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Sleep Assessment in Critically Ill Adults: Established Methods and Emerging Strategies

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OBJECTIVES: Sleep is a biological mandate with an integral role in optimizing functions that maintain psychological and physical health. During critical illness, however, sleep may be disrupted at best and elusive at worst. Sleep improvement efforts and research endeavors evaluating interventions to improve sleep in critically ill adults are hampered by limited methods available to measure sleep in this setting. This narrative review summarizes available modalities for sleep assessment in the ICU, describes new ICU sleep assessment methods under development, and highlights features of the ideal ICU sleep measurement tool.

DATA SOURCES: The most relevant literature and author experiences were assessed for inclusion from PubMed and textbooks.

STUDY SELECTION: The authors selected studies for inclusion by consensus.

DATA EXTRACTION: The authors reviewed each study and selected appropriate data for inclusion by consensus.

DATA SYNTHESIS: Currently available tools to measure sleep in critically ill adults have important flaws. Subjective measurements are limited by recall bias, the inability of many patients to communicate, and poorly correlate with objective measures when completed by surrogates. Actigraphy does not consider the effects of sedating medications or myopathy leading to an over estimation of sleep time. Polysomnography, the gold standard for sleep assessment, is limited by interpretation issues and practical application concerns. Single and multiple channel electroencephalogram devices offer real-time physiologic data and are more practical to use than polysomnography but are limited by the scope of sleep-specific information they can measure and poorly characterize the circadian system.

CONCLUSIONS: A measurement tool that offers real-time sleep and circadian assessment and is practical for broad application in the ICU does not exist. Newer sleep assessment devices have shown promise in measuring physiologic data in real time; when used in combination with other assessment modalities, and analyzed by computational techniques, they may revolutionize sleep monitoring in the ICU.

KEY WORDS: actigraphy; assessment; electroencephalography; intensive care; polysomnography; sleep

Most critically ill adults sleep poorly. Patients themselves often report difficulty both initiating and maintaining sleep; nights in the ICU are often described as being interminable. The stress of critical care-associated insomnia is reported by patients to be comparable to pain and the inability to communicate while intubated (1–3). For a long time, the poor sleep of the critically ill was not given the priority it deserves. More recently, the cognitive, psychological, and physical consequences of critical illness have become clearer and poor sleep has taken its place as a potentially modifiable area for ICU care improvement (4).

Sleep is known to be important to information-processing, mood and emotional regulation, protein synthesis, removal of CNS metabolic waste, regulation of inflammation, and both innate and adaptive immunity; testing for each of

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these outcomes may be difficult under the best of circumstances but is considerably more complicated in the context of a critical illness (**Table 1**). Clinicians are often unaware of their patients' sleep quality due to the challenges associated with sleep measurement in the ICU. Even a basic assessment of patients' level of consciousness as an estimate of sleep quality is complicated by the sedating medications frequently administered and critical illness itself. Sleep is a complex, multidomain, neurophysiologic state that requires valid physiologic-based sleep assessment strategies to accurately evaluate it.

This narrative review summarizes currently available modalities for sleep assessment in the ICU, describes new ICU sleep assessment methods under development, and highlights the critical features of the ideal ICU sleep measurement tool.

NORMAL SLEEP

Normal sleep is characterized by two different states that cycle approximately every 90 minutes: 1) nonrapid eye movement (NREM) sleep that progresses through light sleep (i.e., stage N1, N2) to deep sleep (stage N3) and 2) rapid eye movement (REM) sleep. Each sleep state is defined by a unique electrical signal when monitored by electroencephalogram, muscle tone when evaluated with electromyogram, and eye movements when assessed using the electrooculogram. **Table 2** characterizes the electroencephalographic, electromyographic, and electrooculographic features of each sleep phase.

Two distinct forces control the sleep-wake cycle (**Fig. 1*A***):

1) Homeostatic drive: The drive to sleep increases the longer one is awake and is reflected in the dynamic interplay of various neurotransmitters. Sleep is heralded by accumulation of neurotransmitters such as adenosine, exerting a soporific effect. Following sleep, resolution of the drive to sleep leads to wakefulness, occurring with the release of excitatory neurotransmitters such as orexin, histamine, norepinephrine, and acetylcholine.
2) Circadian rhythms: A pacemaker located in the suprachiasmatic nucleus coordinates physiologic systems including the CNS, autonomic nervous system, and immune system to entrain their activity to environmental influences, most notably light.

SLEEP ALTERATIONS IN CRITICAL ILLNESS

Patients with a lower severity of illness may demonstrate characteristic features of normal sleep; however, their sleep quality often remains poor (7). For example, total sleep time may appear normal, but it is often achieved in short intermittent periods (e.g., naps) throughout both the day and night (8, 9). Sleep efficiency (the time designated for sleep actually spent asleep) is reduced,

TABLE 1.
Assessment of Physiologic Systems Regulated by Sleep and the Impact of Critical Illness on Their Measurement

System Regulated by Sleep	Assessment Method	Barriers to Accurate Assessment in the ICU
Protein synthesis	Serum biomarkers of total protein synthesis. Specific proteins may require mass spectroscopy or enzyme-linked immunosorbent assay	Complicated by critical illness-related catabolism and nutritional status
Immunity (innate/adaptive)	Specific aspects of immunity can be measured as deficiencies of cellular or humoral immunity	Results altered by critical illness, medications, infection
Inflammation	Serum biomarkers	Results altered by critical illness and some medications (e.g., steroids)
Hormone release	Serum levels of growth hormone, thyroid-stimulating hormone, cortisol, etc	Levels altered by critical illness, medications
Cognitive function (e.g., memory, executive function)	Neuropsychiatric testing	Frequent use of sedation and presence of delirium
Emotional control/mood	Validated assessment scales	Frequent use of sedation and presence of delirium
Removal of CNS metabolic waste via the "glymphatic" system	Contrast-enhanced MRI; still mostly in animal models and experimental	Impractical in critically ill patients; unknown the effects of critical illness

TABLE 2.
Features of Normal Sleep Stages When Evaluated by Electroencephalogram, Electromyogram, or Electrooculogram

Sleep Stage	Electroencephalogram	Electromyogram	Electrooculogram
Nonrapid eye movement			
N1	Low voltage, mixed frequency. Vertex sharp waves present	Below relaxed wakefulness	Slow rolling eye movements
N2	Low voltage, mixed frequency, at least one sleep spindle present, K complex present	Lower muscle tone	Slow eye movements less evident compared with stage NI sleep
N3	Delta waves > 20% of a 30 s epoch	Lower muscle tone	No eye movements
REM	Low voltage, mixed frequency. "Sawtooth waves." No vertex sharp waves present	Muscle atonia; lowest electromyogram signal of all the sleep stages	REMs

REM = rapid eye movement.

fragmentation (disruption) increased, and light sleep heavily predominates over deep, NREM sleep and REM sleep (10). While circadian rhythm is maintained, it is characterized by a "phase delay" where sleep onset occurs later than normal (**Fig. 1*B***) (11–13). Abnormal circadian timing occurs as a result of altered zeitgebers (literally "time givers") in the ICU such as relatively dim light during the day and bright light at night, altered feeding schedules, and lack of physical activity (among others) compared with normal timing that is based on the 24-hour rotation of the earth and social behaviors.

It may be most accurate to think of critically ill patients with a higher severity of illness (typically those who are sedated and mechanically ventilated) as having an altered state of consciousness accompanied by variable features of sleep. In these patients, several abnormal sleep patterns have emerged. Some patients who are behaviorally awake have been found to have dissociative electroencephalographic manifestations (e.g., theta and delta waves) more typical of sleep (14, 15). Conversely, low amplitude, high frequency beta, and alpha activity typically seen in the awake state have been observed with electroencephalograms in patients with coma. "Atypical sleep" refers to NREM sleep without spindles or K complexes (electroencephalogram features that define the presence of N2 sleep). "Pathologic wakefulness" is characterized by the general slowing of electroencephalogram frequencies and impaired electroencephalogram reactivity. The absence of sleep spindles may be particularly clinically important. Sleep spindles may facilitate verbal and nonverbal memory consolidation, and their absence is associated with more severe encephalopathy and higher mortality (16–18).

SUBJECTIVE ASSESSMENT

The most accessible measures of sleep are subjective assessment tools. Of the 13 different published ICU sleep questionnaires, 10 are meant to be reported by patients and three by ICU nurses (i.e., their evaluation of their patient's sleep) (19). Among the 10 patient-reported scales, only the Richards Campbell Sleep Questionnaire (RCSQ) has been validated against polysomnography and has undergone extensive reliability testing (20). While accessible and easy to administer, the RCSQ, has only been validated for use in awake, alert, and responsive patients thus and may not be appropriate for use in higher severity of illness ICU patients receiving sedatives or with delirium. For patients who can complete it, such tools capture retrospective self-reports about the sleep characteristics most important to patients and their families; information that is currently unobtainable using "objective" means.

Among the three published nurse-administered subjective assessment tools, only the Sleep Observation Tool (SOT) has been validated against polysomnography; none have undergone reliability testing (19–21). While the SOT may represent a potential strategy to subjectively evaluate sleep in patients' unable to participate in sleep self-assessment, SOT validation studies were small and were conducted in primarily awake, low severity of illness ICU patients. Importantly, clinician assessment

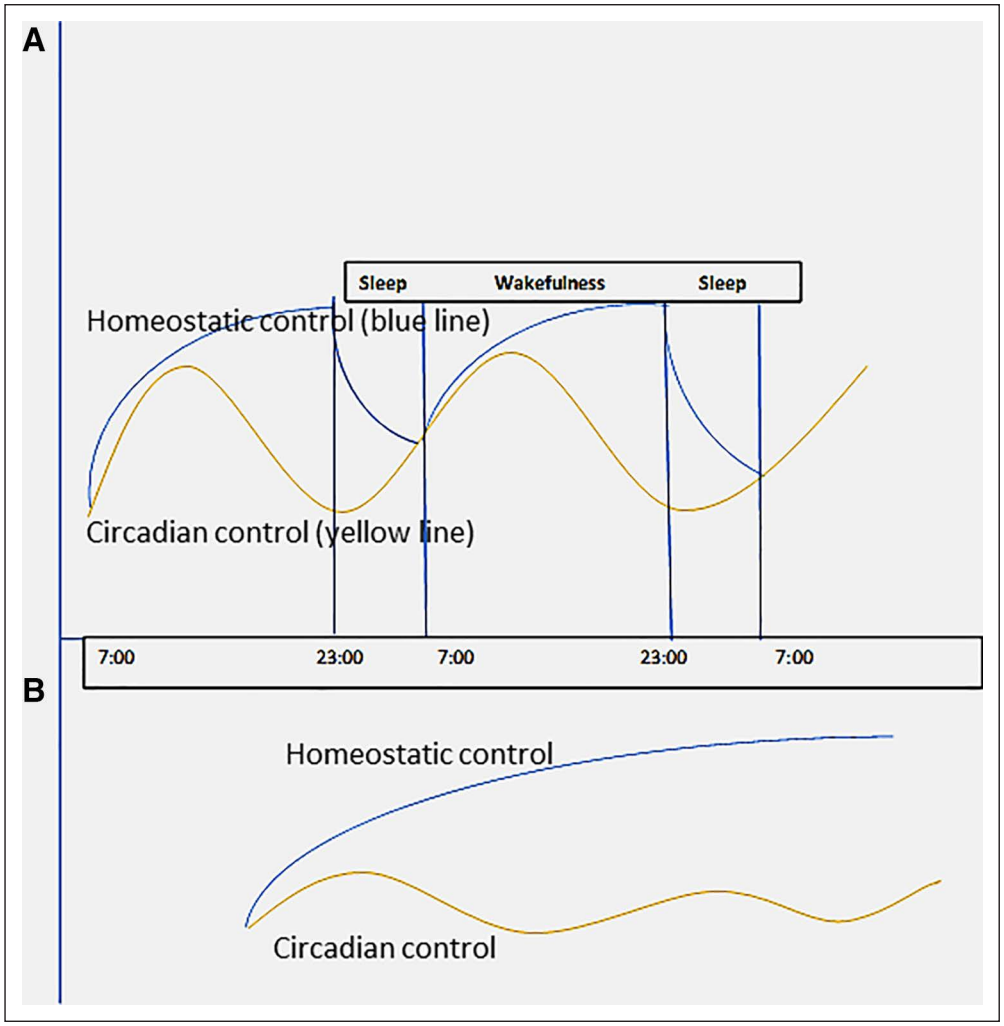

Figure 1. Regulation of the sleep-wake cycle is under the control of both circadian and homeostatic forces. **A**, Illustration of the normal two-process model of the control of sleep (5). Circadian rhythm shown in *yellow* and the homeostatic control of sleep in *blue*. The circadian cycle entrains to external factors such as light. The circadian propensity to sleep corresponds inversely with core body temperature. Homeostatic process builds pressure (as adenosine accumulates) to sleep the longer the patient is awake. **B**, Hypothetical model of what might occur in the ICU when there is a phase delay (note the later rise in the circadian curve), decreased amplitude, and ongoing homeostatic pressure to sleep the longer the patient remains awake (6). Misalignment of these two processes have adverse health consequences.

of patient sleep, such as nursing observation, tends to overestimate total sleep time compared to polysomnography and overestimate sleep quality compared to patients (19). Clearly, more research surrounding ICU subjective sleep instruments is required.

OBJECTIVE ASSESSMENT: ELECTROENCEPHALOGRAM + PHYSIOLOGY-BASED

Polysomnography

Polysomnography has served as the electrophysiologic definition of sleep for more than 60 years and is widely considered the gold standard assessment tool (22). Polysomnography typically involves collection of multiple biosignals, including electroencephalogram, electrooculogram, electromyogram, heart rate, respiration, oxygen saturation, and limb movements and is pictured in **Supplemental Figure 1** (http://links.lww.com/CCX/A905). However, the challenges of conducting polysomnography in the ICU are formidable and the interpretation of results is challenging (10, 14, 15). Standard sleep stage scoring per the original criteria by Rechtschaffen and Kales (23) and updated by the American Academy of Sleep Medicine in 2016 may not accurately describe and measure sleep in these patients.

Polysomnography is costly, labor intensive, often poorly tolerated by patients, may interfere with beside care, and importantly requires skilled personnel to both attend to the recording and to understand the difficulties and nuances of interpretation. Furthermore, recording length needs to be at least 24 hours to account for the almost equal day/night distribution of sleep in ICU patients. As a result, the number of ICU studies that have used polysomnography as the primary sleep assessment tool are relatively few in number and limited in size. Given the above, the 2018 pain, agitation, delirium, immobility, and sleep guidelines pragmatically recommend polysomnography not be routinely used clinically to monitor sleep in the ICU, despite affirming that clinicians should routinely inquire about sleep or use a validated assessment tool to monitor it (4).

Partial Polysomnography: Electroencephalogram Only

Given the challenges of performing complete polysomnographies in the ICU, there has been increasing interest in trying to measure and stage sleep using only some components of the polysomnography. Electroencephalography has received the greatest attention, given that it directly measures brain activity and serves as the foundation for sleep staging. Reduced channel count electroencephalography devices (a single-channel device is pictured in **Supplemental Fig. 2**, http://links.lww.com/CCX/A905) have been applied to bare skin, most typically the forehead, thus avoiding the need for conductive gels or caps to create an electrical pathway through hair (24).

Single-Channel Electroencephalogram

Single-channel electroencephalography (SC-EEG) is typically conducted with one electrode placed in the middle of the forehead and the other on the left mastoid. In healthy adults, the SC-EEG was able to recognize consolidated sleep (i.e., total sleep time TST], stage N2 and N3 sleep, and time spent in REM sleep) as well as polysomnography assessment but performed worse than polysomnography in patients where sleep stage transitions were frequent (25).

Spectral analysis using a single channel was compared with standard (Rechtschaffen and Kales) sleep scoring for reproducibility in a cohort of mechanically ventilated patients (26). Spectral analysis is a method of electroencephalogram analysis based on frequency; the amount of rhythmic activity at different electroencephalogram frequencies is quantified. The proportion of theta (3–7 Hz) and delta waves (0–3 Hz) (associated with deeper sleep) is compared to the proportion of alpha activity (8–13 Hz) and gamma activity (30–48 Hz) (associated with lighter, nonrestorative sleep). In this study, spectral electroencephalogram analysis proved more reliable and reproducible than manual methods of electroencephalogram analysis; however, there remains no reliable reference standard for spectral analysis, and it has not been correlated with sleep outcomes.

One small study compared SC-EEG to polysomnography to evaluate depth of sleep using spectral analysis in five critically ill adults ($n = 2$ mechanically ventilated) and five healthy adults (27). In this proof-of-concept study, the average sensitivity and specificity for detecting slow wave sleep compared with simultaneous polysomnography was 0.68 and 0.59, respectively. This technology currently has numerous limitations for ICU use including the limited scope of information it provides and thus is only appropriate for research use at present.

While many spectral analyses of electroencephalograms in sleep seek to identify correlates of sleep states, such as wake versus NREM versus REM, new analyses have been proposed to derive continuous and quantitative measures of sleep depth, such as the odds ratio product (ORP) (28). Applicable to low-channel count electroencephalograms, the ORP quantifies power across four frequency ranges in short 3-second windows to predict sleep or wakefulness, and this digital index has been used to investigate the effects of sedatives on sleep architecture in critically ill patients.

Multichannel Electrophysiologic Devices

Electrophysiologic devices may be equipped with multiple frontopolar electroencephalogram electrodes. The electroencephalogram elements needed to stage sleep can be detected in frontopolar electroencephalograms, including spindles, K complexes, slow waves, and cortical rhythmic activity. Frontopolar devices may facilitate portable sleep monitoring with better accuracy than SC-EEG devices, and better portability and tolerability in the ICU than full polysomnographies. One frontopolar system with three electroencephalogram channels has been validated with polysomnography in healthy adults (29) and used in both mechanically ventilated and nonintubated ICU patients (30, 31).

Other multichannel devices have also been developed that can record other electrophysiologic parameters simultaneously, including, but not limited to, electromyogram and electrooculogram. Some of these devices have been developed with the intent of improving home sleep monitoring. For example, one wireless sleep monitor with eight electrodes (four forehead for electroencephalogram, two electrooculogram, one mastoid, and one chin) can provide signals comparable to in-laboratory polysomnography (32). The accuracy of multichannel electrophysiologic devices compared with polysomnography in the ICU remains less clear currently. Until they are rigorously evaluated in the

ICU, multichannel electrophysiologic devices should be considered as a promising research tool.

Processed Electroencephalogram

In addition to examination of the raw forehead electroencephalogram data, several devices use proprietary algorithms to monitor the depth of sedation in patients undergoing anesthesia, such as the bispectral index and patient state index. However, current data has not demonstrated that processed electroencephalograms provide a reliable estimate of sleep in the ICU when compared to polysomnography (33).

OBJECTIVE ASSESSMENT: NONELECTROENCEPHALOGRAM, PHYSIOLOGY-BASED

Actigraphy

An actigraph, a small noninvasive device that continuously measures spontaneous limb activity/movement, has been used as a surrogate measure of sleep in the ICU and to diagnose circadian disorders in outpatients (34). However, in mechanically ventilated critically ill adults, it has been shown to correlate poorly with polysomnography indicating a greater TST and sleep efficiency than polysomnography (22, 35), likely due to effects of sedation or critical illness neuropathy and myopathy on decreasing spontaneous movement. The role for actigraphy in ICU clinical practice is still evolving.

NONTRADITIONAL METHODS TO EVALUATE SLEEP

The study of sleep has progressed beyond electroencephalography; the use of other technologies (e.g., functional imaging, circulating micro messenger RNA) have advanced our understanding of sleep and the consequences of sleep deprivation. Although these approaches have not yet found a practical clinical application in the ICU, with further research they could become part of sleep assessment strategies going forward.

Cardiorespiratory Signals

Several groups have applied deep learning, artificial intelligence analysis to cardiac and respiratory signals to stage sleep (36, 37). These have only recently been applied in the ICU (38), although with only partial agreement between cardiac and respiratory staging in patients. These techniques are also likely to be limited in applicability for patients receiving adrenergic agents or patients who are mechanically ventilated.

Biomarkers of the Circadian System

Biomarkers are used to estimate the circadian function given that the circadian clock cannot be measured directly in humans. Core body temperature, plasma cortisol, and metabolites of melatonin are the most commonly measured surrogates (39). In the ICU, multiple factors affect the circadian system including the ICU environment (noise and especially light exposure), timing of feeding, medication administration, patient care interactions, and severity of illness. Although circadian function has implications for the proper functioning of vital biologic systems such as response to injury and illness and also has implications for the optimal timing of medication administration, it is impractical to measure in clinical practice and does not give direct information about sleep quality.

Functional Imaging

Functional imaging has been used to investigate both sleep physiology and the consequences of sleep disruption, primarily in healthy individuals. Functional MRI measurement of regional CNS blood-oxygen-level-dependent signals has revealed decoupling of frontal cortex from the default-mode network during deep sleep, but not light sleep (40, 41). Measuring a full night of sleep in an MRI scanner, however, remains challenging.

In contrast, functional imaging has been more revealing in studying the consequences of sleep disruption. In healthy individuals deprived of even one night of sleep, there are demonstrable changes in regional CNS vascular and metabolic function. Associated with these changes is the compromise of functional connectivity between areas of the brain necessary to integrate and process information (42, 43). Interactions between brain hemispheres are necessary for the integration of emotional, cognitive, motor, and sensory information. These studies suggest sleep loss impairs connectivity between the hippocampus and multiple other brain regions critical to memory and executive function and support further clinical investigation (42, 43). In

critically ill adults, functional imaging studies have been used to investigate disorders of consciousness such as delirium but have yet to been applied to the study of sleep or consequences of its disruption (44).

Circulating MicroRNAs

MicroRNAs are post-transcriptional regulators of gene expression. Recent advances in microRNA technology have enabled the use of these circulating gene signatures to detect sleep disorders (e.g., sleep-disordered breathing, habitual short sleep) in ambulatory adults. One outpatient study, using these signatures as a circulating biomarker of the consequences of sleep disruption, was able to distinguish patients with poor sleep from patients with normal sleep (45). Although this technology has not been studied for use in ICU, biomarker technology holds potential for identifying patients with preexisting, undiagnosed sleep disorders and the resulting poor quality sleep who are known to

TABLE 3.
Comparison of Different Methods to Evaluate Sleep in Critically Ill Adults

Measurement Tool	Outcome Measured	Advantages	Disadvantages
Traditional			
Subjective[a]	Patients' or surrogate's subjective assessment of their sleep	Most accessible, least costly	Recall bias. Altered recall due to delirium or sedation. Variable relationship with results of polysomnography
Actigraphy	Motion detector	Simple, not intrusive, little cost	Measures only motion so the effects of sedation and ICU care on motion not considered
Electroencephalogram-focused			
Processed electroencephalogram	Analysis of electroencephalogram waveform as surrogate for depth of sedation	Easy to use and available	Not validated against polysomnography as a measure of sleep
Polysomnography	Electroencephalogram Electrooculogram Electromyogram	Gold standard for measuring sleep in all patient settings	Limited by cost, requires skilled personnel to apply, interpretation difficult in the ICU, very intrusive
Single-channel electroencephalogram	Mostly delta power Frontal electrode	Uses delta waves to detect acute encephalopathy and/or ICU "depth of sleep" Mildly intrusive, easily applied. Real-time data	Crude assessment of level of consciousness. Likely cannot distinguish between different states of altered consciousness
Multichannel electroencephalogram	Several channel electroencephalogram (frontal) and also capable of collecting electrooculogram and electromyogram	Includes electroencephalogram but also with ability to do sleep staging Mildly intrusive, easily applied. Real-time data	Not as good as polysomnography for sleep staging
Newer physiologic-based methods of sleep assessment: not yet tested in the critically ill			
Functional imaging	CNS blood flow (functional MRI) CNS metabolism (positron emission tomography)	Records very specific physiologic measurements	Costly. Difficult/even risky to transport critically ill adults to conduct these studies. Studied in the critically ill for disorders of consciousness but not specifically sleep
MicroRNA	Experimental use for detecting or predicting poor sleep quality	Could become available serum biomarker	Currently untested for clinical use and in the critically ill

[a]Examples include validated questionnaires such as Richards Campbell Sleep Questionnaire.

be at risk for poor quality sleep both during and after the ICU.

Table 3 summarizes the advantages and disadvantages of the different methods used to measure sleep.

FUTURE DIRECTIONS

One of the current deficiencies in ICU care is the lack of an objective, scalable, continuous, real-time way to monitor and assess patients' sleep during their critical illness. Medication effect, metabolic dysregulation, CNS infection and vascular insult, seizures, and some psychiatric disorders can mimic sleep. Technologies to differentiate these factors and sleep states are not currently available in real time, thus often leading to consultation with specialists and procedures that may introduce risk. A scalable system akin to hemodynamic monitoring for cardiovascular function designed to monitor moment-to-moment alteration in CNS function, interpretable by intensivists, and with the ability to discriminate among these disorders of consciousness would be an invaluable improvement to ICU care.

Reliable measures of sleep quality in the ICU are lacking. At present, objective assessment tools measure mostly fidelity to electroencephalogram patterns known to be characteristic of the sleep/wake cycle of normal healthy individuals. Subjective measures are sometimes unreliable and other times unobtainable in ICU patients.

There needs to be development and testing of objective tools that measure sleep but are not affected by critical illness or its treatments and can reliably determine if the restorative functions of sleep have been achieved. Further, integration of measures of circadian biology would enhance our understanding of the alterations in each patient, which is requisite to formulating a personalized care plan. It may be through combinations of existing and evolving complementary strategies, such as multichannel electroencephalogram in combination with a subjective tool and circadian biomarker, and/or new evolving technologies leveraging machine learning algorithms and quantitative electroencephalogram that progress is made (6, 37, 46).

CONCLUSIONS

Sleep is essential to the normal functioning of the brain and numerous physiologic systems. Dysregulated sleep is common in ICU patients, particularly those with a high severity of illness. For many adults, sleep may not be recognizable by available diagnostic tools including the gold standard polysomnography. It is important to consider both what is being measured and what is not being measured as part of sleep assessment. Currently available objective, physiology-based assessment tools generally measure one or more physiologic parameters, that is, electrical signal from specific region (s) of the brain, patient movement, biomarkers of circadian rhythm. What is not being measured are the outcomes dependent on sleep for optimal functioning and which may be the most patient-centered outcomes. Subjective measurement tools do try to quantify the ill-defined restorative function of sleep by patient self-assessment and currently stand as the only readily available, practical, recommended assessment tool for use in the ICU. Subjective assessment of patients further validates patients' and family members' concerns and provides information about patient experience and ICU quality of life that cannot be gained in any other way; however, it is limited in scope and applicability. There is a need for technologic advance that would fill this important void in critical care diagnostics and management.

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