, rodents presented memory impairment evaluated by step-down inhibitory avoidance (aversive memory), habituation to open field (locomotor and exploratory activities), the continuous multiple-trials step-down inhibitory avoidance task (learning), the novel object recognition task (short-term and long-term memories), the forced swimming task (depressive-like behavior), elevated plus-make (anxiety-like behavior), sweet consumption (anhedonia-like behavior), and decreased contextual freezing time in a fear conditioning test (fear memory) [27–31]. CLP sepsis presented impairment of numbers of crossings and rearings in the open field task on day 15 after surgery [32]. After 28 days of LPS administration, C57BL/6 mice presented cognitive impairment evaluated by the novel object recognition, elevated plus maze, and tail-suspension tasks [33]. One month after LPS administration, C57BL/6 mice presented a reduction in sucrose preference, which is a measure of anhedonia [34]. On day 30 after CLP surgery, Wistar rats presented cognitive impairment evaluated by step-down inhibitory avoidance, the continuous multiple-trials step-down inhibitory avoidance task, and habituation to open field [35–38]. However, in another study, researchers observed no differences in the recognition memory indicator between CLP and sham groups, which demonstrate a rescue of short-term memory after 30 days of sepsis induction [26]. Sepsis survivor mice did not show impairment in contextual fear conditioning or trace fear conditioning at 50 days after CLP surgery; however, they demonstrated impairment in extinction of conditioned fear [39]. On day 60 after CLP surgery, Wistar rats did not show impairment of aversive, habituation, and novel object recognition memories, nor did the rodents present depressive-like behavior [37, 40, 41]. Patients may also develop neuropsychiatric manifestations, such as anxiety, depression, or post-traumatic stress disorder (PTSD), which can have an intense effect on their lives and reduce their probability of returning to work [42]. Thus, pre-clinical models of sepsis help better understand long-term outcomes following sepsis and possible new therapeutic approaches to prevent cognitive impairment triggered by sepsis.

Pathophysiology of Cognitive Impairment in Pre-Clinical Sepsis Model

Sepsis is a severe clinical condition associated with high host immune response to infection [43]. After infection, PAMPs are recognized by Toll-like receptors (TLR), and their interaction markedly upregulates the transcription of genes involved in pro-inflammatory responses [5]. Thus, this activation leads the nuclear translocation of the transcription factor nuclear factor-κB (NF-κB) to produce and deliver pro-inflammatory mediators. A number of pre-clinical studies have shown an auto amplification of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, in the first few hours after sepsis induction [44], followed by BBB disruption [45]. The disruption of BBB and elevated levels of matrix metalloproteinases (MMP)-9 and MMP-2 activities were observed in the micro vessels of the cortex and hippocampus of rodents subjected to CLP surgery [45]. Consistent with the immune response,

DAMPs, which are latter endogenous constituents produced or delivered by damaged tissue, bind to different receptors and exacerbate the host immune response. HMGB-1 may act on brain micro vasculature endothelial cells to disrupt BBB integrity, thus facilitating the entry of neurotoxic substances into the brain [46]. Elevated serum levels of HMGB-1 were noted from 4 to 12 weeks after CLP [46, 47], and among septic patients, serum HMGB-1 levels were significantly lower in survivors than in non-survivors patients [48]. The anti-HMGB-1 monoclonal antibody improved memory impairment and brain pathology in the CLP sepsis model [46]. There are other receptors involved in the sepsis immune activation, such as c-type lectin receptors (CLR), nucleotide binding oligomerization domain (NOD)-like receptors (NLR), receptors for advanced glycation end-products (RAGE), RIG-I-like receptors (RLR), and intra-cytosolic DNA sensors [49]. RAGE expression increased in the hippocampus and the pre-frontal cortex at 30 days after CLP sepsis, when rats were showing cognitive impairment [50]. Serum level of sRAGE amplified with the development of disseminated intravascular coagulation and the severity of sepsis in patients [51]. HMGB-1, AGEs, and S-100 proteins also bind to RAGE, leading to its activation and subsequent neuroinflammation by targeting NF-κB and increasing the expression of early growth response protein-1 (ERG-1) [52, 53]. In another study, amyloid-beta peptide interacted with RAGE-bearing cells in the vessel wall that resulted in transport of amyloid-beta peptide across the BBB and increased pro-inflammatory cytokines and endothelin-1 (ET-1) expression. Inhibition of RAGE-ligand interaction blocked accumulation of amyloid-beta peptide in brain parenchyma in a genetically manipulated mouse [54]. At 30 days after CLP surgery in rodents, there is an increase in hippocampal and pre-frontal cortex levels of amyloid-beta peptide and a decrease in synaptophysin levels associated with simultaneous cognitive impairment. Together, these results imply in the pre-clinical sepsis model that HMGB1-RAGE-signaling activation may lead to long-term cognitive impairment observed during post-sepsis [38]. The inflammasome gene profile was modulated in septic patients with an increase of NLR family CARD domain containing-4 (NLRC-4) and NLR family pyrin domain containing-3 (NLRP-3) and a decrease of NOD-1 and NLRP-1 expression in septic patients compared to healthy controls; the expression levels of the pro-inflammatory cytokines IL-1β and IL-18 were higher in septic patients with a greater magnitude in non-survivors [55]. NLRP-3 is a multiprotein complex formed by the adaptor protein apoptosis-associated speck-like protein containing CARD (ASC) and pro-caspase-1 that regulates the activation of caspase-1, which proteolytically maturates IL-1β and IL-18. Mice with genetic deficiency of NLRP-3 presented inhibition in inflammatory responses and enhanced survival rates after CLP surgery [56]. Another study showed that NLRP-3 deleted mice subjected to CLP surgery had increased survival rates and decreased autophagy and enhanced phagocytosis [56]. LPS-induced mice presented long-term depressive-like behavior and recognition memory deficit. Additionally, NLRP-3, ASC, and caspase-1 expressions and IL-1β, IL-18, and TNF-α levels increased followed by microglial activation in an LPS-induced sepsis model. These effects were blocked by a selective irreversible inhibitor of caspase-1 (Ac-Tyr-Val-Ala-Asp-chloromethylketone) [57]. In another study, mice subjected to CLP surgery presented an increase of Iba-1, IL-1β, and NLRP-3 expression and apoptosis in the hippocampus followed by spatial memory impairment evaluated by the Morris water maze. Inhibition of microglia decreased pro-inflammatory markers and prevented the memory impairment [58]. Microglial gene expression showed an increase of anti-microbial genes and the S-100A family of genes for at least 2 weeks after CLP sepsis surgery; however, the genes did not express cytokines that were observed in the entire brain. CLP-induced sepsis resulted in long-term neuroinflammation sustained due to interactions among various cell types, including resident microglia and peripheral myeloid cells [39]. A pre-clinical systematic review evaluated the effect of peripheral inflammatory activation on microglia. A total of 51 studies were identified with different doses of LPS (0.33 to 200 mg/kg) and live or heat-killed pathogens as a peripheral infectious stimulus. After LPS administration, microglial activation was noted 6 h after challenge, which persisted for at least 3 days. Live *E. coli* triggered microglial activation after 2 days and heat-killed bacteria after 2 weeks. Microglial activation was associated with TLR-2, TLR-4, TNF-α, and IL-1β expression [59]. Consistent with pre-clinical studies, three cases of post-mortem sepsis, when patients' right frontal pole was removed and studied at autopsy, the expression of the astrocyte marker glial fibrillary acidic protein (GFAP), cluster of differentiation 68 (CD68), and CD45 microglial markers were all increased in the brain [60]. Thus, in addition to inflammatory markers, HMGB-1/RAGE, NLRP-3, and activation of microglia play roles in the pathophysiology of post-sepsis cognitive impairment.

Intervention to Prevent Cognitive Impairment in Pre-Clinical Sepsis Model

Adjunctive Dexamethasone Therapy This study evaluated the effect of dexamethasone on mortality, circulating corticosterone and adrenocorticotropin hormone (ACTH) levels, body and adrenal gland weight, anhedonia-like behavior, and aversive memory in CLP sepsis survivor rats. Wistar rats received dexamethasone as an adjuvant treatment for 7 days. Ten days after CLP sepsis, the rats were evaluated for aversive memory, sweet food consumption, and body and adrenal gland weight. Sepsis caused anhedonia-like behavior, memory impairment, increased adrenal gland weight, and increased plasma levels of corticosterone and ACTH. Dexamethasone treatment

normalized the adrenal gland weight and plasma levels of corticosterone and ACTH. Additionally, dexamethasone decreased mortality and anhedonia-like behavior and prevented aversive memory impairment [30]. In this study, on days 10 and 30 after CLP surgery, the Wistar rats were subjected to training for an inhibitory avoidance task. Immediately after the training session, the animals received a single injection of saline, epinephrine, naloxone, dexamethasone, or glucose, and 24 h later the animals were subjected to the test. The CLP sepsis survivor rats that received adjuvant treatment with the different aforementioned drugs presented a difference between the training and test sessions, showing retention of aversive memory [40].

Antidepressant Drugs (Fluoxetine and Imipramine) Antidepressant drugs demonstrate an increase in neurogenesis in the adult rodent hippocampus, and there is also some evidence that antidepressant drug treatment increases peripheral brain-derived neurotrophic factor (BDNF) levels in patients [61, 62]. After 28 days of LPS administration and fluoxetine treatment, C57BL/6 mice were subjected to novel object recognition, elevated plus maze, and tail-suspension tasks. The LPS mice presented cognitive impairment in all the tasks; however, fluoxetine treatment prevented behavioral changes. After the behavioral tasks, fluoxetine treatment was discontinued for 7 days to evaluate biochemical markers. Fluoxetine decreased the Iba-1 microglia marker in the hippocampus, early growth response protein 1 (EGR1) immunoreactivity in the CA1, and bromodeoxyuridine (Brdu) immunoreactive cells in the dentate gyrus [33]. Wistar rats subjected to CLP presented with decreased consumption of sucrose, showing anhedonia-like behavior. Additionally, there were decreases in hippocampus weight and BDNF levels and increases in adrenal gland weight and plasma levels of corticosterone and ACTH. Imipramine treatment prevented depressive-like behavior, decreased corticosterone and ACTH plasma levels, increased BDNF levels, and normalized hippocampal and adrenal gland weight [30]. This study suggested that depressive-like behavior and hypothalamic–pituitary–adrenal axis (HPA) axis changes induced by sepsis may be prevented with antidepressant treatment. In another study from the same research group, it was demonstrated that depressive-like behavior in CLP sepsis survivor rats was reversed after imipramine administration [63]. When LPS-treated C57BL/6 mice were assessed after 1 month, they presented immobility in the tail suspension task and showed a decrease in sucrose preference. Fluoxetine administered 90 min before the behavioral tasks decrease the immobility in the tail suspension task in post-septic animals. However, the authors did not evaluate the effect of fluoxetine on the sucrose preference task [34]. Thus, the antidepressant-like fluoxetine and imipramine indicated a beneficial effect post-sepsis in neuropsychiatric manifestations.

Erythropoietin Treatment Sprague-Dawley rats were subjected to CLP surgery. The rodents were treated with exogenous recombinant human erythropoietin at a dose of 5 units per day infused consecutively for 7 days into the left lateral ventricle. Seven days after CLP surgery, the animals were subjected to open field exploration, the inhibitory avoidance training and test, and the Morris water maze for spatial learning and memory functions. These tasks indicated sepsis-induced emotional and cognitive deficits; however, recombinant human erythropoietin adjuvant treatment prevented impairment of aversive and spatial memories. AKT/mTOR pathway-mediated neuronal protective effects of erythropoietin were observed in the CLP sepsis group [64]. In another study, Wistar rats were subjected to CLP and treated with a single dose of recombinant human erythropoietin and killed at 6 and 24 h after CLP surgery. Treatment with erythropoietin decreased lipid peroxidation, catalase (CAT), superoxide dismutase (SOD), and creatine kinase activity in the hippocampus of rats subjected to CLP. To study the behavior, erythropoietin was administered once a day for 4 days after CLP surgery, and aversive memory was evaluated on day 10. Mortality was decreased only during erythropoietin adjuvant treatment. After the treatment, the mortality rate was equal between the CLP saline group and CLP erythropoietin group; however, erythropoietin prevented cognitive impairment, as evidenced by improvement in aversive memory in a step-down inhibitory avoidance task [65].

Heparins (Dalteparine, Enoxaparine, or Nadroparine) Treatment Sepsis is commonly complicated by coagulopathy by disseminated intravascular coagulation [66]. Heparin and low-molecular weight heparin decreased mortality and end-organ failure following experimental sepsis [22, 66]. In this study, i.p. LPS challenge produced sepsis in BALB/c mice. The mice were treated with nadroparine, orenoxaparine, or dalteparine. Nadroparine pretreated 2 h before LPS challenge, but not synchronous injection, inhibited the hypothermic response. Nevertheless, pretreatment with equal doses of enoxaparine or dalteparine had no significance on the hypothermia. The high dose of LPS (60 mg/kg) increased the hypothermia and inhibited spontaneous locomotor activity 24 h after treatment. Synchronous nadroparine treatment reduced the hypothermia and eliminated the reduction in spontaneous locomotor activity [22].

HMG-CoA Reductase Inhibitor (Atorvastatin, Lovastatin, or Simvastatin) Statin is a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor that can control hypercholesterolemia. In an experimental model, simvastatin prevented LPS-induced septic shock in rats [67]. Additionally, experimental sepsis was induced in Swiss Webster mice by i.p. injection of fecal material (feces from naïve Swiss Webster, 5 mg/mL). Atorvastatin or simvastatin did not prevent mortality in septic

mice; still, survivors presented lower clinical scores. The atorvastatin or simvastatin treatments decreased pro-inflammatory cytokines, brain lipid peroxidation myeloperoxidase levels, and microglial activation in septic mice. Intravital examination of the brain vessels showed a decrease of functional capillary density and an increase of leukocyte adhesion that were prevented by both atorvastatin and simvastatin. At 15 days after sepsis, mice survivors presented cognitive dysfunction related to hippocampal and aversive amygdala-dependent memories. Statin treatments prevented cognitive impairment assessed by step-down inhibitory avoidance and Morris water maze tasks [68]. In another study from the same research group, the authors showed that sepsis survival with simvastatin treatment was improved in Swiss Webster mice but not in C57BL/6 mice, compared to controls, whereas statins reduced sepsis severity in both mice types at 24 h after induction. Lovastatin or simvastatin retained avoidance memory compared to the control group [19].

Inhibition of Indoleamine 2,3-Dioxygenase Pathway Kynurenine pathway activation has been reported in several neurological diseases as an effect of host immune response [69–71]. The enzyme indoleamine 2,3-dioxygenase (IDO) is the most important connection between the immune system and the kynurenine pathway [72]. The kynurenine pathway is the main route for tryptophan metabolism in mammals. In its first step, tryptophan is converted to kynurenine in a reaction catalyzed by IDO and tryptophan 2,3-dioxygenase (TDO). Then, IDO converts tryptophan into kynurenine that is metabolized into other catabolites through the activity of enzymes within the kynurenine pathway [73]. In this study, sepsis induced hippocampus-dependent cognitive impairment, evidenced by decreased contextual freezing time in a fear conditioning test along with an increase in the hippocampal microglial marker, Iba-1, TNF-α, IL-1β, IL-6, kynurenine, the ratio of kynurenine/tryptophan, and IDO activity and a decreased tryptophan level in mice subjected to the CLP model. A single peripheral administration of L-kynurenine, a metabolite of the amino acid L-tryptophan that is produced by many cells in response to immune activation, induced a deficit in the cognitive impairment in the control group. Nevertheless, mice treated with 1-methyl-D, L-tryptophan (IDO inhibitor) did not experience these changes [31, 74]. In another study, polymicrobial sepsis increased the activity of mitochondrial complexes I, II-III, and IV at 24 h after CLP. However, IDO-1/2 inhibition normalized the activity of these complexes in the hippocampus. Additionally, Wistar rats presented impairment of habituation and aversive memories 10 days after CLP, while the adjuvant treatment with the IDO-1/2 inhibitor prevented these alterations [75]. The results suggest that IDO-dependent neurotoxic kynurenine metabolism was a cause of sepsis-induced cognitive impairment, and IDO inhibitors might be a new avenue as adjuvant treatment for sepsis-associated encephalopathy.

Inhibition of Histone Deacetylase (Sodium Butyrate, Suberoylanilide Hydroxamic Acid, Trichostatin A, or Valproic Acid) The authors investigated the effect of class I histone deacetylase (HDAC) inhibitor (valproic acid) and suggested that it can prevent cognitive deficits in a sepsis mouse model. The C57BL/6 mice received valproic acid once daily for 14 uninterrupted days commencing either immediately or 2 weeks after CLP surgery. No difference in mortality rate was observed between valproic acid and saline-treated sepsis groups, when valproic acid was administered immediately after CLP for 14 days. However, treatment with valproic acid increased BDNF concentration and IL-1β levels and decreased the activity of caspase-3 with simultaneous increases in acetyl-H3K9 and acetyl-H4K12 levels, compared to the saline-treated sepsis group. Valproic acid prevented cognitive impairment in spatial learning memory, as seen in Morris water maze and Y-maze tasks [76]. In this study, Wistar rats subjected to CLP presented aversive memory impairment. The animals presented an increase of HDAC activity in the hippocampus and cortex 24 h after CLP and in the pre-frontal cortex and hippocampus 10 days after CLP. The adjuvant treatment with sodium butyrate, a class I HDAC inhibitor, prevented memory impairment. Additionally, sodium butyrate presented a late inhibitory effect on HDAC activity in the pre-frontal cortex and in the hippocampus after 10 days of CLP surgery, with no influence of HDAC expression at 24 h after CLP surgery [77]. A study by Fang et al. investigated whether a septic brain was epigenetically modulated by HDACs, using the CLP model in Sprague-Dawley rats. The rats were treated with trichostatin A (TSA) or suberoylanilide hydroxamic acid (SAHA) inhibitors of classes I and II of the HDAC family, respectively, for 7 days after CLP surgery. The HDACs' inhibition improved spatial learning and memory dysfunction on the Morris water maze task in septic rats. Hippocampal acetylated histone 3 (AcH3), acetylated histone 4 (AcH4), cytoplasmic HDAC4, and B cell lymphoma-extra-large (Bcl-XL) were inhibited in the brain of septic animals. Hippocampal bcl-2-like protein 4 (Bax) and nuclear HDAC4 expressions were increased in CLP group; however, the treatment with HDAC inhibitors preserved the changes of Bcl-XL and Bax [78].

Inhibition of Matrix Metalloproteinases Matrix metalloproteinases are important for tissue formation, neuronal cell renovation, and BBB homeostasis. During inflammation, MMPs may digest tight junctions and basement membrane proteins, contributing to an increase in the BBB permeability, thus affecting brain homeostasis [79]. Thirty-five hours after CLP induction, Wistar rats presented aversive memory impairment

assessed by the inhibitory avoidance task. An intracerebroventricular (i.c.v.) administration of MMP-2 and MMP-9 inhibitors in a single dose after sepsis induction prevented cognitive impairment and BBB disruption [45]. In another study from the same research group, Wistar rats presented aversive memory impairment at 30 days after CLP surgery. Adjuvant treatment with MMP-2/9 inhibitors prevented cognitive impairment and decreased the amyloid-β deposition in the rat brain [38].

Inhibition of Pro-Inflammatory Cytokines Pro-inflammatory cytokines are essential for a strong host inflammatory response. Nevertheless, early sepsis mortality is caused by an acute and harmful pro-inflammatory response, while the second sepsis phase is associated with acute immunosuppression, which make the patients susceptible to long-term risk for life-threatening secondary infections [80]. The IL-1β receptor antagonist (IL-1ra) prevented the BBB disruption in the pre-frontal cortex, hippocampus, and striatum; decreased the levels of IL-1β, IL-6, and TNF-α in the pre-frontal cortex and striatum at 24 h; and prevented cognitive impairment assessed by habituation to an open field and step-down inhibitory avoidance tasks at 10 days in Wistar rats subjected to CLP [81]. IL-1ra administration also ameliorated long-term potentiation (LTP) in the hippocampus in a CLP mouse model [82]. In another study, wild-type mice presented memory impairment in the novel object recognition task at 10 days after sepsis induced by CLP. However, these deficits were not observed in tumor necrosis factor receptor-1 (TNFR1) knockout mice, and the absence of TNFR1 in mice subjected to CLP surgery triggered a higher BDNF expression in the hippocampus [83].

Mechanistic Target of Rapamycin Inhibitor Rapamycin is a mechanistic target of rapamycin (mTOR) inhibitor. The mTOR-C1 signaling stimulates cell growth by inducing and inhibiting anabolic and catabolic processes is responsible for cell cycle development, and it is sensitive to rapamycin. mTOR-C2 signaling is insensitive to acute rapamycin treatment; however, chronic rapamycin contact can disrupt its structure [84]. The purpose of this research strategy was to study the neuroprotective effect of rapamycin in Kunming mice subjected to CLP. Fourteen days after CLP surgery, mice were subjected to the Morris water maze, and then the hippocampus was dissected to evaluate mTOR expression. Rapamycin prevented cognitive impairment in the CLP group but did not affect the total mTOR targets. Phosphorylated mTOR targets decreased (p-mTOR-Ser2448, p-p70S6k-Thr389, and p-AKT-S473), autophagy indicators increased (LC3-II, Atg5, Atg7), and P62 decreased in the hippocampus of the rapamycin-treated CLP mice [85]. Sepsis by CLP model enhanced the phosphorylation of Akt, mTOR, and p70S6K along with hippocampal neuronal loss, abnormal neuronal morphology, and impaired long term cognitive performance, suggesting that sepsis-induced hippocampal neurodegeneration triggers Akt/mTOR signaling pathway. However, rapamycin rescued cognitive deficits in acute phase, 14 days after CLP surgery, with no influence on chronic phase cognitive impairment, 60 days after CLP surgery, or long-term neuronal loss in hippocampal CA1 region [86].

Nonconventional Antibiotic Treatment (Minocycline or Tigecycline) Minocycline is a tetracycline derivative that can cross the BBB and present anti-inflammatory activity with neuroprotective characteristics that limit inflammation and oxidative stress [87]. Although tigecycline is architecturally similar to minocycline, the modifications to the molecule resulted in a prolonged spectrum of its activity and reduced susceptibility to the development of resistance, compared with other tetracycline antibiotics [88]. Sprague-Dawley rats were subjected to traumatic brain injury and CLP procedure to induce sepsis. Immediately following injury, the animals received minocycline, tigecycline, or saline. Mortality in the animals subjected to combined traumatic brain injury and CLP was reversed by both minocycline and tigecycline administration. Minocycline, but not tigecycline, decreased the extent of cortical tissue damage, TNF-α expression in the pericontusional cortex, and microglial activation. Both antibiotics had effects on recovery of cognitive deficits observed following combined traumatic brain injury and CLP surgery [89]. Sepsis also decreased hippocampal Neuregulin-1 (NRG-1) concentrations, which was reversed by minocycline adjuvant treatment. Minocycline also reduced microglia activation and prevented cognitive impairment in C57BL/6 mice subjected to CLP [31] and LTP in the hippocampus of C57BL/6 mice with sepsis [82]. In another study, sepsis increased oxidative damage, pro-inflammatory cytokines, BBB permeability, and cognitive impairment, while these alterations were prevented by minocycline treatment with simultaneous improvement in long-term cognitive impairment evaluated by the inhibitory avoidance task and habituation to open field [90].

Inhibition of Leukocyte Influx into Central Nervous System In this study, female C57BL/6 (B6; H-2 Kb) mice were treated with anti-NK1.1 monoclonal antibody to deplete natural killer (NK) cells prior to LPS or CLP sepsis induction. In the LPS sepsis model, after disruption of the BBB, conventional CD11b(+) CD27(+) NK cells migrated into the brain. Additionally, depletion of NK cells previous to LPS treatment decreased neutrophil recruitment, IL-1β, IL-6, and TNF-α levels in the brain. NK cell depletion reduced depression-like behavior in LPS-treated mice, as indicated by reduced sucrose preference and changes in serotonin metabolism-associated enzymes and proteins, including tryptophan hydroxylase 2 (TPH2), monoamineoxidase (MAO-A), and serotonin transporter in the mice's brains. The NK depleted CLP

group presented a decrease of TNF-α and IL-1β levels in the brain. Depressive-like behavior was prevented by NK depletion treatment prior to CLP surgery, showing a result similar to that found in the LPS-induced sepsis model [23]. Wistar rats subjected to CLP surgery presented increased levels of IL-1β, IL-6, TNF-α, thiobarbituric acid reactive species (TBARS), nitrosative stress, and BBB dysfunction. After CLP surgery, the Wistar rats received anti-CD40 as a treatment or isotype immunoglobulin (Ig) IgG as a control. The inhibition of CD40-CD40 ligand activation by anti-CD40 (CD40 molecule, TNF receptor superfamily member-5) did not influence the mortality rate but decreased CD40–CD40L levels, cytokines, oxidative damage, and BBB dysfunction. Additionally, anti-CD40 prevented aversive and non-aversive long-term memory impairment 10 days after CLP surgery in sepsis survivor rats compared to the CLP/IgG group [90].

Phytotherapeutic Compounds

Physostigma venenosum: Physostigmine is an AChE inhibitor in the beginning extracted from *P. venenosum* (Calabar bean) and *Hippomane mancinella* (Manchineel tree) [91]. The LTP in the excitatory synapses of the hippocampal neurons was affected in septic rats compared to controls, suggesting that synaptic plasticity is affected by sepsis and that hippocampal neurons are involved in septic delirium. Physostigmine, the cholinesterase inhibitor improved the LTP suggesting that cholinergic neurotransmission is linked to septic encephalopathy [92].

Huperzia serrata: Huperzine-A is an acetylcholinesterase inhibitor and *N*-methyl-D-aspartate (NMDA) receptor antagonist extracted from *Huperzia serrata*. Wistar rats were treated with huperzine-A and then subjected to LPS-induced sepsis. Then memory was evaluated at 3, 12, and 24 h after LPS administration by Morris water maze task. Huperzine-A treatment prevented impairment of spatial memory induced by LPS. Huperzine-A also improved cholinergic function by augmenting hippocampal levels of (ChAT), muscarinic acetylcholine receptor-1, and acetylcholine (ACh). In addition, TNF-α and IL-1β protein and gene expression decreased in the hippocampus at 3, 12, and 24 after LPS-induced sepsis in rats treated with huperzine-A [93].

Panax ginseng: Ginsenosides are a class of steroid glycosides, and triterpene saponins, found *Panax ginseng*. Ginsenosides modulated expressions and functions of receptors such as tyrosine kinase receptors, serotonin receptors, NMDA receptors, and nicotinic acetylcholine receptors [94]. C57BL/6 mice were subjected to CLP and treated with Ginsenoside-Rg1 1 h before the CLP. The ginsenoside-Rg1 improved the survival rate and rescued from the learning and memory deficits as noted on Morris Water maze. This adjuvant treatment also decreased microglial marker Iba-1, reduced the expression of TNF-α, IL-1β, and IL-6; activation of caspase 3; expression of microtubule-associated protein 1A/1B-light chain 3 (LC3) and nucleoporin p62 (p62) in hippocampus [24].

Resveratrol: Resveratrol is a polyphenol that has antioxidant activity and decreases the activation of SIRT-1 [95]. In another study, C57BL/6 mice were subjected to CLP surgery and presented an increase of Iba-1, IL-1β, NLRP-3 expression, and apoptosis in the hippocampus followed by spatial memory impairment evaluated by Morris water maze [58]. However when the rodents were treated with resveratrol, there is a decrease in microglial markers and pro-inflammatory markers with simultaneous reduction in in memory impairment. Resveratrol protected against sepsis-associated encephalopathy by inhibiting the NLRP-3/IL-1β axis in microglia [58].

Radical Scavenging

Alpha-lipoic acid: This study evaluated the effect of α-lipoic acid (ALA; 200 mg/kg) an antioxidant compound on brain dysfunction in Wistar rats subjected to CLP. Animals were divided into sham + saline, sham + ALA, CLP + saline, and CLP + ALA groups. Twelve, 24 h, and 10 days after surgery, the hippocampus, prefrontal cortex, and cortex were assayed for TNF-α and IL-1β, BBB permeability, nitrite/nitrate concentration, MPO activity, TBARS formation, protein carbonyls, SOD and CAT activity, and neurotrophins levels. Treatment with ALA decreased TNF-α and IL-1β levels, MPO activity, nitrite/nitrate concentration, and lipid peroxidation with simultaneous increase in CAT activity. ALA also enhanced NGF levels in hippocampus and cortex and prevented cognitive as measured in novel object recognition test after sepsis [96].

N-acetylcysteine and/or deferoxamine: On days 10 and 30 after CLP surgery, Wistar rats were subjected to inhibitory avoidance task, habituation to an open field, and continuous multiple-trials step-down inhibitory avoidance task. The sepsis group presented memory impairment that was prevented by use of *N*-acetylcysteine plus deferoxamine (NAC/DFX) adjuvant treatment [27]. In another study from the same research group, CLP sepsis inhibited mitochondrial electron transport chain complexes I and II; however, treatment with NAC/DFX, taurine, or RC-3095 (gastrin-releasing peptide receptor antagonist) prevented these changes on complexes I and II in the rat brain. CLP sepsis also increased creatine kinase (CK) activity in hippocampus, cerebral cortex, cerebellum, and striatum that were prevented by the NAC/DFX or taurine treatments [97–99].

Nicotinamide adenine dinucleotide phosphate (*NADPH*) *oxidase inhibitor* (*apocynin*): For this interventional study, C57BL/6 mice were subjected to CLP and treated with a NADPH oxidase inhibitor knows as apocynin. The time consumed in the center of the arena was reduced on day 13 but not on day 29 in the CLP/vehicle group compared with the control, whereas apocynin treatment prevented the decrease in

the CLP group. On day 14, apocynin treatment also prevented the decrease in the freezing time of CLP mice group. Sepsis triggered cognitive impairment, which was followed by selective phenotype loss of parvalbumin interneurons and increased gp91 (phox), 4-hydroxynonenal, MDA (malondialdehyde), IL-1β, and IL-6 expressions; however, apocynin treatment reduced these inflammatory and oxidative markers [100]. In another study, CLP sepsis caused hypotension, hyperlactatemia, renal and hepatic dysfunction, along with an increase in the levels of IL-6, IL-1β, macrophage inflammatory protein (MIP), and late-cognitive deficits. Apocynin decreased the levels of H_2O_2 and reduced the oxidative stress [101]. Sepsis was induced in wild-type and gp91 (phox) knockout mice by CLP. The absence of NOX2 in gp91 ($phox^{-/-}$) mice prevented glial cell activation. Alternatively, experimental sepsis was induced in C57BL/6 mice by an i.p. injection of the fecal slurry for behavioral studies to avoid surgery and the mice were treated with apocynin. Pharmacological inhibition of NOX2 with apocynin prevented hippocampal oxidative stress and development of long-term cognitive impairment assessed by step-down inhibitory avoidance task and Morris water maze [102]. Wild-type C57/BL6 mice and mice deficient for the inducible nitric oxide synthase gene ($NOS_2^{-/-}$) were subjected to sepsis model by LPS administration. LPS increased NOS_2 expression in wild-type mice compared to $NOS_2^{-/-}$mice. Wild-type mice showed more behavioral impairment in eight-arm radial maze and open field tasks on LPS treatment compared to $NOS_2^{-/-}$mice, suggesting that LPS-induced NOS_2 linked NO production. LPS-treated wild-type mice had increased brain mRNA levels of TNF-α, IL-1β, and RANTES [103].

Hydrogen gas: Hydrogen gas (H_2) is an antioxidant that decrease toxic reactive oxygen species (ROS) such as hydroxyl radical ($^{\bullet}OH$); however, hydrogen-rich saline (HRS) is more appropriate for clinical application [104, 105]. In this study, the survival rate was superior among Wistar rats submitted to CLP that had received HRS compared with those that had received no treatment. CLP group presented cognitive impairment evaluated by Morris water maze, cell damage categorized by histopathologic changes and oxidative damage in the hippocampus. These changes were attenuated by HRS dose-dependent treatment [106]. ICR mice underwent CLP or sham operation and were treated with 2% H_2 for 60 min. The H_2 treatment reduced the levels of pro-inflammatory cytokines and oxidative products and increased activities of antioxidant enzymes in serum and hippocampus. Further, the H_2 treatment stimulated the expression and transposition of nuclear factor erythroid 2-related factor 2 (NRF2) and the expression of cytoplasmic heme oxygenase-1 (HO-1). In addition, H_2 prevented cognitive impairment in sepsis group evaluated by Y-maze and fear conditioning test [25].

Disufenton sodium (*NXY-059*): NXY-059 is a disulfonyl derivative of the neuroprotective spin trap phenylbutynitrone (PBN) and its hydrolysis/oxidation product MNT are very powerful scavengers of free radicals. In this study, NXY-059 showed no improvement on mortality rate of Swiss Webster mice subjected to CLP sepsis. On cognitive evaluation, the animals treated with NXY-059 improved when compared to controls, by a reduction in the numbers of crossings and rearings in the open field test [32].

Miscellaneous (Agonists, Antagonists, and Inhibitors of Different Receptors)

Acetylcholinesterase inhibitor (*Rivastigmine*): Wistar rats were subjected to CLP sepsis and 3 days after surgery the animals received rivastigmine as adjuvant treatment or saline for 7 days. Ten days after surgery, rats were submitted to habituation to an open-field memory test. CLP group presented habituation memory impairment; however, CLP rats treated with rivastigmine presented a reduction in the number of crossings and rearings on the open field habituation between test and training session, indicating memory acquisition [107].

β2 adrenergic receptor agonist (*Salmeterol*): Mice received pre-treatment with salmeterol 1 h before LPS sepsis induction reduced the expression of hippocampal pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. Subsequently, the cognitive impairment induced by systemic LPS stimulation was attenuated by salmeterol treatment [108].

$CB_1$and CB_2 (cannabidiol) receptor agonist: The pharmacological effects of cannabinoid type I (CB_1) and cannabinoid type II (CB_2) are mediated through G protein coupled receptors [109]. Cannabidiol improved cognition in multiple pre-clinical models such as schizophrenia, Alzheimer's disease, brain ischemia, cerebral malaria, hepatic encephalopathy, bacterial meningitis, and sepsis [97–99, 110, 111]. CLP Wistar rats treated with cannabidiol at different doses reduced the mortality, MDA levels, carbonyl levels, and prevented cognitive impairment as evidenced by aversive memory improvement on inhibitory avoidance task compared to CLP plus vehicle group in both acute and chronic phases of sepsis [97–99].

Cholinesterase inhibitor (*eserine*) *and selective CB_2receptor agonist* (*JWH-133*): In this study, the authors evaluated the effect of a cholinesterase inhibitor (eserine), a selective CB_2 receptor agonist (JWH-133), on LPS-induced sepsis. Wistar rats received LPS injection and 30 min after the injection, the animals were treated with eserine, JWH-133, or eserine plus JWH-133. At 24 h after LPS administration and adjuvant treatment, the animals were subjected to the habituation to T maze, rota rod, and activity cage tests. The adjuvant treatments improved the cognitive skills, locomotor and exploratory activity, and motor co-ordination that were impaired with LPS when compared to LPS plus vehicle. Eserine, JWH-133, or eserine plus JWH-133 also prevented an increase of IL-6, vascular cell adhesion molecule-1 (VCAM-1), and oxidative-nitrosative stress in terms of MDA and iNOS gene expression [21].

Acetylation of cyclophilin D (*CypD*): C57BL/6J mice were subjected to CLP surgery and assigned in six groups: sham group, CLP group, CypD siRNA transfection (CypD-si) group, CypD control siRNA transfection (CypD-c) group, Sirtuin (SIRT) 3 overexpression vector pcDNA3.1 (SIRT3-p) group, and SIRT3 empty vector pcDNA3.1 (SIRT3-v) group. The CypD-si and CypD-c groups were transfected with CypD siRNA and CypD control siRNA. In addition, the SIRT3-p and SIRT3-v groups received SIRT3 pcDNA3.1 and vector pcDNA3.1, respectively. CypD and acetylation of CypD levels increased in the hippocampus of mice subjected to CLP surgery. In addition, increasing SIRT3 and decreasing CypD prevented cognitive impairment, apoptosis, and protected the integrity of mitochondrial membrane. Activated SIRT3-mediated deacetylation of CypD reduced the learning and memory impairment evaluated by Morris water maze in CLP sepsis [112].

D-Arg-2', 6'-dimethyltyrosine-Lys-Phe-NH2 (*SS-31 peptide*): The aim of this research strategy was to evaluate the effects of the mitochondria-targeted peptide SS-31 on mitochondrial function and cognition in CLP sepsis model. C57BL/6 mice were treated with peptide SS-31 (5 mg/kg) administrated after surgery and later on once daily for six uninterrupted days. Seven days after CLP surgery, surviving mice were subjected to open field and fear conditioning tests and the hippocampus was collected for biochemical analysis. SS-31 treatment improved survival rate, ameliorated the behaviour performance on open field test, and increased the freezing time in 24 h context test. SS-31 treatment prevented a decrease of mitochondrial complexes I and III enzyme activities, prevented an increase of ROS, and a reduction of ATP content in the hippocampus of CLP-induced mice. In addition, SS-31 protected the integrity of mitochondrial membrane, prevented apoptosis and neuronal damage, decreased the levels of IL-1β, and NLRP-3 expression in the hippocampus of CLP-induced mice [113].

D-Serine (*The NMDA receptor co-agonist D-serine*): Sepsis was induced by CLP or by a single intraperitoneal injection of LPS, 8 mg/kg in C57BL/6J mice. Sepsis reduced the protein and mRNA levels of NMDA receptor subunits GluN2A, GluN2B, and GluN1 but not synaptophysin levels or the hippocampal neuronal number in both CLP and LPS mice in the first week. D-serine, co-agonist of NMDA receptors, limited the LPS induced damage, including the cognitive impairment, NMDA receptor subunits loss, neuro-inflammation, oxidative stress, and the hippocampal decrease of p-CREB. As sepsis-induced NMDA receptor loss is interfering with hippocampal changes, NMDA receptors are target platform for future interventions [114].

Electroacupuncture: Sprague-Dawley rats were pre-treated with different waveforms of electroacupuncture (Baihui and bilateral Tsusanli acupoints). After electroacupuncture pre-treatment, the animals were subjected to CLP surgery. The survival rates increased in the CLP rats pre-treated with continuous wave, dilatational wave, and intermittent wave compared to CLP group. All waveforms prevented memory impairment evaluated by Morris water maze task in septic survivor rats. Electroacupuncture pre-treatment decreased the production of TNF-α, IL-6, MDA, and increased the activity of SOD and CAT in serum and hippocampus at 48 h after CLP surgery. Electroacupuncture pre-treatment also decreased the expression of TLR-4, NF-κB, and Iba-1 in the hippocampus of CLP sepsis rats [115].

Neuregulin (*NRG*)*-1*: NRG-1 is a ligand for the receptor tyrosine-protein kinase (erbB)-3 and erbB4 members of the epidermal growth factor receptor (EGF) family receptors. The NRG-1 is produced from neurons to stimulate the formation and maintenance of radial glial cells. CLP sepsis-induced anxiety-like behavior and hippocampal-dependent cognitive impairment, as demonstrated by significantly augmented distance spent in the open field task and reduced freezing time to context in the fear conditioning task [31]. The NRG1-β1 adjuvant treatment prevented the sepsis-induced cognitive impairment; however, the treatment with the EGFR inhibitor, AG1478, nullified the NRG1-β1 effect on behaviour task.

Glutamatergic neurotransmission inhibitor (*Riluzole*): Riluzole is a glutamate release inhibitor drug. Wistar rats were subjected to CLP surgery and received riluzole, 30 min after the surgery, and every 12 h as continuing treatment. The outcome of riluzole on the survival rate, body weight and temperature, leukocyte amount, neurological investigation scores, and brain edema were evaluated at 6 and 48 h after CLP surgery. CLP rats presented survival rates of 89, 50, and 28% at 6, 24, and 48 h, respectively. In CLP rats treated with riluzole, the survival rate improved to 94, 72, and 50% at the same time points. Riluzole also decreased MDA, and increased glutathione (GSH) levels in the rat brain and improved weight loss, body temperature, brain edema, and BBB permeability. In addition, Bederson's neurological examination scores [116] decreased in the CLP rats treated with riluzole [117].

[*Gly14*]*-Humanin* (*HNG*): HNG is a derivative of humanin (HN). The HN is a liberated bioactive peptide that decreases cell toxicity by inhibiting c-JunNH2-terminal kinase [118]. In this study, ICR mice were subjected to CLP surgery and treated with HNG peptide. The HNG treatment reduced IL-1β, IL-6, and TNF-α levels; GFAP-positive astrocytes and Iba-1-positive microglia biomarkers that were elevated 16 h after CLP sepsis. On day 21 after sepsis surgery, mice were subjected to Y-maze task and they presented impairment in working memory. HNG treatment prevented cognitive impairment in working memory and also improved basal forebrain cholinergic neuronal loss and reduced synaptic plasticity caused by sepsis [119].

Guanosine: Guanosine is a purine nucleoside thought to have neuroprotective properties [120]. Wistar rats subjected to CLP

were treated with i.p. guanosine injection. Twelve and 24 h after CLP surgery, TBARS and protein carbonyls formation were evaluated. Guanosine treatment decreased TBARS and carbonyl levels in the brain. On day 10, another group of rats were subjected to habituation to an open-field apparatus, inhibitory avoidance ask, object recognition task, and forced swimming task. Guanosine treatment prevented memory impairment and depressive-like behavior [121].

High mobility group box 1 (HMGB-1) inhibitor: Polymicrobial sepsis was induced by CLP in BALB/c mice. Sepsis survivor mice presented an increase of HMGB-1 levels in the serum for at least 12 weeks after CLP, along with learning and memory impairment. The anti-HMGB-1 monoclonal antibody was provided once a day for 3 days. Animals were subjected to SHIRPA, open-field task, black-and-white alley test, and navigational test. Administration of anti-HMGB-1 antibody improved memory impairment and brain pathology. To test their hypothesis, recombinant HMGB-1 was administrated to naïve mice and memory was evaluated. Interestingly, administration of recombinant HMGB-1 to naïve mice caused memory impairment [46].

Intermittent fasting diet: Wistar rats on intermittent fasting diet were deprived of food for 24 h every other day for 30 days. On day 31, the rats had access to food for 24 h and received LPS intravenously for sepsis induction. Intermittent fasting diet improved cognitive deficits by decreasing the pro-inflammatory cytokine expression, and enhancing neurotrophic support. LPS administration exhibited impairment in cognitive performance in the Barnes maze and inhibitory avoidance tasks, without changes in locomotor activity, that were improved in intermittent fasting diet rats [122].

Immunoglobulin therapy: Wistar rats were subjected to CLP surgery and received IgG or immunoglobulins enriched with IgA and IgM (IgGAM) at 5 min after the CLP surgery. On days 10, 30, and 60, the animals were subjected to open field, elevated plus maze, and forced swimming tasks. In IgG and IgGM groups, the mortality decrease to 30 and 20%, respectively. On day 10, the rats presented depressive-like behavior that was prevented by both treatments. However, on day 30 and on day 60 after CLP surgery, the rodents did not present depressive-like behavior [123].

Metformin: It is a drug used to treat type-2 diabetes and it exerts anti-inflammatory and anti-oxidant effect [124, 125]. Metformin treatment increased the survival rate, protected BBB integrity, attenuated neuronal apoptosis, brain edema, oxidative damage, and pro-inflammatory cytokine levels, and improved cognitive function along with an increase in Akt phosphorylation. However, LY294002, a phosphatidylinositol-3-kinase (PI3K) inhibitor reverted the metformin's neuroprotective effect theorizing that metformin's neuroprotective effect might be from activation of PI3K/Akt signaling pathway [126].

N-acetyl-5-methoxy tryptamine (*melatonin*): Melatonin is a hormone that is produced by the pineal gland in animals and is an important physiological sleep regulator in humans that presented anti-inflammatory and antioxidant properties in preclinical models [127–129]. Melatonin treatment immediately after surgery improved survival rate with no behavioral change and reduced plasma IL-1β levels, whereas melatonin treatment 7 days after surgery improved cognitive assessments by reverting hippocampal BDNF and GDNF levels, suggesting that melatonin could be a novel therapeutic solution for sepsis associated encephalopathy [130].

N-Methyl-D-aspartate (*NMDA*) *receptor antagonist* (*MK-801*): Sepsis was induced by CLP surgery in Wistar rats. Animals were treated with a single dose of MK-801 and 10 days after the surgery, memories were evaluated by different tasks. MK-801 adjuvant treatment prevented impairment in aversive memory and short and long-term memories as evaluated by inhibitory avoidance task and novel object recognition task respectively [29].

Nicotinic acetylcholine receptor agonist (*nicotine*): Wistar rats were subjected to CLP sepsis and received an adjuvant treatment with nicotine. The animals were treated with nicotine or vehicle every day per 1 week before and/or 1 week after sepsis surgery. At 30 min after the last administration of nicotine, the rats were subjected to the open field, elevated plus-maze, and step-down inhibitory avoidance tasks. The constant nicotine treatment did not change the survival rate in the sepsis group. Moreover, while sepsis group showed no significant changes on locomotor activity, the treatment with nicotine during 1 week after CLP decreased the locomotion of sepsis-surviving rats in the open field. Both nicotine treatments (prior and/or after CLP surgery) enhanced the sepsis-induced anxiety-like behavior. Nicotine also was able to recover short-term and long-term inhibitory avoidance memory impairments, detected in sepsis survivors, only when administered during two successive weeks (prior and after CLP surgery) [131].

RAGE antagonist: Rat polyclonal anti-RAGE (RAGEab) (100 μg/kg saline) was administered bilaterally into the hippocampus at days 15, 17, and 19 after CLP. Control animals received 100 μg/kg of isotype IgG. Serum proinflammatory markers (TNFα, IL-1β, and IL-6), levels of RAGE, RAGE ligands (S100B, Nε-[carboxymethyl]lysine, HSP70, and HMGB1), brain levels of TLR4, GFAP, neuronal NOS, Aβ, and p-tauSer202 all increased during post-CLP period. Intracerebral administration of RAGE antibody post-CLP reversed these changes and also attenuated the cognitive deficits that resulted from sepsis. The data suggest that RAGE induces neuronal damage that might be alleviated with anti-RAGE treatments [132] .

Serine/threonine kinase glycogen synthase kinase 3β (*GSK3β*) *inhibitor*: TDZD-8 is a thiadiazolidine derivative that acts as a non-ATP competitive inhibitor of the serine/threonine kinase glycogen synthase kinase 3β (GSK3β) [133]

Glucagon-like peptide (*GLP-1*): Liraglutide is an equivalent of human GLP-1 and acts as a GLP-1 receptor agonist with insulinotropic activity [134]. Swiss mice were subjected to sepsis by CLP and on day 30 post-surgery, the animals presented memory impairment evaluated by novel object recognition and step-down inhibitory avoidance task, but they demonstrated normal performance when re-evaluated on day 45 after CLP surgery. Cognitive impairment in post-septic animals were accompanied by decreased hippocampal levels of synaptophysin, cAMP response element-binding protein (CREB), CREB phosphorylated at serine residue 133 (CREBpSer133), and GluA1 phosphorylated at serine residue 845 (GluA1pSer845). Expression of TNF-α increased, IRS-1 phosphorylation at serine 636 (IRS-1pSer636) increased, and phosphorylation of IRS-1 at tyrosine 465 (IRS-1pTyr465) decreased in the hippocampus of mice on day 30 after CLP surgery. Phosphorylation of Akt at serine 473 (AktpSer473) and of GSK3 at serine 9 (GSK3βpSer9) were also diminished in hippocampus of post-septic mice. Post-septic mice were treated with liraglutide for 10 days or TDZD-8 for 5 days that began on day 20 and on day 25 after CLP surgery. Both treatments prevented memory impairment evaluated by novel object recognition task [135].

Vitamin B_6: Wistar rats subjected to CLP who received a treatment with vitamin B_6 prevented BBB disruption, neuroinflammation, oxidative stress, and energy metabolism changes and decreased long-term cognitive impairments by improving learning and memory deficits. Vitamin B_6 might have brought these changes by decreasing tryptophan metabolism changes via kynurenine pathway [136], Table 1.

Clinical Studies

Neuropsychiatric Manifestations and Long-Term Cognitive Decline in Sepsis Survivor Patients

A study by Iwashyna et al. evaluated the total number of Medicare beneficiaries surviving at least 3 years after severe sepsis and to evaluate the burden of their cognitive impairment and disability. Severe sepsis was evaluated by a standard administrative definition. A total of 637,867 Medicare beneficiaries were alive at the end of 2008 who had survived severe sepsis 3 or more years earlier. An estimated 476,862 had functional disability, with 106,311 survivors having moderate to severe cognitive dysfunction [167]. Another study determined the changes in cognitive dysfunction and physical behavior among patients who survived severe sepsis. Individual interviews were performed with respondents or proxies using validated surveys to assess the presence of cognitive dysfunction and to determine the number of activities of daily living (ADL) and instrumental activities of daily living (IADL) with which patients needed assistance. The prevalence of moderate to severe cognitive dysfunction increased by 10.6% among patients who survived severe sepsis, and a high rate of new functional restrictions was seen following sepsis. Patients with no limits before sepsis presented a mean of 1.57 new limitations, and for those patients with mild to moderate limitations before sepsis, a mean of 1.50 new limitations was found. In contrast, non-sepsis general hospitalizations were related with no change in moderate to severe cognitive dysfunction and with the evolution of fewer new limitations [168]. In a prospective case study, a woman patient contributed in clinical interviews, comprehensive neuropsychological testing, and neurological magnetic resonance imaging (MRI) at approximately 8 months and 3.5 years after ICU discharge. Compared to pre-ICU baseline test data, her intellectual function deteriorated nearly 2 standard deviations from 139 to 106 (from the 99th to the 61st percentile) on a standardized intelligence test 8 months post-discharge. Initial diffusion tensor brain magnetic resonance imaging (DT-MRI) at the end of ICU hospitalization presented diffuse unusual hyper-intense areas connecting predominately white matter in both hemispheres and the left cerebellum. A brain MRI 3.5 years after ICU discharge confirmed the development of profound atrophy with sulcal widening and ventricular enlargement [169]. In another prospective case-control study, researchers compared the neurodevelopmental and behavioral outcomes of 50 children with sepsis-associated encephalopathy. Children with sepsis-associated encephalopathy demonstrated worse mean verbal IQ, full-scale IQ, and General Development Score, as well as the physical, adaptive, social-emotional, cognitive, and communication subscales of the latter. The proportion of sepsis cases with low intelligence was 52 versus 32% in controls. The most common behavior changes were decline in school performance (44%), disobedience (28%), and stubbornness/irritable behavior (26%). Children with Glasgow Coma Scale scores ≤ 10 and ≤ 8 presented impairments in full-scale IQ. In summary, children who had survived sepsis-associated encephalopathy presented delayed neurodevelopment, low verbal IQ, weakening in school performance, and low intelligence at short-term follow-up. Irritability, shock, and duration of sedation were associated with reduced behavioral outcomes [170]. This prospective cohort evaluated the long-term changes in neurobehavioral parameters, brain morphology, and electroencephalography of sepsis and non-septic patients. Twenty-five septic and 19 non-septic ICU survivors were enrolled to evaluate brain morphology, standard electroencephalography, cognition and psychiatric behavior, and health-related quality of life (HRQoL). Sepsis survivors presented cognitive damage in verbal learning and memory and a decrease of left hippocampal volume compared to healthy controls. The sepsis group and to some extent the non-septic ICU patients presented more low-frequency activity in the EEG indicating brain impairment.

Table 1 Characteristics of the included pre-clinical studies

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
Adembri et al. [137]	Rats. Sex and strain: no information	CLP	TBI induced by controlled cortical impact (CCI)	Cerebromorphological changes, cerebral metabolism, and lesion volume histology	None	Computerized tomography (CT) and histology revealed no difference between CCI and CCI + CLP. PET imaging showed a decrease in cerebral metabolism in the perilesional area in CCI + CLP rats, when compared to CCI rats, suggesting that PET imaging can spot the early changes in the dual injury (Adembri et al. [137])
Adembri et al. [89]	Adult male Sprague-Dawley rats	Cecal ligation and puncture/-perforation (CLP)	Minocycline (45 mg/kg, i.p.) or tigecycline (7.5 mg/kg, i.p.) every 12 h, for 3 days	Growth of peritoneal microbes, mortality, body weight, cytokine in cortex, lesion volume, and viable neurons count in hippocampus, microglial migration, and activation in cortex	Beam balance at 2, 7, and 14 days and Morris water maze (MWM) tasks at 10 to 14 days after CLP	Minocycline and tigecycline improved survival rate ($p < 0.01$), body weight ($p < 0.01$), and attenuated microbial growth, without affecting vestibulomotor or cognitive functions. Only minocycline decreased traumatic brain injury (TBI) cortical lesion volume ($p < 0.05$), hippocampal CA3 neuronal death ($p < 0.05$), TNF-α levels ($p < 0.01$), and microglial activation and infiltration ($p < 0.01$) when compared to TBI + CLP rats (Adembri et al. [89])
Akyol et al. [22]	Adult male BALB/c mice	Lipopolysaccharide (LPS) low dose (1 mg/kg, i.p.) or high dose (60 mg/kg, i.p.)	Low-dose LPS: Nadroparine (11.875, 23.75, 47.5, 95.0, or 190.0 U/kg, s.c.) and enoxaparin (11.90 or 23.8 U/kg, s.c.) or dalteparine (12.01 or 24.03 U/kg, s.c.) and unfractionated heparin (500 IU/kg, s.c.) 2 h before LPS. High-dose LPS: Nadroparine (23.75 U/kg, s.c.) 2 h before or with LPS. In another group of mice, a test dose of nadroparine was injected 5 h after LPS	Rectal temperature (Trectal)	Open field task 1 day after LPS injection	Low-dose LPS-induced hypothermia was inhibited on pretreatment with nadroparine ($p < 0.05$), but not with enoxaparine or dalteparine. High-dose LPS caused hypothermia as well as impaired spontaneous locomotor activity, which were both prevented with synchronous nadroparine ($p < 0.05$) (Akyol et al. [22])
Alexandre et al. [138]	Swiss Webster mice. Sex and age: no information	Fecal-induced peritonitis (FIP)	Atorvastatin and simvastatin (20 mg/kg, p.o.), 1 h before and 6, 24, and 48 h after CLP	Mortality rate, sepsis severity score, cytokines, chemokines and oxidative damage, microglial activation, and blood-brain barrier (BBB) dysfunction	Inhibitory avoidance and MWM tasks 15 days after FIP	Statin treatment lowered IL-1, IL-6, KC, and MCP-1 levels, reduced the oxidative damage in brains at 6 h after sepsis and curtailed cognitive damage, both avoidance and spatial memory in septic mice. The

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						mortality was not affected (Alexandre et al. [138])
Anderson et al. [34]	Adult male C57BL/6 mice	LPS (5 mg/kg, i.p.).	PDTC (200 mg/kg, i.p.), 10 min prior to LPS and fluoxetine (20 mg/kg, i.p.) 90 min before behavioral tasks	Microglial and astrocyte activation, cytokines iNOS, nuclear factor-kappa B (NF-κB) pathway components, immediate early gene products and cell proliferation	Marble burying, open field, hyponeophagia, sucrose preference, forced swim, tail suspension, novel object recognition, MWM, radial 8-arm maze, and elevated plus maze tasks 30 days after LPS injection	Post-septic mice demonstrated increased immobility on the tail suspension task ($p < 0.001$), anxiety-like behavior in the elevated plus maze ($p < 0.05$), decreased preference to sucrose ($p < 0.05$), and reduced exploratory behavior in the novel object recognition task ($p < 0.05$), with no impairment visualized in the MWM, the radial 8-arm maze or the novel object recognition task, when compared to control group. Fluoxetine attenuated the increase in immobility in the tail suspension task in post-septic animals ($p < 0.05$), compared to LPS + saline mice. Post-septic mice showed upregulation of the microglial activation markers [CD-11b ($p < 0.05$), F4/80 ($p < 0.01$), and IBA-1 ($p < 0.05$)] in the hippocampus, downregulation of the plasticity-related immediate early gene products [ARC and EGR1 ($p < 0.05$)], and decrease in neural stem cell proliferation marker (BrdU) in the dentate gyrus ($p < 0.05$), while astrocyte activation marker GFAP, iNOS, cytokines, and NF-κB components were not altered. Treatment with the NF-κB pathway inhibitor, PDTC, ameliorated most of the LPS-induced changes ($p < 0.05$), except neural stem cell proliferation (Anderson et al. [34])
Anderson et al. [33]	Adult male C57BL/6 mice	LPS (5 mg/kg, i.p.)	Fluoxetine (10 mg/kg, p.o.) in drinking water, 7 days after LPS, for 28 days	Rate of hippocampal cell proliferation in the hippocampus and microglial activation	Novel object recognition, elevated plus maze and tail suspension tasks 28 days after LPS injection	Fluoxetine attenuated the increase in immobility in the tail suspension task ($p < 0.001$) and decreased the object exploration in the probe trial of a novel object exploration task ($p < 0.05$). It also reverted the increases in IBA-1 positive activated microglia in hippocampus

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						($p < 0.001$), EGR1 immunoreactivity in the CA1 region ($p < 0.05$), and Brdu immunoreactive cells in the dentate gyrus ($p < 0.001$) (Anderson et al. [33])
Barichello et al. [35]	Adult male Wistar rats	CLP	None	None	Step-down inhibitory avoidance, continuous multiple-trials step-down inhibitory avoidance, and open field tasks 10 days after CLP	10 days after CLP surgery, sepsis group showed a significantly decrease in the step-down latency ($p < 0.01$) and an increase in both crossing and rearings in the open field test session ($p < 0.001$), compared to sham group. When training and test sessions are compared, there is no difference in sepsis group, indicating memory impairment. Sepsis group showed a significant increase in the number of training trials to reach the acquisition criterion in continuous multiple-trials step-down inhibitory avoidance task, compared to sham group ($p < 0.05$) (Barichello et al. [35])
Barichello et al. [36]	Adult male Wistar rats	CLP	None	None	Step-down inhibitory avoidance, continuous multiple-trials step-down inhibitory avoidance and open field tasks 30 days after CLP	30 days after CLP surgery, sepsis group significantly decreased latency on step-down inhibitory avoidance task, compared to sham group ($p < 0.01$) in the test session. In the continuous multiple-trials step-down inhibitory avoidance task, sepsis group showed a significant increase in the number of training trials to reach the acquisition criterion, compared to sham group ($p < 0.001$) (Barichello et al. [36])
Barichello et al. [27]	Adult male Wistar rats	CLP	*N*-acetylcysteine (NAC) (20 mg/kg, s.c.) at 3, 6, 12, 18, and 24 h after CLP, deferoxamine (DFX) (20 mg/kg, s.c.) at 3 and 24 h after CLP, or both	Thiobarbituric acid reactive substances (TBARS) and protein carbonyls in hippocampus	Step-down inhibitory avoidance, open field and continuous multiple-trials step-down inhibitory avoidance tasks at 10 or 30 days after CLP	NAC plus DFX treatment, but not its isolate use, prevented memory impairment ($p < 0.01$) and attenuated oxidative damage in hippocampus at 6 h after sepsis ($p < 0.01$), when compared to CLP group (Barichello et al. [27])
Barichello et al. [28]	Adult male Wistar rats	CLP	None	None	Novel object recognition, elevated plus-maze, forced swim and open field tasks 10 days after CLP	Sepsis group presented a significant impairment of short- and long-term novel object recognition memory

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						($p < 0.05$), an increase in immobility time in the forced swimming test ($p < 0.05$), suggesting depressive-like behavior, with no significant difference on elevated plus-maze task, suggesting no anxiety-like behavior (Barichello et al. [28])
Bian et al. [139]	Adult male Kunming mice.	LPS (5 or 10 mg/kg, i.p.) daily, for 7 days	None	Body weight, microglia and astrocyte activation, neurotrophin, and cytokines	MWM task 8, 30, and 90 days after the last LPS injection	Both low (5 mg/kg) and high (10 mg/kg) doses of LPS induced weight loss, spatial learning, and memory impairment on MWM ($p < 0.05$), increase in Iba-1 and GFAP positive cells in the CA3 layer of hippocampus, and enhanced GDNF, IL-1β, and IL-6 levels. Low-dose LPS rats needed 30 days to recovery, whereas high-dose LPS rats required 90-day recovery. Spatial learning and memory impairment in high dose LPS rats were permanent (Bian et al. [139])
Biff et al. [140]	Adult male Wistar rats	CLP	None	TBARS and cytokines in cerebrospinal fluid (CSF), neurotrophin levels in hippocampus	Step-down inhibitory avoidance task 30 days after CLP	Sepsis increased the CSF levels of TBARS ($p < 0.05$), IL-1β and TNF-α ($p < 0.05$), and BDNF levels at 6 h after CLP in hippocampus. At 24 h, septic group showed increased levels of IL-1β, IL-10, and TNF-α with worse cognitive function and lower hippocampal BDNF levels ($p < 0.05$) (Biff et al. [140])
Bozza et al. [141]	Adult male C57BL/6 mice	CLP	None	Magnetic resonance imaging (MRI) and in vivo proton spectroscopy at baseline, 6 and 24 h after CLP, total creatinine (Cr), choline (Ch), and *N*-acetylaspartate (NAA) levels, Cr/Ch ratio and NAA/Ch ratio	None	Diffusion-weighted T2 images showed hyperintense areas representing vasogenic edematic fluid at the brain base at 6 and 24 h after CLP ($p < 0.05$). The water apparent diffusion coefficients were decreased in the hippocampus, thalamus, and cortex, suggesting a cytotoxic edema in septic brains ($p < 0.05$). A slight increase in Cr/Ch ratio and a significant decrease in NAA/Ch ratio were noted in septic mice, indicating neuronal damage (Bozza et al.

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						[141])
Bozza et al. [19]	Swiss mice and C57BL/6 mice	FIP (5 mg/kg in Swiss mice; 2.5 mg/kg in C57BL/6 mice)	Lovastatin and simvastatin (20 mg/kg, p.o.) 1 h before to 48 h after CLP	Mortality, sepsis severity	Inhibitory avoidance task 15 days after CLP	Simvastatin decreased mortality in Swiss mice, but not in C57BL/6 mice, compared to control group, whereas statins reduced sepsis severity in both mice types after 24 h and prevented cognitive deficits at 15 days after CLP (Bozza et al. [19])
Calsavara et al. [83]	Adult male C57BL/6 and TNFR1$^{-/-}$ mice	CLP	None	Mortality, cytokines in brain and serum, gene expression of cytokines, and neurotrophins in hippocampus	Novel object recognition task 10 days after CLP	Mortality rate did not differ among mice strains. WT mice showed short- and long-term memory impairment ($p < 0.05$) but TNFR1$^{-/-}$ mice did not present short-term ($p < 0.05$) and long-term ($p < 0.01$) memory alterations. Sham TNFR1$^{-/-}$ mice had high levels of TNF-α and IL-1β in serum ($p < 0.05$) than WT mice. CLP TNFR1$^{-/-}$ mice showed higher levels of IL-6 in serum ($p < 0.05$) than WT mice, while TNF-α, IL-1β, IL-6 and IFN-γ in brain were significantly increased due to CLP in both WT ($p < 0.05$) and TNFR1$^{-/-}$ ($p < 0.01$) mice. There was an increase in BDNF expression in CLP operated TNFR1$^{-/-}$ mice ($p < 0.01$) (Calsavara et al. [83])
Cassol-Jr et al. [97]	Adult male Wistar rats	CLP	NAC (20 mg/kg, s.c.) plus DFX (20 mg/kg, s.c.) 3 h after CLP, taurine (50 mg/kg, s.c.) immediately after CLP and RC-3095 (3 mg/kg, s.c.) immediately after CLP	Mitochondrial respiratory chain/electron transport chain (ETC) enzymes and creatine kinase activities in cerebral cortex, hippocampus, striatum, and cerebellum	None	CLP inhibited complexes I and II, and all treatments reversed this action on complexes I ($p < 0.05$) and complexes II ($p < 0.05$) in all brain areas. Sepsis increased CK activity in all brain structures that was reversed by NAC/DFX ($p < 0.05$) and taurine ($p < 0.05$), while RC-3095 decreased CK activity ($p < 0.05$) (Cassol-Jr et al. [97])
Cassol-Jr et al. [98])	Adult male Wistar rats	CLP	Dexamethasone (0.2 or 2 mg/kg, i.p.) daily, for 7 days after CLP	Mortality, body weight, corticosterone in serum and ACTH in plasma and adrenal gland weight	Inhibitory avoidance, anhedonia, and open field tasks 10 days after CLP	Sepsis decreased sucrose intake ($p = 0.00$) and body weight change, while increased mortality rate ($p = 0.04$), adrenal gland weight ($p = 0.00$), corticosterone ($p = 0.00$), and ACTH levels ($p = 0.00$) and impaired aversive

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						memory ($p = 0.06$), compared with sham rats. Both dexamethasone doses reversed the decrease in sweet food consumption ($p = 0.00$), normalized adrenal gland ($p = 0.00$), body weight, corticosterone ($p = 0.00$), and ACTH levels ($p = 0.00$). Dexamethasone at 0.2 mg/kg reversed memory impairment ($p = 0.00$). Treatment with 2 mg/kg of dexamethasone increased mortality ($p = 0.04$) (Cassol-Jr et al. [97])
Cassol-Jr et al. [99]	Adult male Wistar rats	CLP	Cannabidiol (CBD) (2.5, 5, or 10 mg/kg, i.p.) once or daily, for 9 days after CLP	Mortality, TBARS, and protein carbonyls in lung, liver, kidney, heart, spleen, and brain (hippocampus, striatum, and cortex) at 6 h and 10 days after CLP	Inhibitory avoidance task 10 days after CLP	At 6 h after CLP, TBARS was increased in the lung, kidney, and heart of CLP animals, and all three doses of CBD significantly reduced TBARS, mainly in the lung and heart. In the brain, only the striatum showed increased TBARS levels ($p = 0.025$) and all doses of CBD diminished it. There was an increase in carbonyl levels in the liver, kidney, heart, and spleen, and 5 or 10 mg/kg of CBD significantly reduced it in the liver, heart, and spleen. In the brain, all structures presented higher levels of protein carbonyls, and the striatum was the only structure with significant reduction of protein damage after treatment with all CBD doses. At 10 days after CLP, TBARS was increased in the kidney and both CBD at 2.5 and 10 mg/kg reversed it. In the brain, only the hippocampus had increased levels of TBARS, and all CBD doses prevented it. Protein carbonyls were increased in kidney, heart, liver, and spleen, and higher doses of CBD reversed it. All doses of CBD prevented memory impairment, but only 10 mg/kg of CBD decreased mortality (Cassol-Jr et al. [98])

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
Cassol-Jr et al. [29]	Adult male Wistar rats	CLP	MK-801 (0.025 mg/kg, s.c.) after CLP	Neurotrophin and DARPP-32 expression in hippocampus	Step-down inhibitory avoidance and novel object recognition tasks 10 days after CLP	CLP group showed short- and long-term memory impairment visualized in the step-down inhibitory avoidance and in novel object recognition tasks. Treatment with MK-801 prevented impairment in aversive memory ($p = 0.005$), short-term ($p = 0.002$), and long-term memories ($p = 0.002$). MK-801 did not influence the hippocampal BDNF expression, but DARPP-32 expression was increased ($p = 0.009$), compared to sham group (Cassol-Jr et al. [29])
Chavan et al. [46]	Adult male BALB/c mice	CLP	Anti-high mobility group box 1 (HMGB1) antibody (50 μg/mouse, i.p.) once a day on days 7, 9, and 11 after CLP and purified recombinant HMGB1 (500 μg in 350 μL of PBS, i.p.) once a day, for 3 weeks	HMGB1 in serum and histological changes in hippocampus	Primary screen and the first stage of the SHIRPA procedure, open field, rotarod, black-and-white alley, and navigational tasks 30 and 120 days after CLP	Sepsis induced a late phase increase in serum levels of HMGB1 ($p < 0.05$), that remained elevated until 12 weeks after CLP, along with learning and memory impairment ($p < 0.01$), and reduced spine density on dendritic processes in hippocampal CA1 area ($p < 0.05$). The administration of Anti-HMGB1 antibody 7, 9, and 11 days after sepsis decreased HMGB1 levels ($p < 0.05$), improved cognitive deficits ($p < 0.01$), and dendritic spine density. Administration of recombinant HMGB1 to naive mice caused significant memory decline ($p < 0.05$) (Chavan et al. [46])
Chen et al. [115]	Adult male Sprague-Dawley rats	CLP	Electroacupuncture (EA) pretreatment with different waveforms (continuous wave—CW, dilatational wave—DW, or intermittent wave—IW) at Baihui (GV20) and bilateral Tsusanli (ST36) acupoints for 30 min	Encephaledema and BBB permeability, catalase (CAT), malondialdehyde (MDA), superoxide dismutase (SOD), and cytokines in serum and hippocampus, Toll-like receptor 4 (TLR-4), NF-κB, and microglial activation and neuronal apoptosis in hippocampus	MWM task 5 days before and 2 days after CLP	EA pretreatment with three waveforms ameliorated sepsis-induced damage by improving survival rate to 85% ($p < 0.01$ DW vs. CW), cognitive dysfunction ($p < 0.05$, DW vs. CLP), inhibiting microglial activation (by downregulated TLR-4, NF-κB, and Iba-1 expressions), and attenuating brain edema ($p < 0.01$, DW vs. CLP), BBB dysfunction ($p < 0.01$, DW vs. CLP), neuronal apoptosis

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						($p < 0.01$, DW vs. CLP), decreasing the levels of TNF-α and IL-6 ($p < 0.01$, DW vs. CLP, both), MDA ($p < 0.01$, DW vs. CLP) and increasing the activity of SOD and CAT ($p < 0.01$, DW vs. CLP, both). Among the three waveforms, dilatational was most effective, followed by intermittent and then the continuous wave form (Chen et al. [115])
Coelho et al. [142]	Male Wistar rats	CLP	500 μL of nNOS activity inhibitor, 7-nitroindazole (7-NI) (50 mg/kg, i.p.), or vehicle (sesame oil 10%) were given to rats 30 min prior to CLP or sham	At 0, 4, 6, 18, and 24 h after CLP, vasopressin levels and NOS activity of the neurohypophysis and hypothalamus were analyzed in decapitated rats, respectively. Hematocrit, serum sodium, osmolality, proteins and plasma vasopressin hormone (AVP), and survival rate were calculated	None	CLP decreased sodium and plasma proteins levels, neurohypophyseal AVP, plasma AVP levels at 12 and 24 h, increased the osmolality, hypothalamic NOS activity at 4 and 24 h, plasma AVP at 6 h after CLP. All these changes were delayed or reversed with 7-NI, except AVP levels, concluding that nNOS has no major role in vasopressin secretion and its inhibition does not impact AVP levels in septic rats (Coelho et al. [142])
Comim et al. [107]	Adult male Wistar rats	CLP	D-amphetamine (AMPH) (0.5, 1, or 2 mg/kg, i.p.) 10 days after CLP	None	Open field task 10 days after CLP	Sepsis did not affect locomotor and exploratory behavior visualized in the open field task. AMPH at 1 and 2 mg/kg increased crossing and rearings in sham rats, while only 2 mg/kg caused this alteration in CLP rats (Comim et al. [107])
Comim et al. [107]	Adult male Wistar rats	CLP	Rivastigmine (0.5 mg/kg, i.p.) daily, from days 3 to 10 after CLP, or rivastigmine (0.5 mg/kg, i.p.) 30 min before the open field training session	None	Open field task 10 days after CLP	Sepsis-induced animals presented similar crossing and rearing activities among training and test sessions, indicating impaired memory acquisition. Rivastigmine treatment reversed these alterations in crossing ($p < 0.001$) and rearing ($p < 0.001$) behaviors (Comim et al. [107])
Comim et al. [30]	Adult male Wistar rats	CLP	Imipramine (10 mg/kg, i.p.) daily, for 14 days, starting 3 days after CLP	Body weight, adrenal gland, and hippocampal weight, corticosterone levels in serum, ACTH levels in plasma, neurotrophin in hippocampus	Anhedonia and open field tasks 10 days after CLP	CLP rats presented decreased sucrose intake ($p = 0.002$), hippocampal weight ($p = 0.0001$), and BDNF levels ($p = 0.042$) and increased adrenal gland weight ($p = 0.001$), plasma corticosterone ($p = 0.042$), and ACTH levels ($p = 0.039$) with

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						no increase in body weight ($p = 0.451$). Treatment with imipramine reverted the decrease in sucrose intake ($p = 0.001$), adrenal gland weight ($p = 0.0001$), and body weight recovery after surgery ($p = 0.0001$), decreased the levels of corticosterone ($p = 0.037$), and ACTH ($p = 0.0001$), while reverted the loss of hippocampal weight ($p = 0.0001$), and BDNF levels ($p = 0.004$) (Comim et al. [30])
Comim et al. [37]	Adult male Wistar rats	CLP	None	None	Inhibitory avoidance, memory of extinction, inhibitory avoidance-two trainings paradigm, and posttraumatic memory tasks 10, 30, and 60 days after CLP	The aversive memory was impaired at 10, 30, but not 60 days after CLP, but no damage was found in aversive memory after two training sessions. Also, there was no damage to the memory of extinction at 60 days after CLP. Posttraumatic memory impairment was also observed up to 10 days after induction (Comim et al. [37])
Comim et al. [37]	Adult male C57BL/6 mice and adult male Wistar rats	CLP	None	Number of rolling and adherent leukocytes after intravital microscopy, cytokines, chemokines, and myeloperoxidase (MPO) in plasma and hippocampus, striatum, cortex and pre-frontal cortex, BBB permeability, and brain histopathological analysis	SHIRPA test 6, 12, and 24 h after CLP	CLP sepsis caused a decrease in leukocyte levels at 6, 12, and 24 h, an increase in leukocyte rolling and adhesion in the brain blood vessels, followed by an increase in brain MPO activity, indicating neutrophil infiltration, and increased BBB permeability. There was an increase in both brain and plasma cytokines and chemokines; however, the levels increased earlier in the brain than plasma, except CXCL1/Kc. On SHIRPA test, there was no significant difference in reflex, sensory, and motor behavior. However, there was a decrease in the neuropsychiatric state ($p < 0.05$) and muscle tone and strength only at 6 h ($p < 0.05$), and a decrease in the autonomous function ($p < 0.01$; $p < 0.01$) and a decrease in total scores ($p < 0.01$; $p < 0.05$) at 6 and 12 h, when compared to sham group, respectively (Comim et al. [37])

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
Comim et al. [143]	Adult male Wistar rats	CLP	Ketamine (5, 15, or 25 mg/kg, i.p.) 30 days after CLP	None	Open field, inhibitory avoidance, stereotyped behavior, and social interaction tasks 30 days after CLP	High doses of ketamine (15 and 25 mg/kg), but not low dose (5 mg/kg) enhanced locomotor activity ($p < 0.05$), latency to first contact in the social interaction ($p < 0.05$), and stereotyped behavior ($p < 0.05$), compared to CLP + saline rats. Individually, ketamine induced similar changes in a lower intensity, but sepsis alone did not, suggesting that sepsis has an add-on effect to ketamine induced schizophrenia rat model (Comim et al. [143])
Comim et al. [144]	Neonatal male C57BL/6 mice	LPS (25 μg, s.c.).	None	None	Open field, step-down inhibitory avoidance, continuous multiple trials step-down inhibitory avoidance, novel object recognition, elevated plus-maze, and forced swimming tasks 60 days after LPS injection	Neonatal sepsis-induced mice presented impairment in locomotor and exploratory behavior visualized in the open field task ($p < 0.05$), aversive memory and learning in both inhibitory avoidance tasks ($p < 0.05$), novel object recognition memory during short and long term ($p < 0.05$), and an increase of immobility time in the forced swimming task ($p < 0.05$) (Comim et al. [144])
da Cunha et al. [145]	Swiss mice	CLP associated with intra- tracheal instillation of *P. aeruginosa*	None	Mortality rate, neutrophil infiltration, and cytokines in peritoneal cavity, apoptosis marker expression in lung	Passive avoidance task 15 and 21 days after CLP or until 96 days after CLP	Sepsis caused a high mortality rate (70%), hypoglycemia, increased levels of CCL2, IL-1b, and IL-10 and neutrophil accumulation in the peritoneal cavity along with subsequent cognitive deficits that recovered after 21 days. The CLP animals exposed to *P. aeruginosa* showed a decrease in caspase-1, but increase in caspase-12 expressions in the lungs, associated with low count of neutrophil. Animals subjected to CLP and *P. aeruginosa* instillation required longer recovery period (96 days) compared to only sepsis induction (21 days) to recover from cognitive damage (da Cunha et al. [145])
da Cunha et al. [145]	Wild type and $CCR2^{-/-}$ mice. No	CLP	None	Survival rate, sepsis severity, cell proliferation, neurotrophin, amyloid-β (Aβ), and apoptosis	Open field, MWM and passive avoidance tasks 15 days after CLP	$CCR2^{-/-}$ mice, including sham and CLP groups, had severe cognitive impairment, compared to wild-type

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
	information about age and sex			marker expression in hippocampus and cortex		animals. CCR2$^{-/-}$ naive mice showed impaired aversive and contextual memory, associated with decreased hippocampal BDNF levels, increased β-amyloid protein expression, and increased cortical and hippocampal caspase-3 and caspase-12 expression (da Cunha et al. [145])
Dal-Pizzol et al. [50]	Adult male Wistar rats	CLP	None	Receptor for advanced glycation end products (RAGE) in hippocampus and prefrontal cortex	None	RAGE levels were increased in the hippocampus and prefrontal cortex at 30 days after sepsis (Dal-Pizzol et al. [50])
Dal-Pizzol et al. [45]	Adult male Wistar rats	CLP	Nonselective MMP-2/9 inhibitor (0.3 mg/kg, i.c.v.), selective MMP-2 inhibitor (250 μg/kg, i.c.v.), selective MMP-9 inhibitor (15 μg/kg, i.c.v.), or MMP-2 and MMP-9 selective inhibitors together, immediately after CLP	BBB permeability, gelatinases, protein carbonyl, and cytokine in hippocampus and cortex	Step-down inhibitory avoidance and open field tasks 36 h after CLP	Sepsis increased the BBB permeability in cortex and hippocampus along with an increase of MMP-9 expression in both structures until 24 h after sepsis ($p < 0.05$), while MMP-2 expression was only increased in the cortex at 12 h ($p < 0.05$). The administration of nonselective or specific gelatinases inhibitors reverted these changes ($p < 0.05$) and lowered oxidative damage ($p < 0.05$) and brain levels of IL-6 ($p < 0.05$). Sepsis-induced cognitive damage ($p < 0.05$) was reverted only with dual MMP-2/9 inhibitor (Dal-Pizzol et al. [45])
Danielsky et al. [136]	Adult male Wistar rats	CLP	Vitamin B_6 (600 mg/kg, s.c.) or same volume of saline immediately after CLP	Kynurenine, tryptophan, tryptophan/kynurenine ratio in the hippocampus and pre-frontal cortex, levels of cytokines TNF-α, IL-1β and IL-6, BBB permeability, nitrite/nitrate concentration, MPO activity, TBARS formation, protein carbonyls, SOD and CAT activity, mitochondrial electron transport chain enzyme activity, and protein determination	Habituation to open field and object recognition task	Vit B_6 attenuated BBB permeability, neuroinflammation, oxidative stress, and energy metabolism changes and decreased long-term cognitive impairments by improving learning and memory deficits. Vit B6 might have brought these changes by decreasing tryptophan metabolism changes via kynurenine pathway (Danielsky et al. [136])
D'Avila et al. [146]	Adult male Swiss mice	CLP	None	Oxygen consumption, mitochondrial membrane potential, mitochondrial cytochromes contents, ETC activity, hydrogen peroxide (H_2O_2)	None	Septic animals presented significative uncoupling of oxidative phosphorylation, compared to control rats, altered oxidative phosphorylation efficiency ($p < 0.01$) in the mitochondrial

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						membrane potential analysis, depletion of cytochromes, reduction in the complex IV activity ($p = 0.02$), and H_2O_2 generation ($p = 0.03$) (D'Avila et al. [146])
D'Avila et al. [101]	Murine model No mention about sex, age and strain	LPS and FIP in different batches No mention about dosage	Apocynine No mention about dosage	Glucose uptake, oxygen consumption, 4-hydroxynonenal (4-HNE), H_2O_2, and cytokines	No clear mention of the type and timing of behavioral analysis	Sepsis induced by FIP caused hypotension, hyperlactatemia, renal and hepatic dysfunction, increases in IL-6, IL-1β, and MIP, and late-cognitive deficits. Also, acute brain slices uptake more glucose and consume more oxygen at 6 h after fecal peritonitis induction, compared to control. Endotoxemia increased brain glucose uptake before peripheral organs, in 2 h and peaked around 6 h after LPS injection. Apocynine, an NADPH oxidase inhibitor, attenuated the H_2O_2 levels and reduced the oxidative stress (D'Avila et al. [101])
Della Giustina et al. [96]	Adult male Wistar rats (60 days old)	CLP	200 mg/kg of alpha-lipoic acid (ALA) or the same volume of saline by oral gavage soon after CLP or sham surgery in 12 h experiment, soon after and 12 h after in 24 h experiment, and daily dose for 10 days in long-term cognitive experiment	Hippocampus, prefrontal cortex, and cortex assayed for the levels of TNF-α and IL-1β, blood-brain barrier (BBB) permeability, nitrite/nitrate concentration, MPO activity, TBARS formation, protein carbonyls, SOD and CAT activity, and BDNF and NGF levels	Habituation to open field test, object recognition test	ALA reverted CLP sepsis induced changes by decreasing BBB permeability in hippocampus, cytokines such as TNF-α and IL-1 β and MPO levels in hippocampus and prefrontal cortex, nitrite/nitrate levels in hippocampus, prefrontal cortex, and cortex and protein carbonyl levels in hippocampus and cortex and an increase in CAT activity and NGF levels in hippocampus and cortex along with cognitive improvement in terms of habituation, short-term and long-term memory improvement. In conclusion, ALA protects BBB integrity, prevents neuro-inflammation, oxidative stress, and improves cognition (Della Giustina et al. [96])
De Souza Constantino et al. [147]	Adult male Wistar rats	CLP	*N*-acetylcysteine (20 mg/kg, s.c.) every 6 h, for 24 h with deferoxamine (20 mg/kg, s.c.), single	Immunocontent of Aβ and synaptophysin in hippocampus and prefrontal cortex	Inhibitory avoidance task 30 days after CLP	Sepsis induced an increase in Aβ levels ($p < 0.05$) in the hippocampus and prefrontal cortex at 30 days after CLP, which was correlated with a decrease in

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
			dose, or a MMP2–9 inhibitor (0.3 mg/kg, i.c.v.)			synaptophysin ($p < 0.05$) in both structures. Both treatments reverted Aβ levels in the two structures while affected sunaptophysin only in the prefrontal cortex. Sepsis impaired aversive memory ($p < 0.05$) that was prevented with both treatments (De Souza Constantino et al. [147])
Esen et al. [148]	Sprague-Dawley rats	CLP	Human IgG or IgGAM, (250 mg/kg, i.v.) via the penile vein 5 min after CLP	Serum total, complement 3 (C3), and soluble complement C5b-9. Cerebral complement and its receptor, NF-κB, Bax, and Bcl-2 expressions. Immune cell infiltration and gliosis by using CD3, CD4, CD8, CD11b, CD19, and GFAP antibodies and apoptotic neuronal death by terminal deoxynucleotidyl transferase (TdT) dUTP nick-end labeling (TUNEL) staining	None	Immunoglobulins IgG and IgGAM reduced the serum complement activity, cerebral C5a and C5a receptor expression, glial cell proliferation, mRNA expression levels of proapoptotic molecules NF-κB and Bax, increased the anti-apoptotic Bcl-2 expression, thus reducing neuronal apoptosis. This concludes that immunoglobulin therapy might reduce neuronal dysfunction and behavioral deficits by reducing apoptosis, gliosis, inflammation, and complement activation (Esen et al. [148])
Fang et al. [78]	Adult male Sprague-Dawley rats	CLP	Trichostatin A (TSA) (10 mg/kg, i.p.) or suberoylanilide hydroxamic acid (SAHA) (25 mg/kg, i.p.) daily, for 7 days	Histones and acetylated histones, histone deacetylases (HDAC), and apoptosis markers in hippocampus	MWM task 7 days after CLP	Sepsis inhibited hippocampal AcH3, AcH4, cytoplasmic HDAC4, and Bcl-XL ($p < 0.05$) but enhanced hippocampal Bax and nuclear HDAC4 expressions ($p < 0.05$) and spatial learning and memory deficits on MWM task ($p < 0.05$). Treatment with TSA or SAHA reversed the changes of Bcl-XL and Bax, and decreased neuronal apoptosis as seen on MTT assay ($p < 0.05$) and improved cognition ($p < 0.05$) (Fang et al. [78])
Gamal et al. [21]	Adult male Wistar rats	LPS (4 mg/kg, i.p.)	Eserine (0.6 mg/kg, i.p.), JWH-133 (1.3 mg/kg, i.p.), or both, 30 min after LPS	Cytokine, levels and expression of vascular cell adhesion molecule 1 (VCAM-1), iNOS, E-selectin, and MDA	T maze, rotarod, and open field tasks 24 h after LPS injection	Eserine, JWH-133, or Eserine + JWH-133 reverted the LPS-induced increases in the levels and gene expression of interleukin-6, VCAM-1, iNOS, MDA, and E-selectin ($p < 0.05$), and improved alterations in the exploratory behavior, locomotor activity, and co-ordination

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						evaluations ($p < 0.05$) that were impaired after LPS injection, when compared to LPS + vehicle (Gamal et al. [21])
Gao et al. [74]	Adult male C57BL/6 mice	CLP	Neuregulin 1 (NRG1-β1) (10 μM, i.c.v.) and/or AG1478 (5 mM, i.c.v.) 1 h before each behavior task. Minocycline (50 mg/kg, i.p.) 1 h after CLP and for 2 days	Cytokines, microglial activation, NRG1, receptor tyrosine-protein kinase 4 (ErbB4), parvalbumin, and local field potential recordings in hippocampus	Open field, contextual fear conditioning, tone fear conditioning, and MWM tasks 10, 12, and 15 days after CLP	Sepsis caused anxiety-like behavior and hippocampal-dependent cognitive impairment, as evidenced by increased distance on open field test and decreased contextual freezing time in fear conditioning task ($p < 0.05$), along with an increase in hippocampal IBA1-positive cells, IL-1β and IL-6 levels, and decrease in NRG1 ($p < 0.05$), ErbB4 ($p = 0.012$), parvalbumin levels, and stimulus-evoked gamma activity ($p < 0.05$). NRG1 treatment reverted these changes ($p < 0.05$), but its effects were abolished by AG1478 administration ($p < 0.05$). Minocycline also showed similar results as NRG1 ($p < 0.05$) (Gao et al. [74])
Gao et al. [31]	Adult male C57BL/6 mice	CLP	1-methyl-D, L-tryptophan (5 mg/ml, p.o.) in drinking water, 1 day before and 7 days after CLP, L-kynurenine (100 mg/kg, i.p.) 30 min before behavioral tasks	Mortality, L-tryptophan, L-kynurenine, cytokines, indoleamine 2, 3-dioxygenase (IDO), neurotrophin, and microglial activation marker in brain and plasma	Open field, contextual fear conditioning and cued fear conditioning tasks 13 days after CLP	Sepsis induced cognitive impairment as evidenced by decreased contextual freezing time ($p < 0.05$) along with an increase in hippocampal IBA1-positive cells, TNF-α, IL-1β and IL-6 ($p < 0.05$), kynurenine, kynurenine/tryptophan ratio, IDO activity, and decreased tryptophan level ($p < 0.05$). Similarly, single peripheral administration of L-kynurenine, the metabolic product of IDO, induced cognitive impairment in the sham mice. However, treatment with IDO inhibitor 1-methyl-D, L-tryptophan reverted all these changes ($p < 0.05$) (Gao et al. [31])
Gasparotto et al. [132]	Adult Wistar rats	CLP	Rat polyclonal anti-RAGE (RAGE*ab*) (100 μg/kg saline) was administered bilaterally into the hippocampus at days 15, 17, and 19 after CLP.	Hippocampus and prefrontal cortex levels of amyloid-β (Aβ) and Ser-202phosphorylated tau (p-tauSer202), RAGE, RAGE ligands (S100B, Nε [carboxymethyl] lysine, HSP70,	Inhibitory avoidance tasks 30 days after CLP, object recognition task	Serum proinflammatory markers (TNFα, IL-1β, and IL-6), levels of RAGE, RAGE ligands (S100B, Nε-[carboxymethyl]lysine, HSP70, and HMGB1), brain levels of TLR4, GFAP, neuronal NOS, Aβ,

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
			Control animals received 100 μg/kg of isotype IgG	and HMGB1) and TLR-4, GFAP and neuronal nitric oxide synthase, serum levels of TNFα, IL-1β, and IL-6		and p-tauSer202 all increased during post-CLP period. Intracerebral administration of RAGE antibody post-CLP reversed these changes and also attenuated the cognitive deficits that resulted from sepsis. The data suggest that RAGE induces neuronal damage that might be alleviated with anti-RAGE treatments (Gasparotto et al. [132])
Granger et al. [149]	Adult male BALB/c mice	CLP	Telemeter implantation for core body measurement	Mortality rate and morbidity, cytokines mRNA, and protein expressions in brain	Cage activity and social exploration tasks immediately after CLP	Sepsis caused a mortality rate of 44%. Body temperature rhythms and cage activity of remaining mice were severely compromised for up to 23 days, food and water consumption were reduced for 2–3 days, and body weight dropped for 7 days post-CLP sepsis. In addition, sepsis decreased social interactions 24–72 h ($p \leq 0.05$). Early response to sepsis (6–72 h) included upregulation of mRNA and protein for IL-1β, IL-6, and TNFα in the hypothalamus, hippocampus, and brainstem ($p \leq 0.05$) (Granger et al. [149])
Guo et al. [86]	66 specific-pathogen--free male Kunming mice (1 M old, 18-22 g outbred mice	CLP	Rapamycin (specific inhibitor of mTOR complex I (0.5 mL solution) (1 mg/kg, i.p.) or equal volume of saline from day 5 to 9 after CLP	Akt, mammalian target of rapamycin (mTOR), and p70S6K, β-actin, neuronal count in the cornu ammonis 1 (CA1) region of the hippocampus morphology	Morris Water Maze Test	CLP sepsis enhanced phosphorylation of Akt, mTOR, and p70S6K along with hippocampal neuronal loss, abnormal neuronal morphology, and impaired long term cognitive performance, suggesting that sepsis-induced hippocampal neurodegeneration triggers Akt/mTOR signaling pathway. However, rapamycin (specific inhibitor of mTOR complex I) rescued cognitive deficits in acute phase with no influence on chronic phase cognitive impairment or long-term neuronal loss in hippocampal CA1 region (Guo et al. [86])
He et al. [23]	Adult female C57BL/6 mice	CLP and LPS (2 mg/kg, i.p.) in	Anti-NK1.1 mAb (25 μg, i.p.), twice, prior to LPS or CLP	NK cells count and function, cytokines, microglial activation, and BBB permeability	Sucrose preference task 4 days after CLP or LPS injection	LPS increased IL-1β, IL-6 and TNF-α levels ($p < 0.001$), neutrophil attracting chemokines ($p < 0.01$),

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
		different batches of animals				and several types of leukocytes infiltration, microglial activation, and BBB disruption, compared to control animals. NK cells depletion with anti-NK1.1 prior to LPS treatment reversed all these changes ($p < 0.05$). Also, infiltrated NK cells attracted neutrophils by chemotactic activity with higher expression of chemokines, such as CXCL1, CXCL2, and CXCL3 (especially CXCL2), along with help from microglia to upregulate pro-inflammatory cytokines. NK cells depletion could significantly reduce depression-like behavior in LPS-treated mice ($p < 0.05$) and changes in serotonin metabolism-associated enzymes and proteins (Chen et al. [115])
Hernandes et al. [102]	Adult male C57BL/6 mice and Gp91$^{phox\ -/-}$ mice	CLP	Apocynin (20 mg/kg, s.c.) 30 min prior to CLP in C57Bl/6 mice and apocynin (5 mg/kg, s.c.) at 1, 6, 24 and 48 h after CLP	4-HNE, NADPH oxidase (Nox) activity, and gene expression, glial activation, plasma, and peritoneal cavity levels of cytokine/chemokine	Inhibitory avoidance and MWM tasks 15 days after CLP	Sepsis increased 4-HNE, along with an increase in Nox2 gene expression ($p < 0.05$), microglia, and astrocyte activation with cellular process thickening up to 5 days in hippocampus. Nox2 inhibition with apocynin attenuated oxidative stress ($p < 0.05$) and astrogliosis ($p < 0.001$). Apocynin inhibition of Nox2 or the absence of Nox2 in gp91phox$^{-/-}$ mice prevented glial cell activation. Apocynin prevented the development of long-term memory deficits ($p < 0.05$) (Hernandes et al. [102])
Hoshino et al. [82]	Adult male C57BL/6J mice	CLP	Minocycline (MINO) (60 mg/kg, i.p.) daily, for 3 days after CLP. Mouse recombinant IL-1 receptor antagonist (IL-1ra) (50 ng/mL)	Mortality, endotoxin levels in blood, synaptic plasticity in the hippocampus	None	Sepsis increased the mortality rate (56.2%; $p < 0.05$) and endotoxin levels in the blood ($p < 0.05$). In the hippocampal CA1 region, synaptic plasticity was severely impaired ($p < 0.05$) in the sepsis group, which was prevented with MINO. IL-1ra attenuated synaptic plasticity impairment in the CLP + vehicle group ($p < 0.05$), with no added influence in the CLP +

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						MINO group (Hoshino et al. [82])
Huang et al. [20]	Adult male Sprague-Dawley rats	CLP	*N*-[*N*-(3,5-difluorophenacetyl)-1-alanyl]-*S*-phenylglycine t-butyl ester (DAPT) (10 μmol/Kg, i.p.) 30 min before CLP	Notch receptor intracellular domain (NICD), Poly [ADP-ribose] polymerase 1 (PARP-1), cytokine in CSF, neuronal apoptosis	Novel object recognition task with no mention about the timing of behavioral analysis	Sepsis increased the expression of NICD ($p < 0.05$) and PARP-1 ($p < 0.05$) in hippocampus, TNF-α levels ($p < 0.05$), neuronal apoptosis ($p < 0.01$), and cognitive dysfunction ($p < 0.01$). Treatment with DAPT reverted the levels of NICD and PARP-1, reduced hippocampal neuronal apoptosis ($p < 0.05$), TNF-α levels ($p < 0.05$), and improved the cognitive deficits caused by sepsis (Huang et al. [20])
Huerta et al. [150]	Adult male C57BL/6 mice	CLP	None	Brain histology	SHIRPA test with modifications 30 days after CLP and contextual fear conditioning task 45 days after CLP	CLP mice showed comparable behavioral results to sham mice in SHIRPA test, but presented deficits in contextual fear memory up to 22 weeks ($p < 0.01$). This was associated with fewer dendritic spines in the excitatory neurons in the basolateral nucleus of the amygdala and granule cells in the dentate gyrus, with no significant difference in hippocampal CA1 pyramidal neurons (Huerta et al. [150])
Jeppsson et al. [151]	Adult male Sprague-Dawley rats	CLP	1.0 PCi of carbon-14-labeled amino acid in Krebs-Ringer buffer and 10 mM Hepes, (0.2 mL, i.v.) 15 s before decapitation	Plasma and brain amino acids, brain uptake index and brain influx rate, white blood cell count, ammonia, albumin, and glucose assay	None	Both early and late septic groups showed a decrease in plasma albumin, glucose levels and plasma amino acids, such as arginine, glycine, lysine, proline, and serine, brain amino acids, such as arginine and serine and an increase in neutral amino acids histidine, phenylalanine and tyrosine, brain uptake indices (except for lysine) and brain influx rates for all neutral amino acids and plasma ammonia levels. Only late septic rats showed a decrease in branched chain amino acids and white blood cell count, compared to controls. Septic brain microvessels had a higher uptake of carbon-14-labeled leucine and tyrosine, with no change in lysine uptake between the groups (Jeppsson et al. [151])

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
Jeremias et al. [152]	Adult male BALB/c mice	CLP	None	Mortality, S100β in plasma, weight of spleens and splenic lymphocytes analysis, cytokine levels in spleen, hippocampus and plasma	SHIRPA test 6 and 12 h after CLP	Sepsis severity significantly impacted the survival rate, as severe sepsis caused a higher mortality rate than mild sepsis ($p < 0.05$), impaired behavior on SHIRPA test ($p < 0.05$), and elevated plasma S100β levels ($p < 0.05$) in moderate and severe sepsis groups, compared to both sham and mild sepsis groups. There was no notable change in splenic weight and splenocytes profile 6 h after CLP. However, there was an increase in splenic and plasma IL-6, IL-10, and IL-1β levels ($p < 0.05$) (Jeremias et al. [152])
Ji et al. [100]	Adult male C57BL/6 mice	CLP and neuronal culture	Apocynin (2.5, 5, or 10 mg/kg, i.p.) daily, for 10 days after CLP. For neuronal cultures, apocynin (0.5 mM) alone or with LPS (1 μg/ml)	Parvalbumin, $gp91^{phox}$, 4-HNE, MDA, SOD, and cytokines	Open field and contextual and tone fear conditioning tasks 13 and 29 days after CLP	Sepsis resulted in anxiety-like behavior and a decrease in associative memory ($p < 0.05$), along with an increase in 4-HNE, MDA, IL-1β, and IL-6 levels ($p < 0.05$) and selective phenotype loss of parvalbumin interneurons, $gp91^{phox}$ activation and a decrease in post-synaptic density protein 95 (PSD-95) puncta numbers in parvalbumin interneurons, compared to sham group ($p < 0.05$). Apocynin treatment reverted all these changes ($p < 0.05$), compared to CLP + vehicle group (Ji et al. [100])
Ji et al. [130]	Adult male C57BL/6 mice	CLP	Melatonin dissolved in 1% ethanol and then diluted in normal saline (10 mg/kg, i.p.) daily, for 3 consecutive days (early) immediately or at 7 days (late) after sham or CLP, followed by an additional treatment in drinking water until the end of behavioral tests	Serum levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-10), and levels of MDA, SOD, reactive oxygen species (ROS), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF)	Open field test, novel object recognition, and fear conditioning tests	Early melatonin treatment improved survival rate with no behavioral change and reduced plasma IL-1β levels, whereas deferred melatonin treatment improved cognitive assessments by reverting hippocampal BDNF and GDNF levels, suggesting that melatonin could be a novel therapeutic solution for sepsis associated brain derailment (Ji et al. [130])
Leite et al. [131]	Adult male Wistar rats	CLP	Nicotine bitartrate (0.1 mg/kg, s.c.) daily, for 7 days before CLP or 7 days before and 7 days after CLP	None	Open field, elevated plus maze and step-down inhibitory avoidance tasks 7 days after CLP	Nicotine did not impact the survival rate while impaired the locomotor activity 1 week after CLP. However, nicotine treatment (both

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						before and/or after CLP) rescued the sepsis induced anxiety-like responses seen on elevated plus maze ($p < 0.05$), but only nicotine treatment before and after CLP improved short- and long-term memory loss seen on inhibitory avoidance task ($p < 0.05$) (Leite et al. [131])
Li et al. [153]	30-day-old male Wistar rats	CLP	Ethyl pyruvate (EP) (40 mg/kg, i.p.) dissolved in 2 ml of lactate ringer solution or lactate ringer solution was administered at 30 min after CLP to CLP + EP and CLP + Sham groups respectively	Cortical pathological changes with H&E, cellular HMGB1 localization with immunofluorescence staining, HMGB1 cortical levels, HMGB1 receptor for advanced glycation end-products (RAGE), and downstream effecter, nuclear factor kappa-β (NF-κB) sub-unit p65 with Western blot analysis	None	CLP induced edema and a reduction in cortical neuronal numbers, increased HMGB1 translocation from the nucleus to cytoplasm and also increased the RAGE levels and nuclear NF-κB p65 expression, which were all reverted back with EP administration, suggesting that inhibition of HMGB1 translocation via HMGB1 inhibitors such as EP might be neuroprotective in sepsis (Li et al. [153])
Li et al. [24]	Adult male C57BL/6 mice	CLP	Ginsenoside Rg1 (40 or 200 mg/kg, i.p.) 1 h before CLP	Cytokines levels and expression in hippocampus, microglial activation, neuronal apoptosis, and autophagy pathway	MWM task 4 days after CLP	Rg1 improved the survival rate ($p < 0.05$), diminished the learning and memory deficits, ameliorated brain histopathologic changes, microglial Iba1 activation ($p < 0.01$), TNF-α, IL-1β and IL-6 expression ($p < 0.05$), caspase 3 activation ($p < 0.05$), and decreased the expression of light chain 3-II and p62 in hippocampus, but not beclin 1 (Li et al. [24])
Liu et al. [25]	Adult male ICR mice	CLP	2% hydrogen (H_2) (4 L/min) for 60 min at 1 h and 6 h after CLP	H_2 concentration in blood and brain, survival rate, histopathology, and neuronal apoptosis in hippocampus, BBB permeability, brain water content, cytokines SOD, CAT, MDA and 8-iso-PGF2α in serum and hippocampus, expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and cytoplasmic heme oxygenase-1 (HO-1) in hippocampus	Y-maze task and contextual fear conditioning task	H_2 treatment ameliorated survival rate from 30 to 70% ($p < 0.05$), attenuated sepsis induced histopathological changes, neuronal apoptosis, BBB disruption ($p < 0.001$), brain edema ($p < 0.01$), pro-inflammatory cytokine levels, prevented oxidative stress and up-regulated Nrf2 and HO-1 expression in CLP mice. H_2 also remarkably improved cognitive dysfunction observed in both behavioral tasks (Liu et al. [25])
Liu et al. [85]		CLP			MWM task 14 days after CLP	

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
	Adult male Kunming mice		Rapamycin (1, 5, or 10 mg/kg, i.p.) daily, for 5 days after CLP	Glial infiltration, mTOR targets, and autophagy indicators in hippocampus		Sepsis resulted in neuronal loss and increased glia infiltration in hippocampus. Rapamycin protected against the cognitive decline caused by sepsis ($p < 0.05$) by inhibition of mTOR and improved learning by enhancing autophagy. Though Rapamycin did not affect total mTOR targets, it decreased phosphorylated mTOR targets (p-mTOR-Ser2448, p-p70S6k-Thr389, p-AKT-S473) ($p < 0.05$) and P62 and increased autophagy indicators (LC3-II, Atg5, Atg7), compared to control group ($p < 0.05$) in hippocampus (Liu et al. [85])
Magno et al. [154]	C57BL/6 mice	Pneumo sepsis intra tracheal instillation of 10^5 CFU of *P. aeruginosa*	None	Bronchoalveolar lavage fluid for cell migration and cytokine, cells count in blood, MPO in lung, lung permeability, and survival rate	Freezing task 13 and 50 days after instillation	Pneumosepsis resulted in with leukocyte infiltration, predominantly neutrophils, as evidenced by increased levels of MPO, enhanced IL-6 and protein levels along with an intense cell infiltration in the lung and reduced survival rate, associated with deficit of aversive memory that persisted for 50 days (Magno et al. [154])
Michels et al. [90]	Adult male Wistar rats	CLP	Anti-CD40 (1, 10, or 100 μg/kg, i.c.v.) or minocycline (100 μg/kg, i.c.v.) after CLP	CD40 and CD40 ligand, cytokines, MPO, nitrite/nitrate (N/N) in brain, BBB permeability	Inhibitory avoidance and open field tasks 10 days after CLP	Microglial activation by in vivo CLP sepsis or in vitro LPS induces CD40–CD40L pathway with increased CD40 expression and CD40 L secretion ($p < 0.05$). Sepsis also increased IL-1β, IL-6, and TNF-α levels that leaded to TBARS and N/N increases, neutrophil infiltration, and BBB dysfunction ($p < 0.05$), compared to sham group. Anti-CD40 treatment had no influence on mortality rate, however decreased CD40–CD40L levels, as well as neuroinflammation, oxidative damage and BBB dysfunction and improved both aversive and non-aversive long-term memory deficits in sepsis survivors ($p < 0.05$) (Michels et al. [90])

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
Michels et al. [155]	Adult male Wistar rats	CLP	Minocycline (100 μg/kg, i.c.v.) once, after CLP	BBB permeability, cytokines, TBARS, and protein carbonyls in hippocampus	Inhibitory avoidance and open field tasks 10 days after CLP	Sepsis increased TBARS and protein carbonyls levels ($p < 0.05$), IL-6 and TNF-α ($p < 0.05$), caused BBB dysfunction ($p < 0.05$), and impaired cognitive function ($p < 0.05$). Minocycline administration inhibited microglial activation and reverted all these changes along with an improvement in long-term cognitive impairment ($p < 0.05$) (Michels et al. [155])
Mina et al. [81]	Adult male Wistar rats	CLP	IL-1ra (10 μg, i.c.v.) once, after CLP	BBB permeability, cytokines, TBARS, protein carbonyls, and ETC activity	Open field and step-down inhibitory avoidance tasks 10 days after CLP	Sepsis increased the BBB permeability ($p < 0.05$) in the prefrontal cortex, hippocampus and the striatum, and the levels of IL-1β, IL-6, and TNF-α ($p < 0.05$) in the prefrontal cortex and hippocampus, enhanced the activity of complex 1 ($p < 0.05$), TBARS and protein carbonyl levels ($p < 0.05$), associated with an impairment in habituation and aversive memory. All these effects were reverted with IL-1ra treatment ($p < 0.05$) (Mina et al. [81])
Moraes et al. [26]	Adult male Swiss mice	CLP and astrocytes, microglial, and neuronal cell culture	IL-1Ra (1 μg/mL) in neuronal culture	Astrocyte, microglial and neuronal activation, synapse quantification and cytokines in hippocampus and cortex	Novel object recognition task 9 and 30 days after CLP	Septic mice showed short-term memory impairment at 9 days after CLP ($p < 0.05$) and reduced numbers of hippocampal and cortical excitatory synapses ($p < 0.05$), along with microglial activation and reactive astrogliosis ($p < 0.05$) that were reverted within 30 days ($p < 0.05$). Neuronal cultures treated with conditioned medium derived from cultured astrocytes (ACM) and microglia (MCM) increased the number of synapses between cortical neurons ($p < 0.05$). When stimulated with LPS, in MCM there was reduced number of synapses by 50% and increased levels of IL-1β, while in ACM the synapses increased by 500%. Treatment with IL-1Ra decreased IL-1β levels and reduced

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						synaptic deficits ($p < 0.05$) (Moraes et al. [26])
Neves et al. [135]	Adult male Swiss mice	CLP	Liraglutide (50 nmol/kg, s.c.) daily, at 20 days after CLP, for 10 days, or TDZD-8 (5 mg/kg, i.p.) daily, at 25 days after CLP, for 5 days	Synaptophysin, cAMP response element-binding protein (CREB), insulin receptor substrate pathway, cytokine, and p-tau	Open field, novel object recognition, and step-down inhibitory avoidance tasks 15, 25, 30, and 45 days after CLP	Sepsis impaired aversive and recognition memories that were associated with damage to the hippocampal synaptic integrity and function, visualized by reduction of CREB, synaptophysin, increased expression of TNF-α and inhibition of IRS-1pathway. Treatment with liraglutide or TDZD-8 improved object recognition memory (Neves et al. [135])
Oliveira et al. [32]	Adult male Swiss mice	CLP	NXY-059 (50 mg/kg, i.p.) daily, for 5 days after CLP	Mortality, sepsis severity, glucose levels in blood	Open field task 15 days after CLP	NXY-059 did not improve mortality rate. Animals displayed a moderate sepsis at 24 h and mild sepsis with a slight restoration of glucose levels at 48 h after sepsis. Treatment with NXY-059 reduced the numbers of crossings and rearings in the open field task ($p < 0.05$) (Oliveira et al. [32])
Ozcan et al. [123]	Adult male Wistar rats	CLP	Human IgG (250 mg/kg, i.v.) or IgGAM (250 mg/kg, i.v.) after CLP	None	Open field, elevated plus maze and forced swimming tasks 10, 30, and 60 days after CLP	Sepsis caused a mortality rate of 50% that was reduced to 30 and 20% after treatment with IgG and IgGAM, respectively. Sepsis altered behavior in the open field task at days 10 and 30, which was improved with IgGAM at day 10 ($p < 0.01$) and 30 ($p < 0.05$), and with IgG at day 10 ($p < 0.01$). CLP rats showed anxiety-like behavior ($p < 0.01$) and depressive-like behavior ($p < 0.01$), both of which improved with IgG and IgGAM treatments (Ozcan et al. [123])
Petronilho et al. [121]	Adult male Wistar rats	CLP	Guanosine (GUA) (8 mg/kg, i.p.) daily and through the experiment duration	TBARS and protein carbonyl in hippocampus, striatum, cerebellum, prefrontal cortex, and cortex	Inhibitory avoidance, open field, novel object recognition and forced swimming tasks 10 days after CLP	Guanosine treatment reduced TBARS and protein carbonyl levels between 12 and 24 h after CLP. Also, GUA improved memory deficits and depressive-like behavior that were altered at 10 days after CLP (Petronilho et al. [121])
Santos-Junior et al. [156]	Male Wistar rats	CLP	Osmotic challenge with hypertonic saline (ip; 2 mol/L NaCl) in a volume	Plasma levels of osmolality, nitrite, interleukin (IL)-1β, IL-6, arginine AVP, and oxytocin (OT) levels and	None	Sepsis survivor rats showed systemic inflammatory changes such as high nitrite and IL-1β levels which

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
			corresponding to 1% of body weight and isotonic saline (ip; 0.01 mol/L NaCl) to controls 5 days after CLP	c-fos expression analysis of hypothalamic supraoptic nuclei (SON). In another group of sepsis survivor rats, water intake was measured for 240 min after the osmotic stimulus		demonstrated no change with osmotic challenge. Though osmotic challenge increased osmolality, neurohypophyseal hormones AVP and OT in controls and sepsis survivors, AVP and OT levels, but not the osmolality and c-fos expression in SON are more reduced in sepsis group than naïve rats. To conclude, sepsis induced inflammatory damage impaired neurohypophyseal osmoregulatory reflex blocking its hormonal secretion (Santos-Junior et al. [156])
Schwalm et al. [38]	Adult male Wistar rats	CLP	NAC (20 mg/kg, s.c.), every 6 h for 24 h with deferoxamine (20 mg/kg, s.c.) single dose, or MMP2–9 inhibitor (0.3 mg/kg, i.c.v.)	Aβ and synaptophysin levels in hippocampus and prefrontal cortex	Step-down inhibitory avoidance task 30 days after CLP	Sepsis increased Aβ content ($p < 0.05$) and decreased synaptophysin levels ($p < 0.05$) in the hippocampus and prefrontal cortex, that was correlated to impaired cognitive performance ($p < 0.05$). Treatments with antioxidants or MMP2–9 inhibitor reverted Aβ content in both structures ($p < 0.05$), but synaptophysin levels were reverted only in prefrontal cortex ($p < 0.05$) (Schwalm et al. [38])
Semmler et al. [157]	Adult male Wistar rats	LPS (10 mg/kg, i.p.)	None	Quantitative analysis of hippocampal, entorhinal and parietal cortex neurons, vesicular acetylcholine transporter (VAChT)	Open field, 8-arm radial maze and passive avoidance tasks 90 days after CLP	LPS-induced rats exhibited changes in the open field activity ($p < 0.05$), memory deficits in the radial maze ($p < 0.05$), with no change in the passive avoidance task. These impairments correlated with reduced density on NeuN-staining in the CA1 and CA2 regions of the hippocampus ($p < 0.01$) and the prefrontal cortex ($p < 0.01$) and reduced cholinergic innervation in the parietal cortex as measured by VAChT ($p < 0.05$) (Semmler et al. [157])
Shimizu et al. [158]	Adult male Wistar rats	CLP	None	Cells count, endotoxin, ammonia and aminoacids in blood, monoamines and their metabolites in brain	Step-through passive avoidance and Hargreaves' planter tasks 24 and 48 h before and 24 h after CLP	Sepsis caused a mortality rate of 44% at 48 h after CLP, increased endotoxin levels ($p < 0.05$), but decreased white blood cell count ($p < 0.01$) and the concentrations of

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						tyrosine and arginine ($p < 0.05$) in plasma. Also, sepsis impaired retention performance 24 h after CLP ($p < 0.05$), while did not alter nociceptive responses. Sepsis decreased 3,4-dihydroxyphenylacetic acid (DOPAC) at 48 h after sepsis in the striatum. The levels of 5-hydroxytryptamine (5-HT) increased in the cortex, striatum and hippocampus at 48 h after CLP ($p < 0.05$). Norepinephrine (NE) concentration in the hypothalamus was decreased at 24 h after CLP, while the cortical NE was increased at 48 h after CLP (Shimizu et al. [158])
Singer et al. [159]	Adult male C57BL/6 mice	CLP	None	Microglial activation, cell infiltration and cytokines in brain	None	Sepsis caused microglial activation identified as $CD45^{mid}/CD11b+$ population, decreased the microglial expression of chemokine receptor, with no influence over IL-1β levels. There was a persistent presence of neutrophils and $Ly6C^{high}$ and $Ly6C^{low}$ monocytes (Singer et al. [159])
Singer et al. [160]	Adult male C57BL/6 mice and $CCR2^{-/-}$ mice	CLP	None	Cell count, cell infiltration, and microglial activation in brain	Contextual fear conditioning, trace contextual fear conditioning and extinction learning tasks 50 days after CLP	Sepsis impaired extinction memory up to 50 days after CLP, induced microglia, neutrophil and monocyte infiltration at 14 days, which is independent of CCR2 gene (Singer et al. [160])
Singer et al. [39]	Adult male C57BL/6 and $CCR2^{-/-}$ mice	CLP	None	Brain histology, dendritic spine density, immunoglobulins, cell infiltration, cytokines, chemokines, and microglial expression	Contextual fear conditioning, trace tone conditioning and extinction of conditioned fear tasks 50 days after CLP	Sepsis causes deficits in extinction of conditioned fear nearly two months after CLP ($p = 0.038$), without neuronal loss or changes in synaptic density in the hippocampus. Sepsis also resulted in infiltration of monocytes and neutrophils into the CNS at least 2 weeks after sepsis in a CCR2 independent manner, accompanied by long-term expression of cytokines and chemokine ($p < 0.05$) genes in whole brain.

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						Also, while microglia does express anti-microbial genes and damage-associated molecular pattern molecules at least 2 weeks after sepsis, they do not express the cytokines observed in brain (Singer et al. [39])
Steckert et al. [161]	Adult Male Wistar rats	CLP	None	Cytokines in CSF, TBARS and protein carbonyl, creatinine kinase activity and ETC enzymes	None	Sepsis increased IL-6 levels ($p = 0.005$) in CSF, TBARS levels ($p = 0.002$) in prefrontal cortex with a reduction in hippocampus ($p = 0.002$), striatum ($p = 0.009$) and cortex ($p = 0.009$), a decrease in protein carbonyl ($p = 0.008$) in prefrontal cortex with an increase in striatum ($p = 0.029$), along with an increase in hippocampal complex IV activity ($p = 0.034$), all at 30 days after CLP. At 60 days after CLP, septic rats showed an increase in TNF-α levels ($p = 0.005$) in CSF, a decrease in hippocampal TBARS levels ($p = 0.005$) with an increase in protein carbonyl in striatum ($p = 0.012$) and a decrease of complex I activity in prefrontal cortex ($p = 0.038$), striatum ($p = 0.043$) and hippocampus ($p = 0.016$ (Steckert et al. [161])
Steckert et al. [77]	Adult male Wistar Rats	CLP	Sodium butyrate (SB) (10 mM in 5 μL) once, before CLP	HDAC activity in prefrontal cortex, hippocampus, striatum and cortex	Inhibitory avoidance task 10 days after CLP	Sepsis impaired aversive memory ($p = 0.002$) at 10 days after CLP, increased HDAC activity in hippocampus ($p = 0.023$) and cortex ($p = 0.026$) at 24 h after CLP and in prefrontal cortex ($p = 0.003$) and hippocampus ($p = 0.006$) at 10 days after CLP. SB treatment reverted memory impairment ($p = 0,002$) and showed late inhibitory effect on HDAC activity in the prefrontal cortex and hippocampus at 10 days after CLP, with no early influence at 24 h (Steckert et al. [77])
Steckert et al. [162]	Male Wistar rats (60 days old)	CLP	Chronic mild stress (CMS) protocol prior to sepsis induction by CLP	Body weight, water and food intake, mortality until 10 days after sepsis, TBARS, protein carbonyl levels	Open field locomotor and exploratory activity, splash test for anhedonia, forced swim test	When more specific depressive-like grooming behavior is tested on splashing sucrose solution, CLP +

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
				and cytokines such as TNF-α, IL-1β and IL-6 levels		control and CMS + sham rats showed a decrease in grooming time. However, CMS + CLP rats depicted no decrease in grooming time, along with a decrease in inflammatory brain cytokines, but with no expected oxidative parameter results, suggesting that CMS prior to sepsis might be neuroprotective against sepsis related systemic stress and inflammation (Steckert et al. [162])
Sun et al. [112]	Adult male C57BL/6 mice	CLP	Cyclophilin D (CypD) siRNA (50 μL, i.c.v.) and Sirtuin-3 (SIRT3)-Flag (i.c.v.) 3 days before CLP	Apoptotis, mitochondrial membrane potential, mitochondrial permeability transition pore (mPTP) opening, cytokines	MWM task with no clear mention about the timing of behavioral analysis	Sepsis increased hippocampal levels of CypD and its acetylation, caused cognitive damage and cell apoptosis, decreased threshold for mPTP opening and mitochondrial membrane potential, and increased the expressions of IL-6, TNF-a and caspase-3 ($p < 0.05$). Increasing SIRT3 and decreasing CypD in SIRT3-p and CypD-si groups ameliorated cognitive impairment, neuroapoptosis, rescued mitochondrial membrane and reduced the expressions of IL-6, TNF-a, and caspase-3 ($p < 0.05$) (Sun et al. [112])
Sui et al. [58]	Adult male C57BL/6 mice	CLP and BV2 cell culture	Resveratrol (10 or 30 mg/kg, i.p.) 1 h before and at 6, 12, and 18 h after CLP. For cell culture, LPS (100 ng/mL) and resveratrol (30 μM)	Apoptosis, microglial activation, gene expression of NLRP3, and IL-1홱	MWM task 4 days after CLP	CLP mice treated with both doses of resveratrol presented a better spatial memory ($p < 0.05$), decreased rates of apoptosis, and number of iba-1 positive microglia ($p < 0.05$) in the hippocampus. NLRP3 expression and IL-1홱 cleavage were inhibited by resveratrol, dose-dependently. In the BV2 cell lines, resveratrol prevented ATP-induced NLRP3 activation and IL-1홱 cleavage (Sui et al. [58])
Tang et al. [126]	Male C57/BL6 mice	CLP	Metformin dissolved in normal saline or equal amounts of normal saline (100 mg/kg, i.p.) immediately after CLP. 10 μL of LY solution (50 mmol/L dissolved in	Survival percentage, brain water content, levels of inflammatory markers (IL-1β, IL-6, and TNFα), BBB permeability, neuronal apoptosis, and expression of Akt, p-Akt, and β-actin	Morris Water Maze test. One hour before CLP, 10 μL of LY solution (50 mmol/L dissolved in 25% DMSO in phosphate-buffered saline [PBS]) was injected into the left ventricle ((bregma; 1.0 mm lateral, 0.3 mm posterior, 2.6 mm	Metformin enhanced the survival percentage, protected BBB integrity, attenuated neuronal apoptosis, brain edema, oxidative damage, and proinflammatory cytokine levels, and improved cognitive function along with an

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
			25% DMSO in phosphate-buffered saline [PBS]) was injected into the left ventricle ((bregma; 1.0 mm lateral, 0.3 mm posterior, 2.6 mm deep) at a rate of 1 μL/min in the CLP+ Met+ LY group) or equal amount of normal saline 1 h before CLP		deep) at a rate of 1 μL/min in the CLP+ Met+ LY group. Other groups received an equal amount of normal saline	increase in Akt phosphorylation. However, LY294002, a phosphatidylinositol-3-kinase (PI3K) inhibitor reverted the metformin's neuroprotective effect theorizing that metformin's neuroprotective effect might be from activation of PI3K/Akt signaling pathway (Tang et al. [126])
Toklu et al. [117]	Adult male and female Wistar rats	CLP.	Riluzole (6 mg/kg, s.c.) 30 min after CLP and twice daily as continuous treatment	Mortality, weight loss, fever, leukocyte count, cytokine in plasma, brain edema, BBB permeability, MDA, glutathione (GSH) and histological analysis	Bederson's modified neurological examination 6 and 48 h after CLP	Sepsis caused high mortality rate ($p < 0.001$), weight loss ($p < 0.01$), hypothermia ($p < 0.05$), brain edema ($p < 0.001$), an increase in BBB permeability ($p < 0.001$), increased MDA levels ($p < 0.001$), and decreased GSH ($p < 0.001$) levels, along with impaired neurological scores on Bederson's neurological exam. Riluzole treatment attenuated mortality rate ($p < 0.001$), weight loss ($p < 0.01$), body temperature ($p < 0.01$), brain water content ($p < 0.001$), BBB permeability ($p < 0.05$ to 0.01), decreased MDA ($p < 0.001$) and increased GSH ($p < 0.01$) levels, along with an improvement in the neurological scores ($p < 0.05$–0.01) (Toklu et al. [117])
Tuon et al. [63]	Adult male Wistar rats	CLP	Imipramine (10 mg/kg, i.p.) 10 days after CLP	None	Forced swimming and open field tasks 10 days after CLP	Sepsis caused depressive-like behavior ($p < 0.05$), which was ameliorated with the use of imipramine ($p < 0.05$) (Tuon et al. [63])
Tuon et al. [40]	Adult male Wistar rats	CLP	Epinephrine (25 μg/kg, i.p.), nalaxone (0.4 mg/kg, i.p.), dexamethasone (0.3 mg/kg, i.p.), or glucose (320 mg/kg, i.p.) after training, 10 or 30 days after CLP	None	Inhibitory avoidance task 10 and 30 days after CLP	All treatments exhibited memory improvement effect with different statistical significance at10 days post-sepsis, EPI ($p = 0.001$), NAL ($p = 0.002$), DEX ($p = 0.002$), or GLU ($p = 0.002$) and at 30 days post-sepsis, EPI ($p = 0.001$), NAL ($p = 0.002$), DEX ($p = 0.003$), or GLU ($p = 0.002$) (Tuon et al. [40])
Tuon et al. [40]	Adult male Wistar rats	CLP	None	None	Open field, step-down inhibitory avoidance, continuous multiple trials step-down inhibitory	Sepsis caused impairment after 10 and 30 days in the step-down inhibitory avoidance task ($p = 0.002$,

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
					avoidance, novel object recognition, elevated plus-maze and forced swimming tasks 10, 30, and 60 days after CLP	$p = 0.003$), continuous multiple trials step-down inhibitory avoidance task ($p < 0.05$) and forced swim test ($p = 0.01$, $p < 0.001$) and after 10 days on habituation to open field ($p < 0.001$) and object recognition test ($p < 0.05$) but no difference in the elevated plus maze task. After 60 days, there was no significant difference between sepsis and control groups (Tuon et al. [40])
Vasconcelos et al. [122]	Adult male Wistar rats	LPS (1 mg/kg, i.v.)	Intermittent fasting (IF), consisted of food deprivation for 24 h every other day, for 30 days	Body weight, expression of NF-κB, Toll-like receptor 4 (TRL4), iNOS and neurotrophin in hippocampus, cytokines, and chemokines in serum and hippocampus	Open field, rotarod, Barnes maze, and inhibitory avoidance tasks 1 day after LPS injection	IF prevented memory impairment induced by LPS in the Barnes maze task ($p < 0.001$) and inhibitory avoidance task ($p < 0.05$), diminished the expression of TLR-4 mRNA ($p = 0.016$) and iNOS mRNA ($p = 0.045$), but increased NF-κB translocation ($p < 0.05$) and biding activity ($p < 0.05$), while reduced the hippocampal levels of IL-1β ($p < 0.001$) and RANTES ($p < 0.05$), compared to LPS group, and serum levels of TNF-α ($p < 0.01$), IL-6 ($p < 0.01$), RANTES ($p < 0.05$), and IFN-γ ($p < 0.05$), also compared to LPS group. IF + LPS animals did not display reduction in BDNF levels ($p < 0.05$) (Vasconcelos et al. [122])
Venturi et al. [163]	Adult male Sprague-Dawley rats	CLP	TBI by CCI model	Mortality, body weight, lesion volume, cell count, and microglia and glia activation	Beam balance and MWM tasks 2, 7, and 14 days after CLP	Sepsis associated with TBI increased mortality rate (37.7%, $p < 0.01$) compared to all groups, reduced weight gain at 14 days after surgery ($p < 0.05$), compared to CLP group, and induced motor function impairment visualized in the beam balance task at 7 days ($p < 0.01$), compared to all groups. Also, CLP + CCI animals presented learning, but not memory, impairment ($p < 0.05$), compared to CCI group, increased neuronal cell loss in the hippocampal CA3 region ipsilateral

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
						to trauma ($p < 0.05$), compared to CCI group and enhanced microglial activation, with no alteration in astrocyte activation and lesion volume (Venturi et al. [163])
Wang et al. [64]	Adult male Sprague-Dawley rats	CLP	Recombinant human erythropoietin (rhEPO) (5 U/ day, i.c.v.) daily, for 7 days after CLP	Neuronal apoptosis, protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway	Open field, inhibitory avoidance and MWM tasks 7 days after CLP	Sepsis induced neuronal apoptosis by inhibiting Bcl-2 and increasing Bad ($p < 0.05$). CLP rats showed a suppressed expression of phosphorylated AKT ($p < 0.05$), mTOR ($p < 0.05$), and p70S6k ($p < 0.05$). The administration of rhEPO reverted neuronal apoptosis in septic rats ($p < 0.05$), increased the expression of phosphorylated AKT ($p < 0.05$), mTOR, and p70S6k ($p < 0.05$), and improved the emotional and spatial cognitive defects visualized in CLP rats ($p < 0.05$) (Wang et al. [64])
Weberpals et al. [103]	Adult male C57BL/6 and $NOS2^{-/-}$ mice	LPS (5 mg/kg, i.p.)	None	Microglial and glial activation, iNOS, synaptosomal proteins and cytokines	Open field and eight arm radial maze tasks 60 days after LPS injection	LPS increased NOS2 expression in hippocampus and prefrontal cortex and activated myeloid cells ($p < 0.05$). Wild-type mice showed more behavioral impairment after LPS treatment, compared to $NOS2^{-/-}$ mice ($p < 0.05$), suggesting that LPS induces NOS2 linked nitric oxide production that leads to cognitive dysfunction. Also, LPS-treated *wild type* mice had increased brain mRNA levels of TNF-α, IL-1β, and RANTES ($p < 0.01$), with distinct changes in the synaptic proteins ($p < 0.01$) (Weberpals et al. [103])
Wu et al. [20]	Adult male mice. No mention about strain	LPS (no mention about dosage)	Salmeterol (1–0.1 mg/kg) 1 h before LPS	Cytokines in serum, cytokine expression in hippocampus and microglial activation	Radial arm maze task with no mention about the timing of behavioral analysis	Salmeterol reduced microglial activation in the hippocampus and the expression of TNF-α, IL1β, and IL6 following sepsis and attenuated the cognitive deficits (Wu et al. [108])
Wu et al. [76]	Adult male C57BL/6 mice	CLP	Valproic acid (VPA) (100 mg/kg, i.p.) daily, for 14 days after CLP or VPA (100 mg/kg, i.p.) plus K252a (1 mg/kg, i.p.) daily,	Expression of histones, HDACs, neurotrophin, apoptosis marker, phospho-TrkB, and postsynaptic density (PSD) 95 in hippocampus, ammonia in serum, cytokines,	Open field, MWM and Y-maze tasks 29 days after CLP	VPA reverted the damage to spatial learning seen on MWM ($p = 0.011$) and Y-maze ($p = 0.008$) tasks, reduced IL-1β ($p = 0.018$) and caspase-3 levels ($p < 0.001$),

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
			for 14 days 2 weeks after CLP	MDA, and neurotrophin in hippocampus		increased the expressions of BDNF ($p < 0.05$), phospho-TrkB (pTrkB) ($p < 0.05$), postsynaptic density 95 ($p = 0.024$) and the number of synapses ($p < 0.05$), enhanced acetyl-H3K9 ($p = 0.048$) and acetyl-H4K12 levels ($p = 0.015$). There was no difference in serum ammonia and MDA levels among groups. TrkB antagonist K252a blocked the VPA effects with regard to cognition, pTrkB expression ($p = 0.044$), and hippocampal synapses ($p = 0.046$) (Wu et al. [76])
Wu et al. [113]	Adult C57BL/6 male mice	CLP	Peptide SS-31 (5 mg/kg, i.p.) daily, for 6 days after CLP	ETC enzymes, mitochondrial membrane potential level, mPTP, Cyt C, apoptosis marker NLR Family Pyrin Domain Containing 3 (NLRP3), cytokine, and neuron-specific enolase (NSE) levels in hippocampus	Open field and fear conditioning tasks 7 days after CLP	SS-31 treatment improved survival rate (53.33%; $p < 0.05$) and cognitive deficits visualized by increased distance traveled in the open field task and freezing time in the fear conditioning task ($p < 0.05$), reverted the mitochondrial dysfunction by increasing the activity of ETC complexes I and III ($p < 0.05$), decreased ROS production ($p < 0.05$) and mPTP ($p < 0.05$), increased ATP ($p < 0.05$) and mitochondrial membrane potential levels ($p < 0.05$), decreased the release of Cyt C and cleavage of caspase-3 ($p < 0.05$), neuronal injury ($p < 0.05$) and inflammation ($p < 0.05$) (Wu et al. [113])
Yamada et al. [164]	Adult male ICR mice	CLP and astrocyte cell culture	None	Cytokines, histological changes, inflammatory cells, and β-amyloid levels	Y-maze task with no mention about the timing of behavioral analysis	Sepsis impaired working memory, increased neuroinflammatory morphological indices, and b-amyloid levels in the cortex and hippocampus. Combined treatment with β-amyloid and LPS of primary astrocytes increased the expression of TNF-α and IL-6, compared to those treated with β-amyloid or LPS alone (Yamada et al. [164])
Yamada et al. [119]	ICR mice.	CLP	S14G-humanin (HNG) (0.75 mg/kg, i.p.), daily, for	Cytokines, microglial and astrocyte activation, and brain histology	Open field and Y-maze tasks 21 days after CLP	Treatment with HNG acutely reduced the levels of IL-1β, IL-6, and

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
	No mention about sex and age		4 days, starting at 2 h after CLP			TNFα and the activation of astrocytes and microglia that were elevated 16 h after CLP. In chronic phase, it improved the working memory that was impaired at 21 days after CLP. In addition, HNG also improved basal forebrain cholinergic neuronal loss and reduced synaptic plasticity caused by sepsis (Yamada et al. [164])
Zaghloul et al. [165]	Murine model No mention about Strain, sex, age	CLP	None	Choline acetyltransferase (ChAT), activity of acetylcholinesterase (AChE), expression of muscarinic M1 acetylcholine receptor gene, cytokines, and microglia morphology	None	Sepsis decreased the number of ChAT positive neurons, expression of muscarinic M1 acetylcholine receptor coding gene in the hippocampus ($p < 0.05$), increased the activity of AChE in cortex, hippocampus and hypothalamic areas innervated by cholinergic neurons ($p < 0.05$), along with microglial morphological changes, increased IL-1b and IL-6 gene expression in brain areas ($p < 0.05$) with a simultaneous increase in serum levels of IL-1b and IL-6 ($p < 0.05$) (Zaghloul et al. [165])
Zhai et al. [166]	Adult male wild-type C57BL/6 mice and ChAT-ChR2-EYFP (ChAT) transgenic mice	CLP	Photostimulation of basal forebrain cholinergic neurons, left cervical vagotomy and chemical splenic denervation by injecting 6-hydroxydopamine (6-OHDA) (60–120 μg) or saline into exteriorized spleens	Serum and tissue protein levels of TNF-α, IL-6, and IL-10	None	Photoactivation of basal forebrain cholinergic neurons in the CLP mice reduced the levels of TNF-α and IL-6 in the serum and spleen, which are slightly reversed with left cervical vagotomy. It also increased the c-Fos expression in the basal forebrain, the dorsal motor nucleus of the vagus, and the ventral part of the solitary nucleus. This suggests that optogenetic activation of basal forebrain cholinergic neurons activated dopaminergic neurons in dorsal motor nucleus of the vagus further transferring the signals to the spleen via the vagus nerve attenuating septic inflammation through cholinergic pathway, which was reverted with vagotomy (Zhai et al. [166])
Zhang et al. [114]	C57BL/6J male mice	CLP and LPS	D-serine (500 mg/kg/day, i.p.), LPS (8 mg/kg/day, i.p.,) or	Hippocampal levels of synaptophysin, GAPDH and NMDA receptor	Open Field Test and Barnes Maze Test	Sepsis reduced the protein and mRNA levels of NMDA receptor subunits

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
			normal saline (NS) daily for 3 days. The mice were divided into control (NS), LPS + NS and LPS + D-serine groups	subunits GluN2A, GluN2B and GluN1 (by Western blot and RT-PCR); the number of CA1 neurons (by Nissl staining); neuronal activity (by p-CREB staining); neuroinflammation (by staining of Iba-1 and inflammatory factors IL-1β, TNF-α, NLRP3); and oxidative stress [by levels of dihydroethidium (DHE)]		GluN2A, GluN2B, and GluN1 but not synaptophysin levels or the hippocampal neuronal number in both CLP and LPS mice in the first week. D-serine, co-agonist of NMDA receptors limited the LPS induced damage, including the cognitive impairment, NMDA receptor subunits loss, neuro-inflammation, oxidative stress, and the hippocampal decrease of p-CREB. As sepsis induced NMDA receptor loss is interfering with hippocampal changes, NMDA receptors are target platform for future interventions (Zhang et al. [114])
Zhou et al. [106]	Adult male Wistar rats	CLP	Hydrogen-rich saline (HRS) (2.5 or 10 mL/kg, i.p.) 10 min before CLP	Mortality, reactive oxygen species (ROS), MDA, and SOD in hippocampus, neuronal apoptosis, and histopathologic changes in hippocampus and hydrogen levels in blood	MWM task 4 and 7 days after CLP	CLP sepsis resulted in high mortality ($p < 0.05$), increased hippocampal levels of ROS ($p < 0.01$) and MDA ($p < 0.01$) and decreased SOD ($p < 0.01$), increased neuronal apoptosis ($p < 0.05$) and cognitive dysfunction ($p < 0.05$), compared to controls. HRS improved the survival rate ($p < 0.05$), reverted the neuronal apoptosis as seen on immunohistochemical staining of cleaved caspase 3 ($p < 0.01$) and on TUNEL assay ($p < 0.01$), diminished ROS ($p < 0.01$) and MDA ($p < 0.01$) levels and improved cognition ($p < 0.01$) (Zhou et al. [106])
Zhu et al. [93]	Adult male Wistar rats	LPS (10 mg/kg, i.p.)	Huperzine-A (HupA) (0.04 mg/kg, i.p.), once, 30 min prior LPS	ChAT, muscarinic acetylcholine receptor-1 (CHRM1), AChE and acetyl choline (Ach) in hippocampus, cytokines and neuronal apoptosis	MWM task 3, 12, and 24 h after LPS injection	Sepsis induces cholinergic compromise, along with increase in TNF-α and IL-1β levels ($p < 0.05$), neuronal apoptosis ($p < 0.05$), and cognitive damage ($p < 0.05$). HupA improved cholinergic function by augmenting hippocampal levels of ChAT and CHRM1 ($p < 0.01$) and Ach ($p < 0.01$), reduced the levels of cytokines ($p < 0.01$), neuronal apoptosis ($p < 0.01$) and improved spatial learning and memory ($p < 0.01$) (Zhu et al. [93])

Table 1 (continued)

Reference	Strain/Species	Sepsis model	Intervention	Evaluation	Behavioral task	Main findings
Zivkovic et al. [92]	Rats No mention about sex, age, strain	LPS (no mention about dosage)	Physostigmine (no mention about dosage)	Neuronal function in hippocampus	None	Sepsis altered synaptic plasticity in hippocampus verified by long-term potentiation (LTP) in the neuronal excitatory synapses. Physostigmine administration improved the LTP (Zivkovic et al. [92])

BAX Bcl-2-like protein 4, *Bcl-2* B cell lymphoma 2, *BDNF* brain derived neurotrophic factor, *CCL2* (C-C motif) ligand 2, *CCR2* CC-chemokine receptor 2, *CD40* Cluster of differentiation 40, *DARPP-32* dopamine- and cyclic-AMP-regulated phosphoprotein, *EGR1* early growth response protein 1, *GDNF* glial cell line derived neurotrophic factor, *GFAP* glial fibrillary acidic protein, *Iba-1* ionized calcium-binding adapter molecule 1, *IL* interleukin, *iNOS* inducible nitric oxide synthase, *i.p.* intraperitoneal, *KC* C-X-C motif chemokine ligand 1, *MCP-1* monocyte chemoattractant protein-1, *MMP* matrix metalloproteinase, *NGF* nerve growth factor, *NLRP3* NLR family pyrin domain containing 3, *NOS2* nitric oxide synthase 2, *s.c.* subcutaneously, *p.o.* per os, *RANTES CCL5* Chemokine (C-C motif) ligand 5, *TNF-α* tumor necrosis factor-α, *TNFR1* tumor necrosis factor receptor 1, *TrkB* tropomyosin receptor kinase B

No differences were found in HRQoL, psychological functioning or depressive symptoms, and depression could be ruled out as a confusing factor [171]. In this retrospective double-blind pilot randomized controlled trial, primary outcomes of physical function and self-reported HRQoL were recorded at ICU discharge and 6 months post-hospital discharge. A significant increase in patient self-reported physical function and physical role for the SF-36 at 6 months was found in the exercise group. Physical function scores were not significantly different between the groups. IL-10 levels was higher in the exercise group; however, there were no differences between the groups for lactate, IL-6, TNF-α, muscle strength, exercise capacity, fat-free mass, or hospital anxiety [172]. This study targeted to identify diagnoses or events during a hospitalization requiring critical care that are related with a subsequent dementia diagnosis in the elderly. Over the 3-year follow-up period, dementia was again diagnosed in 4519 (17.8%) of 25,368 patients who were treated in intensive care and survived hospital discharge. Infection or a diagnosis of severe sepsis, acute neurologic dysfunction, and acute dialysis were all independently associated with a subsequent diagnosis of dementia [173]. A prospective cohort study using a battery of questions and functional status measured as the number of ADLs and IADLs for which assistance is needed evaluated a total of 1208 members. These members presented with 1548 incident severe sepsis episodes that were associated with an increase in the prevalence of moderate/severe cognitive impairment from 9.8 to 19.4%. On adjusting stable patient clinical features, in fixed-effect regression analysis, incident severe sepsis was associated with a 4.2-fold increase in the odds of developing moderate/severe cognitive impairment. Patients with normal pre-sepsis functionality developed 1.72 new I/ADL limitations post severe sepsis. Patients with mild/moderate functional limitations (requiring assistance with 1–3 I/ADLs) pre-sepsis developed 1.40 new I/ADL limitations. However, patients with severe (> 4 I/ADL) limitations before sepsis did not show much change post-sepsis [174]. In this prospective controlled observational study, evoked oscillatory responses to rhythmic visual stimuli were evaluated and analyzed to study brain synchrony via magnetoencephalography (MEG) in 26 survivors of severe sepsis or septic shock, and 23 healthy individuals and patients diagnosed with liver cirrhosis were evaluated as control group. Dynamic adaptation of cerebral neurons in terms of frequency coupling to the rhythmic flicker stimulation was reduced in sepsis survivors and in liver cirrhosis patients; however, in sepsis survivors, it augmented with time following sepsis. The cognitive injury results from pathologically desynchronized neuronal oscillations and from an altered oscillatory coupling in the brain. This study demonstrates that long-term cognitive injury is still present 1 year after severe sepsis, and it was reflected by an abnormal functional brain synchronicity [175]. Another study was a voluntary, web-based prospective survey of sepsis survivors

distributed via social media and online channels. A total of 1475 completed surveys were analyzed that presented with increases in body numbness, fatigue, pain, chest pain, palpitations, visual disturbances, stomach and eating problems, memory loss, mood changes, and hair loss, together with problems with dentition and nails, compared to before sepsis. Sepsis survivors also presented with decreased ability to perform chores, walk up and down stairs, walk for at least 15 min, run errands, adequately spell when writing, and read for at least 15 min and reduced satisfactory sex drive. In summary, sepsis survivors presented mental, physiological, and functional disabilities for a significant time following their initial episode of sepsis [176].

Major Depressive Disorder in Sepsis Survivor Patients

A study evaluated factors associated with depression symptoms in a prospective cohort of 135 patients after abdominal sepsis. Depression symptoms were evaluated using the Impact of Events Scale-Revised (IES-R) and the Beck Depression Inventory II (BDI-II). Five percent of patients expressed severe depression symptoms [177]. The aim of this study was to measure self-reported HRQoL, anxiety, depression, and cognitive behavior in pediatric septic shock survivors. HRQoL was evaluated with the KIDSCREEN-52, anxiety with the State Trait Anxiety Inventory for Children, depression with the Children's Depression Inventory, and cognitive function with the cognitive scale of the TNO-AZL Children's Quality of Life Questionnaire Child Form. The median age of the children at pediatric intensive care unit admission was 4.2 years old, and the median age at follow-up was 10.7 years old. Depression, quality of life, and anxiety scores were equal than those of the healthy controls, whereas cognitive function was inferior than in healthy controls. Forty-four percent of the children presented cognitive scores < 25% of those of the norm population. In septic shock survivors, HRQoL, anxiety, and depression were equivalent to or superficially better than those of the age-related Dutch norm population; however, cognitive function was decreased [178]. This study evaluated whether incident severe sepsis was associated with augmented risk of depressive symptoms. A total of 439 patients were assessed with an adapted version of the Center for Epidemiologic Studies Depression Scale, and severe sepsis was recognized using an authorized algorithm in Medicare claims. Depressive symptoms were found in 28% of sepsis survivor patients at a median of 1.2 years before sepsis and persisted in 28% of sepsis survivor patients at a median of 0.9 years after sepsis. Neither incident severe sepsis nor severe sepsis-related clinical characteristics were related with succeeding depressive symptoms [179]. One study aimed to evaluate whether pre-sepsis depressive symptoms were linked with risk of new cognitive dysfunction in survivors of severe sepsis. Severe sepsis was identified using a validated algorithm in Medicare claims. A total of 447 patients were evaluated prospectively using an adapted version of the Center for Epidemiologic Studies Depression Scale, and cognitive function was measured using versions of the Telephone Interview for Cognitive Status (TICS). Depressive symptoms in patients with normal cognition before sepsis were 38%, and after severe sepsis, 18% of the survivors had incident cognitive impairment. Depressive symptoms were connected with post-sepsis incident cognitive impairment, and pre-sepsis depressive symptoms remained the strongest factor associated with post-sepsis incident cognitive dysfunction [180]. A retrospective cohort study evaluated physical and mental long-term outcomes of ICU stay for severe sepsis in patients and their spouses. They involved 55 patients who survived severe sepsis and their spouses with a median of 55 months after ICU liberation. The Hospital Anxiety and Depression Scale, the Short Form-12 Health Survey, the Post-traumatic Stress Scale-10, and the Giessen Subjective Complaints List-24 were included. Patients and spouses (26 and 42%, respectively) showed clinically pertinent scores of anxiety and depression; about two thirds of the patients and spouses informed post-traumatic stress symptoms defined as clinically significant. Patients reported anxiety, exhaustion, and poorer mental and physical HRQoL, and the spouses presented impaired mental HRQoL and increased anxiety [181].

Delirium in Sepsis Survivor Patients

In another prospective ancillary study within the SAILS trial, a randomized controlled trial evaluating mortality and ventilator-free days for rosuvastatin versus placebo for patients with sepsis-associated acute respiratory distress syndrome, delirium was evaluated with the validated Confusion Assessment Method (CAM)-ICU method, and cognitive function was evaluated with tests for executive function, language, verbal reasoning and concept formation and working, immediate, and delayed memories. The mean percentage of days with delirium was 34% in the rosuvastatin group and 31% in the placebo group. At 6 months, 19 (36%) of 53 patients in the rosuvastatin group versus 29 (38%) of 77 in the placebo group had cognitive deficiency, with no significant difference between the groups. At 12 months, 20 (30%) of 67 patients versus 23 (28%) of 81 patients had cognitive deficiency, with no significant difference between the groups. The results suggest that delirium may affect a considerable amount of patients, with approximately one third of survivors presenting cognitive deficiency over 1 year of follow-up [182].

Quality of Life in Sepsis Survivor Patients

The aim of this research strategy was to compare the HRQoL of survivors of severe sepsis and septic shock with HRQoL in

others who survived serious disease without sepsis. A follow-up interview was held 6 months after ICU discharge, and a EuroQol five-dimension (EQ-5D) questionnaire was used. A total of 104 sepsis survivors and 133 survivors in the control group responded to the EQ-5D test. Survivors of severe sepsis and septic shock presented almost identical HRQoL to that of survivors of critical illness admitted without sepsis [183]. This prospective observational study aimed to assess long-term survival and quality of life of patients admitted to a surgical ICU for the reason of sepsis or trauma. The patients were separated into sepsis and trauma groups, and quality of life was measured 2 years after ICU admission using the EQ-5D questionnaire. A total of 98 trauma patients and 66 patients with sepsis were involved in the study. There was no difference between the groups in Acute Physiology and Chronic Health Evaluation II score or length of stay in the surgical ICU. Surgical ICU survival, in-hospital survival, post-hospital survival, and cumulative 2-year survival were lesser in the sepsis group than in the trauma group. There was no variation in quality of life in all five magnitudes of the EQ-5D. Sixty percent of the patients presented symptoms of depression, nearly 60% had difficulties in their normal activities, and 56% presented pain [184].

PTSD in Sepsis Survivor Patients

This study evaluated factors related with post-traumatic stress symptoms in a prospective cohort of 135 patients after peritoneal sepsis. PTSD was evaluated using the Impact of Events Scale-Revised (IES-R) and the Post-Traumatic Symptom Scale 10 (PTSS-10). The percentage of patients with moderate PTSD symptom scores was 28% and that of patients with high PTSD symptom scores was 10%. Thirty percent of patients after peritoneal sepsis reported higher levels of PTSD symptoms [177], Table 2.

Very Low Birth Weight Preterm Infants and Neonatal Sepsis

The aim of another prospective cohort was to evaluate whether neonatal infections were related with an elevate risk of unfavorable neurodevelopment at 5 years of age in very preterm children. A total of 2277 live births were qualified for a follow-up assessment at 5 years of age. Cerebral palsy and cognitive injury were considered as a function of early-onset sepsis (EOS) and late-onset sepsis (LOS), after modification for potential confounding influences, in multivariate logistic regression models. At 5 years of age, the occurrence of cerebral palsy was 9% and that of cognitive impairment was 12%. The occurrence of cerebral palsy was higher in infants with isolated EOS or isolated LOS than in uninfected infants, and this risk was even higher in cases of mutual EOS and LOS. There was no association between neonatal infection and cognitive impairment [187]. This prospective cohort evaluated neurodevelopmental and growth deficiency among extremely low-birth-weight infants with neonatal infection. Neurodevelopmental and growth consequences were evaluated at a comprehensive follow-up visit at 18 to 22 months of corrected gestational age and compared by infection group. A total of 6093 infants were studied and classified by type of infection: uninfected ($n = 2161$), clinical infection alone ($n = 1538$), sepsis ($n = 1922$), sepsis and necrotizing enterocolitis ($n = 279$), or meningitis with or without sepsis ($n = 193$). The sepsis group presented a different risk factor of neurodevelopmental impairment according to the infecting microorganism. In the coagulase-negative staphylococci infection group, the OD was 1.3; for other Gram-positive infections, the OD was 1.7; for Gram-negative infections, the OD was 1.4; for fungal infections, the OD was 1.4; and for combined pathogens, the OD was 1.6 [188]. This prospective cohort aimed to identify determinants of neurodevelopmental outcome in preterm children. Gestational age, sex, outborn, illness severity, bronchopulmonary dysplasia, necrotizing enterocolitis, late-onset sepsis, retinopathy of prematurity, abnormal neuroimaging, and site were significantly associated with neurodevelopmental impairment (Bayley-III < 70, severe cerebral palsy, blind or hearing aided, and neurodevelopmental impairments or death). Neurodevelopmental impairment was associated with late-onset sepsis [189]. In a prospective cohort, the authors confirmed previous reports that neonatal sepsis increases the risk of a poor neurodevelopmental outcome in extremely low-birth-weight infants. The sepsis group was associated with poor outcomes and presented an OD of 1.7 [190]. A prospective cohort nested in a double-blind randomized controlled trial included 204 pre-term patients who had survived sepsis and 204 pre-term as a control. The patients were evaluated using Bayley-III and PARCA-R instruments. Both instruments showed cognitive delay (4.4 and 19.6%, respectively) and language delay (8.4 and 12.6%, respectively) in sepsis survivor patients (Martin). A case-control study included 102 low-birth-weight infants as a control group and 18 survivors of sepsis. These infants were prospectively followed for 36 months. Preterm infants who develop sepsis are not at significantly higher risk for triggering neurodevelopmental disability [191]. This population-based prospective cohort involved infants born before 32 weeks of gestation, and cognition was assessed with the K-ABC and behavior with the Strengths and Difficulties Questionnaire (SDQ). In contrast, in these results, 48/342 (14%) premature infants who had survived sepsis were evaluated, and the results showed a non-significant association with cognitive scores and neurodevelopmental impairment [192], Table 3.

Mechanisms by Which Sepsis Could Induce Neurological Sequelae and Declines in Cognitive Function in Survivor Patients

There are several studies demonstrating different brain dysfunctions associated with cognitive impairment in sepsis

Table 2 Characteristics of clinical studies included

Reference (country)	Study design	Sample size	Population characteristics	Cognitive and behavioral outcomes assessed with time of assessment	Method of outcome assessment	Main findings
Boer et al. [177] (Netherlands)	Prospective cohort study	$n = 107$	F = 46% M = 54% Median age = 66.8(57–73)	PTSD and depression symptoms, 12 months after emergency laparotomy	• IES-R • PTSS-10 • BDI-II	• Proportion of patients with - moderate PTSD = 28% (95% CI = 20–37) - severe PTSD = 10% (95% CI 6–17) - severe depression symptoms = 5% (95% CI = 2–12) • Severe PTSD symptoms are associated with younger age, length of ICU stay and having fewer or many traumatic memories of the ICU/hospital stay. • The severe PTSD symptoms were not associated gender or disease related morbidity at 6 month follow-up (Boer et al. [177])
Bronner et al. 2009 [178] (Netherlands)	Retrospective cohort study Behavioral and cognitive function in those with a history of admission to PICU for sepsis	$n = 50$ Comparative group = age-related Dutch normal population	F = 23 M = 27 Median age at ICU admission = 4.2 years (0–17) Median age at outcome assessment = 10.7 years (8–20.4)	HRQoL, anxiety, depression and cognitive function, during 1995–2004, in those ≥ 8 years of age	• KIDSCREEN-52 • State Trait Anxiety Inventory for Children • Children's Depression Inventory • Cognitive scale of the TNO-AZL Children's Quality of Life Questionnaire Child Form	• No statistically significant difference in HRQoL and anxiety scores when compared to the age-related Dutch norm population. • Depression scores were significantly better and cognitive scores were significantly worse than the Dutch norm population. • Cognitive function is reduced with 20 out of 45 children analyzed (44%) having cognitive scores < 25% of the norm population. • Cognitive function impairment is associated with younger age of admission to PICU (Bronner et al. 2009 [178])
Davydow et al. [180] (USA)	Prospective cohort study Pre-sepsis depression associated with post-sepsis cognitive decline	$n = 517$ (hospitalizations of 447 patients for sepsis)	F = 282 M = 235 Mean age = 76.1 years	Depressive symptoms and cognitive function	• CES-D • TICS or a proxy interview, if patient cannot be assessed	• The prevalence of pre-sepsis substantial depressive symptoms was 38% (95% CI = 34–42%) • The incidence of cognitive impairment post severe sepsis = 18% (95% CI = 15–20%) - mild cognitive impairment = 40% (95% CI = 30–50%) -moderate to severe cognitive impairment = 60% (95% CI = 50–70%) • Pre-sepsis depressive symptoms are associated with post-sepsis incident cognitive impairment: OR 2.58, 95% CI = 1.45–4.59 (Davydow et al. [180])

Table 2 (continued)

Reference (country)	Study design	Sample size	Population characteristics	Cognitive and behavioral outcomes assessed with time of assessment	Method of outcome assessment	Main findings
Davydow et al. [179] (USA)	Prospective cohort study Depressive symptoms in sepsis survivors	*n* = 471 (439 patients who had a total of 471 hospitalizations for sepsis)	F = 248 M = 223 Median age at hospitalization = 75.3 years	Symptoms of depression and cognitive impairment	• CES-D • TICS or a proxy interview, if patient cannot be assessed	• The point prevalence of substantial depressive symptoms - At a median of 1.2 years before sepsis = 28% (95% CI = 24–31%) - At a median of 0.9 years after sepsis = 28% (95% CI = 23–32%) • Incident severe sepsis [RR 1.00, (95% CI 0.73–1.34)] was not significantly associated with subsequent depressive symptoms. • Post-sepsis substantial depressive symptoms was independently associated with pre-sepsis substantial depressive symptoms [RR 2.20, 95%CI (1.66, 2.90)], adjusting for post-sepsis cognitive and functional impairment. • Post-sepsis depression is not associated with sepsis (Davydow et al. [179])
Gotz et al. [175] (Germany)	Prospective matched cohort study	Exposed (survivors of severe sepsis /septic shock) *n* = 26 Unexposed (age matched without history of sepsis) *n* = 23 Followed up to one year post sepsis onset		Oscillatory response to visual stimuli and neuro-psychological testing	• Magnetoencephalography • DemTect	• Cognitive processing increases on entrainment of neural oscillations to flickering external stimuli and in sepsis patients it is identified to be increased with duration post sepsis (Gotz et al. [175])
Gotz et al. [185] (USA)	Prospective cohort study MEG over activation in survivors of severe sepsis and correlation with neurophysiological tests	Survivors of severe sepsis or septic shock *n* = 36 Non-sepsis healthy controls *n* = 30	Survivors of severe sepsis or septic shock F = 12(33%) M = 24(67%) Mean age = 58.9 ± 2 years Non-sepsis healthy controls F = 18(60%) M = 12(40%) Mean age = 50.9 ± 3 years	Cognitive function	• DemTect • Clock Drawing Test	• DemTect Test Score - Sepsis survivors 14.7 ± 0.3 - Non-sepsis healthy participants 16.7 ± 0.4 • DemTect combined with clock drawing test score - Sepsis survivors 33.5 ± 0.9 - Non-sepsis healthy participants 37.1 ± 0.6 • Correlation between mental status and resting frequency identified (Gotz et al. [185])

Table 2 (continued)

Reference (country)	Study design	Sample size	Population characteristics	Cognitive and behavioral outcomes assessed with time of assessment	Method of outcome assessment	Main findings
Granja et al. [183] (Portugal)	Prospective cohort study QoL sepsis survivors when compared to non-sepsis survivors	Sepsis survivors $n = 104$ Non-sepsis critical illness survivors $n = 133$		QoL, anxiety and depression—6 months post ICU discharge	• EQ-5D with 5 dimensions (mobility, self--care, usual activities, pain/discomfort and anxiety/depression)	• Sepsis survivors reported fewer problems in all EQ-5D dimensions, but it was statistically significant only in anxiety/depression dimension compared to controls (Granja et al. [183])
Guerra et al. [173] (USA)	Retrospective cohort study Risk factors for dementia after critical illness	Severe sepsis $n = 3145$	F = 80% M = 20% Mean age 47.6 ± 14.0 years	Hazard of getting dementia post sepsis ICU admission	• HR	• Dementia at 3 follow up • $n = 683$ (21.7%) • HR = 1.63 (95% CI 1.50–1.77) • Adjusted HR = 1.40(95% CI 1.28–1.53) (Guerra et al. [173])
Huang et al. [176] (USA and United Kingdom)	Web-based prospective survey	Sepsis survivors $n = 1475$	Patients with sepsis mean age = 76.9 years	Neuropsychological and functional abilities before and after sepsis	• Likert scale survey	• Sepsis survivors have increased bodily symptoms such as fatigue, pain, chest pain, palpitations, visual disturbances, gastrointestinal problems, hair loss, poor dentition and nails, and neuropsychiatric problems (visual disturbances, memory loss, mood changes) compared to before sepsis ($p < 0.01$). • In conclusion, sepsis leaves the survivors with an aftermath of physiological, neuropsychiatric and functional impairment (Huang et al. [176])
Iwashyna et al. [168, 174] (USA)	Prospective cohort study	$n = 1208$		Cognitive function	• Using a battery of questions(instrument not mentioned)	• Severe sepsis was associated with an increase in the prevalence of moderate/severe cognitive impairment from 9.8% (95% CI 8.3%, 11.2%) to 19.4% (95% CI 16.5%, 22.2%). • Incident severe sepsis was associated with development of moderate/severe cognitive impairment: OR = 4.2 (95% CI 2.31, 7.62) (Iwashyna et al. [174])
Iwashyna et al. [168, 174] (USA)	Prospective cohort study	Patients with sepsis $n = 516$ Patients with non-sepsis hospitalization $n = 4517$		Cognitive function	• m-TICS or a proxy interview, if patient cannot be assessed. • IQCODE for those > 65 years who were not able to be interviewed	• The prevalence of moderate/severe cognitive impairment increased from 6.1 to 16.7% among patients who survived severe sepsis. • Incident sepsis was associated with progression to mild/moderate cognitive impairment: OR = 3.33 (95% CI 1.53, 7.25) • Non-sepsis general hospitalizations were associated with no change in

Table 2 (continued)

Reference (country)	Study design	Sample size	Population characteristics	Cognitive and behavioral outcomes assessed with time of assessment	Method of outcome assessment	Main findings
						moderate/severe cognitive impairment: OR = 1.15 (95% CI 0.80, 1.67) (Iwashyna et al. [168])
Iwashyna et al. [167] (USA)	Retrospective cohort study	Medicare beneficiaries with severe sepsis *n* = 637,867	Age = 49 years (F)	Cognitive dysfunction	• Incidence rate • Prevalence	• Moderate-to-severe cognitive impairment developed in 106,311 (95% CI 79,692, 133,930) survivors (Iwashyna et al. [167])
Jackson et al. [169] (USA)	Case study Testing done 8 months and 3.5 years after ICU discharge	*n* = 1 (survivor of sepsis)	F = 27 (54%) M = 23 (46%)	Neuropsychological testing including IQ, memory, depression, PTSD and cognitive status	• WAIS-III • MMSE • WMS-III • TMT-A and TMT-B • GCS Glasgow coma scale • Richmond Agitation and Sedation scale • CAM-ICU • BDI-II • IES-R	• Cognitive IQ scores (WAIS-R) showed substantial decline of 2 standard deviations from 99th to 61st percentile eight months post discharge, with not much improvement at 3.5 years. Overall memory was superior WMS-III General memory index; there is a relative weakness in visual memory with mild deficits in attention and concentration (Trail making Test B) (Jackson et al. [169])
Kaur et al. [170] (India)	Prospective cohort study Neurodevelopmental and behavioral outcomes in SAE survivors discharged from PICU	SAE survivors *n* = 50 Age and sex matched healthy survivors *n* = 50 Age range = 4–12 years	Sepsis with intervention F = 8, M = 18 Sepsis without intervention F = 10, M = 14	IQ, neurodevelopmental and psychological screening 3–9 months after discharge from PICU	• Malin's Intelligence Scale for Indian Children • DP-3 • General Developmental Score • Childhood Psychopathology Measurement Schedule • Behavioral questionnaire developed by investigators	• SAE children had significantly decreased mean verbal IQ, full-scale IQ, "below average" verbal IQ, General Development Score, and DP-3. • In the delayed subgroup of General Development Score < 70, 42% of SAE children were affected compared to 4% of non SAE children. • Among the SAE children 52% had low intelligence compared to 32% non SAE children. • Decline in school performance (44%), disobedience (28%), and stubbornness/irritable behavior (26%) were the most common behavior changes in the SAE children. • On multivariate regression analysis, there is statistical significant association between shock and decline in school performance: OR = 6.5(95% CI = 1.2–33) (Kaur et al. [170])
Kayambu et al. [172] (Australia)	Prospective double-blinded pilot randomized controlled trial	Sepsis syndromes *n* = 50	Sepsis F = 34, M = 32 Trauma F = 28, M = 70	Physical function with acute care index of function (ACIF) and self-reported health-related quality of life (HRQoL) using SF-36 medical	• Anxiety subscale of the Hospital Anxiety and Depression Scale (HADS)	• No significant difference between patients with and without physical rehabilitation in physical function ACIF

Table 2 (continued)

Reference (country)	Study design	Sample size	Population characteristics	Cognitive and behavioral outcomes assessed with time of assessment	Method of outcome assessment	Main findings
		Sepsis with intervention $n = 26$ Age 30–83 years Sepsis without intervention $n = 24$ Age 37–85 years		short-form (SF-36) and anxiety were recorded At ICU discharge and 6 months post discharge, respectively		final scores ($p = .45$) and mobility scores ($p = .67$). • Significant improvement in HRQoL in the aspects of physical function ($p = 0.04$) and physical role ($p = .005$), emotional role ($p = 0.08$), vitality ($p = 0.07$), and general health ($p = 0.06$) for the SF-36 at 6 months was seen in exercise group • No difference in bodily pain, social functioning, or mental health ($p = 0.09$) in intervention group To summarize, early ICU exercise can moderate sepsis attack by improving self-reported physical function and with anti-inflammatory effects (Kayambu et al. [172])
Korosec et al. [184] (Slovenia)	Prospective observational study	Sepsis $n = 66$ Age 64.4 ± 13.5 years Trauma $n = 98$ Age 53.2 ± 21.5 years	Rosuvastatin group F = 44(53%) M = 39(47%) age 49 ± 16 years Placebo group F = 56(53%) M = 50(47%) age 52 ± 14 years	Quality of life assessment Measures of mobility, self-care, usual activities, pain/ discomfort and anxiety/depression At 2 years after ICU admission	• Quality of life was assessed using EuroQol 5D questionnaire and a telephone interview. EuroQoL 5D descriptive system measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression	• EuroQol 5D Index was 0.72 ± 0.24 and did not differ between sepsis and trauma patients. • There was also no significant difference in EuroQol 5D between groups. However in total, 60% of patients had signs of depression, 60% had problems in daily activities, 56% had pain, and 56% had mobility problems. Sepsis patients had more mortality compared to trauma group (Korosec et al. [184]; Needham et al. [182]).
Needham et al. [182] (USA)	Randomized controlled trial Study looked at effect of rosuvastatin versus placebo on cognition in those with sepsis associated ARDS and delirium	Patients with sepsis associated ARDS eligible for long-term cognitive assessment in rosuvastatin group $n = 83$ in placebo group $n = 106$	Patients F = 18 (32.7%) M = 37(67.3%) Mean age = 61.1 ± 11.5 years Spouse F = 37(67.3%) M = 18(32.7%) Mean age = 61.7 ± 12.2 years	Secondary endpoints were cognitive function at six and twelve months	• Hayling Sentence Completion Test scaled score • Verbal Fluency Test score • Similarities age-adjusted scaled score from WAIS-III • Digit Span age-adjusted scaled score from WAIS-III Logical Memory I and II age adjusted scaled scores from WAIS-III	• At 6 months, 36% of patients in the rosuvastatin group versus 38% in the placebo group had cognitive impairment, with no significant difference between groups. • At 12 months, 30% of patients in the rosuvastatin group versus 28% of patients in the placebo group had cognitive impairment, with no significant difference between groups (Needham et al. [182])

Table 2 (continued)

Reference (country)	Study design	Sample size	Population characteristics	Cognitive and behavioral outcomes assessed with time of assessment	Method of outcome assessment	Main findings
Rosendahl et al. [181] (Germany)	Prospective cohort study Patient and spouse mental and physical health post sepsis 55 months after ICU discharge	Patient-spouse dyads analyzed after sepsis intensive care $n = 55$	Sepsis survivors F = 12 M = 13 Mean age = 55.65 ± 1.9 years Non-sepsis survivors F = 8 M = 11 Mean age = 52.15 ± 4.512 years	Anxiety, depression, and posttraumatic symptoms	• HADS (German version) • Posttraumatic symptom scale • Mental HRQoL	• 26–42% of patients and spouses showed clinically relevant scores of anxiety and depression ($p = .85$, $p = .032$ respectively) • 67% showed posttraumatic stress symptoms ($p = .53$). • Patients reported higher depression scores compared to spouses ($p = .031$). • Compared with normal German samples, patients and spouses reported a significant worse mental HRQOL and higher anxiety • Anxiety and depression scores, posttraumatic stress symptoms, and mental HRQOL were significantly related between patients and spouses (Rosendahl et al. [181])
Semmler et al. [171] (Germany)	Prospective cohort study Long-term behavioral and neurological changes in those patients admitted to ICU with and with no sepsis compared to historical normal participants	Sepsis survivors $n = 25$ Non-sepsis survivors $n = 19$ Published historical norms MRI healthy controls $n = 31$ EEG $n = 20$	Septic ICU survivors: F = 12 M = 13 Non-septic ICU-survivors F = 9 M = 17	Cognitive function tests and neuropsychological tests	• Multiple Choice Word Test-B • NeuroCogFx • Neuropsychological profile analysis • SF-36 • Auditory Verbal Learning Test (German version) • RCFT	• Sepsis survivors showed cognitive deficits in verbal learning ($p = 0.028$) and memory ($p = 0.006$) compared to historical norms ($p < 0.05$) (Semmler et al. [171])
Widmann et al. [186] (Germany)	Prospective cohort study Long-term cognitive deficits after sepsis	Septic ICU survivors $n = 25$ Non-septic ICU-survivors $n = 26$		Neuropsychological assessment	• NeuroCogFx • SF-36 • SCL90-R BDI	• ICU survivors with and without sepsis had long-term mild cognitive decline, and had no depression ICU survivors with sepsis had deficits in verbal learning and verbal episodic memory (Widmann et al. [186])

E eligible, *C* completed, *PR* participation rate, *F* female, *M* male, *IES-R* Impact of Events Scale-Revised, *PTSS-10* Post Traumatic Symptom Scale-10, *BDI-II* Beck Depression Inventory II

HRQoL health-related quality of life, *CES-D* Center for Epidemiologic Studies Depression Scale, *TICS* telephone interview for cognitive status, *QoL* quality of life, *EQ-5D* EuroQol five-dimension, *HR* hazard ratio, *NeuroCogFx* neuro cognitive effects, *SF-36* Short Form-36 Health Survey, *SCL90-R* Symptom Check List 90-R, *BDI* Beck's Depression Inventory, *IQCODE* Informant Questionnaire on Cognitive Decline in the Elderly, *m-TICS* modified telephone interview for cognitive status, *OR* odds ratio, *WAIS-III* Wechsler Adult Intelligence Scale-III, *MMSE* mini mental state examination, *WMS-III* Weschler Memory scale-III, *GCS* GCS Glasgow coma scale, *BDI-II* Beck Depression Inventory II, *IES-R* Impact of Events Scale-Revised, *SAE* sepsis-associated encephalopathy, *PICU* pediatric intensive care unit, *IQ* intelligent quotient, *DP-3* development profile-3, *TMT-A* trail-making test A, *TMT-B* trail-making test B, *DST* digit-symbol test, *ARDS* acute respiratory distress syndrome, *HADS* Hospital Anxiety and Depression Scale, *RCFT* Rey Complex Figure Test

Table 3 Characteristics of low-birth weight clinical studies included

Reference (country)	Study design	Sample size	General population characteristics	Sepsis assessment	Cognitive and behavioral outcomes assessed	Method of outcome assessment	Main findings
Bassler et al. [190] (Canada)	Prospective cohort	$n = 944$ in total; $n = 378$ with sepsis	F = 456; M = 454; Mean birth weight = 793 ± 127 g Mean GA = 26.2 ± 1.8 weeks	Blood or CSF culture growing bacteria, fungi or viruses	Cognitive delay	• BSID-II–MDI score < 70	• Cognitive delay was observed in 106 infants with sepsis • Sepsis was associated with poor outcomes at 18 months (OR 1.7; 95% CI 1.3–2.2) (Bassler et al. [190])
Ferreira et al. [193] (Brazil)	Prospective cohort	$n = 194$ in total; $n = 86$ with sepsis	F = 103; M = 91; Mean birth weight = 1119 ± 247 g Mean GA = 29 ± 2 weeks	Blood culture growing bacteria and/or clinical and laboratory signs suggestive of infection	Cognitive delay	• BSID-II–MDI score < 85	• Sepsis was not associated with cognitive delay (Ferreira et al. [193])
Graz et al. [192] (Switzerland)	Prospective cohort	$n = 342$ in total; $n = 48$ with sepsis	F = 167; M = 175; Mean birth weight = 1158 ± 348 g Mean GA = 28.4 ± 6.8 weeks	Blood culture and clinical signs	Cognitive delay and behavioral alterations	• K-ABC • WPPSI-III or McCarthy Scales of Children's Abilities for children with major developmental problems • SDQ to evaluate behavior	• In univariate regression, sepsis was associated with cognitive decline, but it was not sustained after multivariate analysis • Sepsis was not associated with behavior alterations (Graz et al. [192])
Martin et al. [194] (United Kingdom, Australia, Argentina, New Zealand, Serbia, Greece, Denmark, Belgium, Ireland)	Prospective cohort nested in double-blind, randomized, controlled trial	$n = 204$ in total; $n = 204$ with sepsis	F = 100; M = 104; Median birth weight = 910 g (718–1163) Median GA = 27 (5–30) weeks	Current use of antibiotics for the treatment of proven or suspected infection with at least one of the following characteristics: a birth weight less than 1500 g; or need for respiratory support	Cognitive and language delay	• Bayley-III • PARCA-R	• The Spearman correlation between PARCA-R and Bayley-III scales were moderate (0.43) for cognition and more (0.71) for language • With standard scoring for Bayley-III, 9 infants (4.4%; 1.6–7.2%) had moderate cognitive delay and 16 (8.4%; 4.5–12.4%) had moderate language delay • With Australian standards, 40 infants (19.6%; 14.2–25.1%) had cognitive delay, and 24 (12.6%; 7.9–17.4%) had language delay (Martin et al. [194])
Mitha et al. [187] (France)	Prospective cohort	$n = 2277$ in total;	F = 733; M = 762;	Data from neonatal records with standard	Cognitive impairment	• K-ABC score < 70 as severe impairment	• Sepsis was not significantly associated with cognitive impairment (Mitha

Table 3 (continued)

Reference (country)	Study design	Sample size	General population characteristics	Sepsis assessment	Cognitive and behavioral outcomes assessed	Method of outcome assessment	Main findings
		$n = 1495$ with cognitive evaluation; $n = 1083$ with sepsis	$n = 720$ infants born with 31–32 weeks of GA	questionnaire. EOS = infection of maternal origin; LOS = postnatally acquired infection			et al. [195])
Soraisham et al. [191] (Canada)	Case control	Study group $n = 51$ in total; $n = 18$ with sepsis; Control group $n = 102$; $n = 11$ with sepsis	Study group F = 28; M = 23; Mean birth weight = 977 ± 187 g Mean GA = 27.6 ± 2.3 weeks Control group F = 42; M = 60; Mean birth weight = 981 ± 188 g Mean GA = 27.9 ± 2.5 weeks	Blood culture growing bacteria or fungi	Cognitive delay	• BSID-II–MDI score <70 • Stanford-Binet Intelligence scales > 70	• Infants with NEC had more culture-proven sepsis (35.3% vs. 10.8%, $p < 0.001$) • Sepsis did not predict cognitive delay (OR 1.1; 0.3–4.7) (Soraisham et al. [191])
Stoll et al. [188] (United States of America)	Prospective cohort	$n = 6093$ in total; $n = 2337$ with sepsis	F = 3281 M = 2812 $n = 3772$ infants with birth weight of 751–1000 g; $n = 4147$ infants born with 25–28 weeks of GA	Positive blood culture and antibiotic therapy for 5 or more days. Time of sepsis development = EOS (≤ 72 h of birth) or LOS (> 72 h)	Cognitive delay	• BSID-II–MDI score < 70 • Infants with severe delay and untestable received score = 49	• Cognitive delay was visualized in 661 (37%) infants that had only sepsis • Sepsis was associated with cognitive delay (OR 1.3; 1.1–1.6) • Infants with gram-positive bacterial sepsis were 1.4 times more likely to develop cognitive delay (OR 1.4; 1.0–2.0), while the combination of more than 1 sepsis episode or polymicrobial sepsis increased this association (OR 1.5; 1.2–2.0) (Stoll et al. [188])
Synnes et al. [189] (Canada)	Prospective cohort	$n = 2340$. No mention about number of infants with sepsis	F = 1108; M = 1232; Median birth weight = 920 (770–1099) grams	Blood or CSF culture growing bacteria, fungi or viruses with early onset occurring in	Cognitive and language delay	• Bayley-III score < 85 as NDI or score < 70 as sNDI	• Late-onset sepsis was significantly associated with sNDI (OR 1.40; 1.05–1.86) (Synnes et al. [189])

Table 3 (continued)

Reference (country)	Study design	Sample size	General population characteristics	Sepsis assessment	Cognitive and behavioral outcomes assessed	Method of outcome assessment	Main findings
			Median GA = 27 (25–28) weeks	the first 2 days after birth and late-onset sepsis thereafter			

Bayley-III Bayley Scales of Infant and Toddler Development-Third edition, *BSID-II* Bayley Scales of Infant Development-Second edition, *CI* confidence interval, *CSF* cerebrospinal fluid, *EOS* early-onset sepsis, *F* female, *GA* gestational age, *K-ABC* Kaufman Assessment Battery for Children, *LOS* late-onset sepsis, *M* male, *MDI* Mental development index, *n* number of participants, *NDI* neurodevelopmental impairment, *NEC* necrotizing enterocolitis, *OR* odds ratio, *PARCA-R* Parent Report of Children's Abilities–Revised, *SDQ* Strengths and Difficulties Questionnaire, *sNDI* significant neurodevelopmental impairment, *WPPSI-III* Wechsler Intelligence for Preschool and Primary School Third edition

survivor patients, such as delirium, lower cerebral blood flow index, neuroinflammation, BBB permeability, and white matter disruption, among others. Sepsis-associated delirium (SAD) is described in approximately 50% of septic patients, and it is a clinical feature of the participation of the central nervous system (CNS) during sepsis [196]. Additionally, neuroinflammation, abnormal cerebral perfusion, and neurotransmitter disproportions are the central mechanisms underlying the development of SAD that can trigger decline in cognitive functions [197]. This retrospective cohort study aimed to evaluate whether severe sepsis was associated with neuropathological findings of microvascular brain injury. There were 529 subjects who underwent brain autopsy, and among them, 296 experienced a total of 873 hospitalizations during study participation. A total of 89 individuals experienced severe sepsis hospitalizations. In analyses adjusting forage at death, sex, race, history of diabetes mellitus, coronary artery disease, cerebrovascular disease, or hypertension, prior severe sepsis hospitalization was associated with a relative risk of mild to moderate microvascular brain injury of 1.77. Those with severe sepsis were less likely to have evidence of acute or subacute macroinfarcts. Severe sepsis was associated with microvascular brain injury, a finding that may provide insight into the mechanisms of the association between severe sepsis and cognitive impairment [198]. In this prospective study, the cerebral circulatory parameters pulsatility index (PI) and cerebral blood flow index (CBFi) were evaluated based on the measured velocity of the middle cerebral artery, and Acute Physiology and Chronic Health Evaluation (APACHE) II score was assessed to evaluate the severity of illness. Forty septic patients were investigated, with transcranial Doppler on the first and third days of sepsis diagnosis. Twenty-one patients presented confusion, and the mainstream of the patients presented a PI higher than 1.1 (76%). PI on the first day could predict a positive Assessment Method for the Intensive Care Unit (CAM-ICU) test in septic patients. Multivariable analysis demonstrated that PI on the first day is associated to a positive CAM-ICU test independent of age and APACHE II score. On only the first day, the mean blood velocity in the middle cerebral artery and CBFi were identified to be lower in those patients with a high initial PI [199]. In another study from the same research group, patients presented a median pre-ICU IADL score of 6.3, 14 patients had cognitive decline at discharge, 2 patients were in persistent coma despite sepsis resolution, and information recall was the most affected mental function of the other 12 patients. Only on the first day, patients with cognitive decline had higher PI and lower CBFi compared to those without cognitive deficits. Multivariable analysis presented delirium but not PI as an independent prognostic factor for cognitive decline. In summary, delirium, but not cerebral perfusion changes, was an independent risk factor for cognitive injury in septic patients who were released from the ICU [200]. This prospective

Table 4 Bias summary: prospective observational studies

Criteria	Rosendahl et al. [181]	Boer et al. [177]	Bronner et al. [178]	[179]	[180]	Granja et al. [183]	Guerra et al. [173]	Iwashyna et al. [167]	Iwashyna et al. [168, 174]	Kaur et al. [170]	Rosendahl et al. [181]	Semmler et al. [171]	Götz et al. [185]	Korosec Jagodic et al. [184]
Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the participation rate of eligible persons at least 50%?	N	Y	Y	CD	Y	Y	NA	Y	N	Y	N	N	CD	N
Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y
Was a sample size justification, power description, or variance and effect estimates provided?	Y	N	Y	N	N	N	NA	NA	Y	N	Y	N	N	N
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y	Y	Y	Y	CD	Y	Y	Y	CD	Y	Y	Y	Y
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the exposure(s) assessed more than once over time?	N	N	N	Y	Y	N	N	N	CD	N	N	N	N	N
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the outcome assessors blinded to the exposure status of participants?	N	N	N	N	N	N	N	N	N	N	N	CD	N	N
Was loss to follow-up after baseline 20% or less?	NA	NA	NA	Y	Y	N	NA	NA	Y	N	NA	NA	N	N
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	N	Y	Y	Y	Y	CD	Y	NA	Y	Y	NA	Y	NA	N

Y yes, *N* no, *NA* not applicable for study design, *CD* cannot determine. Quality assessment of included studies was performed using the NIH Quality Assessment Tool for controlled intervention trials and the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Table 5 Bias summary: experimental trial

Criteria	Needham et al. [182]	Kayambu et al. [172]
Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	Y	Y
Was the method of randomization adequate (i.e., use of randomly generated assignment)?	Y	Y
Was the treatment allocation concealed (so that assignments could not be predicted)?	Y	Y
Were study participants and providers blinded to treatment group assignment?	Y	Y
Were the people assessing the outcomes blinded to the participants' group assignments?	Y	N
Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	Y	Y
Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	?	N
Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	?	N
Was there high adherence to the intervention protocols for each treatment group?	Y	Y
Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	Y	Y
Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Y	Y
Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	NA	Y
Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	Y	Y
Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	N	Y

Y yes, *N* no, *NA* not applicable for study design, *CD* cannot determine

representative neuroimaging study was nested within an ongoing prospective cohort study to evaluate the association among delirium duration, white matter integrity, and cognitive impairment in ICU survivors. Delirium was evaluated with the CAM-ICU, and cognitive consequences were tested at 3- and 12-month follow-up. Greater duration of delirium of 3 versus 0 days was connected with lower fractional anisotropy in the genu and splenium of the corpus callosum and anterior limb of the internal capsule at hospital discharge. These associations persisted at 3 months for the genu and splenium. Lower fractional anisotropy in the anterior limb of the internal capsule at discharge and in the genu of the corpus callosum at three months were associated with worse cognitive scores at 3 and 12 months. In summary, delirium duration in the ICU was associated with white matter disruption, and white matter disruption was associated with worse cognitive scores up to 12 months later [201].

Elderly patients are frail and afflicted by worse outcomes, which are most likely associated with reduced functional status at baseline and serious deconditioning during acute illness. This prospective study aimed to describe the differences between nonagenarians and other age groups in patients admitted to internal medicine departments with sepsis and to assess predictors of survival in patients older than 90 years of age. One thousand eighty patients who were nonagenarians constituted 10.93% of this cohort. Of these, 70.48% had a cognitive injury and 82.60% had reduced functional state. Complications secondary to sepsis at admission and throughout hospitalization and mortality rates were higher in the nonagenarian population, at 61.86 vs. 51.14%, respectively, and survival rate was lower in the nonagenarian population, at 40.68 vs. 66.84%. In summary, nonagenarians presented worse outcomes associated with reduced functional status at baseline and strong deconditioning during acute disease [202].

Limitations

Our review may be limited by pre-clinical studies that did not present statistical data to identify the effect of the adjuvant treatment on cognition. Additionally, the majority of clinical studies are observational, and hence, causation cannot be established. The clinical articles presented moderate amounts of bias, which is expected given the designs of the included clinical studies, please see Tables 4 and 5.

Conclusions

Pre-clinical studies have shown an auto amplification of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, in the first few hours after sepsis induction, increased BBB permeability, elevated levels of MMPs, increased levels of DAMPs, such as HMGB-1, S-100 protein, and AGEs. Additionally, NLRP-3, RAGE, and NF-kB signaling, astrocytes and microglia cells were also activated during sepsis. The rodents presented long-term cognitive impairment that was prevented by blocking the aforementioned pro-inflammatory mediators and immune pathways in the first

hours after sepsis induction. Clinical studies showed that sepsis survivors presented increased bodily symptoms, such as fatigue, pain, visual disturbances, gastrointestinal problems, and neuropsychiatric problems (mood changes, relative weakness in visual memory with mild deficits in attention and concentration, development of moderate and severe cognitive impairment) compared to before sepsis. Sepsis leaves survivors with an aftermath of physiological, neuropsychiatric, and functional impairment.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

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