

Sleep and Delirium: Physiologic and Clinical Implications
Presenters: Ben Palanca, MD, PhD, MSCI and Melissa Knauert, MD, PhD

Time	Section
02:53	<p><u>Objectives (Ben Palanca)</u></p> <ul style="list-style-type: none"> • Appreciate the importance of high-quality sleep in maintaining normal physiologic and cognitive functions • Understand the electroencephalographic and phenotypical changes associated with delirium that implicate disrupted sleep processes • Appreciate associations between disrupted sleep and delirium risk • Consider pharmacologic and non-pharmacologic approaches for modulating sleep structure in future delirium research
03:29	<p><u>Delirium: Significance and Impact</u></p> <ul style="list-style-type: none"> • Costly, common, cognitive decline?, poor prognostic sign (high mortality, morbidity, and poorer longer term outcomes)
03:51	<p><u>Delirium: Core Features</u></p> <ul style="list-style-type: none"> • Awareness, attention, cognition, fluctuating
04:14	<p><u>Comparisons of Delirium and Sleep Deprivation</u></p> <ul style="list-style-type: none"> • Delirium (CAM-S) → long CAM categories • Sleep deprivation → contains a very similar list to the CAM
05:52	<p><u>Reasons to Study Sleep in Elucidating Delirium Pathophysiology</u></p> <ul style="list-style-type: none"> • Critical for maintain consciousness and cognition • Common • Incompletely understood • Clinically relevant • Modifiable
06:33	<p><u>Importance of Sleep Health with Modifiers Across Societal Levels</u></p> <ul style="list-style-type: none"> • Societal Level: globalization, 24/7 society, technology, policy, discrimination, geography, environment • Social Level: neighborhood, work, family, culture, social networks, socioeconomic status, safety • Individual Level: genes, age, sex/gender, race/ethnicity, beliefs, behaviors, emotions
07:37	<p><u>Bidirectionality of Sleep and Immunity: Likely Contributor to Delirium Pathogenesis</u></p> <ul style="list-style-type: none"> • Strong immune activation could have disturbed sleep and fatigue • Abnormal sleep can impact the immune system in a bad way <ul style="list-style-type: none"> ○ Systemic inflammatory mediators
09:21	<p><u>Normal Overnight Sleep Macrostructure</u></p> <ul style="list-style-type: none"> • Hypnograph across sleep states over the course of the night • REM vs. Non-REM sleep • Cycles are about 60-90 minutes long • N1: Transition from wakefulness to sleep ~5% TST (total sleep time) • N2: Bulk of sleep, 50% TST • N3: Slow Wave Sleep, 20% TST (declines with age) • REM: rapid eye movement sleep ~25% TST
11:15	<p><u>States of Sleep May Aid in Clearance of AD Pathology</u></p> <ul style="list-style-type: none"> • Glymphatic system hypothesized to clear out
12:08	<p><u>Sleep: Microstructure and Physiologic Roles</u></p> <ul style="list-style-type: none"> • Defined by different EEG markers • N2 sleep → sleep spindles (learning and memory, facilitates deeper sleep)

	<ul style="list-style-type: none"> • N3 sleep (SWS)→ delta waves (resetting of synapses, neurohumoral homeostasis, release of growth hormone, glymphatic system function)
13:36	<p><u>Pathologic Wakefulness/ Atypical Sleep?</u></p> <ul style="list-style-type: none"> • Not consistent with “normal” EEG patterns
14:25	<p><u>Do EEG Changes During Delirium Reflect Damage or a Healing Process?</u></p> <ul style="list-style-type: none"> • Escalating severity of sepsis encephalopathy (see emergence of slower waves- theta, delta)
15:09	<p><u>Markers of Sleep Pressure During Wakefulness are Associated with Delirium Features</u></p> <ul style="list-style-type: none"> • Awake theta (sleep pressure) • Occipital alpha (posterior dominant rhythm)
16:30	<p><u>Is Delirium a Disorder of Sleep and Wakefulness?</u></p> <ul style="list-style-type: none"> • Does delirium consist of intrusions of sleep processes into wakefulness to heal ischemic, metabolic, or inflammatory insults?
17:07	<p><u>Approaches to Probe Relationships Between Delirium and Sleep Relationships</u></p> <ul style="list-style-type: none"> • Actigraphy watches to measure • Wearables (can get really complex)
17:57	<p><u>Associations Between Sleep Disturbances on Delirium</u></p> <ul style="list-style-type: none"> • Meta-analysis • Preoperative sleep disturbance was associated with a 3 to 5 time risk of delirium
19:34	<p><u>Sleep Structural Measures and Delirium Outcomes</u></p> <ul style="list-style-type: none"> • 2017 study→ sleep EEG on postoperative day 1 <ul style="list-style-type: none"> ◦ Found that greater sleep time was associated with lower delirium severity • 2021 study→ found that greater sleep efficiency was associated with a potential effect of delirium risk (but not statistically significant due to a small sample size)
21:26	<p><u>Actigraphy Measures and Postoperative Delirium Outcomes</u></p> <ul style="list-style-type: none"> • Intact/no delirium had greater movement during day relative to night compared to those with hypoactive delirium • Looking at number of awakenings and wakefulness after sleep onset (WASO)
22:12	<p><u>Contributions of Obstructive Sleep Apnea Revisited</u></p> <ul style="list-style-type: none"> • Could contribute to blood brain barrier and brain physiology that could contribute to delirium • Mixed results and very limited evidence about obstructive sleep apnea playing a role in post-operative neurocognitive disorders
22:52	<p><u>Non-pharmacologic and Pharmacologic Interventions Targeting Sleep</u></p> <ul style="list-style-type: none"> • Sleep hygiene • Melatonin/receptor agonists • Orexin receptor antagonists • Dexmedetomidine • Sleep slow wave or sleep spindle promotion?
23:36	<p><u>A Few of Many Outstanding Questions</u></p> <ul style="list-style-type: none"> • Do deficiencies in preoperative sleep constitute risk factors for postoperative delirium across a broad population? • What are the important measures of sleep that are protective factors for conferring protection and mitigating injury? • What are molecules/neurons/circuits that are involved in delirium pathophysiology and sleep/immune system cross-talk? Can we intervene on sleep microstructure to disrupt the processes?
24:25	<p><u>Conclusions</u></p> <ul style="list-style-type: none"> • Postoperative delirium is an important clinical problem • Sleep, a fundamental process for promoting healing, is a potential target for improving delirium outcomes. More work is needed to evaluate associations at a larger scale

	<ul style="list-style-type: none"> • Sleep microstructure has associated physiologic benefits • Pharmacologic and non-pharmacologic approaches to improve delirium outcomes through modulation of sleep structure are under development
25:40	<p><u>Our Objective?... To Understand: How did we get here? Where are we going? (Melissa Knauert)</u></p> <ul style="list-style-type: none"> • ICU delirium → sleep... and (finally) circadian disruption → outcomes → treatment
28:13	<p><u>Delirium in the (medical) ICU is common and challenging</u></p> <ul style="list-style-type: none"> • Risk factors: sedatives, age, dementia, prior coma, pre-ICU emergency surgery/trauma, APACHE severity of illness scores, ASA score • Prevalence: 50 to 80% on the medical ICU • Outcomes: impact on cognition, hospital LOS, mortality • Treatment: limited pharmacologic treatment; sleep and mobility bundles recommended
29:11	<p><u>Sleep in the ICU is Severely Disrupted</u></p> <ul style="list-style-type: none"> • Cycle: Impaired daytime function → short duration → poor quality → abnormal timing
30:58	<p><u>ICU Sleep Disruption is Associated with Poor Outcomes</u></p> <ul style="list-style-type: none"> • Poor sleep is associated with delirium • Delirium is associated with poor sleep and decreased melatonin levels • Poor sleep is associated with an increased risk of death
31:53	<p><u>Getting unstuck from the sleep opportunity perspective</u></p> <ul style="list-style-type: none"> • Add environmental control and/or cluster care to avoid overnight interruptions • Necessary but not sufficient
32:31	<p><u>The timing and duration of sleep is controlled by the 2-process model</u></p> <ul style="list-style-type: none"> • Sleep drive “S” vs. Wake drive “C” <ul style="list-style-type: none"> ○ In tandem, synchronicity, balancing out
34:10	<p><u>Circadian Rhythms are (also) abnormal in the ICU</u></p> <ul style="list-style-type: none"> • (left) measured body temperature • (right) measured serum melatonin (critically ill are more delayed)
35:44	<p><u>Using continuous heartrate data from telemetry to estimate circadian phase (diurnal variation)</u></p> <ul style="list-style-type: none"> • Looked to see if aligned, misaligned in terms of circadian rhythm or if they lacked a circadian variation
37:27	<p><u>ICU sleep and circadian disruption has many domains</u></p> <ul style="list-style-type: none"> • Quality of wake, daytime function, perceived sleep, sleep timing, sleep duration, circadian alignment, circadian amplitude, sleep continuity, sleep architecture, sleep regularity
38:01	<p><u>Circadian framework suggests key targets for sleep promotion and beyond</u></p> <ul style="list-style-type: none"> • Photic cue: light (day-night) → central clock → nonphotic cues, peripheral clocks, improved function
39:17	<p><u>Where does this potential lead us</u></p> <ul style="list-style-type: none"> • Sleep bundles likely improve delirium outcomes <ul style="list-style-type: none"> ○ Scoping review: 20 studies of bundled care, sleep measures, delirium measures, study design, outcomes • Eye masks and ear plugs may improve delirium outcomes <ul style="list-style-type: none"> ○ Scoping review: 5 studies of eye masks, ear plugs, sleep measures, delirium measures, study design, outcomes • Bright light therapy?? Delirium outcomes <ul style="list-style-type: none"> ○ Scoping review: 5 light studies, sleep and circadian measures, delirium measures, study design, outcomes • Melatonin??? Delirium outcomes <ul style="list-style-type: none"> ○ Scoping review: 8 studies melatonin rx, sleep and circadian measures, delirium measures, study design, outcomes • Other pharma??? Delirium outcomes <ul style="list-style-type: none"> ○ Scoping review: 11 pharma studies, outcomes

43:20	<p><u>Gaps and Challenges</u></p> <ul style="list-style-type: none"> • Mixed interventions • Mis-timed or mis-dosed interventions • Challenging sleep and circadian measurement • Varied outcome measures
43:57	<p><u>Light</u></p> <ul style="list-style-type: none"> • Timing, duration, intensity, spectra, history
44:05	<p><u>Where does this potential lead us... daytime light as a case study</u></p> <ul style="list-style-type: none"> • Non-circadian light patterns are present...dim daytime light is a key problem • ICU light is artificial
45:45	<p><u>Can we arrive at a best practice for light intervention</u></p> <ul style="list-style-type: none"> • Patients are likely delayed • Daytime 4 or 8 hour block bright light • 10,000 lux at source • High blue light content, e.g. 5000 Kelvin • Nighttime minimal light • Light and spectra monitoring
46:44	<p><u>Where does this potential lead us... other zeitgebers</u></p> <ul style="list-style-type: none"> • Non-photic cues: sleep & exercise/mobility, feeding timing
47:30	<p><u>The immediate future of ICU Sleep and Circadian Research</u></p> <ul style="list-style-type: none"> • Low hanging fruit <ul style="list-style-type: none"> ○ TX: light, sleep, feeding & mobility → improve: delirium, sleep, metabolism, strength • Moonshot(s) <ul style="list-style-type: none"> ○ Large scale and/or bedside measures, peripheral clock measures, pharmacotherapy
48:42	<p><u>Questions and Answers</u></p>