Nature and Science of Sleep

Elevate Series

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REVIEW

Bidirectional Interaction of Sepsis and Sleep Disorders: The Underlying Mechanisms and Clinical Implications

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Abstract: Sepsis is defined as life-threatening organ injury induced by infection, with high incidence and mortality. Sleep disorder is prevalent in septic patients and approximately 50% of patients with sepsis may develop atypical sleep patterns, but many of them may have been underdiagnosed by physicians. Sleep disorders and sepsis exhibit a close bidirectional relationship, with each condition significantly influencing the other. Conversely, sleep deprivation, sleep dysrhythmia and sleep fragmentation have been shown to impact the outcome of sepsis. This review endeavors to offer a comprehensive understanding of the intricate mechanisms that underpin the interplay between sepsis and sleep disorders, in addition to exploring potential clinical intervention strategies that could enhance outcomes for patients suffering from sepsis.

Keywords: sepsis, sleep disorders, cytokines, clock genes, sepsis associated encephalopathy

Introduction

Sepsis, a syndrome characterized by deregulated immune responses to infection leading to multiorgan dysfunction, is a leading cause of mortality associated with infections.[1] It poses a significant global public health challenge, affecting millions of individuals worldwide and ranking as one of the primary causes of death.[2] More and more studies have indicated that sleep quality is severely impaired in septic patients and sleep disorder may worsen the outcome of septic patients. Approximately 20% of the working population suffers from sleep disturbances, with the incidence escalating to over 50% in critically ill patients.[3] It was estimated that sepsis may double the risk of insomnia in septic patients,[4] and a PSG study revealed that approximately 50% of patients with sepsis exhibited atypical sleep patterns.[5]

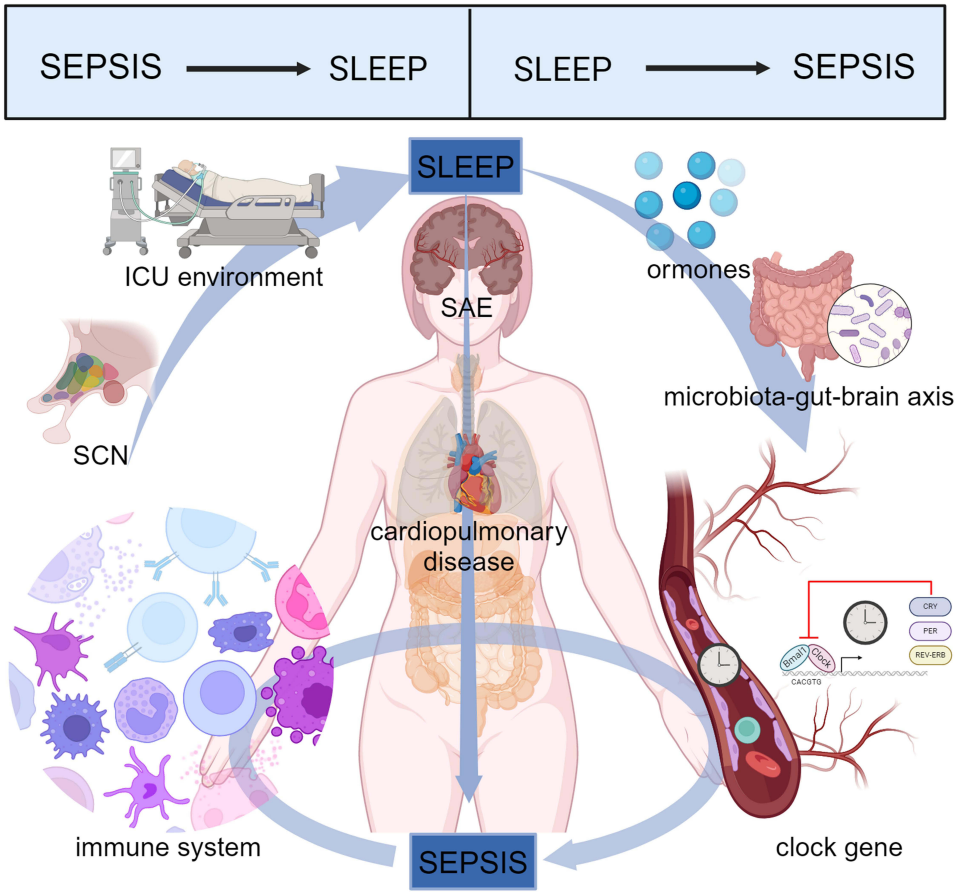
In the past three decades, the intricate relationship between the immune system and the central nervous system (CNS) has been established and characterized.[6–8] Sleep deprivation has been reported to compromise immune function by suppressing natural killer cell activity and cellular immune responses, thereby facilitating bacterial invasion and reducing immune reactivity.[9–11] Thus, sleep disorder is associated with poorer prognosis in septic patients and may serve as an important therapeutic target. Therefore, this review aims to comprehensively discuss the interaction of sepsis and sleep and the potential mechanisms (Figure 1).

Physiological Function and Regulation of Normal Sleep

Normal sleep comprises two primary phases: nonrapid eye movement (NREM) and rapid eye movement (REM), which alternate approximately every 90 minutes.[12] Sleep exhibits a homeostatic nature, where deprivation over an extended period leads to an increase in both the duration and intensity of subsequent sleep sessions. Additionally, independent of prior wakefulness, the circadian system regulates the timing of sleep, representing a separate regulatory mechanism.[13,14] This circadian process ensures uninterrupted sleep during the primary hours of the night.[15] Physiological and cellular processes operate in a cyclic manner, adhering to a 24-hour rhythm that is driven by an endogenous mechanism known as

Received: 7 July 2024
Accepted: 13 October 2024
Published: 19 October 2024

Graphical Abstract



the circadian rhythm. This rhythm underlies the life cycle of virtually all organisms.[16] The mammalian circadian system comprises a hierarchical network of multiple oscillators designed to synchronize internal rhythms with external cycles.[17]

Almost every cell in the human body exhibits a circadian rhythm, with clocks within tissues and organs operating in synchrony.[18] The dual-process model of sleep regulation, underpinned by adenosine levels and governed by the hypothalamic suprachiasmatic nuclei (SCN), identifies homeostasis and circadian rhythm as two pivotal factors. The SCN plays a crucial role in regulating several neurotransmitter systems, including the HPA axis and melatonin secretion from the pineal gland.[19,20] For instance, melatonin synthesis is triggered by β-adrenergic stimulation of pineal cells, which peaks during sleep and wanes during wakefulness, thereby communicating nocturnal cues to the body. These processes ebb and flow in cyclic patterns, with peaks occurring approximately every 24 hours. The circadian system is responsible for regulating a wide range of vital physiological functions throughout the body, such as brain arousal, sympathetic tone, cardiovascular function, coagulation, immune cell activity, glucose control, and metabolism.[21–23] Circadian rhythms are inherent biological oscillations that can adapt to periodic environmental changes.[24] A robust circadian rhythm primes the body to meet increased energy demands or stress, thereby enhancing the functionality of individual cells, organ systems, and even the entire organism.[20,25,26]

Substantial evidence indicates that interleukin-1 and TNF are implicated in the modulation of spontaneous NREM sleep.[27,28] For example, interleukin-1 directly alters the firing patterns of neurons in the hypothalamus and brainstem, regions that are known to play a role in regulating sleep-wake cycles.[29]

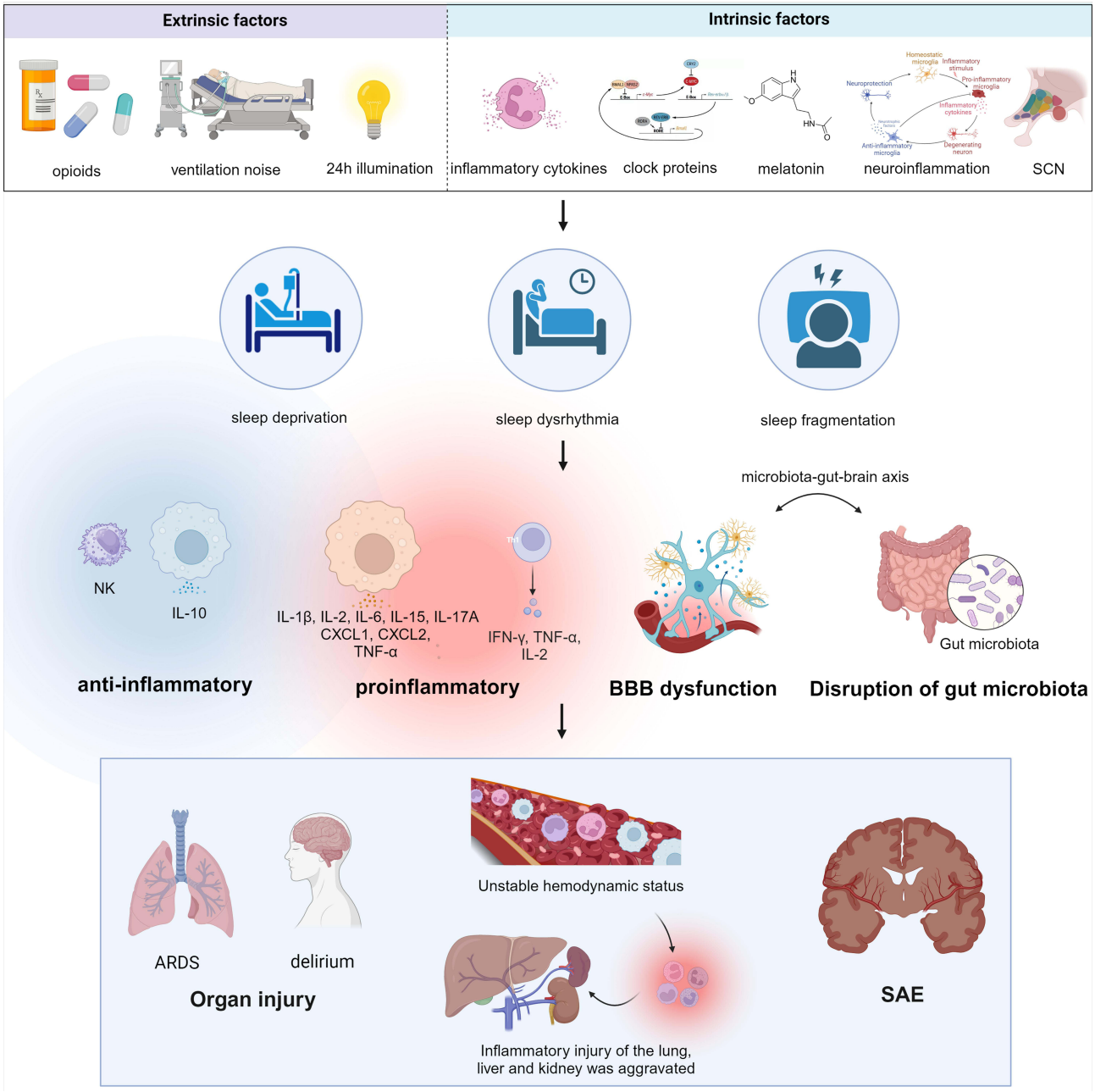


Figure 1 The schematic diagram illustrates the relationship between sleep disorders in sepsis patients and various factors that influence sleep quality. These factors lead to alterations in the state of sleep, which subsequently impact inflammation and immune status and ultimately result in clinical changes. Created with Biorender.com.

Effect of Sepsis on Sleep Quality

Manifestation of Sleep Disorders in Patients with Sepsis

Sepsis may induce acute alterations in sleep, including dysregulated REM-NREM sleep cycle and fragmented sleep. Studies in septic animals have shown that sepsis increases the duration of NREM sleep during the active phase (dark phase) but not during the inactive phase (light phase). Moreover, REM sleep is suppressed for a significant period after sepsis induction, indicating a disruption in the normal REM-NREM sleep cycle.[30] Lipopolysaccharide (LPS) is a common mediator of sepsis induced by Gram-negative bacteria, it may disrupt the normal brain oscillatory activity regulating REM and NREM sleep state.[31] In human patients, sepsis can also induce changes in electroencephalogram (EEG) rhythms, characterized by low-pressure mixed-frequency waves with intermittent theta and delta waveform

activity.[32,33] Fragmented sleep induced by sepsis was characterized by discontinuous sleep periods that are fragmented by frequent awakenings[31] and increased times of transitions from one behavioral state to another.[30] It has emerged as a crucial factor in the manifestation of neurological symptoms in acute systemic inflammation and post-sepsis syndrome.[34] There are numerous clinical studies evaluating the sleep status of septic patients and supporting that sleep was severely disordered in sepsis (Table 1).

Factors Contributing to Sepsis-Induced Sleep Disturbance

Hypothalamic Suprachiasmatic Nuclei

Neural inflammation during sepsis may impair the light responsiveness of hypothalamic suprachiasmatic nuclei (SCN), which serves as the primary circadian pacemaker. Palomba et al demonstrated that weekly administration of LPS impaired the light responsiveness of the SCN, as measured through c-FOS induction.[38] Furthermore, LPS showed an acute and long-lasting effect in SCN region. Acutely, 24 hours after LPS treatment there is a marked upregulation of SCN EGR-1, and an upregulation of $F4/80^{+}$ microglia with activated morphology. The activation in SCN regions could persisted for a long period since the SCN harvested 3 month after LPS stimulation showed a persistent upregulation of the microglial markers CD-11b and F4/80, indicating that the SCN responds to peripheral inflammation and stimuli and induce sleep disorders during sepsis.[39]

Clock Genes

At the molecular level, there is a profound correlation between disturbances in clock genes and immune alterations.[16] During sepsis, the expression patterns of clock genes and the broader transcriptome become aberrant.[40] Diaz et al conducted a study on the circadian rhythms of 11 patients in a neurointensive care unit and observed that after one week, the circadian rhythm of the clock gene CLOCK was disrupted.[41] Furthermore, research has extracted blood from patients

Table 1 Overview of Clinical Studies on the Impact of Sepsis on Sleep

Study	Design	Subjects	Assessment tool	Result
In-Ae Song 2021[34]	Retrospectively data analyses	45,826 survivors of sepsis	ICD-10 codes of G47* (G47.0: primary insomnia, and G47.1–9) in the NHIS database	2935 (6.4%) were newly diagnosed with a sleep disorder within 1 year after the date of sepsis diagnosis.
Cynthia Y Huang 2019[35]	Prospective, observational online international survey	827 survivors of sepsis within the last year from 41 countries	Likert Scale	7 days before survey: Survivors reported anxiety, depression, fatigue, sleep issues ranging from 'never' to 'always'.
Kimberly R. Boer 2008[36]	Prospective cohort	107 abdominal sepsis patients	IES-R, PTSS-10, BDI-II	Up to 38% of abdominal sepsis patients show PTSD symptoms, possibly linked to sleep issues.
Matthew B Maas 2020[37]	Prospective cohort	112 critically ill patients (53 with sepsis and 59 with ICH)	wrist actigraphy, melatonin profile	Critically ill patients rapidly enter a state of behavioral quiescence proportionate to their illness severity with concomitant disturbance of rest-activity rhythms within the circadian.
Y Boyko 2018	Descriptive study	16 patients with severe sepsis	PSG	Half of the patients in the severe sepsis group had atypical sleep.
N S Freedman 2001[32]	Cross-sectional study	22 patients were in the ICU for primarily medical problems (5 patients with sepsis)	PSG	All 22 patients demonstrated sleep-wake cycle abnormalities.

Abbreviations: NHIS, National Health Insurance Service; ICU, intensive care unit; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; IES-R=Impact of Events Scale–Revised; PTSS-10=the Post-Traumatic Symptom Scale 10, BDI-II=Beck Depression Inventory II.

with sepsis and isolated CD14-positive cells, finding that the rhythmic expression of positive regulators, such as CLOCK and ARNTL, is weakest in septic patients, whereas the rhythmic expression of negative regulators, including NR1D1, NR1D2, and CRY2, is most pronounced. Additionally, compared to healthy individuals, patients with septic shock exhibit suppressed expression of the clock genes CRY1, NR1D1, NR1D2, DBP, and PER2, while CRY2 expression is significantly upregulated.[42]

Melatonin

Melatonin, a hormone predominantly produced by the pineal gland, plays a pivotal role in regulating the sleep-wake cycle.[43] However, growing evidence indicates that the circadian rhythm of melatonin secretion is disrupted during severe sepsis.[44–47] Numerous studies have demonstrated that septic patients often exhibit aberrations in melatonin production and other circadian rhythm biomarkers, ranging from decreased amplitude to complete abolition of rhythm.[48] Additionally, research points to the severity of brain disorders and exposure to adrenergic agonist medications as significant factors contributing to disturbances in the melatonin rhythm.[49]

Inflammation

Animal studies have revealed that inflammatory cytokines potentially play a role in regulating sleep disturbances during sepsis. Notably, TNF-α and various proinflammatory cytokines, including IL-1, TNF, IFN-γ, IL-2, IL-6, and IL-15, are recognized for their ability to promote NREM sleep, whereas anti-inflammatory cytokines tend to have the opposite effect, suppressing NREM sleep.[29,50–55] Furthermore, numerous studies have demonstrated that the upregulation of proinflammatory mediators by LPS can also influence the expression of clock genes.[56–59] These findings highlight the intricate interplay between immune responses, inflammation, and circadian rhythms in sepsis-induced sleep disturbances.

ICU Environment

ICU patients frequently suffer from sleep deprivation, which is primarily attributed to environmental factors such as excessive noise and continuous lighting. Moreover, augmented patient care activities and invasive monitoring techniques contribute significantly to sleep disruption.[60] Research has demonstrated that ICU patients experience severe sleep fragmentation, manifesting as a heightened arousal index, shortened sleep duration, and a reduced proportion of slow-wave sleep.[61] Notably, patients with sepsis or those requiring mechanical ventilation in medical ICUs often exhibit minimal or no REM sleep, particularly within the first 1–2 postoperative days, potentially linked to the administration of high-dose opioids.[62] However, there are also some contrary findings, which suggest that ICU conditions, such as prolonged exposure to high light levels, do not necessarily disrupt the circadian rhythms of septic patients, as nonseptic ICU patients display normal rhythmic expression of clock genes.[63]

The Impact of Sleep Disorders on the Outcome of Sepsis

Systemic Effects of Sleep Disorders in Humans

Sleep abnormalities can potentially trigger systemic disturbances via inflammatory and immunological alterations, oxidative stress, and changes in glucocorticoid levels. Following sleep deprivation, patients with sepsis often exhibit shorter latencies to the onset of fever, more severe febrile reactions, and prolonged recovery periods for physiological functions.[64] A large number of studies have established a significant association between habitually shortened sleep duration and a range of adverse health outcomes, including obesity, diabetes mellitus, cardiovascular disease, neuropsychiatric symptoms, and pain. Furthermore, population-based studies have indicated an elevated risk of mortality among individuals with shortened sleep durations.[65,66]

The release of growth hormone, prolactin, melatonin, and leptin triggers the activation, proliferation, differentiation, and production of proinflammatory cytokines in immune cells. This synergistic action significantly potentiates the immune system's response. Notably, in both humans and animals, peaks in the levels of proinflammatory factors and Th1 cytokines are observed during the early slow-wave sleep (SWS) phase, which dominates during certain stages of sleep across various tissues.[67] Studies have also revealed the impact of alterations in signalling molecules, including melatonin, ROS, cortisol, epinephrine, norepinephrine, growth hormone, metabolites resulting from changes in the

intestinal microbiota, and adipokines derived from adipose tissue, all of which are associated with sleep, on immune cell function.[68]

Effect of Sleep Disorders on Encephalopathy in Sepsis

The brain serves as a pivotal mediator of the immune response and a prime target for pathophysiological processes in sepsis.[69] Sepsis-associated encephalopathy (SAE), a diffuse brain dysfunction that occurs secondary to infection in the body without overt CNS infection,[70] has been well recognized by physicians as one of the first organs affected by sepsis with clinical manifestations,[71] and changes in mental status have been identified as a key indicator in three sepsis screening programs.[72] Clinically, SAE is characterized by attention deficits, decreased concentration, and impairments in learning and memory.[73] Systemic inflammatory processes can lead to blood–brain barrier (BBB) dysfunction, enabling the infiltration of proinflammatory mediators into the CNS and subsequent inflammation throughout the brain. These pathophysiological alterations, including neuroinflammation, vascular changes, and tissue lesions due to metabolic failure, are observed in both animal models and humans.[71]

Chronic sleep deprivation has been linked to the promotion of neuroinflammation, synaptic loss, mood disorders, and cognitive impairments in various neurodegenerative and neurobehavioral diseases,[74–77] similar to SAE. Sleep disorders may also contribute to the development of SAE. Sepsis is associated with several metabolic changes in the brain, such as ATP depletion, increased ROS production, and antioxidant consumption.[78,79] As an important regulator of sleep, melatonin has been reported to increase the antioxidant activity of antioxidant enzymes by activating NRF2 and upregulating sirtuins, which have neuroprotective effects.[80–82] Disruption of the BBB is among the primary etiologies of SAE. Wang et al[83] showed that pretreatment with melatonin preserved the integrity of the BBB in mice with sepsis induced by LPS. Zhao et al[84] reported that melatonin treatment in septic animals reduced the brain concentrations of proinflammatory cytokines, such as TNF-α and IL-1β. However, since melatonin is an antioxidant, whether it improves the prognosis of sepsis patients by regulating sleep quality remains unclear.

Effects of Sleep Disorders on Inflammatory and Immune Responses in Sepsis

Multiple studies have demonstrated an interactive relationship between sleep disorders and inflammatory or immunological responses.[68,74,85] Diseases characterized by an inflammatory component exhibit diurnal variations in their severity, with the circadian rhythm playing a pivotal role in modulating immune responses at various levels.[86] Rats subjected to total sleep deprivation (TSD) exhibit compromised defenses against bacterial invasion. This leads to infection at critical levels, resulting in sepsis, hypothermia, and ultimately death. Notably, during the early stages of infection, rats are not susceptible to aerobic bacteria; thus, antibiotics cannot prevent the initial adverse effects of TSD. However, restoring sleep has been shown to reverse the deleterious effects of TSD.[87] This reversal is attributed to the fact that sleep disorders lead to a decrease in the production of inflammatory and immunological factors, highlighting the intricate connection between sleep and immune function.

Multiple cytokines are involved in sleep deprivation-related systemic inflammation.[88,89] In sleep-deprived mice, the expression of most proinflammatory regulators was significantly elevated, with IL-6 and IL-17A being the most notable Both cytokines have the potential to induce cytokine storms. Additionally, the levels of the proinflammatory chemokines CXCL1 and CXCL2 were markedly increased. These molecules are crucial for facilitating neutrophil recruitment and extravasation.[90] Furthermore, the serum levels of chemokine (C-C motif) ligand 20 (CCL20), which can be upregulated by IL-17A,[91] are also increased following sleep deprivation (SD). Chronic disruption of the circadian rhythm or long-term sleep restriction can increase the plasma expression of IL-6, TNF-α, and CRP.[76,85,92,93] Post-septic SD elevates plasma levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), reduces IL-10 plasma levels, amplifies spleen weight, and exacerbates inflammatory injury in the lungs, liver, and kidneys.[94] Furthermore, normal sleep following vaccination has been demonstrated to potentiate the natural immune response against invading antigens, resulting in a notable increase in the proportion of T cells producing proinflammatory cytokines and Th1 cell factors (IL-2, IFN-γ, TNF-α) as a direct consequence of sleep.[67] In patients hospitalized with sepsis, those experiencing short-term poor sleep quality exhibited significantly lower levels of plasma albumin, atrial natriuretic peptide (ANP), and lymphocyte counts, particularly T cells and NK cells, than did those with good sleep quality.[95] Disrupted sleep increased the

baseline concentrations of inflammatory cytokines in blood, including interleukin-1β, interleukin-6 and tumor necrosis factor-α, and decreased interleukin-10. The imbalance between pro-inflammatory markers and anti-inflammatory IL-10 may promote an excessive inflammatory response to acute sepsis, increasing mortality risk.[96–99]

Immune cells have also been reported to be affected by sleep disorders. Two consecutive days of SD reduced the absolute lymphocyte count (ALC) and the recovery of ALC after 3 days of SD. Additionally, sleep deprivation immediately following sepsis led to a decrease in plasma ANP levels within two days. Notably, subsequent analysis revealed a positive correlation between plasma ANP levels and the recovery of ALC, as well as between the counts of CD3+ T cells and CD3+ CD4+ cells in peripheral blood, on day 5. These findings suggest that short-term disturbances in sleep quality may hinder lymphocyte recovery in critically ill patients.[95] Disrupted sleep was associated with increased circulating monocytes and natural killer (NK) cells. The accumulation of inflammatory monocytes and NK cells may induce a hyper-inflammation response, which is associated with an increased risk of acute sepsis and mortality.[100] Interrupted sleep increased circulating T cell levels at night, possibly due to altered lymph node migration of T cells. If the timely migration of T cells to lymph nodes is disrupted, it may impair the initiation of adaptive immune responses against infection and exacerbate sepsis and mortality in patients.[101,102]

Moreover, sleep disorders significantly modulate the molecular expression patterns of circadian rhythms, such as BMAL1, CLOCK, and REV-ERBα, which play crucial roles in regulating fundamental immune responses. For instance, the heterodimer BMAL1:CLOCK modulates TLR9 expression and suppresses the expression of inflammatory cytokines such as IL-6 and the monocyte chemoattractant protein CCL2.[103] Numerous studies have shown that mice with Clock gene knockout exhibit enhanced survival rates after sepsis induction and increased resilience to septic shock.[104–109] Therefore, sleep disruption and inadequate rest can modulate the expression of circadian rhythm genes involved in regulating the immune response to infection or stress.

Effect of Sleep Disorders on the Cardiopulmonary Function During Sepsis

It has been suggested that diminished REM sleep may serve as an adaptive response to sepsis-induced stress.[110] During sleep, the cardiovascular system undergoes significant modifications, including dynamic fluctuations in blood flow and electrical activity. These alterations have been associated with life-threatening arrhythmias and ischemic events, particularly in patients with preexisting cardiac conditions.[25] During the NREM phase, heart rate increases significantly, correlating with augmented venous return during inspiration, while a decrease in heart rate is observed during expiration, coincident with diminished venous return.[111] REM sleep, on the other hand, is marked by heightened cardiopulmonary variability and hemoglobin oxygen saturation, which may exacerbate hemodynamic instability in already unstable patients.[61] The literature on the impact of sleep deprivation on the respiratory system in critically ill patients is scarce. However, available evidence suggests that prolonged and continuous sleep disruptions, which are characteristic of ICU patients, may have deleterious effects on respiratory function.[112–115] This is particularly pertinent in individuals with preexisting lung conditions and those facing challenges in weaning from mechanical ventilation. At the molecular level, disturbances in normal circadian rhythms have been shown to influence the severity of sepsis-related inflammation, trigger inflammatory responses in obstructive lung disease patients, prolong apnea episodes in obstructive sleep apnea patients, and increase cancer risk.[24]

Clinical Studies Investigating the Role of Sleep Intervention in Sepsis

Given the established correlation between sepsis and circadian rhythms, time-based therapeutic approaches have garnered increasing attention. ICU patients with sepsis often exhibit alterations in their circadian rhythms and sleep patterns, prompting the investigation of phototherapy as a means to modulate these rhythms. Notably, in septic animals, exposure to bright blue light has been demonstrated to enhance bacterial clearance, attenuate systemic inflammation, and minimize organ damage.[116] Melatonin has emerged as a promising natural agent for treating sepsis and its associated complications. Due to its antioxidant potential, anti-inflammatory properties, ability to maintain blood-brain barrier integrity, and ability to restore mitochondrial homeostasis, melatonin is a potential prophylactic or therapeutic agent for sepsis patients.[117,118]

Table 2 Overview of Clinical Studies Examining the Impact of Melatonin Therapy on Sepsis

References	Subjects	Intervention	Control	Design	Outcome (melatonin vs control)
Mansilla-Rosello 2022[120]	29 patients with severe sepsis	IV melatonin dose of 60 mg per day for 5 days	IV Placebo per day	Randomized controlled trial	Mortality: 20.0% vs 35.7% ($p < 0.001$) The SOFA score: reduced in melatonin group ($p<0.001$)
Taher 2022[125]	40 patients with early septic shock	50 mg melatonin per day for 5 days	Placebo per day	Randomized controlled trial	Ventilator-free days: 16.90±9.24 vs 10.00±10.94 over the 28-day ($p=0.035$) The mean reduction in the required dose of vasopressor: 6.2 ±5.12 vs 3.20±3.95 ($p=0.045$) Vasopressor-free days: 12.75±7.43 days vs 10.15±6.12 days ($p=0.046$)
Gitto 2001[126]	30 septic infants	Melatonin orally in two doses of 10 mg each	Blank	Randomized controlled trial	MDA + 4-HAD: significant reduction to the levels in the normal controls at both 1 and 4 h ($p < 0.05$) Mortality: 0 vs 3
Frargy M 2015[127]	50 infants with neonatal sepsis	20 mg melatonin orally for 3 days	blank	Prospective clinical trial	Sepsis score: significant improvement but difference after 24 h($p=0.008$), 48 h($p=0.006$) and 72 h($p=0.002$)
El-Gendy 2016[128]	40 neonates with neonatal sepsis	20 mg melatonin orally for 2 days	blank	Prospective nonrandomized nonblind case–control study	Clinical condition, hs-CRP, and serum parameters: significant improvement in intervention group than control group
Aisa-Alvarez 2023[129]	131 patients with septic shock	50 mg melatonin per day for 5 days	blank	Randomized clinical trial	The SOFA score decreased: 75% vs 33% ($p=0.0001$) melatonin diminished lipid peroxidation (LPO) ($p = 0.01$) and improved total antioxidant capacity (TAC) ($p = 0.04$).
Aisa-Alvarez 2020[123]	97 patients with septic shock	50 mg melatonin for 5 days	No treatment	Randomized clinical trial	Lipid-peroxidation: reduced ($p=0.04$) Procalcitonin levels: reduced ($p=0.04$) multiple organ failure (MOF): decreased ($p=0.007$)
Pérez-Torres 2023[130]	131 patients with septic shock	50 mg melatonin for 5 days	Standard therapy	Randomized clinical trial	IL-6, IL-8, MCP-1, and IL-10 levels: statistically significantly reduced The SOFA score: reduction from 8 to 2 vs remained high

Despite the well-established correlation between sleep and sepsis, clinical trials examining sleep interventions are lacking. The intervention measures regulating sleep in septic patients are mainly focused on melatonin treatment, as outlined in Table 2. A recent trial demonstrated that the intravenous administration of 60 mg/day of a melatonin formulation was beneficial for septic patients. Specifically, it reduced mortality to zero and decreased hospital stays by 40%.[119] Compared to placebo-treated patients, those receiving melatonin showed a decrease in redox status over the five-day treatment period. The melatonin group also exhibited improved procalcitonin levels and a significantly reduced neutrophil-to-lymphocyte ratio, leading to better disease progression.[120] Studies have indicated that the route of

melatonin administration affects its levels and those of its main metabolite, potentially influencing its therapeutic effects.[121] These studies demonstrated that melatonin supplementation might be useful in treating sepsis. However, in adult patients with sepsis, the efficacy of melatonin is influenced by circadian rhythms, resulting in differential effects.[122] Specifically, melatonin does not exert a significant impact on sepsis-induced inflammation or oxidative damage compared to the effects of a placebo on nighttime endotoxemia.[123] Conversely, in sepsis induced during the daytime, melatonin was reported to significantly reduce the release of proinflammatory markers such as IL-1β.[124]

Conclusion

Sleep disturbances are frequently observed in patients with sepsis, and accumulating evidence has established a bidirectional relationship between sleep and the immune system. Immune activation can disrupt sleep patterns, while sleep, in turn, modulates host immunity. However, the molecular mechanisms underlying sleep disruption and circadian rhythm disorders in sepsis remain incompletely understood. Although clinical studies directly investigating the impact of sleep interventions on sepsis prognosis are limited, multiple trials have demonstrated the beneficial effects of blue light and melatonin on sepsis. These findings suggest that sleep regulation may represent a promising therapeutic strategy to improve the outcome of sepsis patients.

Abbreviations

ROS, Reactive oxygen species; CNS, Central nervous system; REM, Rapid eye movement; HPA, Hypothalamic-pituitary -adrenal; NREM, Non-rapid eye movement; SCN, Suprachiasmatic nucleus; EEG, Electroencephalogram; IL, Interleukin; TNF, Tumor necrosis factor; CLP, Cecal ligation and puncture; PRR, Pattern recognition receptors; SWS, Slow-wave sleep; SAE, Sepsis-associated encephalopathy; BBB, Blood-brain barrier; TSD, Total sleep deprivation; ANP, Atrial natriuretic peptide; ALC, Absolute lymphocyte count.

Data Sharing Statement

Not applicable.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Acknowledgments

De-Zhi Guo and Yu Chen are co-first authors for this study. Graphical Abstract was created with BioRender.com. All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Sci-Tech Innovation 2030 Brain Science and Brain-Like Intelligence Technology Project (2022ZD0208100) and the National Natural Science Foundation of China (82072147).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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