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Sleep and critical illness: bridging the two pillars at the ATS 2016

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At the American Thoracic Society Meeting in 2016, a post-graduate session focused on a number of current issues and ideas relevant to sleep in the critical care setting. The prevailing theme was encouraging physicians to consider sleep issues when caring for critically ill patients while recognizing how difficult this focus can be in practice. Emerging evidence shows the importance of sleep to mortality, cognition, and overall wellbeing. The necessities of quality sleep clearly carry over into the inpatient setting.

The effect of ICU on patient sleep

Sleep is necessary in decreasing neuroinflammation, removing unimportant synaptic connections, and in memory formation; these neurologic processes remain necessary even in the critically ill. Although sleep in critical illness is not well understood, we do know that overall sleep quality for ICU patients is poor. Total sleep time is shortened, there are frequent interruptions, and sleep occurs at inappropriate times (1). Impaired sleep decreases vigilance and attention, and may contribute to the widespread problem of ICU delirium.

Additionally, poor sleep in the critically ill may affect ventilatory responsiveness and inspiratory muscle endurance, and potentially affects mortality, although more research is needed in these areas to determine causal relationships.

Mechanical ventilation, often a key component of ICU care, also has effects on how patients sleep. Although some suggest that mechanical ventilation can improve sleep by decreasing work of breathing and maintaining appropriate gas exchange, excessive ventilatory support can lead to

fragmented sleep, increased arousals and central apneas (2). Guidelines regarding optimizing ventilatory support to mitigate sleep quality reductions are currently lacking, but are a work in progress.

Circadian rhythms and the ICU environment

Sleep is integrally linked to the body's natural circadian rhythms (or internal clock), which can be severely disrupted in ICU patients. Electroencephalogram (EEG) data show that sleep in the ICU is highly fragmented and nonconsolidated (1); levels of melatonin are low in ICU patients, also supporting substantial interruption of the internal clock. Some data also show that critically ill patients do not have a diurnal rhythm (3). The background causes of circadian rhythm disruption in the ICU are critical illness itself and the necessary treatments which can often be invasive, intensive and may occur during sleep times. Moreover, light is an important regulator of the circadian rhythm. Thus, lack of sleep opportunity and poor circadian cues largely contribute to the problem.

Improving the ICU sleep environment has been an area of recent interest. Measures as simple as noise reduction (specifically noise peaks), care clustering, and altering light exposure patterns could potentially lead to markedly improved sleep and circadian rhythm cycling. There are additional circadian cues, such as the timing of feeding, which are often ignored in the ICU setting. In order to address these issues, a group at Yale is actively working to implement measures to help promote sleep. In addition to noise reductions these colleagues are trying to reduce the number of care interactions by clustering care, maintaining

appropriate day/night light cycles, and changing tube-feed strategies to better mimic a natural eating pattern better. Although the measures sound simple, the consistent implementation of them on a large scale is a difficult task.

Sedation and sleep in the ICU

It is important to recognize that sleep and sedation are not equivalent, and that sedation type will affect patients' sleep. Benzodiazepines are frequently used for sedation purposes in the ICU, but, in addition potentially to conferring increased mortality (4) and likely causing delirium (5), GABAergic medications do not necessarily promote natural sleep. Wakefulness is in part driven by output from the locus coeruleus (LC), the activity of which is downregulated in the sleep state. Benzodiazepines do not produce the same effect on the LC as does sleep, since LC's activity remains high when under sedation with benzodiazepines (6). Additionally, GABAergic drugs decrease NREM sleep and decrease sleep latency. There has been considerable interest in using dexmedetomidine as a sedation tool in the ICU. Even though a 2015 Cochrane review did not reveal any evidence that the use of dexmedetomidine improved mortality or delirium incidence (7), this agent may be better at promoting sleep than other medications (8).

There are currently no sedating medications that promote true sleep architecture, and the impact of propofol and opiates need more study. Overall, a considerable amount of work remains to be done regarding the integration, or perhaps separation, of sleep and sedation in the critically ill. Some important points, however, include minimization of benzodiazepines when appropriate, and the importance of sedation vacations.

Measuring sleep in the ICU

The importance of measuring sleep in the ICU is becoming more apparent as research progresses and clinical care becomes increasingly sophisticated. However, even when physicians recognize the importance of sleep in the hospitalized patient, there is no standardized method of easily evaluating sleep in the inpatient setting. The gold standard EEG is cumbersome in the ICU setting and does not have a practical role in this arena. Patient and nurse reported measures of sleep quality are subjective and often do not correlate to more objective data; additionally, critically ill patients cannot reliably report their sleep quality when sedated. Overall, we know very little about

sleep, or the brain's function, during critical illness, without appropriate monitoring. One of the first steps towards future improvement in this area is wireless, non-invasive monitoring of sleep and sleep staging, the development of which is currently under investigation.

Delirium in the ICU

Logically, poor sleep and ICU delirium seem related, although causality has not yet been proven. Lack of sleep can produce symptoms very similar to those of delirium, and the high rates of delirium in the ICU setting where quality sleep is scarce make the relationship impossible to ignore; sleep deprivation impairs cognition and attention (9) which are key features of delirium. Importantly, delirium is a predictor of mortality (10,11), and it increases length of stay and leads to longer mechanical ventilation time (12). There is a considerable amount of interest in improving sleep in the ICU potentially to reduce rates of delirium, although, as described above, consistent and widespread sleep interventions are difficult to implement. Interestingly, a 2013 study demonstrated reduced rates of delirium after a sleep-promoting intervention (13), although rates of benzodiazepine use decreased over the same time period as the intervention, so it is difficult to draw mechanistic conclusions. A recent study in *JAMA* showed improved ventilator free days in patients with agitated delirium who received dexmedetomidine *vs.* placebo, but again mechanism is unclear.

Sleep after the ICU

One very important area of emerging research interest is the effect that the ICU has on patients in the long-term; sleep in the post-ICU setting falls in this category as well. Given that insomnia and other sleep disorders are strongly correlated with increased rates of mortality, depression, anxiety and other medical comorbidities (14), it is critical to understand sleep in ICU survivors. Questionnaire data suggest that patients are reporting poor sleep at 6 months following ICU discharge (15), although the details of this finding still need to be evaluated more objectively.

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Footnote

Conflicts of Interest: Dr. Malhotra is PI on NIH RO1 HL085188, K24 HL132105 and co-investigator on R21 HL121794, RO1 HL 119201, RO1 HL081823. As an Officer of the American Thoracic Society, Dr. Malhotra has relinquished all outside personal income since 2012. ResMed, Inc. provided a philanthropic donation to the UC San Diego in support of a sleep center which Dr. Malhotra's division runs. The other authors have no conflicts of interest to declare.

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