

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

De-Zhi Guo<sup>1,\*</sup>, Yu Chen<sup>1,\*</sup>, Yan Meng<sup>2</sup>, Jin-Jun Bian<sup>3</sup>, Yi Wang<sup>3</sup>, Jia-Feng Wang<sup>3</sup>

<sup>1</sup>School of Basic Medicine, Naval Medical University, Shanghai, People's Republic of China; <sup>2</sup>Department of Intensive Care, Changhai Hospital, Naval Medical University, Shanghai, People's Republic of China; <sup>3</sup>Faculty of Anesthesiology, Changhai Hospital, Naval Medical University, Shanghai, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Yi Wang; Jia-Feng Wang, Email 18019054880@163.com; jfwang@smmu.edu.cn

**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

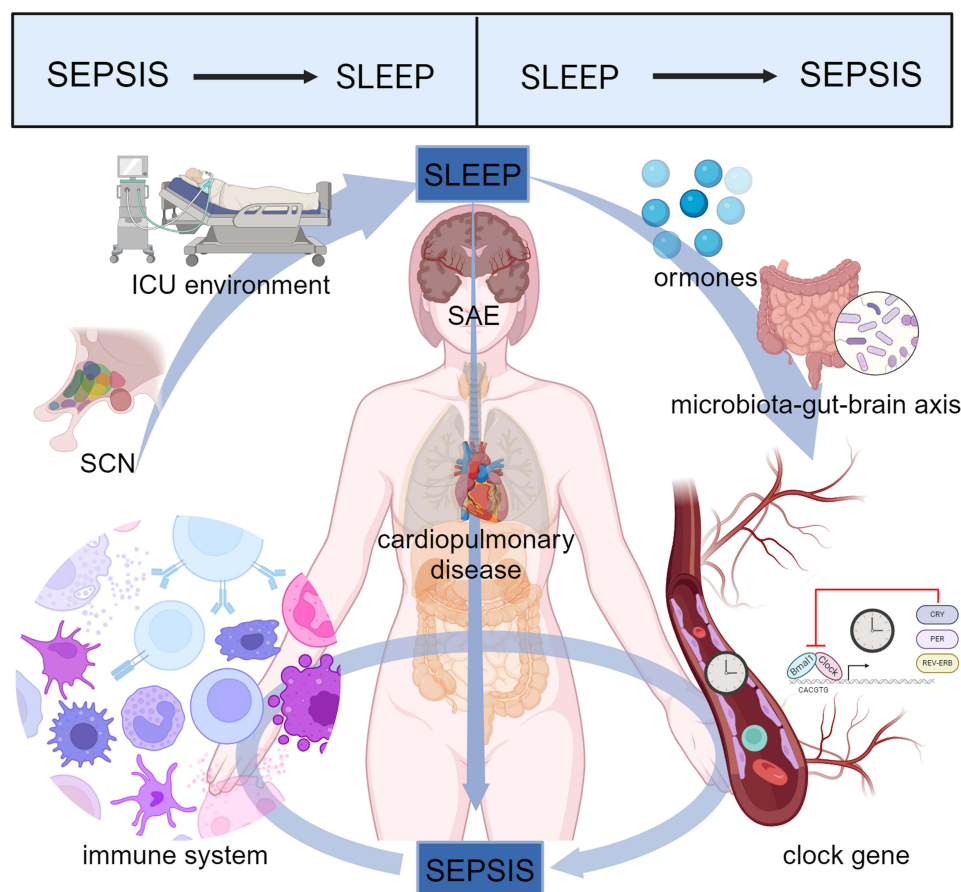
Sepsis, a syndrome characterized by deregulated immune responses to infection leading to multiorgan dysfunction, is a leading cause of mortality associated with infections.<sup>1</sup> It poses a significant global public health challenge, affecting millions of individuals worldwide and ranking as one of the primary causes of death.<sup>2</sup> 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.<sup>3</sup> It was estimated that sepsis may double the risk of insomnia in septic patients,<sup>4</sup> and a PSG study revealed that approximately 50% of patients with sepsis exhibited atypical sleep patterns.<sup>5</sup>

In the past three decades, the intricate relationship between the immune system and the central nervous system (CNS) has been established and characterized.<sup>6–8</sup> 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.<sup>9–11</sup> 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.<sup>12</sup> 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.<sup>13,14</sup> This circadian process ensures uninterrupted sleep during the primary hours of the night.<sup>15</sup> Physiological and cellular processes operate in a cyclic manner, adhering to a 24-hour rhythm that is driven by an endogenous mechanism known as

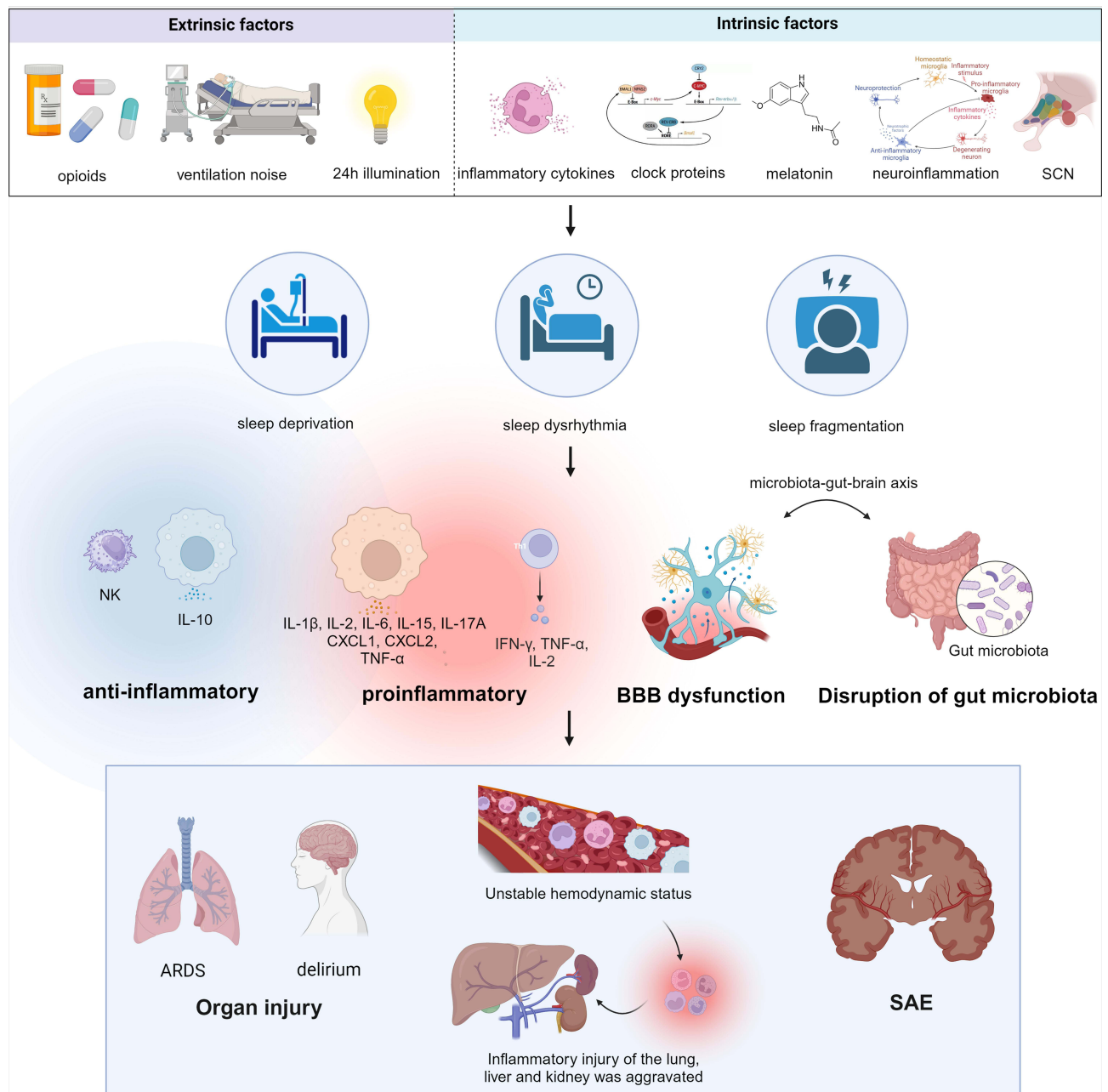
## Graphical Abstract



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

Almost every cell in the human body exhibits a circadian rhythm, with clocks within tissues and organs operating in synchrony.<sup>18</sup> 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.<sup>19,20</sup> For instance, melatonin synthesis is triggered by  $\beta$ -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.<sup>21–23</sup> Circadian rhythms are inherent biological oscillations that can adapt to periodic environmental changes.<sup>24</sup> 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.<sup>20,25,26</sup>

Substantial evidence indicates that interleukin-1 and TNF are implicated in the modulation of spontaneous NREM sleep.<sup>27,28</sup> 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.<sup>29</sup>



**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.<sup>30</sup> 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.<sup>31</sup> 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.<sup>32,33</sup> Fragmented sleep induced by sepsis was characterized by discontinuous sleep periods that are fragmented by frequent awakenings<sup>31</sup> and increased times of transitions from one behavioral state to another.<sup>30</sup> It has emerged as a crucial factor in the manifestation of neurological symptoms in acute systemic inflammation and post-sepsis syndrome.<sup>34</sup> 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.<sup>38</sup> 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<sup>+</sup> 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.<sup>39</sup>

### Clock Genes

At the molecular level, there is a profound correlation between disturbances in clock genes and immune alterations.<sup>16</sup> During sepsis, the expression patterns of clock genes and the broader transcriptome become aberrant.<sup>40</sup> 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.<sup>41</sup> 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 <sup>34</sup>	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 <sup>35</sup>	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 <sup>36</sup>	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 <sup>37</sup>	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 <sup>32</sup>	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.<sup>42</sup>

### Melatonin

Melatonin, a hormone predominantly produced by the pineal gland, plays a pivotal role in regulating the sleep-wake cycle.<sup>43</sup> However, growing evidence indicates that the circadian rhythm of melatonin secretion is disrupted during severe sepsis.<sup>44–47</sup> 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.<sup>48</sup> 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.<sup>49</sup>

### Inflammation

Animal studies have revealed that inflammatory cytokines potentially play a role in regulating sleep disturbances during sepsis. Notably, TNF- $\alpha$  and various proinflammatory cytokines, including IL-1, TNF, IFN- $\gamma$ , 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.<sup>29,50–55</sup> Furthermore, numerous studies have demonstrated that the upregulation of proinflammatory mediators by LPS can also influence the expression of clock genes.<sup>56–59</sup> 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.<sup>60</sup> 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.<sup>61</sup> 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.<sup>62</sup> 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.<sup>63</sup>

## 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.<sup>64</sup> 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.<sup>65,66</sup>

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.<sup>67</sup> 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.<sup>68</sup>

## 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.<sup>69</sup> Sepsis-associated encephalopathy (SAE), a diffuse brain dysfunction that occurs secondary to infection in the body without overt CNS infection,<sup>70</sup> has been well recognized by physicians as one of the first organs affected by sepsis with clinical manifestations,<sup>71</sup> and changes in mental status have been identified as a key indicator in three sepsis screening programs.<sup>72</sup> Clinically, SAE is characterized by attention deficits, decreased concentration, and impairments in learning and memory.<sup>73</sup> 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.<sup>71</sup>

Chronic sleep deprivation has been linked to the promotion of neuroinflammation, synaptic loss, mood disorders, and cognitive impairments in various neurodegenerative and neurobehavioral diseases,<sup>74–77</sup> 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.<sup>78,79</sup> 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.<sup>80–82</sup> Disruption of the BBB is among the primary etiologies of SAE. Wang et al<sup>83</sup> showed that pretreatment with melatonin preserved the integrity of the BBB in mice with sepsis induced by LPS. Zhao et al<sup>84</sup> reported that melatonin treatment in septic animals reduced the brain concentrations of proinflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ . 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.<sup>68,74,85</sup> 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.<sup>86</sup> 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.<sup>87</sup> 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.<sup>88,89</sup> 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.<sup>90</sup> Furthermore, the serum levels of chemokine (C-C motif) ligand 20 (CCL20), which can be upregulated by IL-17A,<sup>91</sup> 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- $\alpha$ , and CRP.<sup>76,85,92,93</sup> Post-septic SD elevates plasma levels of interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), reduces IL-10 plasma levels, amplifies spleen weight, and exacerbates inflammatory injury in the lungs, liver, and kidneys.<sup>94</sup> 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- $\gamma$ , TNF- $\alpha$ ) as a direct consequence of sleep.<sup>67</sup> 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.<sup>95</sup> Disrupted sleep increased the

baseline concentrations of inflammatory cytokines in blood, including interleukin-1 $\beta$ , interleukin-6 and tumor necrosis factor- $\alpha$ , 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.<sup>96–99</sup>

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.<sup>95</sup> 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.<sup>100</sup> 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.<sup>101,102</sup>

Moreover, sleep disorders significantly modulate the molecular expression patterns of circadian rhythms, such as BMAL1, CLOCK, and REV-ERB $\alpha$ , 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.<sup>103</sup> Numerous studies have shown that mice with Clock gene knockout exhibit enhanced survival rates after sepsis induction and increased resilience to septic shock.<sup>104–109</sup> 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.<sup>110</sup> 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.<sup>25</sup> 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.<sup>111</sup> 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.<sup>61</sup> 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.<sup>112–115</sup> 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.<sup>24</sup>

## 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.<sup>116</sup> 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.<sup>117,118</sup>

**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 <sup>120</sup>	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 <sup>125</sup>	40 patients with early septic shock	50 mg melatonin per day for 5 days	Placebo per day	Randomized controlled trial	Ventilator-free days: $16.90 \pm 9.24$ vs $10.00 \pm 10.94$ over the 28-day ( $p = 0.035$ ) The mean reduction in the required dose of vasopressor: $6.2 \pm 5.12$ vs $3.20 \pm 3.95$ ( $p = 0.045$ ) Vasopressor-free days: $12.75 \pm 7.43$ days vs $10.15 \pm 6.12$ days ( $p = 0.046$ ) 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
Gitto 2001 <sup>126</sup>	30 septic infants	Melatonin orally in two doses of 10 mg each	Blank	Randomized controlled trial	Sepsis score: significant improvement but difference after 24 h ( $p = 0.008$ ), 48 h ( $p = 0.006$ ) and 72 h ( $p = 0.002$ )
Frangy M 2015 <sup>127</sup>	50 infants with neonatal sepsis	20 mg melatonin orally for 3 days	blank	Prospective clinical trial	Clinical condition, hs-CRP, and serum parameters: significant improvement in intervention group than control group
El-Gendy 2016 <sup>128</sup>	40 neonates with neonatal sepsis	20 mg melatonin orally for 2 days	blank	Prospective nonrandomized nonblind case-control study	The SOFA score decreased: 75% vs 33% ( $p = 0.0001$ ) melatonin diminished lipid peroxidation (LPO) ( $p = 0.01$ ) and improved total antioxidant capacity (TAC) ( $p = 0.04$ ). Lipid-peroxidation: reduced ( $p = 0.04$ ) Procalcitonin levels: reduced ( $p = 0.04$ ) multiple organ failure (MOF): decreased ( $p = 0.007$ )
Aisa-Alvarez 2023 <sup>129</sup>	131 patients with septic shock	50 mg melatonin per day for 5 days	blank	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
Aisa-Alvarez 2020 <sup>123</sup>	97 patients with septic shock	50 mg melatonin for 5 days	No treatment	Randomized clinical trial	
Pérez-Torres 2023 <sup>130</sup>	131 patients with septic shock	50 mg melatonin for 5 days	Standard therapy	Randomized clinical trial	

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%.<sup>119</sup> 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.<sup>120</sup> Studies have indicated that the route of



melatonin administration affects its levels and those of its main metabolite, potentially influencing its therapeutic effects.<sup>121</sup> 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.<sup>122</sup> 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.<sup>123</sup> Conversely, in sepsis induced during the daytime, melatonin was reported to significantly reduce the release of proinflammatory markers such as IL-1 $\beta$ .<sup>124</sup>

## 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.

## References

1. Singer M. The new sepsis consensus definitions (Sepsis-3): the good, the not-so-bad, and the actually-quite-pretty. *Intensive Care Med.* 2016;42(12):2027–2029. doi:10.1007/s00134-016-4600-4
2. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis. current estimates and limitations. *Am J Respir Crit Care Med.* 2016;193(3):259–272. doi:10.1164/rccm.201504-0781OC
3. Walder B, Haase U, Rundshagen I. Sleep disturbances in critically ill patients. *Anaesthesist.* 2007;56(1):7–17. doi:10.1007/s00101-006-1086-4
4. Thorkildsen MS, Gustad LT, Mohus RM, et al. Association of genetically predicted insomnia with risk of sepsis: a Mendelian randomization study. *JAMA Psychiatry.* 2023;80(10):1061–1065. doi:10.1001/jamapsychiatry.2023.2717
5. Boyko Y, Jennum P, Oerding H, Lauridsen JT, Nikolic M, Toft P. Sleep in critically ill, mechanically ventilated patients with severe sepsis or COPD. *Acta Anaesthesiol Scand.* 2018;62(8):1120–1126. doi:10.1111/aas.13140
6. Dantzer R. Neuroimmune Interactions: from the brain to the immune system and vice versa. *Physiol Rev.* 2018;98(1):477–504. doi:10.1152/physrev.00039.2016
7. Kipnis J. Multifaceted interactions between adaptive immunity and the central nervous system. *Science.* 2016;353(6301):6301:766–771. doi:10.1126/science.aag2638
8. Prinz M, Masuda T, Wheeler MA, Quintana FJ. Microglia and central nervous system-associated macrophages-from origin to disease modulation. *Annu Rev Immunol.* 2021;39(1):251–277. doi:10.1146/annurev-immunol-093019-110159
9. Everson CA, Toth LA. Systemic bacterial invasion induced by sleep deprivation. *Am J Physiol Regul Integr Comp Physiol.* 2000;278(4):R905–R916. doi:10.1152/ajpregu.2000.278.4.R905
10. Irwin M, McClintick J, Costlow C, Fortner M, White J, Gillin JC. Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *FASEB J.* 1996;10(5):643–653. doi:10.1096/fasebj.10.5.8621064
11. Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. *JAMA.* 2002;288(12):1471–1472. doi:10.1001/jama.288.12.1469
12. Patel AK, Reddy V, Shumway KR, Araujo JF. Physiology. *Sleep Stages.* 2023.
13. Borbely AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. *J Sleep Res.* 2016;25(2):131–143. doi:10.1111/jsr.12371
14. Borbely AA, Achermann P. Sleep homeostasis and models of sleep regulation. *J Biol Rhythms.* 1999;14(6):557–568. doi:10.1177/074873099129000894
15. Pavlova M. Circadian rhythm sleep-wake disorders. *Continuum (Minneapolis).* 2017;23(4, Sleep Neurology):1051–1063. doi:10.1212/CON.0000000000000499
16. Lee EY, Wilcox ME. Sleep in the intensive care unit. *Curr Opin Pulm Med.* 2022;28(6):515–521. doi:10.1097/MCP.0000000000000912
17. Yamazaki S, Numano R, Abe M, et al. Resetting central and peripheral circadian oscillators in transgenic rats. *Science.* 2000;288(5466):682–685. doi:10.1126/science.288.5466.682
18. Welsh DK, Logothetis DE, Meister M, Reppert SM. Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. *Neuron.* 1995;14(4):697–706. doi:10.1016/0896-6273(95)90214-7
19. Franken P, Dijk DJ. Circadian clock genes and sleep homeostasis. *Eur J Neurosci.* 2009;29(9):1820–1829. doi:10.1111/j.1460-9568.2009.06723.x
20. Papaioannou V, Mebazaa A, Plaud B, Legrand M. ‘Chronomics’ in ICU: circadian aspects of immune response and therapeutic perspectives in the critically ill. *Intensive Care Med Exp.* 2014;2(1):18. doi:10.1186/2197-425X-2-18
21. Chan MC, Spieth PM, Quinn K, Parotto M, Zhang H, Slutsky AS. Circadian rhythms: from basic mechanisms to the intensive care unit. *Crit Care Med.* 2012;40(1):246–253. doi:10.1097/CCM.0b013e31822f0abe
22. Dang-Vu TT, Desseilles M, Peigneux P, Maquet P. A role for sleep in brain plasticity. *Pediatr Rehabil.* 2006;9(2):98–118. doi:10.1080/13638490500138702
23. Haspel JA, Anafi R, Brown MK, et al. Perfect timing: circadian rhythms, sleep, and immunity - an NIH workshop summary. *JCI Insight.* 2020;5(1). doi:10.1172/jci.insight.131487
24. Truong KK, Lam MT, Grandner MA, Sassoos CS, Malhotra A. Timing matters: circadian rhythm in sepsis, obstructive lung disease, obstructive sleep apnea, and cancer. *Ann Am Thorac Soc.* 2016;13(7):1144–1154. doi:10.1513/AnnalsATS.201602-125FR
25. Kamdar BB, Needham DM, Collop NA. Sleep deprivation in critical illness: its role in physical and psychological recovery. *J Intensive Care Med.* 2012;27(2):97–111. doi:10.1177/0885066610394322
26. Weinhouse GL, Kimchi E, Watson P, Devlin JW. Sleep assessment in critically ill adults: established methods and emerging strategies. *Crit Care Explor.* 2022;4(2):e0628. doi:10.1097/CCE.0000000000000628
27. Kapsimalis F, Richardson G, Opp MR, Kryger M. Cytokines and normal sleep. *Curr Opin Pulm Med.* 2005;11(6):481–484. doi:10.1097/01.mcp.0000183062.98665.6b
28. Imeri L, Opp MR. How (and why) the immune system makes us sleep. *Nat Rev Neurosci.* 2009;10(3):199–210. doi:10.1038/nrn2576
29. Opp MR. Cytokines and sleep. *Sleep Med Rev.* 2005;9(5):355–364. doi:10.1016/j.smrv.2005.01.002
30. Baracchi F, Ingiosi AM, Raymond RJ, Opp MR. Sepsis-induced alterations in sleep of rats. *Am J Physiol Regul Integr Comp Physiol.* 2011;301(5):R1467–R1478. doi:10.1152/ajpregu.00354.2011
31. Kala A, Leemburg S, Jezek K. Sepsis-induced changes in spectral segregation and kinetics of hippocampal oscillatory states in rats. *eNeuro.* 2023;10(6):ENEURO.0002–23.2023. doi:10.1523/ENEURO.0002-23.2023
32. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med.* 2001;163(2):451–457. doi:10.1164/ajrccm.163.2.9912128

33. Nilius G, Richter M, Schroeder M. Updated perspectives on the management of sleep disorders in the intensive care unit. *Nat Sci Sleep*. 2021;13:751–762. doi:10.2147/NSS.S284846
34. Song IA, Park HY, Oh TK. Sleep disorder and long-term mortality among sepsis survivors: a nationwide cohort study in South Korea. *Nat Sci Sleep*. 2021;13:979–988. doi:10.2147/NSS.S319769
35. Huang CY, Daniels R, Lembo A, et al. Life after sepsis: an international survey of survivors to understand the post-sepsis syndrome. *Int J Qual Health Care*. 2019;31(3):191–198. doi:10.1093/intqhc/mzy137
36. Boer KR, van Ruler O, van Emmerik AA, et al. Factors associated with posttraumatic stress symptoms in a prospective cohort of patients after abdominal sepsis: a nomogram. *Intensive Care Med*. 2008;34(4):664–674. doi:10.1007/s00134-007-0941-3
37. Maas MB, Lizza BD, Kim M, et al. Stress-induced behavioral quiescence and abnormal rest-activity rhythms during critical illness. *Crit Care Med*. 2020;48(6):862–871.
38. Palomba M, Bentivoglio M. Chronic inflammation affects the photic response of the suprachiasmatic nucleus. *J Neuroimmunol*. 2008;193(1–2):24–27. doi:10.1016/j.jneuroim.2007.09.002
39. O'Callaghan EK, Anderson ST, Moynagh PN, Coogan AN. Long-lasting effects of sepsis on circadian rhythms in the mouse. *PLoS One*. 2012;7(10):e47087. doi:10.1371/journal.pone.0047087
40. Maas MB, Iwanaszko M, Lizza BD, Reid KJ, Braun RI, Zee PC. Circadian gene expression rhythms during critical illness. *Crit Care Med*. 2020;48(12):e1294–e1299. doi:10.1097/CCM.0000000000004697
41. Diaz E, Diaz I, Del BC, Escudero D, Perez S. Clock genes disruption in the intensive care unit. *J Intensive Care Med*. 2020;35(12):1497–1504. doi:10.1177/0885066619876572
42. Lachmann G, Ananthasubramaniam B, Wunsch VA, et al. Circadian rhythms in septic shock patients. *Ann Intensive Care*. 2021;11(1):64. doi:10.1186/s13613-021-00833-5
43. Jarratt J. Perioperative melatonin use. *Anaesth Intensive Care*. 2011;39(2):171–181. doi:10.1177/0310057X1103900205
44. Li CX, Liang DD, Xie GH, et al. Altered melatonin secretion and circadian gene expression with increased proinflammatory cytokine expression in early-stage sepsis patients. *Mol Med Rep*. 2013;7(4):1117–1122. doi:10.3892/mmr.2013.1331
45. Mundigler G, Delle-Karh G, Koreny M, et al. Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Crit Care Med*. 2002;30(3):536–540. doi:10.1097/00003246-200203000-00007
46. Olofsson K, Alling C, Lundberg D, Malmros C. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. *Acta Anaesthesiol Scand*. 2004;48(6):679–684. doi:10.1111/j.0001-5172.2004.00401.x
47. Verceles AC, Silhan L, Terrin M, Netzer G, Shanholtz C, Scharf SM. Circadian rhythm disruption in severe sepsis: the effect of ambient light on urinary 6-sulfatoxymelatonin secretion. *Intensive Care Med*. 2012;38(5):804–810. doi:10.1007/s00134-012-2494-3
48. Billings ME, Watson NF. Circadian dysrhythmias in the intensive care unit. *Crit Care Clin*. 2015;31(3):393–402. doi:10.1016/j.ccc.2015.03.006
49. Maas MB, Lizza BD, Abbott SM, et al. Factors disrupting melatonin secretion rhythms during critical illness. *Crit Care Med*. 2020;48(6):854–861. doi:10.1097/CCM.0000000000004333
50. Hogan D, Morrow JD, Smith EM, Opp MR. Interleukin-6 alters sleep of rats. *J Neuroimmunol*. 2003;137(1–2):59–66. doi:10.1016/S0165-5728(03)00038-9
51. Krueger JM, Majde JA. Cytokines and sleep. *Int Arch Allergy Immunol*. 1995;106(2):97–100. doi:10.1159/000236827
52. Kubota T, Brown RA, Fang J, Krueger JM. Interleukin-15 and interleukin-2 enhance non-REM sleep in rabbits. *Am J Physiol Regul Integr Comp Physiol*. 2001;281(3):R1004–R1012. doi:10.1152/ajpregu.2001.281.3.R1004
53. Kubota T, Fang J, Brown RA, Krueger JM. Interleukin-18 promotes sleep in rabbits and rats. *Am J Physiol Regul Integr Comp Physiol*. 2001;281(3):R828–R838. doi:10.1152/ajpregu.2001.281.3.R828
54. Kubota T, Majde JA, Brown RA, Krueger JM. Tumor necrosis factor receptor fragment attenuates interferon-gamma-induced non-REM sleep in rabbits. *J Neuroimmunol*. 2001;119(2):192–198. doi:10.1016/S0165-5728(01)00382-4
55. Walker WE. GOODNIGHT, SLEEP TIGHT, DON'T LET THE MICROBES BITE: a REVIEW OF SLEEP AND ITS EFFECTS ON SEPSIS AND INFLAMMATION. *Shock*. 2022;58(3):189–195. doi:10.1097/SHK.0000000000001976
56. Cavadini G, Petrzilka S, Kohler P, et al. TNF-alpha suppresses the expression of clock genes by interfering with E-box-mediated transcription. *Proc Natl Acad Sci U S A*. 2007;104(31):12843–12848. doi:10.1073/pnas.0701466104
57. Motzkus D, Albrecht U, Maronde E. The human PER1 gene is inducible by interleukin-6. *J Mol Neurosci*. 2002;18(1–2):105–109. doi:10.1385/JMN:18:1-2:105
58. Petrzilka S, Taraborrelli C, Cavadini G, Fontana A, Birchler T. Clock gene modulation by TNF-alpha depends on calcium and p38 MAP kinase signaling. *J Biol Rhythms*. 2009;24(4):283–294. doi:10.1177/0748730409336579
59. Tong X, Buelow K, Guha A, Rausch R, Yin L. USP2a protein deubiquitinates and stabilizes the circadian protein CRY1 in response to inflammatory signals. *J Biol Chem*. 2012;287(30):25280–25291. doi:10.1074/jbc.M112.340786
60. Lewis SR, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF. Melatonin for the promotion of sleep in adults in the intensive care unit. *Cochrane Database Syst Rev*. 2018;5(5):CD012455.
61. Weinhouse GL, Schwab RJ. Sleep in the critically ill patient. *Sleep*. 2006;29(5):707–716. doi:10.1093/sleep/29.5.707
62. Tiruvoipati R, Mulder J, Haji K. Improving sleep in intensive care unit: an overview of diagnostic and therapeutic options. *J Patient Exp*. 2020;7(5):697–702. doi:10.1177/2374373519882234
63. Acuna-Fernandez C, Marin JS, Diaz-Casado ME, et al. Daily changes in the expression of clock genes in sepsis and their relation with sepsis outcome and urinary excretion of 6-sulfatoxymelatonin. *Shock*. 2020;53(5):550–559. doi:10.1097/SHK.0000000000001433
64. Lapshina KV, Ekimova IV. Effects of sleep deprivation on measures of the febrile reaction and the recovery of somatovisceral functions and sleep in endotoxemia. *Neurosci Behav Physiol*. 2010;40(4):381–388. doi:10.1007/s11055-010-9268-6
65. Grandner MA. Sleep, health, and society. *Sleep Med Clin*. 2017;12(1):1–22. doi:10.1016/j.jsmc.2016.10.012
66. Watson NF, Badr MS, Belenky G, et al. Joint consensus statement of the American academy of sleep medicine and sleep research society on the recommended amount of sleep for a healthy adult: methodology and discussion. *Sleep*. 2015;38(8):1161–1183. doi:10.5665/sleep.4886
67. Besedovsky L, Lange T, Born J. Sleep and immune function. *Pflugers Arch*. 2012;463(1):121–137. doi:10.1007/s00424-011-1044-0
68. Garbarino S, Lanteri P, Bragazzi NL, Magnavita N, Scoditti E. Role of sleep deprivation in immune-related disease risk and outcomes. *Commun Biol*. 2021;4(1):1304. doi:10.1038/s42003-021-02825-4

69. Zampieri FG, Park M, Machado FS, Azevedo LC. Sepsis-associated encephalopathy: not just delirium. *Clinics (Sao Paulo)*. 2011;66(10):1825–1831. doi:10.1590/S1807-59322011001000024
70. Goffon TE, Young GB. Sepsis-associated encephalopathy. *Nat Rev Neurol*. 2012;8(10):557–566. doi:10.1038/nrneurol.2012.183
71. Mazeraud A, Pascal Q, Verdonk F, Heming N, Chretien F, Sharshar T. Neuroanatomy and Physiology of Brain Dysfunction in Sepsis. *Clin Chest Med*. 2016;37(2):333–345. doi:10.1016/j.ccm.2016.01.013
72. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315(8):762–774. doi:10.1001/jama.2016.0288
73. Catarina AV, Branchini G, Bettoni L, De Oliveira JR, Nunes FB. Sepsis-Associated Encephalopathy: from Pathophysiology to Progress in Experimental Studies. *Mol Neurobiol*. 2021;58(6):2770–2779. doi:10.1007/s12035-021-02303-2
74. Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in health and disease. *Physiol Rev*. 2019;99(3):1325–1380. doi:10.1152/physrev.00010.2018
75. Kincheski GC, Valentim IS, Clarke JR, et al. Chronic sleep restriction promotes brain inflammation and synapse loss, and potentiates memory impairment induced by amyloid-beta oligomers in mice. *Brain Behav Immun*. 2017;64:140–151. doi:10.1016/j.bbi.2017.04.007
76. Manchanda S, Singh H, Kaur T, Kaur G. Low-grade neuroinflammation due to chronic sleep deprivation results in anxiety and learning and memory impairments. *Mol Cell Biochem*. 2018;449(1–2):63–72. doi:10.1007/s11010-018-3343-7
77. Zhu Y, Zhan G, Fenik P, et al. Chronic sleep disruption advances the temporal progression of tauopathy in P301S mutant mice. *J Neurosci*. 2018;38(48):10255–10270. doi:10.1523/JNEUROSCI.0275-18.2018
78. Huang ZS, Xie DQ, Xu LJ, et al. Tetramethylpyrazine ameliorates lipopolysaccharide-induced sepsis in rats via protecting blood-brain barrier, impairing inflammation and nitrous oxide systems. *Front Pharmacol*. 2020;11:562084. doi:10.3389/fphar.2020.562084
79. Zhang H, Slutsky AS, Vincent JL. Oxygen free radicals in ARDS, septic shock and organ dysfunction. *Intensive Care Med*. 2000;26(4):474–476. doi:10.1007/s001340051185
80. Rahim I, Sayed RK, Fernandez-Ortiz M, et al. Melatonin alleviates sepsis-induced heart injury through activating the Nrf2 pathway and inhibiting the NLRP3 inflammasome. *Naunyn Schmiedeberg's Arch Pharmacol*. 2021;394(2):261–277. doi:10.1007/s00210-020-01972-5
81. Shah SA, Khan M, Jo MH, Jo MG, Amin FU, Kim MO. Melatonin Stimulates the SIRT1/Nrf2 Signaling Pathway Counteracting Lipopolysaccharide (LPS)-induced oxidative stress to rescue postnatal rat brain. *CNS Neurosci Ther*. 2017;23(1):33–44. doi:10.1111/cns.12588
82. Xu S, Li L, Wu J, et al. Melatonin attenuates sepsis-induced small-intestine injury by upregulating SIRT3-mediated oxidative-stress inhibition, mitochondrial protection, and autophagy induction. *Front Immunol*. 2021;12:625627. doi:10.3389/fimmu.2021.625627
83. Wang X, Xue GX, Liu WC, et al. Melatonin alleviates lipopolysaccharide-compromised integrity of blood-brain barrier through activating AMP-activated protein kinase in old mice. *Aging Cell*. 2017;16(2):414–421. doi:10.1111/ace.12572
84. Zhao L, An R, Yang Y, et al. Melatonin alleviates brain injury in mice subjected to cecal ligation and puncture via attenuating inflammation, apoptosis, and oxidative stress: the role of SIRT1 signaling. *J Pineal Res*. 2015;59(2):230–239. doi:10.1111/jpi.12254
85. Wright KJ, Drake AL, Frey DJ, et al. Influence of sleep deprivation and circadian misalignment on cortisol, inflammatory markers, and cytokine balance. *Brain Behav Immun*. 2015;47:24–34. doi:10.1016/j.bbi.2015.01.004
86. Arjona A, Silver AC, Walker WE, Fikrig E. Immunity's fourth dimension: approaching the circadian-immune connection. *Trends Immunol*. 2012;33(12):607–612. doi:10.1016/j.it.2012.08.007
87. Bergmann BM, Gilliland MA, Feng PF, et al. Are physiological effects of sleep deprivation in the rat mediated by bacterial invasion? *Sleep*. 1996;19(7):554–562. doi:10.1093/sleep/19.7.554
88. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry*. 2016;80(1):40–52. doi:10.1016/j.biopsych.2015.05.014
89. Kroller-Schon S, Daiber A, Steven S, et al. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. *Eur Heart J*. 2018;39(38):3528–3539. doi:10.1093/eurheartj/ehy333
90. Sang D, Lin K, Yang Y, et al. Prolonged sleep deprivation induces a cytokine-storm-like syndrome in mammals. *Cell*. 2023;186(25):5500–5516. doi:10.1016/j.cell.2023.10.025
91. Kao CY, Huang F, Chen Y, et al. Up-regulation of CC chemokine ligand 20 expression in human airway epithelium by IL-17 through a JAK-independent but MEK/NF-kappaB-dependent signaling pathway. *J Immunol*. 2005;175(10):6676–6685. doi:10.4049/jimmunol.175.10.6676
92. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep*. 2007;30(9):1145–1152. doi:10.1093/sleep/30.9.1145
93. Zielinski MR, Kim Y, Karpova SA, McCarley RW, Strecker RE, Gerashchenko D. Chronic sleep restriction elevates brain interleukin-1 beta and tumor necrosis factor-alpha and attenuates brain-derived neurotrophic factor expression. *Neurosci Lett*. 2014;580:27–31. doi:10.1016/j.neulet.2014.07.043
94. Zhang Y, Xie B, Chen X, Zhang J, Yuan S. A key role of gut microbiota-vagus nerve/spleen axis in sleep deprivation-mediated aggravation of systemic inflammation after LPS administration. *Life Sci*. 2021;265:118736. doi:10.1016/j.lfs.2020.118736
95. Zhang Y, Wu Y, Xu D, et al. Very-short-term sleep deprivation slows early recovery of lymphocytes in septic patients. *Front Med Lausanne*. 2021;8:656615. doi:10.3389/fmed.2021.656615
96. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metab*. 1999;84(8):2603–2607. doi:10.1210/jcem.84.8.5894
97. Dimitrov S, Besedovsky L, Born J, Lange T. Differential acute effects of sleep on spontaneous and stimulated production of tumor necrosis factor in men. *Brain Behav Immun*. 2015;47:201–210. doi:10.1016/j.bbi.2014.11.017
98. Burgos I, Richter L, Klein T, et al. Increased nocturnal interleukin-6 excretion in patients with primary insomnia: a pilot study. *Brain Behav Immun*. 2006;20(3):246–253. doi:10.1016/j.bbi.2005.06.007
99. Wang Z, Chen WH, Li SX, et al. Gut microbiota modulates the inflammatory response and cognitive impairment induced by sleep deprivation. *Mol Psychiatry*. 2021;26(11):6277–6292. doi:10.1038/s41380-021-01113-1
100. Born J, Lange T, Hansen K, Molle M, Fehm HL. Effects of sleep and circadian rhythm on human circulating immune cells. *J Immunol*. 1997;158(9):4454–4464. doi:10.4049/jimmunol.158.9.4454



101. Besedovsky L, Dimitrov S, Born J, Lange T. Nocturnal sleep uniformly reduces numbers of different T-cell subsets in the blood of healthy men. *Am J Physiol Regul Integr Comp Physiol*. 2016;311(4):R637–R642. doi:10.1152/ajpregu.00149.2016
102. Lange T, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. *Ann N Y Acad Sci*. 2010;1193(1):48–59. doi:10.1111/j.1749-6632.2009.05300.x
103. Curtis AM, Bellet MM, Sassone-Corsi P, O'Neill LA. Circadian clock proteins and immunity. *Immunity*. 2014;40(2):178–186. doi:10.1016/j.immuni.2014.02.002
104. Curtis AM, Fagundes CT, Yang G, et al. Circadian control of innate immunity in macrophages by miR-155 targeting Bmal1. *Proc Natl Acad Sci U S A*. 2015;112(23):7231–7236. doi:10.1073/pnas.1501327112
105. Deng W, Zhu S, Zeng L, et al. The circadian clock controls immune checkpoint pathway in sepsis. *Cell Rep*. 2018;24(2):366–378. doi:10.1016/j.celrep.2018.06.026
106. Geiger SS, Traba J, Richoz N, et al. Feeding-induced resistance to acute lethal sepsis is dependent on hepatic BMAL1 and FXR signalling. *Nat Commun*. 2021;12(1):2745. doi:10.1038/s41467-021-22961-z
107. Liu J, Malkani G, Shi X, et al. The circadian clock Period 2 gene regulates gamma interferon production of NK cells in host response to lipopolysaccharide-induced endotoxic shock. *Infect Immun*. 2006;74(8):4750–4756. doi:10.1128/IAI.00287-06
108. Wang CY, Hsieh MJ, Hsieh IC, et al. CLOCK modulates survival and acute lung injury in mice with polymicrobial sepsis. *Biochem Biophys Res Commun*. 2016;478(2):935–941. doi:10.1016/j.bbrc.2016.08.054
109. Wang J, Luo Y, Wang K, et al. Clock-controlled StAR's expression and corticosterone production contribute to the endotoxemia immune response. *Chronobiol Int*. 2015;32(3):358–367. doi:10.3109/07420528.2014.982284
110. Parthasarathy S, Tobin MJ. Sleep in the intensive care unit. *Intensive Care Med*. 2004;30(2):197–206. doi:10.1007/s00134-003-2030-6
111. Collop NA, Salas RE, Delayo M, Gamaldo C. Normal sleep and circadian processes. *Crit Care Clin*. 2008;24(3):449–460. doi:10.1016/j.ccc.2008.02.002
112. Cooper KR, Phillips BA. Effect of short-term sleep loss on breathing. *J Appl Physiol Respir Environ Exerc Physiol*. 1982;53(4):855–858. doi:10.1152/jappl.1982.53.4.855
113. Phillips B, Cooper KR, Newsome HH, Dewey WL. Effect of sleep loss on beta-endorphin activity, epinephrine levels, and ventilatory responsiveness. *South Med J*. 1987;80(1):16–20. doi:10.1097/00007611-198701000-00004
114. Series F, Roy N, Marc I. Effects of sleep deprivation and sleep fragmentation on upper airway collapsibility in normal subjects. *Am J Respir Crit Care Med*. 1994;150(2):481–485. doi:10.1164/ajrccm.150.2.8049833
115. White DP, Douglas NJ, Pickett CK, Zvillich CW, Weil JV. Sleep deprivation and the control of ventilation. *Am Rev Respir Dis*. 1983;128(6):984–986. doi:10.1164/arrd.1983.128.6.984
116. Lewis AJ, Zhang X, Griepentrog JE, et al. Blue light enhances bacterial clearance and reduces organ injury during sepsis\*. *Crit Care Med*. 2018;46(8):e779–e787. doi:10.1097/CCM.00000000000003190
117. Alamili M, Bendtzen K, Lykkesfeldt J, Rosenberg J, Gogenur I. Pronounced inflammatory response to endotoxaemia during nighttime: a randomised cross-over trial. *PLoS One*. 2014;9(1):e87413. doi:10.1371/journal.pone.0087413
118. Sieminski M, Szaruta-Raflesz K, Szypienbejl J, Krzyzaniak K. Potential neuroprotective role of melatonin in sepsis-associated encephalopathy due to its scavenging and anti-oxidative properties. *Antioxidants*. 2023;12(9):1786. doi:10.3390/antiox12091786
119. Acuna-Castroviejo D, Escames G, Figueira JC, de la Oliva P, Borobia AM, Acuna-Fernandez C. Clinical trial to test the efficacy of melatonin in COVID-19. *J Pineal Res*. 2020;69(3):e12683. doi:10.1111/jpi.12683
120. Mansilla-Rosello A, Hernandez-Magdalena J, Dominguez-Bastante M, et al. A Phase II, single-center, double-blind, randomized placebo-controlled trial to explore the efficacy and safety of intravenous melatonin in surgical patients with severe sepsis admitted to the intensive care unit. *J Pineal Res*. 2023;74(2):e12845. doi:10.1111/jpi.12845
121. Galley HF, Allen L, Colin PJ, Galt SP, Webster NR. Dose assessment of melatonin in sepsis (DAMSEL2) study: pharmacokinetics of two doses of oral melatonin in patients with sepsis. *J Pineal Res*. 2022;73(4):e12830. doi:10.1111/jpi.12830
122. Liu R, Luo X, Li J, et al. Melatonin: a window into the organ-protective effects of sepsis. *Biomed Pharmacother*. 2022;154:113556. doi:10.1016/j.biopha.2022.113556
123. Alamili M, Bendtzen K, Lykkesfeldt J, Rosenberg J, Gogenur I. Effect of melatonin on human nighttime endotoxaemia: randomized, double-blinded, cross-over study. *Vivo*. 2014;28(6):1057–1063.
124. Alamili M, Bendtzen K, Lykkesfeldt J, Rosenberg J, Gogenur I. Melatonin suppresses markers of inflammation and oxidative damage in a human daytime endotoxemia model. *J Crit Care*. 2014;29(1):184–189. doi:10.1016/j.jcrc.2013.09.006
125. Taher A, Shokoohmand F, Abdoli E, Mohammadi Y, Mehrpooya M. A pilot study on the melatonin treatment in patients with early septic shock: results of a single-center randomized controlled trial. *Ir J Med Sci*. 2022;191(4):1913–1924. doi:10.1007/s11845-021-02758-1
126. Gitto E, Karbownik M, Reiter RJ, et al. Effects of melatonin treatment in septic newborns. *Pediatr Res*. 2001;50(6):756–760. doi:10.1203/00006450-200112000-00021
127. El FM, El-Sharkawy HM, Attia GF. Use of melatonin as an adjuvant therapy in neonatal sepsis. *J Neonatal Perinatal Med*. 2015;8(3):227–232. doi:10.3233/NPM-15814072
128. El-Gendy FM, El-Hawy MA, Hassan MG. Beneficial effect of melatonin in the treatment of neonatal sepsis. *J Matern Fetal Neonatal Med*. 2018;31(17):2299–2303. doi:10.1080/14767058.2017.1342794
129. Aisa-Alvarez A, Perez-Torres I, Guarner-Lans V, et al. Randomized clinical trial of antioxidant therapy patients with septic shock and organ dysfunction in the ICU: SOFA score reduction by improvement of the enzymatic and non-enzymatic antioxidant system. *Cells*. 2023;12(9):1330. doi:10.3390/cells12091330
130. Perez-Torres I, Aisa-Alvarez A, Casarez-Alvarado S, et al. Impact of treatment with antioxidants as an adjuvant to standard therapy in patients with septic shock: analysis of the correlation between cytokine storm and oxidative stress and therapeutic effects. *Int J Mol Sci*. 2023;24(23):16610. doi:10.3390/ijms242316610



## Nature and Science of Sleep

Dovepress

**Publish your work in this journal**

Nature and Science of Sleep is an international, peer-reviewed, open access journal covering all aspects of sleep science and sleep medicine, including the neurophysiology and functions of sleep, the genetics of sleep, sleep and society, biological rhythms, dreaming, sleep disorders and therapy, and strategies to optimize healthy sleep. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/nature-and-science-of-sleep-journal>