AJRCCM Articles in Press. Published on 16-January-2015 as 10.1164/rccm.201411-2099CI

Sleep in the Intensive Care Unit
Concise Clinical Review
American Journal of Respiratory and Critical Care Medicine

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All authors contributed to the review of the literature, writing and revision of the manuscript.

Key Words: sleep disruption, critical illness, polysomnography, circadian rhythm

Abstract

Sleep is an important physiologic process and lack of sleep is associated with a host of adverse outcomes. In addition, both basic and clinical research has documented the important role circadian rhythm plays in biologic function. Critical illness is a time of extreme vulnerability for patients and the important role sleep may play in recovery for ICU patients is just beginning to be explored. This concise clinical review will focus on the current state of research examining sleep in critical illness. We will discuss sleep and circadian rhythm abnormalities that occur in ICU patients and the challenges to measuring alterations in circadian rhythm in critical illness. In addition we will review methods to measure sleep in the ICU including polysomnography, actigraphy and questionnaires. We will discuss data on the impact of potentially modifiable disruptors to patient sleep, such as noise, light and patient care activities, and report on potential methods to improve sleep in the setting of critical illness. Finally we will review the latest literature on sleep disturbances that persist or develop after critical illness.

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Background

Sleep is a complex process influenced by both biologic and environmental factors. Despite spending one-third of our life asleep, the exact physiologic purpose of sleep is still to be elucidated.(1) There is growing evidence that sleep disturbances are associated with adverse outcomes.(2-4) The impact of sleep deprivation in critically ill patients is gaining attention, as is the link between sleep loss and delirium.(5, 6) This review article will focus on what is known about sleep in patients admitted to an intensive care unit (ICU). We will briefly review etiologies of sleep disruption and circadian rhythm abnormalities in the ICU; tools available to measure sleep in critically ill patients, sleep promoting interventions in the ICU, and sleep problems that may persist in survivors of critical illness.

Sleep Abnormalities in ICU Patients

Sleep abnormalities occur frequently in the intensive care unit (ICU).(7) These abnormalities include sleep deprivation and disruption, as well as abnormal sleep architecture. Factors impacting sleep in the ICU are numerous and detailed below. Compared to healthy adults, studies characterizing sleep disturbances in ICU patients utilizing polysomnography (PSG) have demonstrated prolonged sleep latency, sleep fragmentation, decreased sleep efficiency, numerous arousals, a preponderance of stage 2 sleep, decreased or absent stage 3 (“deep”) sleep, and decreased or absent REM sleep.(8-11) While mean total sleep time does not differ markedly from healthy adults, approximately 50% of ICU sleep occurs during the daytime hours with a marked shift toward light stages of sleep. These studies which have been performed in a varying ICU settings and demonstrate remarkable consistency (multiple short bouts of sleep during the day and night, a relatively normal total sleep time, significant sleep fragmentation and severe reductions in stage 3 and REM sleep). (7, 12)

Determining the best methods to score and stage sleep in critically ill patients has been the focus of recent research studies. Studies that have utilized PSG and standard R&K scoring reveal that sleep in ICU patients is abnormal with less slow wave and rapid eye movement sleep, increased arousals, and altered circadian timing.(10, 11, 13, 14) Some studies have also noted EEG patterns that do not reliability fit into any stage rendering R&K less useful. This is due to an absence of K complexes or sleep spindles in 20-44% of ICU patients, making classification of stage 2 sleep challenging.(15-17) In fact interobserver reliability using R&K is poor for scoring Stage 1 and 2 sleep with better agreements for scoring rapid eye movement sleep.(15) Third, drugs used for sedation, analgesia and vasopressors disrupt sleep and may affect EEG patterns.(18-20) As a result of these challenges, alternative methods to classify sleep using EEG are being explored.

Visual categorization of EEG. Visual sleep staging using the sleep-wakefulness organization pattern classifies sleep into one of five patterns based on frequency and voltage of the EEG and recognition of classical sleep elements, for example sleep spindles, rapid eye movements, or saw tooth waves. Prior application of scoring sleep using the sleep-wake organization pattern has been limited primarily to patients with head injury. When applied to patients in the ICU, interobserver reliability was only

moderate and found to be worse when sleep was less typical of NREM or REM and appeared rudimentary or monophasic.(15) Regardless, inter-observer reliability using the sleep-wake organization pattern was still better than R&K.

Spectral Analysis of EEG. Due to the inadequate agreement using visualization methods, computerized methods of scoring EEG were devised. Spectral analysis of EEG signals with Fast Fourier Transform quantifies EEG based on frequency with expression of sleep as a proportion of spectral frequency of theta, alpha, delta and beta power.(15) In one study, interobserver agreement for spectral analysis of sleep in critically ill patients revealed 100% agreement that was significantly better than visual methods which staged sleep based on R&K and the sleep-wake organization pattern.(15) In addition to reporting proportions of spectral frequency, spectral analysis can be used to measure the spectral edge frequency 95% (SEF95), which is defined as the frequency below which 95% of the spectral power resides with lower SEF95 indicating sleep and higher values indicating wakefulness.(13) The SEF95 has also been used to assess for circadian rhythmicity.(13) Limitations include inconsistencies in the selection of epochs to include for analysis. While spectral analysis seems to provide reliable agreement compared to other methods, further studies comparing spectral analysis alone or in conjunction with other methods to evaluated sleep in the ICU are needed.

Alternative Scoring Strategies. Because abnormal EEG patterns are common in ICU patients, alternative scoring strategies beside R&K are needed. Drouot et al devised a new classification for sleep analysis that incorporates both visual scoring and spectral analysis of the EEG.(21) Two new states of sleep are proposed: pathologic wakefulness and atypical sleep. Pathologic wakefulness is determined and graded visually by assessment of the EEG reactivity.(21) This method visually examines the background EEG rhythm in the occipital channel while the patient is awake with eyes closed followed by the patient's EEG reactivity to eye opening plus the peak EEG frequency using spectral analysis. Atypical sleep is defined by the absence of K complexes and sleep spindles with the presence of high amplitude, continuous irregular delta frequency EEG without superimposed fast frequencies or rapid eye movements and with low amplitude chin EMG.(21, 22) This system was devised in ICU patients who were not on any sedation. Such a strategy for sleep analysis expands upon existing strategies using visual inspection and quantitative spectral analysis of EEG. Using this approach in the ICU, atypical sleep was predicted with a sensitivity of 100% and a specificity of 97%.(21)

In addition to PSG findings of abnormal sleep, surveys of patients surviving critical illness indicate that sleep disturbances during their ICU course are one of the most frequent complaints.(7, 12) These sleep abnormalities in critical illness may contribute to altered mental status and impact on patient recovery in the acute setting. A summary of sleep disturbances noted in critically ill patients is presented in Table 1.

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Circadian Rhythm Alterations in Critically Ill Patients

Two primary processes, the endogenous circadian rhythm and homeostatic processes control the normal sleep-wake cycle. The “biologic clock” or circadian rhythm controls the timing and duration of daily sleep-wake cycles. The homeostatic process regulates the length and depth of sleep and is determined by the previous timing, duration and quality of sleep. Sleep and wakefulness result from an interaction between homeostatic mechanisms and endogenous circadian rhythms. The circadian timing system is comprised of a central pacemaker located in the suprachiasmatic nucleus (SCN) and peripheral clocks located in tissues throughout the body. Circadian misalignment occurs when there is a mismatch between the endogenous circadian rhythm and behavioral cycles of sleep and wakefulness, as occurs in jet lag or shift work. This can result in sleep disruption when sleep is desired and decrements in alertness and performance when it is not.

There are compelling reasons to believe that disruptions of circadian rhythmicity may harm the critically ill patient in very specific ways. Abnormalities of circadian rhythmicity may disrupt sleep-wake cycles, resulting in sleep disruption and poor sleep quality. In addition, alterations in circadian rhythmicity may impair recovery by disrupting the coordinated activity of normal physiologic processes.(23) Recent data suggest that endotoxin alters circadian clock gene expression in peripheral blood leukocytes, potentially uncoupling this expression from the activity of the central clock and interfering with the coordinated expression of the immune response.(24)

Historically, the analysis of circadian rhythmicity in humans has relied on the analysis of the temporal patterns of one or more of the following phase markers: (1) core body temperature, (2) plasma melatonin or its metabolite urinary 6-sulfatoxymelatonin (6SMT), or (3) plasma cortisol. While these are robust markers of circadian rhythmicity in healthy subjects in highly controlled circumstances, there are particular challenges to their use in critically ill patients. Recent data support the use of core body temperature or 6SMT as phase markers in critically ill patients. Fever, organ dysfunction, and medications may, however, render these measurements unreliable.(13, 25)

A typical ICU presents numerous threats to circadian rhythmicity, including low daytime and high nighttime light. In addition, patients may enter the ICU with significant alterations in circadian rhythmicity due their underlying illness, medications, or preexisting sleep schedule. Older patients may be at particular risk for ICU circadian disruption because of a greater propensity for sleep abnormalities as well as age-related declines in circadian rhythmicity.(26) There are no data on whether the circadian rhythm of critically ill patients can be entrained to the environment or if efforts to achieve this would result in improved outcomes. Such an effort would necessitate improving the ICU environment for sleep and wakefulness through a multifaceted intervention designed not only to improve sleep but also to enhance daytime light exposure

Hormones, Cytokines and Sleep Regulation

The neurochemical regulation of sleep is an emerging field of sleep research. Investigators are evaluating the effects of peptides, hormones, and cytokines on sleep regulation including the consequences of sleep deprivation on circulating levels of these

neurochemical modulators.(27) A number of cytokines have been hypothesized to influence sleep regulation including both sleep promotion and inhibition(28, 29) (they are listed in Table 2). For a more detailed discussion of individual mechanisms and pathways of the cytokines and hormones and their effect of sleep regulation see reviews by Krueger et al and Frenette et al.(30, 31)

Although the complexity of critical illness makes this a particularly challenging physiology to study, there are many examples where the interaction between sleep and neurohumoral regulation could be clinically important to the recovery of the critically ill. Insulin resistance, for example, is common among the critically ill; it also occurs with experimental models of sleep loss and may be augmented by circadian misalignment.(32) This potential relationship could be important in the ICU where hyperglycemia has been linked to poor clinical outcomes.

Risk Factors for ICU Sleep Deprivation

As depicted schematically in Figure 1, both patient specific factors and ICU environmental factors contribute to ICU sleep disruption.

Major patient factors for sleep deprivation in ICU patients are the type and severity of underlying illness, the pathophysiology of the acute illness, pain (from l procedures or the underlying condition) and stress/anxiety.(10, 12, 33) While the exact relationship between sleep and ICU severity of illness is still uncertain, it is likely important. One group demonstrated that increased sleep fragmentation is associated with increasing severity of illness. Another study which compared ICU patients with healthy volunteers exposed to the same ICU environment found that the critically ill patients had decreased total sleep time and a lower percentage of slow wave sleep.(34) This relationship between severity of illness and the ICU environment on sleep disturbance is complicated and needs more study.

While patient related factors likely play a large role in sleep disruption one cannot discount the impact of the ICU environment. Noise in the ICU arises from multiple sources including alarms, staff conversations, mechanical ventilators, pagers, and televisions. Noise has been implicated as an etiology of sleep disturbance in the ICU. Numerous studies have demonstrated peak noise levels in excess of recommendations by the Environmental Protection Agency (EPA) (45 decibels (dB) during the day and above 35 dB at night). Mean noise levels in the ICU have been shown to be as high as 55-65 dB over a 24-hour period and peak levels as high as 80 dB have been documented.(17, 35) Studies have demonstrated a correlation with elevated noise levels and the number of patients awake on the wards.(36) While baseline noise is elevated above EPA levels for most of a 24-hour period in the ICU, sound peaks $\geq$80dB have been associated with arousals from sleep.(37) Noise levels in the ICU are frequently well above acceptable levels; however, there are only a handful of studies that have attempted to link environment noise to arousals and awakenings. Those studies that have correlated noise with arousals by PSG have found noise to be the etiology of the disturbance between 11-24% of the total number of arousals.(17, 38) These data indicate that most of the arousals in patients in the ICU are not caused by noise suggesting that other factors must be important in the sleep disruption in ICU patients.

One such factor is abnormal light exposure. Nocturnal light levels in the ICU also contribute to sleep disruption. Light is important to maintaining a normal circadian

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rhythm. Studies which have measured light in the ICU have documented levels of over 1000 lux.(39) Nocturnal light levels as low as 100-500 lux can affect melatonin secretion and nocturnal levels between 300-500 lux may disrupt the circadian pacemaker.(40) Despite high levels of light, when ICU survivors were surveyed they reported that light did not disturb sleep as much as noise and patient care activities.(12)

Patient care activities such as nursing procedures, lab draws, vital signs, imaging, as well as procedures all contribute to sleep disruption in the ICU. ICU patients can experience up to 60 interruptions nightly related to patient care activities.(34, 41) Questionnaires devised by Freedman et al,(12) and by Little et al(42) have aimed to identify factors associated with poor sleep in the ICU. In general, patients report sleep quality in the ICU to be poor and that sleep is disrupted by noise, care activities such as phlebotomy and monitoring of vital signs, and pain.(12, 42) A majority of patients reported having abnormal sleep/wake cycles while in the ICU.(42)

Mechanical ventilation and medications also may contribute to the sleep disruption of critically ill patients. Sleep in mechanically ventilated patients is highly fragmented.(16) Additionally, ventilated patients may experience dyssynchrony with especially during periods of NREM sleep.(43) The ventilator mode may also play a role in sleep disruption. While pressure support ventilation allows the patient to determine their own respiratory rate and tidal volume there are descriptions of central apneas when using this mode of ventilation. These central apneas may be prevented by increasing dead space which can result in an increase in the arterial partial pressure of carbon dioxide.(44) A recent study demonstrated that nocturnal proportional assist ventilation resulted in less episodes of patient-ventilator dyssynchronies and was superior to pressure support ventilation in relation to sleep quality.(45)

Several medications including vasopressors, antibiotics, as well as sedatives and analgesics may have a negative impact on sleep quality and architecture. While benzodiazepines have been shown to increase total sleep time, they result in abnormal sleep architecture. They prolong stage 2 NREM and decrease slow wave sleep as well as REM sleep. In critically ill patients propofol has been shown to suppress REM sleep and worsen sleep quality.(46) Analgesics have also been associated with abnormal sleep architecture when given at doses higher than 10 mg/hour (morphine equivalent).(16) Inotropic medications can affect sleep through their effects on adrenergic receptors. Beta blockers, which are a frequently used medication in the ICU, can negatively impact sleep and may cause insomnia and nightmares due to suppressed REM sleep.(47) Quinolone antibiotics have been reported to disrupt sleep by inhibition of gamma aminobutyric acid (GABA) type A receptors in the brain.(48)

While all of these variables may contribute to the poor sleep of these patients, their importance lies in the fact that they are potentially modifiable. As such, interventions to limit these sleep-disruptors may serve as the basis for future sleep-promoting protocols in the ICU.

Physiologic Effects of Sleep Deprivation in the ICU

Sleep deprivation can affect the immune system, hormone levels, pulmonary mechanics and neurocognition. Although controversial, sleep loss impairs defense mechanisms and may render ICU patients more susceptible to infection.(49) Multiple

studies have shown a modulation of immune function secondary to changes in sleep patterns.(50, 51) The changes in the immune system with sleep deprivation in normal subjects are well described but whether these immune changes impact the ability of patients to recover from illness or increase susceptibility to illness are not known.

Sleep deprivation results in extensive changes to homeostatic mechanisms and alters neuroendocrine control systems and has been shown to cause increases in thyroid hormone, norepinephrine and cortisol levels with decreases in growth hormone levels and insulin resistance.(52) The impact of sleep disturbance on glucose metabolism is critical since glucose regulation can have an impact on patient morbidity and mortality in select ICU populations.(53)

Studies have shown that after 30 hours of sleep deprivation inspiratory muscle endurance is reduced, while FEV1 and FVC are unaltered.(54) Exercise performance has been shown to be negatively impacted by sleep deprivation. Such data suggest that sleep deprivation may affect respiratory muscle function of critically ill patients and impact weaning in mechanically ventilated patients.

Delirium is common in intensive care units.(55, 56) Many of the cognitive consequences of sleep loss are similar to those found in the delirious state. In healthy volunteers sleep deprivation has been shown to impair memory, attention, response time, and other aspects of neurologic function.(5) The relationship between sleep deprivation and delirium in the ICU is currently unproven.(57) However, since sleep deprivation impacts cognitive function a connection between delirium and sleep deprivation in critically ill patients may exist.(6)

Tools to measure sleep in critically ill patients

Sleep in the critically ill can be assessed using a variety of tools. While polysomnography (PSG) is the gold standard for sleep assessment in the outpatient setting, its utility in the ICU is met with numerous challenges.(10, 11) First, performance of EEG requires skilled personnel to apply equipment and interpret data. Additional expenses can be incurred due to the need for extended PSG recordings as sleep may not be isolated to nocturnal periods. Second, there are numerous challenges in scoring sleep in ICU patients. While the traditional scoring of sleep in ambulatory patients uses Rechtschaffen and Kales (R&K), such scoring rules are difficult to apply in ICU patients.

Actigraphy. Actigraphy measures body movement via an internal accelerometer and sleep time using the manufacturer's proprietary algorithm. The actigraph is an automated watch that can be worn on the wrist or ankle and is a valid tool to measure rest-wake patterns and total rest time.(58, 59) In normal healthy adult populations, actigraphy has significant correlation and agreement with PSG.(60) Its primary use in clinical practice is in the assessment of circadian rhythms in a non-critically ill population; however, a few studies have employed actigraphy to measure sedation/agitation in the ICU.(61) These studies indicate that actigraphy correlates with nurse directed observation of agitation, sleep, and sedation in alert and calm patients.(62) Actigraphy also correlates with validated assessments tools for sedation.(63) Its greatest potential for use may be as an objective measurement of sedation/agitation levels over a continuum allowing clinicians to identify increased

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agitation and to prompt further investigation; however additional research is still needed. (64)

Sleep Assessment by Survey. Patient and nurse assessments of sleep by questionnaires have been utilized in the ICU. The Richards-Campbell Sleep Questionnaire (RCSQ) is a brief 5 item questionnaire that uses a visual analog scale to assess sleep depth, latency, awakenings, percentage time awake, and quality of sleep.(65) The RCSQ has been validated against PSG in alert and oriented critically ill male patients, and the questionnaire can be completed by either the patient or the nurse.(65) (66)Studies examining reliability measures between patient and nurse assessments of sleep using the RCSQ are mixed. Two studies indicate that nurses overestimate sleep quality compared to their patients,(67, 68) while another study reported a high degree of correlation between patient and nurse assessments of sleep quality.(69) Nurse derived assessments of sleep overestimate total sleep time, sleep efficiency and underestimate the number of awakenings compared to PSG.(70) The pitfalls of patient reporting of sleep are potential inaccuracies in data due to the use of sedation and delirium.(71)

Despite ongoing research, limited scoring methods currently exist to assess and interpret sleep in ICU patients with most studies reporting small sample sizes and study related variability in the ICU population. As ongoing research imparts understanding of how environmental and pathophysiological factors affect sleep, the field of sleep analysis will continue to evolve. For the clinician at the bedside using sleep survey questionnaires is the easiest method to get assess patients sleep despite their limitations.

Sleep Promoting Interventions in the ICU

A critical next step is to test the effect of both non-pharmacologic and pharmacologic strategies to improve sleep and strengthen circadian rhythmicity of critically ill patients. A challenge for ICU sleep research is the need to deliver timely and appropriately aggressive 24-hour care to critically ill patients while identifying strategies that allow for the preservation of sleep and the enhancement of day-night routines.

The impact of noise reduction strategies on sleep in the ICU remains controversial and not well studied. Some studies have reported improvements in sleep with less arousals and increased REM duration, with use of earplugs.(72) However, another study demonstrated that while reduction in noise increased sleep quantity it did not change sleep architecture or arousal index.(34)

In healthy patients exposed to simulated ICU noise and light, provision of earplugs and eye masks resulted in increase in REM sleep, shorter REM latency, less arousals and elevated melatonin levels.(73) Studies in non-sedated, non-ventilated critically ill patients have demonstrated subjective improvements in sleep with the use of earplugs.(72) Several small studies have examined a variety of relaxation techniques to improve sleep in ICU patients. Critically ill male patients demonstrated improved quantity and quality of sleep when provided a 6-minute back massage.(74) A study of patients undergoing surgery were exposed to ocean sounds to simulate white noise and

compared to a usual care control group the intervention patients demonstrated subjective improvements in sleep measured by the RCSQ.

Various investigators have studied the introduction of quiet times. A non-randomized controlled trial of quiet time demonstrated reductions in noise and increased sleep in patients in the experimental group.(36) Patients, visitors and healthcare providers also reported satisfaction with the quiet time intervention. A pre-post observational sleep promoting quality improvement project in the ICU demonstrated a decrease in perceived noise and a reduction in delirium days, but not improved sleep as measured by the RCSQ.(75)

Circadian rhythm abnormalities and reduced levels of melatonin have been documented in critical illness. A randomized controlled trial in a small number of patients showed that patients who received 10mg of oral melatonin vs. placebo demonstrated improved nocturnal sleep efficiency as measured by BIS (bispectral index).(76)

Sleep promoting interventions will need to be multi-pronged and focus on reducing nighttime sleep disruption and maintaining a normal circadian rhythm.(77) Such a protocol may necessarily need to limit daytime sleep. It is important to note that hypnotics have not been well studied in the critically ill. Many of them have, however, been associated with delirium and should be avoided. Antipsychotics and antidepressants are sometimes used leveraging their sedating side effects, however, such medications have significant side effects including delirium making their use problematic.(78) Their effect on the sleep of critically ill patients is unknown.

Implementation of ICU sleep protocols will require culture change which will need to be individualized to accommodate the work-flows of each institution and critical care setting. This will require education of ICU physicians, nurses, and other ancillary staff along with the measurement of performance and compliance with the protocol.

Sleep after Critical Illness

Poor sleep, which develops during an acute illness, can persist for an extended period of time after discharge and is one of the most frequently cited stressful experiences for patients who have been critically ill.(12, 42, 68, 79) The etiology of abnormal sleep during recovery from critical illness is multi-factorial. Until recently, however, the sleep and circadian rhythms of survivors of critical illness had received little scrutiny. There is accumulating evidence that sleep disturbances are common in this patient population.(80-82) McKinley et al documented moderate to severe self-reported sleep problems in 50% of all respondents one week after hospital discharge.(80) While sleep quality generally improved over time, nearly one-third of all subjects continued to experience moderate to severe problems at 26 weeks.

Sleep disturbances can be distressing to patients and have been shown to be associated with reduced quality of life in survivors of acute lung injury.(82) Physical and cognitive rehabilitation may also be impaired when patients suffer from excessive sleepiness and low energy. In addition, sleep and circadian processes have been implicated in the pathogenesis of a variety of neuropsychiatric diseases that occur commonly after critical illness, including cognitive impairment, depression, anxiety, and posttraumatic stress disorder.(83) In the study by McKinley the presence of sleep

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problems at week 26 was independently associated with poor psychological recovery.(80) Orwelius similarly noted a relationship between poor sleep at 6 and 12 months and low quality of life scores.(81)

The causes of these sleep disturbances are not clear. Given that ICU survivors frequently suffer from a number of active medical problems, it is possible that the presence of sleep disturbances in this population simply marks unresolved illness. Evidence to support this assertion comes from a study in which subjects reported that sleep quality after being in the ICU was similar to *retrospectively* assessed sleep quality prior to critical illness.(81) However, it is possible that the modern critical care experience—including acute illness, a nontherapeutic environment for sleep and wakefulness, and exposure to multiple medications affecting neurotransmitter balance—engenders new sleep disturbances that persist in some subjects after intensive care. This is similar to the development of new or worsening cognitive function after critical illness and reflects shared mechanisms in the brain.(84) Thus there is a need for well-designed prospective studies that characterize sleep and circadian disruption throughout critical illness and recovery while examining their relationship to long-term neuropsychiatric outcomes.

Conclusion:

The relationship between the poor sleep in critically ill patients and their ultimate outcomes remains unknown but potentially important. Poor sleep may contribute to the larger problem of brain dysfunction in the ICU of which delirium is a manifestation. A multidisciplinary approach to understanding and treating the problem will require commitment both on the part of ICU practitioners and hospital administrators which, in turn, may lead to significant improvement in ICU care and patient outcomes.

Acknowledgments: The authors would like to acknowledge the members of the Sleep in the ICU Task Force for their expert contribution to this manuscript. Linda Chlan MD, Nancy Collop MD, Carolyn D'Ambrosio MD, Xavier Druout MD, Biren Kamdar MD, Melissa Knauert MD, PhD, Theresa Krupski, Vipin Malik MD, Robert Owens MD, Sairam Parthasarathy MD, Elizabeth Parsons, MD, Nancy Redeker PhD, RN, Kathy Richards PhD, RN, Paula Watson MD, Klar Yaggi MD

AJRCCM Articles in Press. Published on 16-January-2015 as 10.1164/rccm.201411-2099CI

Figure 1 Factors Related to Sleep Deprivation in Critically Ill Patients

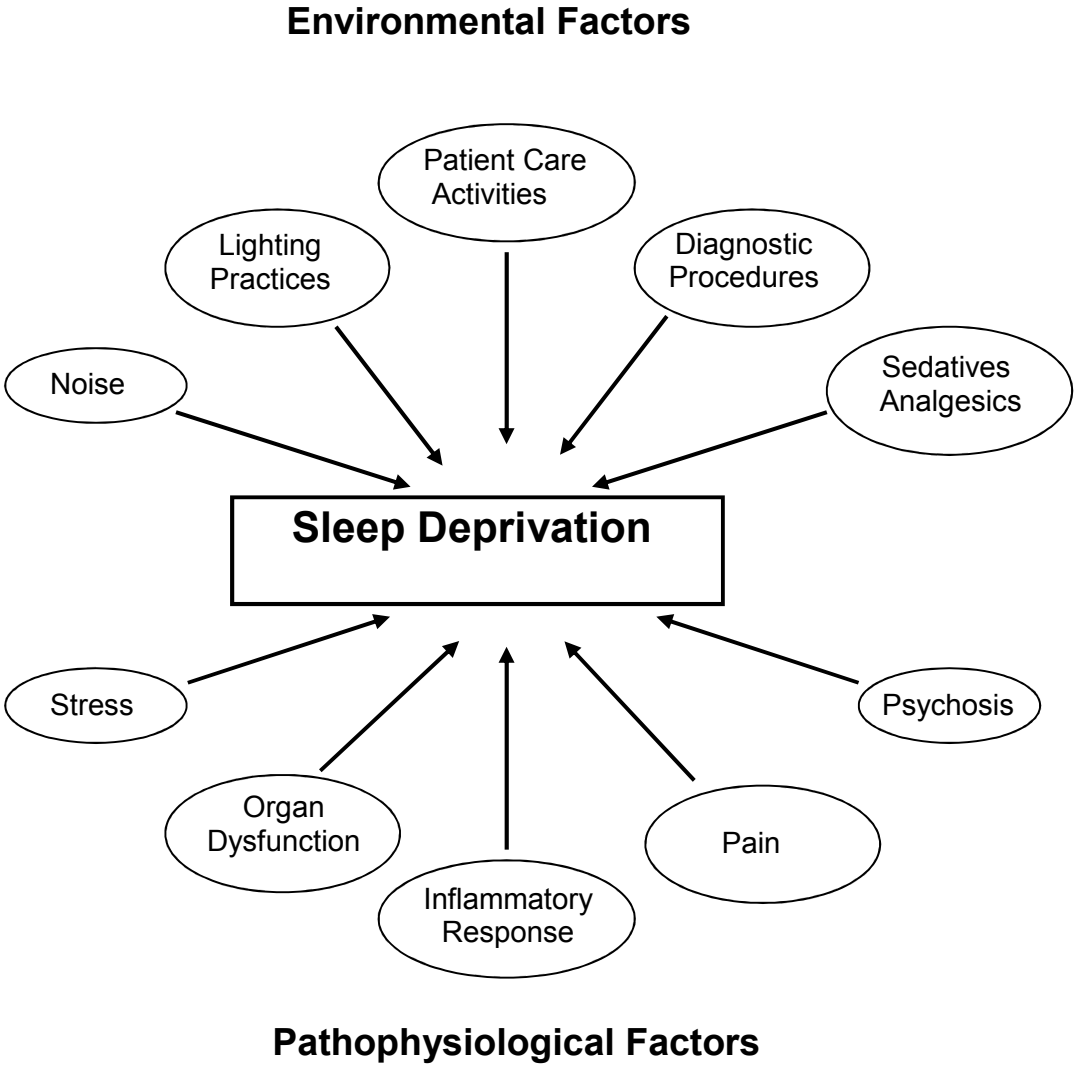

Table 1 Sleep Disturbances in Critically Ill Patient

Patient Related Factors	
Preexisting sleep disorders	
Pain	
Anxiety	
ICU Related Factors	
Noise	
Light	
Patient care activities	
Polysomnographic (PSG) findings in critically ill patients	
Total Sleep Time (TST)	Unchanged/Decreased
TST occurring during daytime hours	50%
Sleep Latency	Unchanged/Increased
Sleep Efficiency	Decreased
Sleep Fragmentation	Increased
Arousals	Increased
NREM Stage 1 (N1)	Increased
NREM Stage 2 (N2)	Increased
NREM Stage 3 (N3)	Decreased
Rapid Eye Movement (REM)	Decreased
Challenges with scoring PSG in critically ill patients	
NREM Stage 1 & 2	Poor interobserver reliability with R&K
NREM Stage 2	Difficulty classifying
Absence of K Complexes	20-44%
Absence of Sleep Spindles	20-44%
Use of sedating medications	
Alternative PSG Scoring Strategies	
Pathologic wakefulness	Visual assessment of EEG reactivity using spectral analysis with eyes open and closed
Atypical sleep	Absence of K complexes and sleep spindles High amplitude continuous irregular delta frequency EEG No fast frequencies, no REM Low amplitude chin EMG

NREM-Non Rapid Eye Movement, R&K-Rechtschaffen & Kales

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Table 2. Cytokines and Neurohumoral Regulators of Sleep (References (27, 29, 85-91))

	Effect on NREM Sleep
IL-1	Promotion
IL-2	Possibly Promotes*
IL-4	Inhibition
IL-6	Possibly Promotes**
IL-10	Inhibition
IL-18	Promotion
TNF-α	Promotion
TGF-β	Inhibition
IGF-1	Inhibition
GHRH	Promotion
CRH	Inhibition
NO	Promotion
Ghrelin	Promotion
VIP	Promotion

*Sleep induces increased circulating IL-2 levels

**May play a more important role in sleep regulation during pathologic states

NREM- Non Rapid Eye Movement; IL–Interleukin; TNF–Tumor Necrosis Factor; TGF –Transforming Growth Factor; GHRH–Growth Hormone Releasing Hormone; NO – Nitric Oxide; IGF – Insulin Like growth Factor; CRH – Corticotropin Releasing Hormone; VIP – Vasoactive Intestinal Peptide

REFERENCES:

1. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M. Sleep drives metabolite clearance from the adult brain. *Science* 2013; 342: 373-377.
2. Grandner MA, Hale L, Moore M, Patel NP. Mortality associated with short sleep duration: The evidence, the possible mechanisms, and the future. *Sleep Med Rev* 2010; 14: 191-203.
3. Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. *J Sleep Res* 2009; 18: 148-158.
4. Grandner MA, Sands-Lincoln MR, Pak VM, Garland SN. Sleep duration, cardiovascular disease, and proinflammatory biomarkers. *Nature and science of sleep* 2013; 5: 93-107.
5. Weinhouse GL, Schwab RJ, Watson PL, Patil N, Vaccaro B, Pandharipande P, Ely EW. Bench-to-bedside review: delirium in ICU patients - importance of sleep deprivation. *Crit Care* 2009; 13: 234.
6. Kamdar BB, Niessen T, Colantuoni E, King LM, Neufeld KJ, Bienvenu OJ, Rowden AM, Collop NA, Needham DM. Delirium Transitions in the Medical ICU: Exploring the Role of Sleep Quality and Other Factors. *Crit Care Med* 2014.
7. Tembo AC, Parker V, Higgins I. The experience of sleep deprivation in intensive care patients: findings from a larger hermeneutic phenomenological study. *Intensive Crit Care Nurs* 2013; 29: 310-316.
8. Friese RS, Diaz-Arrastia R, McBride D, Frankel H, Gentilello LM. Quantity and quality of sleep in the surgical intensive care unit: are our patients sleeping? *J Trauma* 2007; 63: 1210-1214.
9. Parthasarathy S, Tobin MJ. Sleep in the intensive care unit. *Intensive Care Med* 2004; 30: 197-206.
10. Elliott R, McKinley S, Cistulli P, Fien M. Characterisation of sleep in intensive care using 24-hour polysomnography: an observational study. *Crit Care* 2013; 17: R46.
11. Knauert MP, Yaggi HK, Redeker NS, Murphy TE, Araujo KL, Pisani MA. Feasibility study of unattended polysomnography in medical intensive care unit patients. *Heart Lung* 2014; 43: 445-452.
12. Freedman NS, Kotzer N, Schwab RJ. Patient perception of sleep quality and etiology of sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 1999; 159: 1155-1162.
13. Gehlbach BK, Chapotot F, Leproult R, Whitmore H, Poston J, Pohlman M, Miller A, Pohlman AS, Nedeltcheva A, Jacobsen JH, Hall JB, Van Cauter E. Temporal disorganization of circadian rhythmicity and sleep-wake regulation in mechanically ventilated patients receiving continuous intravenous sedation. *Sleep* 2012; 35: 1105-1114.
14. Hardin KA, Seyal M, Stewart T, Bonekat HW. Sleep in critically ill chemically paralyzed patients requiring mechanical ventilation. *Chest* 2006; 129: 1468-1477.

AJRCCM Articles in Press. Published on 16-January-2015 as 10.1164/rccm.201411-2099CI

15. Ambrogio C, Koebnick J, Quan SF, Ranieri M, Parthasarathy S. Assessment of sleep in ventilator-supported critically Ill patients. *Sleep* 2008; 31: 1559-1568.
16. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ. Sleep in critically ill patients requiring mechanical ventilation. *Chest* 2000; 117: 809-818.
17. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 2001; 163: 451-457.
18. Schweitzer PK. Drugs that disturb sleep and wakefulness. In: Kryger MH, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. Philadelphia: Elsevier/Saunders; 2005. p. 499-515.
19. Murphy M, Bruno MA, Riedner BA, Boveroux P, Noirhomme Q, Landsness EC, Brichant JF, Phillips C, Massimini M, Laureys S, Tononi G, Boly M. Propofol anesthesia and sleep: a high-density EEG study. *Sleep* 2011; 34: 283-291A.
20. Pandharipande P, Ely EW. Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. *Crit Care Clin* 2006; 22: 313-327, vii.
21. Drouot X, Roche-Campo F, Thille AW, Cabello B, Galia F, Margarit L, d'Ortho MP, Brochard L. A new classification for sleep analysis in critically ill patients. *Sleep Med* 2011; 13: 7-14.
22. Watson PL, Pandharipande P, Gehlbach BK, Thompson JL, Shintani AK, Dittus BS, Bernard GR, Malow BA, Ely EW. Atypical sleep in ventilated patients: empirical electroencephalography findings and the path toward revised ICU sleep scoring criteria. *Crit Care Med* 2013; 41: 1958-1967.
23. Silver AC, Arjona A, Walker WE, Fikrig E. The circadian clock controls toll-like receptor 9-mediated innate and adaptive immunity. *Immunity* 2012; 36: 251-261.
24. Haimovich B, Calvano J, Haimovich AD, Calvano SE, Coyle SM, Lowry SF. In vivo endotoxin synchronizes and suppresses clock gene expression in human peripheral blood leukocytes. *Crit Care Med* 2010; 38: 751-758.
25. Gazendam JA, Van Dongen HP, Grant DA, Freedman NS, Zwaveling JH, Schwab RJ. Altered circadian rhythmicity in patients in the ICU. *Chest* 2013; 144: 483-489.
26. Nakamura TJ, Nakamura W, Yamazaki S, Kudo T, Cutler T, Colwell CS, Block GD. Age-related decline in circadian output. *J Neurosci* 2011; 31: 10201-10205.
27. Gomez-Gonzalez B, Dominguez-Salazar E, Hurtado-Alvarado G, Esqueda-Leon E, Santana-Miranda R, Rojas-Zamorano JA, Velazquez-Moctezuma J. Role of sleep in the regulation of the immune system and the pituitary hormones. *Ann N Y Acad Sci* 2012; 1261: 97-106.
28. Kaushal N, Ramesh V, Gozal D. TNF-alpha and temporal changes in sleep architecture in mice exposed to sleep fragmentation. *PLoS One* 2012; 7: e45610.
29. Weikel JC, Wichniak A, Ising M, Brunner H, Friess E, Held K, Mathias S, Schmid DA, Uhr M, Steiger A. Ghrelin promotes slow-wave sleep in humans. *Am J Physiol Endocrinol Metab* 2003; 284: E407-415.
30. Krueger JM, Majde JA, Rector DM. Cytokines in immune function and sleep regulation. *Handbook of clinical neurology* 2011; 98: 229-240.
31. Frenette E, Lui A, Cao M. Neurohormones and sleep. *Vitamins and hormones* 2012; 89: 1-17.

32. Leproult R, Holmback U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes* 2014; 63: 1860-1869.
33. Bihari S, Doug McEvoy R, Matheson E, Kim S, Woodman RJ, Bersten AD. Factors affecting sleep quality of patients in intensive care unit. *J Clin Sleep Med* 2012; 8: 301-307.
34. Gabor JY, Cooper AB, Crombach SA, Lee B, Kadikar N, Bettger HE, Hanly PJ. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med* 2003; 167: 708-715.
35. Salandin A, Arnold J, Kornadt O. Noise in an intensive care unit. *J Acoust Soc Am* 2012; 130: 3754-3760.
36. Gardner G, Collins C, Osborne S, Henderson A, Eastwood M. Creating a therapeutic environment: a non-randomised controlled trial of a quiet time intervention for patients in acute care. *International journal of nursing studies* 2009; 46: 778-786.
37. Aaron JN, Carlisle CC, Carskadon MA, Meyer TJ, Hill NS, Millman RP. Environmental noise as a cause of sleep disruption in an intermediate respiratory care unit. *Sleep* 1996; 19: 707-710.
38. Cabello B, Thille AW, Drouot X, Galia F, Mancebo J, d'Ortho MP, Brochard L. Sleep quality in mechanically ventilated patients: comparison of three ventilatory modes. *Crit Care Med* 2008; 36: 1749-1755.
39. Meyer TJ, Eveloff SE, Bauer MS, Schwartz WA, Hill NS, Millman RP. Adverse environmental conditions in the respiratory and medical ICU settings. *Chest* 1994; 105: 1211-1216.
40. Weinhouse GL, Schwab RJ. Sleep in the critically ill patient. *Sleep* 2006; 29: 707-716.
41. Tamburri LM, DiBrienza R, Zozula R, Redeker NS. Nocturnal care interactions with patients in critical care units. *Am J Crit Care* 2004; 13: 102-112; quiz 114-105.
42. Little A, Ethier C, Ayas N, Thanachayanont T, Jiang D, Mehta S. A patient survey of sleep quality in the Intensive Care Unit. *Minerva Anestesiol* 2012; 78: 406-414.
43. Simon PM, Zurob AS, Wies WM, Leiter JC, Hubmayr RD. Entrainment of respiration in humans by periodic lung inflations. Effect of state and CO(2). *Am J Respir Crit Care Med* 1999; 160: 950-960.
44. Parthasarathy S, Tobin MJ. Effect of ventilator mode on sleep quality in critically ill patients. *Am J Respir Crit Care Med* 2002; 166: 1423-1429.
45. Bosma K, Ferreyra G, Ambrogio C, Pasero D, Mirabella L, Braghiroli A, Appendini L, Mascia L, Ranieri VM. Patient-ventilator interaction and sleep in mechanically ventilated patients: pressure support versus proportional assist ventilation. *Crit Care Med* 2007; 35: 1048-1054.
46. Kondili E, Alexopoulou C, Xirouchaki N, Georgopoulos D. Effects of propofol on sleep quality in mechanically ventilated critically ill patients: a physiological study. *Intensive Care Med* 2012; 38: 1640-1646.
47. Bourne RS, Mills GH. Sleep disruption in critically ill patients--pharmacological considerations. *Anaesthesia* 2004; 59: 374-384.

AJRCCM Articles in Press. Published on 16-January-2015 as 10.1164/rccm.201411-2099CI

48. Unseld E, Ziegler G, Gemeinhardt A, Janssen U, Klotz U. Possible interaction of fluoroquinolones with the benzodiazepine-GABAA-receptor complex. *Br J Clin Pharmacol* 1990; 30: 63-70.
49. Faraut B, Boudjeltia KZ, Vanhamme L, Kerkhofs M. Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. *Sleep Med Rev* 2012; 16: 137-149.
50. Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. *JAMA* 2002; 288: 1471-1472.
51. Benedict C, Dimitrov S, Marshall L, Born J. Sleep enhances serum interleukin-7 concentrations in humans. *Brain Behav Immun* 2007; 21: 1058-1062.
52. Schmid SM, Hallschmid M, Jauch-Chara K, Bandorf N, Born J, Schultes B. Sleep loss alters basal metabolic hormone secretion and modulates the dynamic counterregulatory response to hypoglycemia. *J Clin Endocrinol Metab* 2007; 92: 3044-3051.
53. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345: 1359-1367.
54. Chen HI, Tang YR. Sleep loss impairs inspiratory muscle endurance. *Am Rev Respir Dis* 1989; 140: 907-909.
55. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med* 2007; 33: 66-73.
56. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. *J Am Geriatr Soc* 2003; 51: 591-598.
57. Fitzgerald JM, Adamis D, Trzepacz PT, O'Regan N, Timmons S, Dunne C, Meagher DJ. Delirium: a disturbance of circadian integrity? *Medical hypotheses* 2013; 81: 568-576.
58. Madsen MT, Rosenberg J, Gogenur I. Actigraphy for measurement of sleep and sleep-wake rhythms in relation to surgery. *J Clin Sleep Med* 2013; 9: 387-394.
59. Grap MJ, Hamilton VA, McNallen A, Ketchum JM, Best AM, Arief NY, Wetzel PA. Actigraphy: analyzing patient movement. *Heart Lung* 2011; 40: e52-59.
60. Morgenthaler TI, Lee-Chiong T, Alessi C, Friedman L, Aurora RN, Boehlecke B, Brown T, Chesson AL, Jr., Kapur V, Maganti R, Owens J, Pancer J, Swick TJ, Zak R. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. *Sleep* 2007; 30: 1445-1459.
61. Raj R, Ussavarungsi K, Nugent K. Accelerometer-based devices can be used to monitor sedation/agitation in the intensive care unit. *Journal of critical care* 2014; 29: 748-752.
62. Mistraletti G, Taverna M, Sabbatini G, Carloni E, Bolgiaghi L, Pirrone M, Cigada M, Destrebecq AL, Carli F, Iapichino G. Actigraphic monitoring in critically ill patients: preliminary results toward an "observation-guided sedation". *J Crit Care* 2009; 24: 563-567.
63. Grap MJ, Borchers CT, Munro CL, Elswick RK, Jr., Sessler CN. Actigraphy in the critically ill: correlation with activity, agitation, and sedation. *Am J Crit Care* 2005; 14: 52-60.

64. van der Kooi AW, Tulen JH, van Eijk MM, de Weerd AW, van Uitert MJ, van Munster BC, Slooter AJ. Sleep monitoring by actigraphy in short-stay ICU patients. *Crit Care Nurs Q* 2013; 36: 169-173.
65. Richards KC, O'Sullivan PS, Phillips RL. Measurement of sleep in critically ill patients. *J Nurs Meas* 2000; 8: 131-144.
66. Bourne RS, Minelli C, Mills GH, Kandler R. Clinical review: Sleep measurement in critical care patients: research and clinical implications. *Crit Care* 2007; 11: 226.
67. Kamdar BB, Shah PA, King LM, Kho ME, Zhou X, Colantuoni E, Collop NA, Needham DM. Patient-nurse interrater reliability and agreement of the Richards-Campbell sleep questionnaire. *Am J Crit Care* 2012; 21: 261-269.
68. Nicolas A, Aizpitarte E, Iruarrizaga A, Vazquez M, Margall A, Asiain C. Perception of night-time sleep by surgical patients in an intensive care unit. *Nurs Crit Care* 2008; 13: 25-33.
69. Frisk U, Nordstrom G. Patients' sleep in an intensive care unit--patients' and nurses' perception. *Intensive Crit Care Nurs* 2003; 19: 342-349.
70. Beecroft JM, Ward M, Younes M, Crombach S, Smith O, Hanly PJ. Sleep monitoring in the intensive care unit: comparison of nurse assessment, actigraphy and polysomnography. *Intensive Care Med* 2008; 34: 2076-2083.
71. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, Gordon SM, Canonico AE, Dittus RS, Bernard GR, Ely EW. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med* 2010; 38: 1513-1520.
72. Scotto CJ, McClusky C, Spillan S, Kimmel J. Earplugs improve patients' subjective experience of sleep in critical care. *Nurs Crit Care* 2009; 14: 180-184.
73. Hu RF, Jiang XY, Zeng YM, Chen XY, Zhang YH. Effects of earplugs and eye masks on nocturnal sleep, melatonin and cortisol in a simulated intensive care unit environment. *Crit Care* 2010; 14: R66.
74. Richards KC. Effect of a back massage and relaxation intervention on sleep in critically ill patients. *Am J Crit Care* 1998; 7: 288-299.
75. Kamdar BB, King LM, Collop NA, Sakamuri S, Colantuoni E, Neufeld KJ, Bienvenu OJ, Rowden AM, Touradji P, Brower RG, Needham DM. The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. *Crit Care Med*; 41: 800-809.
76. Bourne RS, Mills GH, Minelli C. Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomised controlled trial. *Crit Care* 2008; 12: R52.
77. Tamrat R, Huynh-Le MP, Goyal M. Non-pharmacologic interventions to improve the sleep of hospitalized patients: a systematic review. *Journal of general internal medicine* 2014; 29: 788-795.
78. Pisani MA, Murphy TE, Araujo KL, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit Care Med* 2009; 37: 177-183.
79. Rotondi AJ, Chelluri L, Sirio C, Mendelsohn A, Schulz R, Belle S, Im K, Donahoe M, Pinsky MR. Patients' recollections of stressful experiences while receiving prolonged mechanical ventilation in an intensive care unit. *Crit Care Med* 2002; 30: 746-752.

AJRCCM Articles in Press. Published on 16-January-2015 as 10.1164/rccm.201411-2099CI

80. McKinley S, Aitken LM, Alison JA, King M, Leslie G, Burmeister E, Elliott D. Sleep and other factors associated with mental health and psychological distress after intensive care for critical illness. *Intensive Care Med* 2012; 38: 627-633.
81. Orwelius L, Nordlund A, Nordlund P, Edell-Gustafsson U, Sjoberg F. Prevalence of sleep disturbances and long-term reduced health-related quality of life after critical care: a prospective multicenter cohort study. *Crit Care* 2008; 12: R97.
82. Parsons EC, Kross EK, Caldwell ES, Kapur VK, McCurry SM, Vitiello MV, Hough CL. Post-discharge insomnia symptoms are associated with quality of life impairment among survivors of acute lung injury. *Sleep Med* 2012; 13: 1106-1109.
83. Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat Rev Neurosci* 2010; 11: 589-599.
84. Jackson JC, Mitchell N, Hopkins RO. Cognitive functioning, mental health, and quality of life in ICU survivors: an overview. *Crit Care Clin* 2009; 25: 615-628, x.
85. Dzaja A, Dalal MA, Himmerich H, Uhr M, Pollmacher T, Schuld A. Sleep enhances nocturnal plasma ghrelin levels in healthy subjects. *Am J Physiol Endocrinol Metab* 2004; 286: E963-967.
86. Irwin M. Effects of sleep and sleep loss on immunity and cytokines. *Brain Behav Immun* 2002; 16: 503-512.
87. Krueger JM, Majde JA. Humoral links between sleep and the immune system: research issues. *Ann N Y Acad Sci* 2003; 992: 9-20.
88. Krueger JM, Obal FJ, Fang J, Kubota T, Taishi P. The role of cytokines in physiological sleep regulation. *Ann N Y Acad Sci* 2001; 933: 211-221.
89. Obal F, Jr., Krueger JM. GHRH and sleep. *Sleep Med Rev* 2004; 8: 367-377.
90. Vgontzas AN, Chrousos GP. Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. *Endocrinol Metab Clin North Am* 2002; 31: 15-36.
91. Vgontzas AN, Papanicolaou DA, Bixler EO, Lotsikas A, Zachman K, Kales A, Prolo P, Wong ML, Licinio J, Gold PW, Hermida RC, Mastorakos G, Chrousos GP. Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metab* 1999; 84: 2603-2607.