# Causes, Consequences, and Treatments of Sleep and Circadian Disruption in the Intensive Care Unit: An Official American Thoracic Society Research Statement

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**Abstract:**

**Background:** Sleep and circadian disruption (SCD) is common and severe in the intensive care unit (ICU). Based on rigorous evidence in non-ICU populations and emerging evidence in ICU populations, SCD is likely to have a profound negative impact on patient outcomes. Thus, it is urgent that we advance understanding of ICU SCD.

**Goal:** To establish ICU SCD research priorities.

**Methods:** We convened a multidisciplinary group with relevant expertise to participate in an American Thoracic Society Workshop. Workshop objectives included identifying ICU SCD sub-topics of interest, key knowledge gaps and research priorities. Members attended remote sessions from March to November 2021. Recorded presentations were prepared and viewed by members prior to Workshop sessions. Workshop discussion focused on key gaps and related research priorities. We used iterative surveys to narrow the list of candidate research priorities; the final set of priorities was established via consensus among Workshop members.

**Results:** We identified the following set of top research priorities: further develop rigorous and feasible ICU SCD measures; establish an ICU SCD definition; test associations between ICU SCD domains and outcomes; promote inclusion of mechanistic and patient centered outcomes within large clinical studies; leverage implementation science strategies to assure intervention fidelity and sustainability; and

collaborate among investigators to harmonize methods and promote multisite investigation.

**Conclusions:** ICU SCD is a complex and compelling potential target for improving ICU outcomes. Given the influence on all other research priorities, further development of rigorous, feasible ICU SCD measurement is a key next step in advancing the field.

## Introduction

Sleep and circadian function are fundamental to health. Thus, intensive care unit (ICU) sleep and circadian disruption (SCD) is an important potential target for improving ICU outcomes. Herein, we report ICU SCD Research Priorities as determined during the American Thoracic Society (ATS) *Workshop on the causes, consequences, and treatments of sleep and circadian disruption in the ICU*. In this Research Statement Executive Summary, we will present each of four identified ICU SCD sub-topics: (1) prevalence, incidence, and risk factors; (2) measurement; (3) outcomes; and (4) treatment. Within each topic we will summarize the state of knowledge and share Workshop discussion content focused on the identification of key gaps and research priorities. Top research priorities are presented in Box 1.

## Methods

Detailed methods are included in the full text version of this document.

## Definitions

Workshop members defined ICU as any environment capable of providing mechanical ventilation and/or invasive hemodynamic monitoring that is not a post-operative recovery unit. The population of interest was defined as any patient admitted to the ICU. Workshop members agreed that there is no established definition of ICU SCD. Given the multiple potential domains, it is likely that ICU SCD will ultimately be defined as a multicomponent syndrome with patients experiencing some or all aspects (Figure 1).

**Sub-Topic 1: Prevalence, incidence, and risk factors**

*Prevalence and Incidence*

The magnitude of ICU SCD has been difficult to quantify due to study heterogeneity, difficulty in measuring sleep, and related limitations in crafting a clinically meaningful ICU SCD definition. Nevertheless, the amount, timing, and quality of sleep in the ICU is highly abnormal (1-7). Studies have also demonstrated that critically ill patients often have misaligned or absent circadian rhythms (8-17). Notably, ICU SCD may differ substantially between individual patients and subgroups and may change over time as patients recover from acute illness. This raises key questions of ICU SCD timing including when to measure and when to intervene upon ICU SCD. These questions were re-discussed several times during ensuing sub-topic discussions.

Additionally, Workshop members discussed whether changes in sleep and circadian rhythms during critical illness are adaptive or harmful. Biologic plausibility suggests that sleep should be extended during infection-related critical illness rather than the shorter sleep duration observed in many studies. It is unlikely that the high degree of sleep fragmentation observed in the ICU due to sound, pain, anxiety, mechanical ventilation, and many unnamed factors is adaptive. Similarly, limited data on circadian alignment and amplitude during acute infection suggest acute infection can alter peripheral clock alignment (18), but it remains unclear if this is harmful or beneficial.

*Baseline Risk Factors*

Baseline risk factors for ICU SCD have been difficult to establish. However, poor sleep and use of sleep medications at home prior to admission are factors that have been consistently implicated in ICU sleep disruption (19). Lack of attention to patient sleep history and sleep preferences has been a gap in treatment of ICU SCD. For example, OSA is common and often goes untreated during hospital admissions (20-22). Discussion during the Workshop highlighted the importance of obtaining a more detailed sleep history. The impact of pre-admission sleep abnormalities on ICU SCD has been understudied, and attention to sleep history may also allow personalization of sleep and circadian promotion interventions.

*ICU and Acute Illness Risk Factors*

Once in the ICU, hypothesized contributors to ICU SCD include environmental factors, illness-related factors, medication exposures, and mechanical ventilation. The ICU environment, especially noise, has been consistently reported to be associated with sleep disruption (23). Numerous studies demonstrate that the ICU environment exceeds recommended sound levels around-the-clock (24-27). Excessive noise contributes to approximately 20% of awakenings in ICU patients (28, 29). Inadequate daytime and excessive nighttime light are also common and may significantly disrupt sleep and circadian rhythms (30-32). Frequent care interruptions also contribute to excessive noise and light exposure and induce pain or anxiety, which have been reported by patients as sleep-disruptive (23, 33, 34). Associations between sleep disruption and severity of illness, admission diagnosis, and/or sedative hypnotic drug therapy have not been supported by most studies (23). Loss of circadian alignment and amplitude has

been variably associated with severity of illness, brain injury, and sepsis in diverse ICU cohorts (8-17).

Workshop members noted that studies to date have generally been small and based at single centers. There has been substantial variability in data collection regarding patient characteristics, exposures, ICU SCD measures, and outcomes. Consequently, the lack of consistent associations between proposed risk factors and ICU SCD may be related to study variability rather than a lack of underlying associations.

**Sub-Topic 2: Measurement of Sleep and Circadian Rhythm in the ICU**

Although advances in portable, wearable devices have improved measures of sleep and circadian function in the ICU, numerous challenges remain. Sleep and circadian measures must have acceptable cost, feasibility, tolerance, and interpretability to allow longitudinal monitoring which will facilitate the development of meaningful ICU SCD definitions, guide timing of interventions, and support rigorous outcome evaluation. Circadian measures carry additional challenges of frequent sampling needs and of being vulnerable to masking, a phenomenon in which environmental factors (i.e., light) directly alter the circadian measure at the time of collection (i.e., serum melatonin). Table 2 lists ICU SCD measures.

*Objective Sleep Measures*

Polysomnography (PSG) monitoring in critically ill patients is challenging and resource intensive. Furthermore, traditional portable PSG devices are poorly tolerated

during prolonged monitoring (2). In ICU patients, electroencephalography (EEG) sleep features may have atypical patterns that make conventional scoring unreliable (3, 5-7). Atypical EEG patterns have been associated with poor outcomes in many (5, 6, 29, 35-40) but not all (41, 42) studies. Alternative rules have been proposed to score sleep in ICU patients and should be used whenever possible (6, 7).

Workshop discussions highlighted the cumbersome nature of PSG-based methodologies which have historically limited study size and duration. The group did touch upon more portable EEG devices (e.g., “dry EEG”) that may be easier to apply, but these emerging technologies are not always able to provide EEG tracings of sufficient quality and do not mitigate scoring challenges.

Automated algorithms which use novel EEG montages have been tried to alleviate the above-described challenges (43-46). The readily available Bispectral Index has been studied as a method to assess the depth of sleep but with poor results in scoring sleep stages (43-45, 47). Other methods using automated EEG algorithms to score sleep depth such as spectral power and the odds ratio product have been studied in a limited number of ICU patients (41, 48, 49). These techniques are promising and may provide a rapid and reproducible analysis of sleep using a small device that is more comfortable for patients and more practical for research or clinical staff.

Workshop members agreed that validation of automated scoring along with development of more comfortable leads is likely a key path forward. These methods need to be validated against PSG and visual scoring in a large cohort of ICU patients. Once accomplished, this would mitigate challenges across the field. Furthermore,

validated measurement methods which include real-time automation could ultimately be leveraged as part of SCD monitoring during routine clinical use.

Actigraphy is an objective non-invasive measure of rest-activity which can be used to infer sleep-wake schedule. In healthy subjects, rest-activity cycle, day-night variation of activity and circadian rhythms can be reliably assessed over days to weeks (50). In ICU patients, sedation, induced paralysis, and/or immobilization will decrease movement and thus reduces the validity of actigraphy (51). However, as we trace the trajectory of ICU SCD, actigraphy might be a key component in studying SCD once patients progress beyond their immediate critical illness (52, 53).

*Subjective Sleep Measures*

Patient perception of sleep quality (i.e., subjective sleep quality) is assessed via questionnaires and is an important domain of sleep (54). Patient perception of sleep quality is correlated with outcomes in non-ICU populations and is pragmatic and cost effective (55). The Richards Campbell Sleep Questionnaire (RCSQ) has been validated against PSG and is the most reliable questionnaire for ICU sleep assessment. Unfortunately, an estimated 50% of patients cannot use the RCSQ due to communication or cognitive barriers (56, 57). Observation by staff would seem like a possible way to overcome some of these challenges, but observers tend to overestimate sleep time and, by definition, do not include the patient perspective (51, 58-61)

The Workshop discussion of patient perception of sleep focused on the tension between the high value of such measures and the limitations of implementing them in

the ICU population. As in the case with actigraphy, questionnaires may be used as soon as possible upon resolution of delirium and/or return of the ability to communicate and then used for longitudinal monitoring during illness recovery.

*Circadian Measures*

Key domains of assessing circadian function include phase (i.e., alignment) and amplitude which are most accurately defined by melatonin levels. In ICU patients who have unpredictable alignment, sampling of melatonin or relevant metabolites must be frequent (i.e., every 1 hour) and around-the-clock, which can be cumbersome and thus limit sample size. Furthermore, melatonin is vulnerable to masking as noted above. To avoid, or at least control for, the impact of zeitgebers such as light, feeding, exercise and sleep, investigators must also track these variables in ICU patients.

Other physiologic signals can help identify circadian phase and have both established norms and known relationships to melatonin onset and offset (62). For example, core body temperature, blood pressure, and heart rate have been used (13, 15, 63); these measures can be problematic in many ICU patients as these can be substantially impacted by sleep-wake, disease processes and/or medications. Actigraphy rest-activity patterns have also been used as a proxy for circadian phase but are limited because rest-activity is a behavioral correlate of circadian phase rather than a direct physiologic measure. As noted above, this disconnect can be exacerbated in the generally immobile ICU population (14, 64).

After considering existing sleep and circadian measures, Workshop discussion turned to the potential of artificial intelligence and machine learning techniques that

could address several of the identified measurement issues. Machine learning techniques could be used to integrate a wide variety of physiologic and environmental monitors at the bedside to identify markers of poor sleep and to identify novel proxies of circadian rhythmicity. Integrated machine learning analyses of the environment in ICU patient rooms is feasible and, as proof of principal, has been used to demonstrate that light, sound, and visitation frequency patterns differ between patients with delirium and those without (65).

**Sub-topic 3: Outcomes of ICU Sleep and Circadian Disruption**

Sleep and circadian rhythms are thought to play an important role in ICU recovery. Emerging data suggests that acute sleep and circadian disruption may be linked to ICU mortality (15, 38). Short-term sleep loss and/or circadian disruption in non-ICU study subjects can negatively influence an array of body functions (66-84) (Figure 2). Though research to date has focused on the associations between ICU SCD, respiratory function, and delirium, impact on cardiovascular, metabolic, and immune functions is also likely. In addition to short term outcomes, sleep disturbances are common post-ICU and may influence rehabilitation capacity and quality of life.

*Respiratory failure and mechanical ventilation*

Sleep deficiency may impair respiratory function in ICU patients. Studies in healthy volunteers have shown that respiratory and peripheral muscle endurance is reduced after sleep deprivation (81-84). Additionally, the subjective experience of dyspnea, especially air hunger, can be intensified by sleep deprivation (84, 85). ICU

studies have shown that sleep disturbances are associated with failure to liberate from non-invasive (5) and invasive mechanical ventilation (86).

Mechanical ventilation is associated with sleep disruption due to increased work of breathing (87), ineffective triggering of the ventilator (i.e., patient-ventilator asynchronies) (4, 88), and ventilatory over-assistance (89) (Figure 3). Studies show sleep improvements associated with provision of ventilator support (87, 88). However, excessive ventilatory support can result in hyperventilation, central apneas, and awakenings or arousals (89-92). Proportional modes of ventilation have been shown to decrease patient-ventilator dyssynchrony and improve sleep quality (4, 93). though this result is not consistent across studies (94).

Key questions remain, such as whether the mode of mechanical ventilation versus the achievement of physiologic principles (e.g., synchrony, respiratory muscle rest, avoidance of hyperventilation) is most important in preventing ventilator-related sleep disruption. Furthermore, though there are associations between sleep disruption and poor respiratory outcomes, it remains to be proven that promoting sleep will positively impact these outcomes. To provide detailed, mechanistic information many of the described studies have included PSG with the aforementioned limitations in scoring, study size, and duration of sleep measurement. It may ultimately prove beneficial to nest small mechanistic studies of sleep promotion via ventilator strategies within larger, randomized studies focused on clinical outcomes.

*Delirium*

ICU SCD is regarded as potentially modifiable risk factor for the development of ICU delirium, and delirium may contribute to sleep disturbance (95, 96). In a systematic review (97), six of the ten identified studies demonstrated a statistically significant reduction in the incidence of ICU delirium associated with sleep promotion interventions (98-103). Similar results were seen in a randomized clinical trial (RCT) in which delirium-free patients receiving sedatives were given either nocturnal intravenous dexmedetomidine or placebo until ICU discharge; nocturnal dexmedetomidine was associated with a greater proportion of patients who remained delirium-free, but patient-reported sleep quality was unchanged (104).

During the Workshop, members highlighted that the mechanisms linking individual domains of ICU SCD and delirium remain unclear. Furthermore, there appears, at this relatively early stage, to be a bidirectional relationship between ICU SCD and delirium. Finally, although sleep interventions seem to be a promising approach for improving delirium and related outcomes, as noted throughout this statement, conclusions are limited by small study sizes, confounding, and varied methodology.

*Post-intensive care syndrome*

Long term outcomes were touched upon during the Workshop but have not been extensively studied. Though sleep disturbances improve over time, more than half of patients (61%) report persistently poor sleep at 6 months follow-up after ICU admission (105). This poor sleep has potential to impact the three domains of post-intensive care

syndrome (PICS): cognition (53), mental health (106, 107), and physical function (108, 109).

**Sub-Topic 4: Treatment of ICU Sleep and Circadian Disruption**

Given the multi-faceted nature of ICU SCD, interventions to promote sleep or circadian function tend to be complex. This leads to implementation and sustainability challenges. Furthermore, issues regarding which ICU SCD domains are most closely linked to ICU outcomes and therefore the best targets for intervention, when interventions should occur, and how to measure hypothesized changes in sleep and circadian processes have limited intervention testing to date. In this section we will discuss gaps and next steps in the development of non-pharmacologic and pharmacologic interventions for ICU SCD.

*Non-pharmacologic interventions*

As noted above, ICU sleep is hampered by multiple patient factors, notably anxiety, pain, and pre-existing sleep disorders (23). These entities are key targets for non-pharmacologic sleep promotion. Relaxation techniques have been associated with improved subjective sleep quality, and, in some studies, an increase in total sleep time (110-112). A systemic review of eleven music therapy studies demonstrated consistent associations between music therapy and reduced anxiety/stress in critically ill patients (113) Data on music's direct impact on sleep is more limited (114, 115). Additionally, incorporation of patient sleep preferences may improve SCD, though robust evidence is lacking. A recent pilot project on a general medical ward helped patients arrange their

room comfortably for sleep (e.g., adjustment of temperature, lights, television, blinds) and offered items from a “comfy cart” (e.g., blankets, tea, snacks); the pilot was associated with subjective sleep improvements (116).

Discussion during the Workshop acknowledged a lack of investigation regarding the impact of incorporating a patient’s sleep history and preferences into ICU SCD interventions. At a minimum, it seems straightforward to continue pre-existing outpatient treatments for sleep disorders whenever feasible. Personalization of sleep promotion interventions is novel and potentially beneficial but adds complexity to already encumbered protocols.

Numerous studies have explored interventions to control the environment and/or cluster care delivery (117), and multicomponent sleep promotion bundles are guideline-recommended for ICU patients (19, 118). Environmental control interventions reduce disturbances including noise, light and care interruptions (34, 119-122); however, not all interventions have been successful (123, 124) and even reduced sound levels continue to exceed recommendations (34, 119). Improvements in sleep outcomes have been difficult to demonstrate. For example, multicomponent protocols that emphasized environmental control demonstrated improvements in delirium but did not show changes in sleep (100, 125). Though not universally tolerated, earplugs and eye masks which block the ICU environment may be a simple, low-cost intervention for ICU SCD (126, 127).

At several points in the Workshop, participants highlighted the importance of using established implementation frameworks (128-130) when designing and testing interventions to promote sleep and circadian rhythms in the ICU. From a research

perspective, such approaches are necessary to support the fidelity of the interventions being evaluated. From a clinical perspective, these frameworks are vital for adapting, scaling, and sustaining such efforts within complex, dynamic ICU settings (131).

*Circadian Cues as Treatment*

ICU SCD interventions also include re-establishment of normal diurnal light variation. Daytime light interventions have demonstrated benefits (132-137) including normalization of circadian phase (138). However, some studies have not shown benefit (139, 140). Non-photic entrainment signals (i.e., zeitgebers) may also be important for managing ICU SCD. For example, the timing of nutrition is an influential circadian time cue (141), and restricting feeding to daytime hours may improve ICU SCD. Recent studies have shown that time-restricted daytime feeding is feasible (142). Further studies investigating time-restricted feeding are ongoing (NCT04437264, NCT04870554). Similarly, critical illness-related immobility interrupts normal entrainment and may be an important target for ICU SCD interventions; however, a single study did not show an association between patient engagement in physical therapy and a change in subjective sleep quality (143). Further investigation of early mobility and related effects on sleep and circadian outcomes may provide evidence for novel, mobility-related methods to promote sleep in the ICU.

Relevant Workshop discussion focused on the logistical challenges of translating fundamental circadian knowledge to bedside care. To successfully test circadian interventions, the many abnormal circadian signals present in the ICU environment must be carefully measured and countered (e.g., light, feeding, sleep and immobility).

Additionally, intervention timing is critically important since incorrectly timed circadian time cues will fail to induce desired changes in alignment. Further research is needed to define optimal circadian intervention protocols in the ICU, including appropriate timing, duration, and intensity of zeitgeber exposures.

*Pharmacologic treatment*

To date, there are no ICU guideline recommendations supporting the use of a pharmacologic treatment to improve ICU SCD (19). Nevertheless, medications are frequently prescribed for sleep in the ICU (144). More recent studies involving sleep promotion through pharmacotherapy have primarily involved melatonin agonists, alpha-2-agonists, and orexin antagonists with mixed results (104, 145-148).

Workshop members noted the high demand for sleep medications from caregivers, surrogates, and patients along with the common misperception that sedation is equivalent to sleep. Given the barriers associated with implementing non-pharmacologic SCD interventions in many ICUs, many bedside clinicians express a strong desire for a safe and effective sleep aid, particularly in patients with concomitant delirium. However, the study of pharmacologic options to promote nighttime sleepiness is limited by small trial sizes, the failure to enroll mechanically ventilated adults with a high severity of illness, the lack of standard approach to non-pharmacologic sleep improvement, and an over-reliance on delirium reduction to define efficacy. In addition, RCTs to date have involved prescribing of pharmacologic agents upon ICU admission or timed in relation to specific clinical events (e.g., surgical procedure) (149-151). However, in practice, clinicians are frequently seeking options to promote sleep after

patients report sleep disruption or have already presented with delirium. This discrepancy raises important questions regarding the timing and patient selection for pharmaceutical interventions. Interestingly, pharmacologic therapies to promote daytime wakefulness in the ICU have not been rigorously studied, and this may be a novel and impactful approach to sleep promotion in the ICU.

**Synthesis and Conclusions from Workshop Discussions**

ICU SCD is a complex and compelling potential target for improving ICU outcomes. Herein, we have reported the findings, discussions, and conclusions of an ATS Workshop on ICU SCD. We note that challenges in defining and measuring ICU SCD have led to a set of related limitations hampering the field's progress. Specifically, study size, brevity in monitoring periods, and heterogeneity in study exposures and outcomes have limited evidence to date. However, emerging technologies that have improved longitudinal wearability and the potential for automation of sleep measures hold promise as a means of moving the field forward. Investigators are eager to increase collaborative infrastructure, foster multi-site study design, test individual domains of ICU SCD for associations with ICU outcomes, and clarify the natural history of ICU SCD. Opportunities such as this ATS Workshop have and will continue to support a rich exchange of information and foster collaboration among expert investigators.

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## Figure Legends

**Figure 1:** Conceptual model of intensive care unit sleep and circadian disruption (ICU SCD). Factors that disrupt sleep are presented in blue with arrows indicating interactions among disruptive factors. Proposed domains of ICU SCD are presented in yellow; we hypothesize that patients may experience changes in some or all domains. Proven and hypothesized patient-centered outcomes are presented in green; delirium and respiratory failure have the best-established association with ICU SCD to-date. Abbreviations: ICU, intensive care unit; Mech Ventilation, mechanical ventilation; PICS, post intensive care syndrome.

**Figure 2:** Connections between primary and secondary zeitgebers, central and peripheral clocks, and body functions. Light is the primary zeitgeber with direct input to the central clock located in the suprachiasmatic nucleus and indirect input into peripheral clocks via neurohormonal pathways. Sleep-wake timing, feeding schedule, exercise and social interaction are secondary non-photic zeitgebers which have input into central and peripheral clocks as well as influence light exposure (e.g., low light exposure while sleeping). Internal and external misalignment contribute to an array of organ dysfunction. Abbreviation: ANS, autonomic nervous system.

**Figure 3:** Proposed mechanisms for the bidirectional relationship between respiratory dysfunction and sleep and circadian disruption in the intensive care unit (ICU SCD). Abnormal patient-ventilator interactions illustrated in the top of the figure (blue)

contribute to ICU SCD. In turn, ICU SCD contributes to respiratory ability and outcomes illustrated in the bottom of the figure (green).

| Table 2: Advantages and Disadvantages of Selected ICU Sleep and Circadian Measures | | | |
|---|---|---|---|
| **Measure** | **Advantages** | **Disadvantages** | **Sample Studies** Author Year (Ref #) |
| **Objective Sleep Measures** | | | |
| Polysomnography | – Gold standard for sleep/wake and sleep architecture including stages, timing, and continuity | – Resource intensive<br>– Poor patient tolerance<br>– Standard scoring limited | Cooper 2000 (3)<br>Bosma 2007 (4)<br>Roche Campo 2010 (5)<br>Drouot 2012 (6)<br>Watson 2013 (7)<br>Elliot 2013 (1)<br>Knauert 2014 (2) |
| Multi-channel EEG: Bispectral Index SedLine® | – Automated<br>– Feasible and tolerable<br>– Familiar to ICU providers<br>– Longitudinal monitoring possible | – Limited accuracy identifying sleep<br>– Poor accuracy identifying sleep stages | Gimenez 2017 (43)<br>Vacas 2016 (46)<br>Nieuwenhuijs 2020 (44)<br>Pedrao 2020 (45) |
| Automated EEG: Odds Ratio Product | – Automated<br>– Feasible and tolerable<br>– Longitudinal monitoring possible<br>– Measures alertness | – Limited accuracy identifying sleep<br>– Poor accuracy identifying sleep stages | Dres 2019 (41) |
| Actigraphy | – Feasible and tolerable<br>– Longitudinal monitoring possible | – Limited accuracy identifying sleep<br>– No identification sleep stages<br>– Limited in immobile ICU patients | Kamdar 2017 (64)<br>Wilcox 2021 (53) |
| **Patient Perceived Sleep Measures** | | | |
| Richards Campbell Sleep Questionnaire | – Validated in ICU patients<br>– Feasible and tolerable<br>– Longitudinal monitoring possible<br>– Patient-centered<br>– Includes 5 sleep domains | – Restricted to patients with cognitive and communication ability | Richards 2000 (54)<br>Kamdar 2012 (58)<br>Aitken 2017 (152)<br>Menear 2017 (153) |
| Pittsburgh Sleep Quality Index | – Validated in non-ICU patients<br>– Feasible and tolerable<br>– Longitudinal monitoring possible<br>– 7 sleep domains<br>– Allows assessment of pre / post acute illness sleep | – Restricted to patients with cognitive and communication ability<br>– High patient burden due to length<br>– Not for inpatient use | Buysse 1989 (154)<br>McKinley 2013 (155)<br>Wang 2019 (156) |
| Insomnia Severity Index | – Validated for patients and proxy<br>– Detailed insight into insomnia<br>– Feasible and tolerable<br>– Longitudinal monitoring possible<br>– Allows assessment of pre / post illness insomnia | – Restricted to patients with cognitive and communication ability<br>– Not for inpatient use | Bastien 2001 (157)<br>McKinley 2013 (155)<br>Elliot 2013 (1) |
| **Circadian Measures** | | | |
| Melatonin<br>– serum<br><br>6-sulfatoxymelatonin<br>– urine | – Gold standard | – Frequent sampling<br>– Masking by ICU environment<br>– Anemia/risk anemia for serum samples<br>– Oliguria/anuria limit urine samples; indwelling catheter needed for urine samples | Mundigler 2002 (9)<br>Frisk 2004 (158)<br>Gehlbach 2012 (12)<br>Verceles 2012 (11)<br>Li 2013 (159)<br>Maas 2020 (17) |
| Heart rate | – Feasible and tolerable<br>– Longitudinal monitoring possible | – Need for specialized data management<br>– Critical illness confounds measure | Knauert 2020 (15) |

| | | | |
|---|---|---|---|
| Core temperature | – Longitudinal monitoring possible | – Invasive<br>– Fever / antipyretics confound | Gazendam 2013 (13) |
| Actigraphy | – Feasible and tolerable<br>– Longitudinal monitoring possible | – Indirect behavioral reflection of circadian measures<br>– Limited in immobile ICU patients | Duclos 2014 (14)<br>Knauert 2021 (160) |
| Abbreviations: EEG, electroencephalography; ICU, intensive care unit; Ref; reference; #, number. | | | |

# Causes, Consequences, and Treatments of Sleep and Circadian Disruption in the Intensive Care Unit: An Official American Thoracic Society Research Statement

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**Abstract:**

**Background:** Sleep and circadian disruption (SCD) is common and severe in the intensive care unit (ICU). Based on rigorous evidence in non-ICU populations and emerging evidence in ICU populations, SCD is likely to have a profound negative impact on patient outcomes. Thus, it is urgent that we advance understanding of ICU SCD.

**Goal:** To establish ICU SCD research priorities.

**Methods:** We convened a multidisciplinary group with relevant expertise to participate in an American Thoracic Society Workshop. Workshop objectives included identifying ICU SCD sub-topics of interest, key knowledge gaps and research priorities. Members attended remote sessions from March to November 2021. Recorded presentations were prepared and viewed by members prior to Workshop sessions. Workshop discussion focused on key gaps and related research priorities. We used iterative surveys to narrow the list of candidate research priorities; the final set of priorities was established via consensus among Workshop members.

**Results:** We identified the following set of top research priorities: further develop rigorous and feasible ICU SCD measures; establish an ICU SCD definition; test associations between ICU SCD domains and outcomes; promote inclusion of mechanistic and patient centered outcomes within large clinical studies; leverage implementation science strategies to assure intervention fidelity and sustainability; and

collaborate among investigators to harmonize methods and promote multisite investigation.

**Conclusions:** ICU SCD is a complex and compelling potential target for improving ICU outcomes. Given the influence on all other research priorities, further development of rigorous, feasible ICU SCD measurement is a key next step in advancing the field.

## Overview

Sleep and circadian function are fundamental to human health. Thus, intensive care unit (ICU) sleep and circadian disruption (SCD) is an important potential target for improving critical illness outcomes. Herein, we report ICU SCD Research Priorities as determined during a Workshop of the American Thoracic Society. During Workshop discussions, there were notable themes regarding research knowledge gaps, challenges, and key next steps. Importantly, technical limitations and feasibility issues have profoundly limited ICU SCD studies in terms of size, duration, and quality. Furthermore, variability in ICU SCD definitions, uncertainty regarding the domain(s) of ICU SCD that are most closely related to patient outcomes, a lack of clarity regarding the natural history of ICU SCD during critical illness and recovery, and inconsistent approaches to ICU SCD risk factor identification remain substantial challenges in the field. While multicomponent ICU SCD interventions have succeeded in decreasing environmental disturbance and delirium, these heterogenous studies have largely failed to demonstrate improvements in sleep or circadian function. It remains unclear if this discrepancy is due to a failure of the interventions per se, a failure to adequately implement these (usually) complex interventions, an inability to accurately measure the intended ICU SCD domains, inappropriate patient selection, or incorrect timing of intervention or measures. *To improve the quality of evidence and to characterize the relative benefit of sleep and circadian interventions, the following six research priorities were identified:*

- Advance the development of ICU SCD measures that are rigorous, feasible, and able to support longitudinal monitoring of SCD in the ICU.
- Characterize the natural history of ICU SCD to determine the optimal timing of ICU SCD interventions across the entire trajectory of acute critical illness through recovery.
- Define associations between individual ICU SCD domains and patient outcomes.
- Maximize research efforts by embedding mechanistic outcomes within larger clinical studies focused on clinically important patient-centered outcomes.
- Leverage implementation science strategies to assure intervention fidelity and sustainability of multicomponent sleep and circadian interventions.
- Increase collaboration among inter-professional and clinical-translational investigators to harmonize research methods and promote multisite investigation.

**Introduction**

This paper reports the proceedings of an American Thoracic Society (ATS) *Workshop on the causes, consequences, and treatments of sleep and circadian disruption in the ICU* designed to achieve the following objectives: (1) Delineate a list of priority ICU SCD sub-topics; (2) Identify, discuss, and critically evaluate current knowledge and knowledge gaps within these sub-topics; and (3) Establish a prioritized research agenda. In this research statement, we will briefly review the importance of sleep and circadian function to human health. We will next discuss our methods and provide definitions of key terms. Thereafter we will discuss each of four identified ICU SCD sub-topics: (1) risk factors, prevalence, and incidence; (2) ICU sleep and circadian

measurement; (3) ICU and post-ICU outcomes; and (4) non-pharmacologic and pharmacologic treatment. Within each topic we will summarize the state of knowledge and share Workshop discussion content focused on the identification of key gaps and next steps (Table 1).

*Sleep, Circadian Rhythms, and Health*

Sleep is an important determinant of physical and mental health, and sleep deficiency is common in modern society (1, 2). Even short-term sleep loss negatively influences cognition (3), alertness (4, 5), mood (6, 7), glucose control (8-10), cardiovascular health (11-15), immune system function (16, 17), and respiratory physiology (18-21). Sleep deficiency includes multiple domains of sleep and circadian functions: sleep duration, timing, architecture, continuity, and regularity, internal and external circadian alignment, circadian amplitude, self-perception of sleep, quality of wakefulness, and daytime function (Figure 1).

Circadian rhythms, generated by central and peripheral biologic clocks, are integral to directing the proper timing of sleep and a broad array of physiologic processes (e.g., promotion of consolidated sleep during the night and effective metabolic processing during the day). Under normal circumstances, cues such as light-dark, feeding, exercise, sleep, and social interaction promote alignment between solar day-night, the central clock, and the multitude of peripheral clocks located in every tissue of the human body. Misalignment leading to organ dysfunction can occur between the external environment and the central clock (i.e., external misalignment)

and/or among clocks in the body (i.e., internal misalignment) (Figure 2) (22).

## Methods

### *Committee Composition*

We convened an international multidisciplinary group with expertise in ICU SCD, critical illness, and related outcomes as well as a patient who had experienced ICU admission. Workshop members then conducted two full group and several sub-group planning sessions to identify priority topics for discussion. Potential conflicts of interest were disclosed and managed in accordance with the policies and procedures of the ATS.

### *Literature Search and Evidence Appraisal*

Targeted literature reviews were conducted, discussed, and summarized within each sub-group. Articles were restricted to adult patients admitted to the ICU, though in some cases evidence from experiments in healthy controls were included. Selected speakers then presented a summary of the literature by sub-topic as a pre-recorded lecture that was watched by all Workshop members in advance of each Workshop session.

### *Workshop Discussions and Research Recommendations*

The in-person Workshop was converted to a series of shorter remote video conference sessions (rather than a single full day) due to the COVID-19 pandemic.

Each Workshop session focused on one of the sub-topics identified during planning. Discussion was focused on the key research gaps and high priority next steps. These gaps and next steps were first proposed by the relevant sub-topic presenter and then refined during the session by Workshop participants. We used iterative surveys to narrow the list of candidate research priorities; the final set of top research priorities was established via consensus among Workshop members.

*Document Development*

The research statement was drafted in parts by each sub-topic working group and then assembled and revised for cohesion by the Workshop chairs. Elements of the statement not directly related to sub-topics were written by the chairs. Completed statement drafts were circulated to each member and discussed via video conference in two rounds before final submission.

**Definitions**

Several definitions were agreed upon by the group for the purpose of this Research Statement. ICU was defined as any environment capable of providing mechanical ventilation and/or invasive hemodynamic monitoring that is not a post-operative recovery unit. Much of the Workshop discussion was focused on the medical ICU; however, evidence was drawn from other adult ICU types as available. The target population of interest was defined as any patient admitted to the ICU. In establishing this definition, it was acknowledged that ICU patients are tremendously heterogenous and may be cared for in diverse locations. Relatedly, and perhaps applicable to the

design of particular studies, some Workshop participants expressed an interest in limiting studies to patients admitted to the ICU with at least one qualifying organ failure or implementing other measures to homogenize study populations.

Notably, the group agreed that there are no established definitions of ICU sleep deficiency or circadian disruption. This lack of definition poses a major challenge for the ICU SCD field. Given the multiple potential domains of sleep and circadian disruption, it is likely that ICU SCD will ultimately be defined as a multicomponent syndrome with patients experiencing some or all aspects of ICU SCD. There was consensus among the Workshop members that the ICU SCD definition(s) should be focused on elements of SCD that are most closely associated with ICU outcomes.

**Sub-Topic 1: Prevalence, incidence, and risk factors**

*Prevalence and Incidence*

The magnitude of ICU SCD has been difficult to quantify due to study heterogeneity, difficulty in measuring sleep (See Sub-topic 2), and related limitations in crafting a clinically meaningful ICU SCD definition. Nevertheless, the amount, timing, architecture, and quality of sleep in the ICU is highly abnormal (23-29). For example, observational polysomnography (PSG) studies show shortened sleep duration over 24 hours and a high proportion of daytime sleep (23, 24). Sleep is also highly fragmented with frequent arousals and a short duration of sleep episodes (e.g., lasting only 3 minutes). Finally, there is a paucity of Stage REM and NREM 3 sleep (23, 24).

Circadian rhythms are similarly disrupted in critical illness. Studies have demonstrated that critically ill patients often have misaligned (usually delayed type) or absent circadian rhythms as defined by melatonin (or its urinary metabolite 6-sulfatoxymelatonin) levels and other circadian phase markers. This finding has been described in multiple critical illness cohorts including patients with sepsis, intracerebral hemorrhage, and those requiring mechanical ventilation (30-41).

Notably, ICU SCD may differ substantially between individual patients and subgroups and may change over time as patients recover from acute illness. This raises key questions of ICU SCD definition and timing including when to measure and when to intervene upon ICU SCD. These questions were re-discussed several times during ensuing sub-topic discussions.

Additionally, the group discussed whether changes in sleep and circadian rhythms during critical illness are adaptive or harmful. For example, infection-related illness and other pro-inflammatory states are known to increase sleepiness and extend sleep timing in non-ICU patients (42). Thus, biologic plausibility suggests that sleep duration should be extended during infection-related critical illness rather than shortened as observed in many ICU studies. Similarly, it does not seem likely that the high degree of sleep fragmentation observed in the ICU due to sound, pain, anxiety, mechanical ventilation, and many unnamed factors is adaptive. In terms of circadian disruption, limited data on circadian alignment and amplitude during acute infection suggest acute infection can alter peripheral clock alignment (43), but it remains unclear if this is harmful or beneficial. Given the high relevance of infection and immune function in the ICU this may be an area of particular interest for future research. In addition to

parsing which domains of ICU SCD may be adaptive during critical illness, there is considerable inter-individual vulnerability to sleep loss which may influence the associations between ICU SCD and critical illness outcomes (44, 45).

*Baseline Risk Factors*

Baseline risk factors for ICU SCD have been difficult to establish. However, reporting poor sleep or using sleep medications at home prior to admission are factors that have been consistently implicated in ICU sleep disruption (46). Concerningly, short sleep duration and poor sleep quality are an increasing, serious global health threat (1, 2, 47-51). The use of sleep aids is also common in the adult population, and use increases with age and in patients with sleep disorders (52). Sleep disruption is more common in some populations based on race/ethnicity, occupation, and social factors such as reduced socioeconomic status (53), substance abuse (54, 55), smoking (1), and psychiatric (47, 56) or medical disorders (including sleep disorders) (57-59). Relatedly, lack of attention to patient sleep history and sleep preferences has been a ICU SCD care gap. For example, OSA is common and often goes untreated during hospital admissions (60-62). Similarly, pre-existing sleep problems such as insomnia and restless legs syndrome (RLS) can be exacerbated or unmasked by factors associated with critical illness including blood loss, anxiety, immobility, sleep deprivation, provoking drugs, or cessation of therapeutic medications (63). Furthermore, pre-existing disrupted sleep and undiagnosed OSA represent significant health disparities in racial and ethnic minorities (64). Such sleep disturbances may play a

fundamental role in health disparities (65) and represent a research gap outside the scope of this document (66).

Discussion during the Workshop highlighted the importance of obtaining a more detailed sleep history to identify patients at highest risk for ICU SCD. The impact of pre-admission sleep abnormalities on ICU outcomes and management has not been well-studied. At the very least, knowledge of these conditions may help guide care (e.g., presence of severe pre-existing OSA, insomnia or RLS). Finally, attention to sleep history may also allow targeted sleep and circadian promotion interventions (e.g., providing a sleep opportunity during a patient's preferred sleep time).

*ICU and Acute Illness Risk Factors*

Once in the ICU, hypothesized contributors to ICU SCD include environmental factors, illness-related factors, medication exposures, and mechanical ventilation. The ICU environment, especially noise, has been consistently reported to be associated with sleep disruption (67). Numerous studies demonstrate that the ICU environment exceeds recommended sound levels around-th- clock (68-71). PSG studies show that excessive noise contributes to approximately 20% of awakenings in ICU patients (72, 73). Though evidence is more limited, inadequate daytime and excessive nighttime light are also common in the ICU and may significantly disrupt sleep and circadian rhythms (74-76). Frequent care interruptions also contribute to excessive noise and light exposure and induce pain or anxiety, which have been reported by patients as sleep-disruptive (67, 77, 78). Associations between sleep disruption and severity of illness, length of stay, admission diagnosis, and/or sedative hypnotic drug therapy have not been supported by

most studies (67). Loss of circadian alignment and amplitude has been variably associated with severity of illness, brain injury, and sepsis in diverse ICU cohorts (30-39). Additional hypothesized sources of circadian disruption include abnormal circadian cues such as altered light exposure, disrupted sleep-wake schedule, immobility, and continuous feeding (79-81).

Workshop members noted that studies to date have generally been small and based at single centers. Furthermore, there has been substantial variability in data collection regarding patient characteristics, exposures, ICU SCD measures, and outcomes. Consequently, the lack of consistent associations between proposed risk factors and ICU SCD may be related to study variability rather than a lack of underlying associations.

**Sub-Topic 2: Measurement of Sleep and Circadian Rhythm in the ICU**

Although advances in portable, wearable devices have improved measures of sleep and circadian function in the ICU, numerous challenges remain. Sleep and circadian measures must have acceptable cost, feasibility, tolerance, and interpretability to allow longitudinal around-the-clock monitoring which will facilitate meaningful ICU SCD definitions, guide timing of interventions, and support rigorous outcome evaluation. Circadian measures carry additional challenges of frequent sampling needs (e.g., hourly) and of being vulnerable to masking, a phenomenon in which environmental factors (i.e., light) directly alter the circadian measure at the time of collection (i.e., serum melatonin). Table 2 lists proposed ICU SCD measures.

*Objective Sleep Measures*

Polysomnography (PSG) is considered the gold standard method to objectively measure sleep. PSG studies in the ICU require electroencephalography (EEG), electrooculography (EOG), and chin electromyography (EMG) to measure sleep-wake, sleep stages, and arousals from sleep; such monitoring in critically ill patients is challenging and resource intensive. Furthermore, the necessary monitors can be uncomfortable for patients and thus poorly tolerated during prolonged monitoring (24). PSG is useful to determine the cause of arousals (26), for pharmacological or pathophysiological studies (27, 82-86), or to test therapeutic sleep interventions (87). In non-ICU patients, sleep scoring is based on rules originally established by Rechtschaffen and Kales (88) and later adapted by American Academy of Sleep Medicine (89). In ICU patients, EEG sleep features may differ with those of non-ICU patients, and atypical patterns have been described. The key EEG features of atypical sleep include loss of sleep spindles and K-complexes, and 'pathological wakefulness' in which EEG features of sleep are present during behavioral wakefulness (25, 27-29). These atypical features make conventional scoring rules unreliable. Atypical EEG patterns have been associated with poor outcomes in many studies (27, 28, 73, 90-95) but not in all studies (86, 96). Alternative rules have been proposed to score sleep in ICU patients and should be used whenever possible (28, 29).

Workshop discussions highlighted the cumbersome nature of PSG-based methodologies. A need for experienced staff to apply and maintain monitoring leads, a need for epoch-by-epoch scoring by experts in ICU sleep, and poor patient tolerance have historically limited study size and duration. These limitations have challenged

efforts to monitor longitudinally on a large scale and have made comparison of data among studies difficult as there is no accepted standard for scoring. The group did touch upon more portable EEG devices (e.g., “dry EEG”) that may be easier to apply, but these emerging technologies are not always able to provide EEG of sufficient quality and do not mitigate scoring challenges.

Automated algorithms which use novel EEG montages have been tried to alleviate the above-described challenges. The readily available Bispectral Index has been studied as a method to assess the depth of sleep (97-99) but with poor results in scoring sleep stages (100); similarly, SedLine® has been evaluated in a single limited study (101). Other methods using automated EEG algorithms to score sleep depth such as spectral power and the odds ratio product have been proposed and studied in a small number of ICU patients (86, 102, 103) These techniques are promising and may provide a rapid and reproducible analysis of sleep quality using a small device that is more comfortable for patients and more practical for research or clinical staff.

Workshop members agreed that validation of automated scoring along with development of more comfortable, miniaturized leads is likely a key path forward. These methods need to be validated against full PSG and visual scoring in a large cohort of ICU patients. Once accomplished, this would mitigate challenges across the field such as ICU SCD definition and timing, intervention testing, and assessment of outcomes. Furthermore, automated real-time sleep measurements would be feasible to use at the bedside to guide clinical care. Aspirationally, sleep could be considered a key clinical parameter, like delirium, and would thus be frequently monitored as part of routine care.

Actigraphy is an objective non-invasive measure of rest-activity which can be used to infer sleep-wake schedule. In healthy subjects, rest-activity cycle, day-night variation of activity and circadian rhythms can be reliably assessed for a prolonged duration (several consecutive days or weeks) (104). In ICU patients, sedation, induced paralysis, and/or immobilization will decrease movement and thus reduces the validity of actigraphy for sleep detection (105). However, as we trace the trajectory of ICU SCD, actigraphy might be a key component in studying sleep once patients progress beyond their immediate critical illness (106, 107).

*Subjective Sleep Measures*

Patient perception of sleep quality (i.e., subjective sleep quality) is assessed via questionnaires and is an important domain of sleep (108). Patient perception of sleep quality is correlated with outcomes in non-ICU populations and is pragmatic and cost effective (109-111). The Richards Campbell Sleep Questionnaire (RCSQ) has been validated against PSG and is the most reliable questionnaire for sleep assessment in ICU patients. The RCSQ uses visual analogue scales (VAS) to evaluate 5 sleep domains of patient perceived sleep quality from the preceding night. As with other domains of ICU SCD, it is not clear how each of these domains relates to ICU outcomes. Unfortunately, an estimated 50% of patients cannot use the RCSQ due to communication or cognitive barriers (i.e., sedation or delirium) (112, 113). Other patient questionnaires include the Numerical Rating Scale – Sleep (112), the Sleep in the ICU Questionnaire (114), the Coronary Care Unit Questionnaire (115), and the Verran Snyder-Halpern Sleep Scale (116, 117). Observation by research staff or bedside

caregivers would seem like a possible way to overcome some of these challenges, but observers tend to overestimate sleep time and, by definition, do not include the patient perspective (105, 117-120). During ICU recovery, sleep can be longitudinally assessed via established outpatient instruments such as the Pittsburgh Sleep Quality Index or the Insomnia Severity Score (23, 121-124).

The Workshop discussion of patient perception of sleep as measured by questionnaires focused on the tension between the high value of such measures and the logistical limitations of implementing them in the ICU population. Nevertheless, it was agreed that it is important to obtain patients' sleep perception whenever possible. Finally, as in the case with actigraphy, questionnaires may be used as soon as possible upon resolution of delirium and/or return of the ability to communicate and then used for longitudinal monitoring during illness recovery.

*Circadian Measures*

Key domains of assessing circadian function include phase (i.e., alignment) and amplitude. Melatonin levels, which rise sharply before habitual bedtime and fall sharply after habitual wake, are considered gold standard measures for circadian phase and amplitude. In the critically ill population, which may have unpredictable alignment, sampling of blood (melatonin) or urine (6-sulfatoxymelatonin) must be frequent (i.e., hourly) and around-the-clock, which can be cumbersome and thus limit sample size. Variations in sampling frequency have limited the interpretation of results in some cases. Furthermore, melatonin is vulnerable to masking as noted above. To avoid, or at

least control for, the impact of zeitgebers such as light, feeding, exercise and sleep, investigators must also track these variables in ICU patients.

Other physiologic signals can help identify circadian phase and have both established norms and known relationships to melatonin onset and offset (125). For example, core body temperature, blood pressure, and heart rate have been used (35, 37, 126); these measures can be problematic in many critically ill patients as these can be substantially impacted by sleep-wake, disease processes and/or medications. Actigraphy rest-activity patterns have also been used as a proxy for circadian phase (127) but are limited because rest-activity is a behavioral correlate of circadian phase rather than a direct physiologic measure. As noted above, this disconnect can be exacerbated in the generally immobile ICU population (36, 128). Novel biomarkers of circadian phase that use RNA expression analysis to estimate melatonin onset have been developed in non-critically ill human populations (129, 130). However, preliminary studies suggest that these measures cannot predict melatonin onset in critically ill patients (38).

After considering existing sleep and circadian measures, Workshop discussion turned to the potential of artificial intelligence and machine learning techniques that could address several of the identified measurement issues. Machine learning techniques could be used to integrate a wide variety of physiologic and environmental monitors at the bedside to identify markers of poor sleep and to identify novel proxies of circadian rhythmicity. Integrated machine learning analyses of the environment in ICU patient rooms is feasible and, as proof of principal, has been used to demonstrate that

light, sound, and visitation frequency patterns differ between patients with delirium and those without (131).

**Sub-topic 3: Outcomes of ICU Sleep and Circadian Disruption**

Sleep and circadian rhythms are thought to play an important role in recovery from injury and illness. Sleep quality and quantity are linked to mortality in the general population (132-134), and emerging data suggests that acute sleep and circadian disruption may be linked to ICU mortality (37, 93). As noted above, even short-term sleep loss and/or circadian disruption in non-ICU study subjects can negatively influence an array of body functions including cognition (3), alertness (4, 5), mood (6, 7), glucose control (8-10), cardiovascular function (11-15), immune response (16, 17), and respiratory physiology (18-21). Though associations between ICU SCD and functional outcomes are challenging to prove in the complex ICU environment, the promise of broad ranging benefits related to promotion of normal sleep and circadian function has motivated the field forward. Research to date has focused on the associations between ICU SCD, respiratory function, and delirium; however, impact on cardiovascular, metabolic, and immune functions is also likely. In addition to short term outcomes, sleep disturbances such as insomnia are common post-ICU and may influence rehabilitation capacity and quality of life beyond the acute phase of critical illness. Opportunities may therefore exist to improve outcomes by improving sleep and circadian function throughout the trajectory of critical illness.

*Respiratory failure and mechanical ventilation*

Sleep deficiency may impair respiratory function in ICU patients. Several studies in healthy volunteers have shown that respiratory and peripheral muscle endurance is reduced after sleep deprivation, and changes in the chemoreflex control system can occur (18-21). Additionally, the subjective experience of dyspnea, especially air hunger, can be intensified by sleep deprivation (21, 135). ICU studies have shown that sleep disturbances are associated with failure to liberate from non-invasive (27) and invasive mechanical ventilation (83). Interestingly, a recent study has highlighted the relevance of having normal wakefulness patterns (intimately related to sleep quality and quantity) at the time of liberation from mechanical ventilation (86).

Relatedly, mechanical ventilation is associated with sleep disruption. Contributing factors to sleep disruption relevant to mechanical ventilation include increased work of breathing (136), ineffective triggering of the ventilator (i.e., patient-ventilator asynchronies) (26, 85), and ventilatory over-assistance (137) (Figure 3). Several studies describe sleep improvements due to optimization of ventilator settings. In patients with acute hypercapnic respiratory failure, sleep quality was improved when patients were supported by non-invasive ventilatory support at night (85). Respiratory muscle rest using pressure control ventilation titrated to achieve passive ventilation was found to improve sleep quality, efficiency, and REM sleep compared to low pressure support (136). However, ventilatory support in excess of a patient´s metabolic need can result in hyperventilation, decreased carbon dioxide levels, and central apneas (138); central apneas can in turn result in frequent awakenings and arousals leading to sleep fragmentation (137, 139, 140). Proportional modes of ventilation (i.e., proportional assist-ventilation [PAV] and neurally-adjusted ventilatory assist [NAVA]) can be used to

deliver pressure proportional to the patient´s instantaneous efforts in terms of amplitude and timing which avoids over- and under-assistance and improves synchrony (141-143). PAV has been shown to decrease patient-ventilator dyssynchrony and improve sleep quality due to the combined effects of fewer arousal per hour, fewer awakenings per hour, and greater proportion of REM sleep (26) though this result is not consistent across studies (144). NAVA has been shown to be superior to pressure support ventilation, resulting in increased REM and lesser sleep fragmentation, possibly due to a lack of ineffective efforts or central apneas events (145).

The above studies, like others in the ICU SCD field, are small and report inconsistent findings. Key questions remain, such as whether the mode of mechanical ventilation versus the achievement of physiologic principles (e.g., synchrony, respiratory muscle rest, avoidance of hyperventilation, comfort/relief of dyspnea) is most important in preventing ventilator-related sleep disruption. Furthermore, though there are associations between sleep disruption and poor respiratory outcomes, it remains to be proven that promoting sleep will positively impact these outcomes. Barriers related to ICU SCD measurement have also impacted outcomes studies. To provide detailed, mechanistic information many of the described studies have included PSG with the aforementioned limitations. It may ultimately prove beneficial to nest small mechanistic studies of sleep promotion via ventilator strategies within larger, randomized studies focused on clinical outcomes. Additional design concerns for future studies include selecting the phase of critical illness for sleep promotion, analytic plans that accommodate the likely bidirectional nature of the sleep and respiratory function, and

integration of alternative ventilator modes with recommended parameters such as low tidal volume ventilation (146).

*Delirium*

Delirium is characterized by inattention, fluctuating mental status, disorganized thinking, and an altered level of consciousness, findings which are also found in severe sleep deprivation. While sleep and circadian rhythm disturbances are regarded as potentially modifiable risk factors for the development of delirium, delirium itself may contribute to sleep disturbances. Studies conducted mainly in cardiac surgical patients indicate that sleep deprivation can cause (147), be a result of (148), or simply lower the threshold for transitioning to delirium. A prospective cohort study of surgical ICU patients demonstrated an association between delirium and severe REM sleep reduction (<6% of total sleep time) (82). Similarly, in a single center case-control study, critically ill patients who developed delirium during their stay experienced less REM sleep compared to those who did not experience delirium (149). Further, peripheral melatonin and cortisol levels were lower in the delirious as compared to non-delirious group suggesting an association between ICU SCD and delirium (149).

Sleep promotion has been tested as a mitigation strategy for ICU delirium. In a systematic review (150), six of the ten identified studies demonstrated a statistically significant reduction in the incidence of ICU delirium associated with a sleep intervention (151-156). Similar results were seen in a randomized clinical trial (RCT) in which delirium-free patients receiving sedatives were given either nocturnal intravenous dexmedetomidine or placebo until ICU discharge; nocturnal dexmedetomidine was

associated with a greater proportion of patients who remained delirium-free, but patient-reported sleep quality was unchanged (157).

During the Workshop, we highlighted that the mechanisms linking individual domains of ICU SCD and delirium remain unclear. Furthermore, there appears, at this relatively early stage, to be a bidirectional relationship between ICU SCD and delirium; however, the details of causality need to be clarified in appropriately designed studies. Finally, although sleep interventions seem to be a promising approach for improving delirium and related outcomes, as noted throughout this statement, conclusions are limited by small study sizes, confounding, and variable methodology.

*Post-intensive care syndrome – Full Version*

ICU SCD likely impacts the three domains of post-intensive care syndrome (PICS): cognition, mental health, and physical function. There is considerable evidence linking poor sleep quality with cognitive impairment in a variety of patient populations (158-161). Despite sleep disturbances improving over time, over half of ICU survivors (61%) report persistently poor sleep at 6 months follow-up (162). To date, few studies have rigorously evaluated the prevalence of sleep disruption after critical illness and its potential association with cognitive impairment. For example, a systematic review reported on 22 studies examining sleep after hospital discharge in survivors of critical illness; however, none of these studies reported on cognitive outcomes (162). A more recent study has shown that sleep fragmentation is associated with worse cognitive performance shortly after ICU discharge (107), suggesting that sleep remains important to address in the ICU, on hospital wards and perhaps later in post-ICU recovery.

Anxiety, depression, and posttraumatic stress disorder are also common among ICU survivors (163), and are known to be associated with poor sleep quality (164, 165). Numerous studies have demonstrated an association between depressive symptoms and increased levels of fatigue, stress, and anxiety in healthy participants subjected to sleep restriction (166, 167). The underlying mechanisms between sleep deficiency, circadian disruption, and mood disturbances are not well understood (168). Further research is needed to understand the contribution of poor post-ICU sleep to the development of anxiety, depression and post traumatic stress disorder.

Persistent sleep loss following ICU admission may also impact physical recovery. Sleep loss leads to significant reductions in energy, activity levels, and muscle strength and function (169, 170), which may impact physical recovery from critically illness. Emerging evidence demonstrates that early and intensive physical rehabilitation in the ICU improves physical function, decreases ICU delirium, and shortens ICU length of stay (171, 172). Initiatives to improve ICU sleep quality might enhance mobilization efforts and thus positively impact functional recovery (173).

To extend our understanding of ICU SCD along the entire trajectory of acute critical illness and recovery, workshop members noted that integration of sleep and circadian outcomes in long term follow-up studies is needed. As with other aspects of ICU SCD investigation, the establishment of core measures to serve as common building blocks for studies and the development of a collaborative network among investigators in ICU SCD and investigators in related fields such as PICS is a high priority.

**Sub-Topic 4: Treatment of ICU Sleep and Circadian Disruption**

Given the multi-faceted nature of ICU SCD and the diversity of hypothesized and identified risk factors, interventions to promote sleep or circadian function tend to be complex and include multiple components. This can lead to challenges for implementation and sustainability. Furthermore, issues regarding which ICU SCD domains are most closely linked to ICU outcomes and therefore the best targets for intervention, when interventions should occur, and how to measure hypothesized changes in sleep and circadian processes have limited intervention testing to date. In this section we will discuss gaps and next steps in the development of non-pharmacologic and pharmacologic interventions for ICU SCD.

*Non-pharmacologic interventions*

As noted above, the ability to initiate or maintain sleep is hampered by multiple patient factors, notably anxiety, pain, and pre-existing sleep disorders (67). These entities have been key targets for non-pharmacologic interventions that promote sleep by eliminating these patient sources of sleep disruption. Diverse relaxation techniques aimed at reducing stress and thus promoting sleep have been associated with improved subjective sleep quality, and, in some studies, an increase in total sleep time (174-176). A systemic review of eleven music therapy studies demonstrated consistent associations between music therapy and reduced anxiety/stress in critically ill patients (177) There is more limited data on music's direct impact on sleep (178, 179). Finally, incorporation of patient sleep preferences may also improve patient sleep, though robust evidence is lacking. A recent pilot project on a general medical ward provided

patients with help arranging their room comfortably for sleep (e.g., adjustment of temperature, lights, television, blinds) and offering sleep promoting items from a “comfy cart” (e.g., blankets, tea, snacks); the pilot was associated with subjective sleep improvements (180).

Discussion during the Workshop acknowledged a lack of information regarding a patient’s sleep history and preferences. It seems straightforward, barring contraindications, to continue pre-existing outpatient treatments for sleep disorders. Personalization of sleep promotion interventions is novel and potentially beneficial but adds complexity to already encumbered protocols. Committee members agreed, based on anecdotal clinical experience, that asking about sleep and empathizing with patients about lack of sleep is helpful to patients. It may also raise awareness of other team members to the problem of ICU SCD and potentially improve healthy sleep promotion behaviors.

*ICU environment*

Control of the ICU environment has historically been a major focus when attempting to reduce sleep disruption; more recently, circadian principles have also been applied. Numerous studies have explored interventions to control the environment, cluster care delivery patterns, or combine elements of both (181). In fact, multicomponent sleep promotion bundles are guideline-recommended for ICU patients (46, 182). Environmental control interventions reduce disturbances including noise, light and care interruptions (78, 183-186); however, not all studies have been successful (187, 188) and, when reduced, sound levels continue to exceed recommendations (78,

183). Improvements in sleep outcomes have been more difficult to demonstrate. For example, multicomponent protocols that emphasized environmental control demonstrated improvements in delirium but did not show changes in sleep (153, 189). Though not universally tolerated, earplugs and eye masks which block the ICU environment may be a simple, low-cost intervention for ICU SCD. Meta-analyses suggest that use of earplugs and eye masks are associated with increased total sleep time as well as lower incidence of delirium in ICU patients (190, 191).

At several points in the Workshop, participants highlighted the importance of using established implementation frameworks (192-194) when designing and testing interventions to promote sleep and circadian rhythms in the ICU. From a research perspective, such approaches are necessary to support the fidelity of the interventions being evaluated. From a clinical perspective, these frameworks are vital for adapting, scaling, and sustaining such efforts within complex, dynamic ICU settings (195). Applying such principles to the design of ICU-based sleep and circadian promotion would involve engaging relevant departments (e.g., nursing, respiratory therapy, physical therapy, pharmacy, laboratory medicine, diagnostic imaging, information services, facilities) to identify environmental, non-pharmacological and pharmacological interventions and to iteratively adopt, evaluate, and redesign these interventions to meet the unique, changing needs of involved ICUs.

*Circadian Cues as Treatment*

More recently some ICU SCD interventions have focused on re-establishing normal diurnal light variation. Effective circadian entrainment depends on exposure to light that has sufficient intensity and duration and has the correct spectral characteristics

(i.e., mimicking natural sunlight) (196, 197). Though sample sizes are small, daytime light interventions have demonstrated benefits (198, 199) including increased subjective patient satisfaction (200), improved early post-operative mobility (201), reduced peri-operative delirium (201-203), and normalization of circadian phase as determined by urine 6-sulfatoxymelatonin acrophase (204). Other daytime light studies have failed to show a benefit. However, high lighting levels in the control group (205) and inappropriate timing, duration, and spectral characteristics of the light intervention (206) may have limited findings in these studies.

There are limited investigations of non-photic circadian cues such as exercise and modifications of feeding schedules. The timing of nutrition is an influential circadian time cue particularly for peripheral clocks in the gut, liver, and pancreas. Misalignment of peripheral clocks (i.e., internal misalignment) is associated with circadian disruption, poor sleep, and poor glucose tolerance (81, 207, 208). Thus, feeding during the day in a time-restricted manner may be more optimal than a continuous feeding schedule. Recent studies have shown that time-restricted daytime feeding is feasible (209) and will improve metabolic parameters (210). Further studies investigating the impact of time-restricted feeding on circadian phase alignment and additional clinical outcomes are ongoing (NCT04437264, NCT04870554).

Similarly, critical illness-related immobility interrupts normal entrainment due to movement or exercise and may be an important target for ICU SCD interventions. Though, in the setting of a multi-component sleep promotion intervention, patient engagement in physical therapy was not associated with any change in subjective sleep quality (211). Further study of early mobility in this population and related effects on

sleep and circadian outcomes may provide evidence for novel, mobility-related methods to promote sleep in the ICU.

Workshop discussion focused on means of improving the implementation of zeitgeber-based interventions to improve circadian alignment in the ICU. Though investigators are familiar with the 2-process model of homeostatic and circadian drives, specialized understanding of entrainment and leveraging of circadian cues is not widespread. Photic zeitgebers are the most potent stimuli for entraining the central circadian clock, while a variety of nonphotic zeitgebers are known to entrain peripheral clocks (such as time-restricted feeding). Interventions addressing these targets may result in distinct and profound improvement in clinical outcomes. Improving circadian alignment may also significantly impact important sleep domains such as timing, duration, architecture, and continuity. Translating fundamental circadian knowledge to bedside clinical care poses logistical challenges. The many abnormal circadian signals present in the ICU environment must be carefully measured and countered (e.g., light, feeding, sleep and immobilty). Additionally, intervention timing is critically important since incorrectly timed zeitgeber signals can fail to produce the desired change in alignment or, more concerningly, may cause a change in the wrong direction. Though outside the scope of this document, we also note that lighting adjustments such as low overnight light impacts the alertness and sleepiness of overnight workers in the hospital environment and considerations such as appropriate spectra bright lighting in work and break rooms are needed. Further research is needed to define optimal circadian intervention protocols in the ICU, including appropriate timing, duration, and intensity of

zeitgeber exposures. We note as well that formalization of light recommendations for circadian entrainment is just emerging (196, 197).

*Pharmacologic treatment*

To date, there are no ICU guideline recommendations supporting the use of a pharmacologic treatment to improve ICU SCD (46). Nevertheless, medications are frequently prescribed for sleep in the ICU (212). Melatonin is the most commonly prescribed medication, followed by ramelteon and quetiapine (212). Among studies of sleep bundles in the ICU, only two allowed use of pharmacologic sleep aids to promote sleep (153, 213); despite inclusion in the protocol, sleep aid use was relatively uncommon in study subjects (16% Kamdar et al, 7% Andrews et al) and therefore impact of pharmacologic sleep aids on sleep was not established by these studies.

More recent studies involving sleep promotion through pharmacotherapy have primarily involved melatonin agonists, alpha-2-agonists, and orexin antagonists. Two recent large RCTs of melatonin in ICU patients showed not association between melatonin use and improvement in delirium and conflicting results regarding sleep outcomes as measured by RCSQ and nursing observation (214, 215). The melatonin agonist ramelteon has been reported to improve both sleep-related (nursing observation) and delirium endpoints (216). Though smaller studies evaluating the role of dexmedetomidine for promoting ICU sleep observed differences in sleep quality, the largest study to date did not (157). Similarly, a retrospective cohort study found administration of the orexin antagonist suvorexant to be associated with a lower

incidence of delirium but no difference in any sleep-related endpoints compared with no suvorexant, after adjustment of confounders (217).

Workshop members noted the high demand for sleep medications from caregivers, surrogates, and patients along with the common misperception that sedation is equivalent to sleep. Bedside clinicians express a strong desire for a safe and effective sleep aid, particularly in patients with concomitant delirium. However, the study of pharmacologic options to promote nighttime sleepiness is limited by small trial sizes, the failure to enroll mechanically ventilated adults with a high severity of illness, and an over-reliance on delirium reduction and/or patient-reported sleep quality to define efficacy. In addition, RCTs to date have involved prescribing of pharmacologic agents upon ICU admission or timed in relation to specific clinical events (e.g., surgical procedure) (218-220). However, in practice, clinicians are frequently seeking options to promote sleep after patients report sleep disruption or have already presented with delirium. This discrepancy raises important questions regarding the timing and patient selection for pharmaceutical interventions. Interestingly, pharmacologic therapies to promote daytime wakefulness in the ICU have not been rigorously studied, and this may be a novel and impactful approach to sleep promotion in the ICU. Finally, we should continue to consider the sleep and circadian implications of medications routinely used in the ICU (e.g., corticosteroids, benzodiazepines, narcotics, antipsychotics).

**Synthesis and Conclusions from Workshop Discussions**

ICU SCD is a complex and compelling potential target for improving critical illness outcomes. Herein, we have reported the findings, discussions, and conclusions of the ATS Workshop, “Causes, consequences, and treatments of sleep and circadian disruption in the ICU” which had the following three objectives: (1) Delineate a prioritized list of ICU SCD sub-topics; (2) Identify, discuss, and critically evaluate existing knowledge gaps within these sub-topics; and (3) Establish a prioritized ICU SCD research agenda. We note that challenges in defining and measuring ICU SCD have led to a set of related limitations hampering the field’s progress. Specifically, study size, brevity in monitoring periods, and heterogeneity in study exposures and outcomes have limited evidence to date. However, emerging technologies that have improved longitudinal wearability and the potential for automation of sleep measures hold promise as a means of moving the field forward. Investigators are eager to increase collaborative infrastructure, foster multi-site study design, test individual domains of ICU SCD for associations with ICU outcomes, and clarify the natural history of ICU SCD. Opportunities such as this ATS Workshop have and will continue to support a rich exchange of information and foster collaboration among expert investigators.

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## Figure Legends

**Figure 1:** Conceptual model of intensive care unit sleep and circadian disruption (ICU SCD). Factors that disrupt sleep are presented in blue with arrows indicating interactions among disruptive factors. Proposed domains of ICU SCD are presented in yellow; we hypothesize that patients may experience changes in some or all domains. Proven and hypothesized patient-centered outcomes are presented in green; delirium and respiratory failure have the best-established association with ICU SCD to-date. Abbreviations: ICU, intensive care unit; Mech Ventilation, mechanical ventilation; PICS, post intensive care syndrome.

**Figure 2:** Connections between primary and secondary zeitgebers, central and peripheral clocks, and body functions. Light is the primary zeitgeber with direct input to the central clock located in the suprachiasmatic nucleus and indirect input into peripheral clocks via neurohormonal pathways. Sleep-wake timing, feeding schedule, exercise and social interaction are secondary non-photic zeitgebers which have input into central and peripheral clocks as well as influence light exposure (e.g., low light exposure while sleeping). Internal and external misalignment contribute to an array of organ dysfunction. Abbreviation: ANS, autonomic nervous system.

**Figure 3:** Proposed mechanisms for the bidirectional relationship between respiratory dysfunction and sleep and circadian disruption in the intensive care unit (ICU SCD). Abnormal patient-ventilator interactions illustrated in the top of the figure (blue)

contribute to ICU SCD. In turn, ICU SCD contributes to respiratory ability and outcomes illustrated in the bottom of the figure (green).

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| Table 2: Advantages and Disadvantages of Selected ICU Sleep and Circadian Measures | | | |
|---|---|---|---|
| **Measure** | **Advantages** | **Disadvantages** | **Sample Studies** Author Year (Ref #) |
| **Objective Sleep Measures** | | | |
| Polysomnography | – Gold standard for sleep/wake and sleep architecture including stages, timing, and continuity | – Resource intensive<br>– Poor patient tolerance<br>– Standard scoring limited | Cooper 2000 (25)<br>Bosma 2007 (26)<br>Roche Campo 2010 (27)<br>Drouot 2012 (28)<br>Watson 2013 (29)<br>Elliot 2013 (23)<br>Knauert 2014 (24) |
| Multi-channel EEG: Bispectral Index SedLine® | – Automated<br>– Feasible and tolerable<br>– Familiar to ICU providers<br>– Longitudinal monitoring possible | – Limited accuracy identifying sleep<br>– Poor accuracy identifying sleep stages | Gimenez 2017 (98)<br>Vacas 2016 (101)<br>Nieuwenhuijs 2020 (100)<br>Pedrao 2020 (99) |
| Automated EEG: Odds Ratio Product | – Automated<br>– Feasible and tolerable<br>– Longitudinal monitoring possible<br>– Measures alertness | – Limited accuracy identifying sleep<br>– Poor accuracy identifying sleep stages | Dres 2019 (86) |
| Actigraphy | – Feasible and tolerable<br>– Longitudinal monitoring possible | – Limited accuracy identifying sleep<br>– No identification sleep stages<br>– Limited in immobile ICU patients | Kamdar 2017 (128)<br>Wilcox 2021 (107) |
| **Patient Perceived Sleep Measures** | | | |
| Richards Campbell Sleep Questionnaire | – Validated in ICU patients<br>– Feasible and tolerable<br>– Longitudinal monitoring possible<br>– Patient-centered<br>– Includes 5 sleep domains | – Restricted to patients with cognitive and communication ability | Richards 2000 (108)<br>Kamdar 2012 (118)<br>Aitken 2017 (111)<br>Menear 2017 (110) |
| Pittsburgh Sleep Quality Index | – Validated in non-ICU patients<br>– Feasible and tolerable<br>– Longitudinal monitoring possible<br>– 7 sleep domains<br>– Allows assessment of pre / post acute illness sleep | – Restricted to patients with cognitive and communication ability<br>– High patient burden due to length<br>– Not for inpatient use | Buysse 1989 (121)<br>McKinley 2013 (122)<br>Wang 2019 (123) |
| Insomnia Severity Index | – Validated for patients and proxy<br>– Detailed insight into insomnia<br>– Feasible and tolerable<br>– Longitudinal monitoring possible<br>– Allows assessment of pre / post illness insomnia | – Restricted to patients with cognitive and communication ability<br>– Not for inpatient use | Bastien 2001 (124)<br>McKinley 2013 (122)<br>Elliot 2013 (23) |
| **Circadian Measures** | | | |
| Melatonin<br>– serum<br><br>6-sulfatoxymelatonin<br>– urine | – Gold standard | – Frequent sampling<br>– Masking by ICU environment<br>– Anemia/risk anemia for serum samples<br>– Oliguria/anuria limit urine samples; indwelling catheter needed for urine samples | Mundigler 2002 (31)<br>Frisk 2004 (40)<br>Gehlbach 2012 (34)<br>Verceles 2012 (33)<br>Li 2013 (41)<br>Maas 2020 (39) |
| Heart rate | – Feasible and tolerable<br>– Longitudinal monitoring possible | – Need for specialized data management<br>– Critical illness confounds measure | Knauert 2020 (37) |
| Core temperature | – Longitudinal monitoring possible | – Invasive<br>– Fever / antipyretics confound | Gazendam 2013 (35) |

| | | | |
|---|---|---|---|
| Actigraphy | − Feasible and tolerable<br>− Longitudinal monitoring possible | − Indirect behavioral reflection of circadian measures<br>− Limited in immobile ICU patients | Duclos 2014 (36)<br>Knauert 2021 (127) |
| Abbreviations: EEG, electroencephalography; ICU, intensive care unit; Ref; reference; #, number. | | | |

| Table 1: High Priority Next Steps to Meet Existing Knowledge Gaps | |
|---|---|
| **Sub-topic** | **Next Steps** |
| **Scope** | – Characterize the natural history of ICU SCD to determine the optimal timing of ICU SCD interventions across the entire trajectory of acute critical illness through recovery.<br>– Increase collaboration among inter-professional and clinical-translational investigators to harmonize research methods and promote multisite investigation.<br>– Define distinct study populations that account for the heterogeneity of ICU patients.<br>– Investigate if changes in sleep and circadian domains during acute illness are adaptive versus maladaptive.<br>– Identify baseline, acute illness, and ICU-based risk factors for ICU SCD.<br>– Include and test the significance of pre-admission sleep history in the diagnosis and treatment of maladaptive domains of ICU SCD. |
| **Measures** | – Advance the development of ICU SCD measures that are rigorous, feasible, and able to support longitudinal monitoring of SCD in the ICU. This includes circadian measures that are robust against masking in the ICU environment.<br>– Pursue automated, real time objective sleep and circadian measures that would allow clinical translation of ICU SCD diagnosis and treatment to the bedside.<br>– Maximize the use of patient perceived sleep measures whenever possible; implement these measures as soon as cognitive and communication barriers resolve. |
| **Outcomes** | – Define associations between individual ICU SCD domains and patient outcomes. This includes but is not limited to cognitive, respiratory, metabolic, cardiac, and immune-related outcomes as well as patient centered outcomes.<br>– Maximize research efforts by embedding mechanistic outcomes within larger clinical studies focused on clinically important patient-centered outcomes. Areas of special interest include the bidirectional interactions of respiratory failure, invasive and non-invasive ventilation, and ICU SCD, and the bidirectional interaction of delirium and ICU SCD.<br>– Identify post-hospital outcomes related to ICU SCD. |
| **Treatment** | – Leverage implementation science strategies to assure intervention fidelity and sustainability of multicomponent ICU SCD interventions.<br>– Personalize inpatient sleep and circadian promotion; when possible, continue treatment of pre-existing sleep disorders.<br>– Translate circadian biology principals to the ICU to promote internal and external synchrony.<br>– Explore daytime wake promotion as a component of ICU SCD interventions.<br>– Advance current knowledge of pharmacologic sleep and circadian promotion while avoiding excessive sedation or increased delirium. |
| **Abbreviation:** ICU SCD, intensive care unit sleep and circadian disruption | |

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|---|---|---|---|
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| Polysomnography | – Gold standard for sleep/wake and sleep architecture including stages, timing, and continuity | – Resource intensive<br>– Poor patient tolerance<br>– Standard scoring limited | Cooper 2000 (1)<br>Bosma 2007 (2)<br>Roche Campo 2010 (3)<br>Drouot 2012 (4)<br>Watson 2013 (5)<br>Elliot 2013 (6)<br>Knauert 2014 (7) |
| Multi-channel EEG:<br>Bispectral Index<br>SedLine® | – Automated<br>– Feasible and tolerable<br>– Familiar to ICU providers<br>– Longitudinal monitoring possible | – Limited accuracy identifying sleep<br>– Poor accuracy identifying sleep stages | Gimenez 2017 (8)<br>Vacas 2016 (9)<br>Nieuwenhuijs 2020 (10)<br>Pedrao 2020 (11) |
| Automated EEG:<br>Odds Ratio Product | – Automated<br>– Feasible and tolerable<br>– Longitudinal monitoring possible<br>– Measures alertness | – Limited accuracy identifying sleep<br>– Poor accuracy identifying sleep stages | Dres 2019 (12) |
| Actigraphy | – Feasible and tolerable<br>– Longitudinal monitoring possible | – Limited accuracy identifying sleep<br>– No identification sleep stages<br>– Limited in immobile ICU patients | Kamdar 2017 (13)<br>Wilcox 2021 (14) |
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| Richards Campbell Sleep Questionnaire | – Validated in ICU patients<br>– Feasible and tolerable<br>– Longitudinal monitoring possible<br>– Patient-centered<br>– Includes 5 sleep domains | – Restricted to patients with cognitive and communication ability | Richards 2000 (15)<br>Kamdar 2012 (16)<br>Aitken 2017 (17)<br>Menear 2017 (18) |
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| Core temperature | – Longitudinal monitoring possible | – Invasive<br>– Fever / antipyretics confound | Gazendam 2013 (30) |
| Actigraphy | – Feasible and tolerable<br>– Longitudinal monitoring possible | – Indirect behavioral reflection of circadian measures<br>– Limited in immobile ICU patients | Duclos 2014 (31)<br>Knauert 2021 (32) |
| Abbreviations: EEG, electroencephalography; ICU, intensive care unit; Ref; reference; #, number. | | | |

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| Table 3: Sleep Promotion Intervention Components | | |
|---|---|---|
| **Domain** | **Strategies** | **Special Considerations** |
| Zeitgeber Optimization | – Bright daytime light<br>– Dim or no light at night<br>– Daytime time-restricted feeding<br>– Mobility | – Light interventions must consider spectra, duration, timing, and light exposure history that reach the angle of gaze. Note that most patients are delayed by day 1 or 2 of ICU admission and therefore light exposure should start later than pre-illness wake times. Providers should mitigate light from screens in the room (e.g., televisions, mobile computers et cetera).<br>– Time-restricted feeding should be structured to deliver food during the day and provide a fast during the night.<br>– Providers should minimize daytime sedation to optimize daytime mobility and wakefulness. |
| Patient Comfort | – Pain control<br>– Anxiolysis<br>– Toileting prior to sleep<br>– Treatment of nausea | – Follow PADIS guideline to optimize non-pharmacologic and pharmacologic analgesic strategies.<br>– Balance pain and anxiety with the need to minimize analgesics and anxiolytics known to disrupt sleep (e.g., narcotics and benzodiazepines) |
| Personalization | – Treat pre-existing sleep disorders<br>– Accommodation of sleep timing preferences<br>– Adjustment of room (e.g., temperature, lights, shades) and bed per patient preferences (e.g., blankets, pillows) | – If patient not able to convey sleep preferences, consider asking surrogate. |
| Environmental Control | – Mitigate noise from both inside and outside room<br>– Offer eye masks<br>– Offer earplugs | – Investigate sources of noise which can be diverse and highly unique to each unit or room; talking and equipment alarms are common sources of noise, however many other sound sources exist.<br>– Discourage nighttime visitors outside of special circumstances (e.g., end of life). |
| Cluster Care Overnight | – Define dedicated sleep period and reschedule non-urgent care including medications, phlebotomy, radiology, bathing, skin or wound care, room maintenance | – Involve stakeholders for all changed workflows.<br>– Restaffing may be needed to increase tasks during non-sleep times.<br>– Dedicated sleep period may not be feasible based on patient acuity, but care can be reduced to urgent tasks.<br>– Reassure patients that while they are being allowed to rest, remote monitoring (e.g., telemetry) is ongoing. |
| Mechanical Ventilation | – Consider assist control instead of spontaneous ventilation modes | – Balance preference for assist control modes with benefit of optimized patient-ventilator synchrony (e.g., may revert to pressure support mode if desynchrony occurs). |
| Medication Use | – Minimize analgesics and anxiolytics known to disrupt sleep (e.g., narcotics and benzodiazepines)<br>– Avoid polypharmacy<br>– Consider withdrawal effects from abrupt discontinuation of home medications on sleep | – Multidisciplinary review of medications daily with critical care pharmacist; dose reduce or discontinue when possible. |
| Medication Timing | – Revise medication timing to avoid administration during protected sleep periods | – Leverage electronic medical record defaults to preferentially schedule medication administration in the daytime.<br>– Strategize continuous infusion bag volumes, concentrations and start times such that bag and tubing changes do not occur during protected sleep periods. |