Sleep Quality in Hospitalized Patients with Infection: An Observational Study

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Hosted by Paul Webber
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www.webbertraining.com February 12, 2015

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Disclosures

The speaker has no relevant disclosure

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Outline

- Background
  - Sleep architecture
  - Impact of sleep deprivation on physiological and psychological functions
  - Impact of sleep deprivation on infections
  - Impact of infections on sleep
  - Sleep in hospitalized patients
- Study of sleep quality in hospitalized patients with infection
  - Methods
  - Results
  - Discussion
- Conclusions

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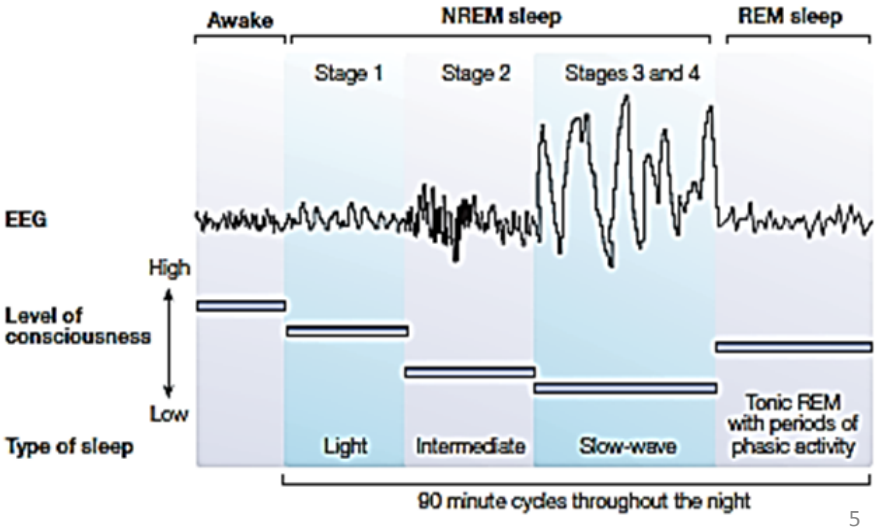
Stages of Sleep

Bryant PA, et al. Nature Reviews 2004;4:457-67



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Hypotheses for the Function of Stages of Sleep

Bryant PA, et al. Nature Reviews 2004;4: 457-67

- NREM sleep
  - Conserves energy; slow heart rate, decreased blood pressure, cardiac output
  - Restores the CNS or components of the CNS e.g. frontal cortex
  - Cools the body and the brain
  - Promotes immune function
- REM sleep
  - Enables psychological and/or emotional adaptation through dreams
  - Endogenous stimulation of the CNS
  - Reverses brain cooling, quiescence or restorative activity
  - Sentinel role by allowing periodic awakenings to survey the environment
  - Information processing

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Potential Impact of Poor Sleep on Physiological and Psychological Health

- Worsening glucose tolerance
- Increased irritability, aggressiveness
- Impaired memory consolidation
- Increased delirium
- Poor balance
- Decreased ventilator drive
- Increased sympathetic cardiovascular activation
- Increased blood pressure
- Immunological abnormalities/susceptibility to infections

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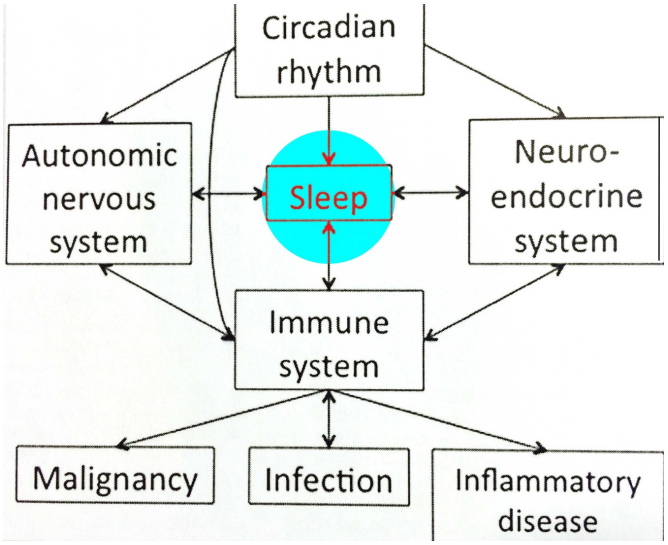
Sleep and Infection

Bryant PA, Curtis N. Ped Infect Dis J 2013;32:1135-37.



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Impact of Sleep on Infection

Bryant PA et al. Nature Reviews 2004;4:457-67

- Partial sleep deprivation (4 hrs) associated with increased TNF and IL-1β production following in vitro stimulation of peripheral blood mononuclear cells
- Acute sleep loss may enhance the immune system
- Chronic sleep loss may be detrimental to the immune system
- Impact of sleep deprivation on cellular and humoral immunity in humans may not be consistent

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Impact of Sleep on Pneumonia Risk in Women

Patel SR et al. SLEEP 2012;35:97-101

- Prospective, observational cohort study of 56,953 female nurses (37-57 yrs of age)
- Pneumonia diagnosis based on physician diagnosis and chest radiograph
- Relative risk to 8-hr sleepers
  - ≤ 5 hrs, 1.4 (1.1-1.8)
  - ≥9 hrs, 1.4 (1.04-1.8)

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Impact of Sleep on Susceptibility to Common Cold

Cohen S et al. Arch Intern Med 2009;169:62-67

- Healthy volunteers
- Challenged with intranasal rhinovirus
- "Dose-response" relationship
  - Those with < 7 hrs average sleep were 3 x more likely to develop cold symptoms than those who had 8 hrs or more.
  - Similar (and stronger) effect with poorer sleep efficiency (proportion of time in bed actually asleep)

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Impact of Acute Sleep Loss on Immune Response to Vaccination

- Influenza A: subjects immunized during a period of partial sleep deprivation had lower virus-specific antibody titers (< 50%) at 10 days post-vaccination compared to those of non-sleep-deprived *(Spiegel K, et al. JAMA 2002;288:1471-2)*
- Hepatitis A: subjects immunized after 1 night of total sleep deprivation had significantly lower virus-specific titers at 4 wks *(Lange T et al. Psychosom. Med 2003;65:831-5)*

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Sleep and Antibody Response to Vaccination

Prather AA, et al. SLEEP 2012; 35:1063-9

- Hepatitis B: subjects immunized with < 7 hr of sleep around the time of vaccination, less likely to achieve protective antibody levels after completion of series

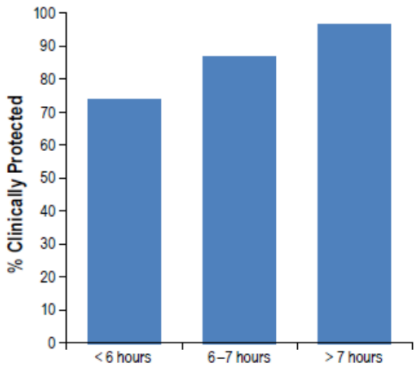

Figure 2—Average actigraphy-based sleep duration predicts likelihood of being clinically protected (i.e. anti-HBs IgG ≥ 10 mIU/ml) 6-months following the third hepatitis B immunization.

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Impact of Sleep Deprivation on Patients

Bryant PA et al. Nature Reviews 2004;4:457-67

- "*Diminished immune responses that result from sleep deprivation in environments such as ICUs might increase the risk of infection…analogous to the proposition that pain has a detrimental effect on the immune response and hospital-acquired infections.*"

- "*The effects of sleep deprivation might be especially important in populations at particular risk of infection: the elderly, the severely unwell, and the immunocompromised*."

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Impact of Infection on Sleep

Majde JA, Krueger JM. J Allergy Clin Immunol 2005;116:1188-98

- The need to rest and sleep often reported subjectively in patients with infection e.g. influenza, infectious mononucleosis
- Increased non-REM sleep and decreased REM sleep are characteristic of many non-neurotropic acute infection in which sleep has been studied, including viral, bacterial, fungal and parasitic infections
- "*Although the evidence is limited, it is likely that maintenance of immune function is one reason why we sleep*."

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Sleep and the Immune System

Bryant PA, et al. Nature Reviews 2004;4:457-67

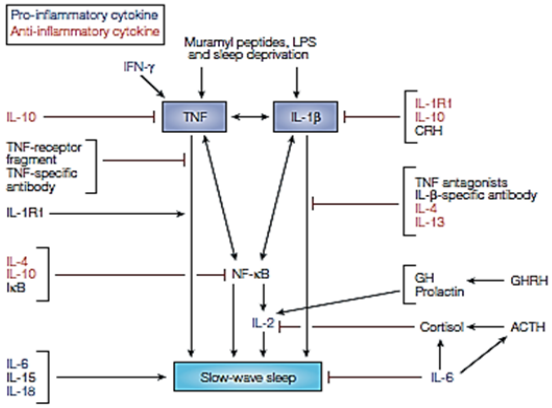

Figure 2 | **Putative pathways of immune-system involvement in sleep.** An attempt to represent (in a single diagram) the results of many of the studies described in the text. This is not intended to be comprehensive but rather to illustrate some of the reciprocal effects of sleep and cytokines. In general, pro-inflammatory cytokines induce sleep, whereas anti-inflammatory cytokines inhibit sleep. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; GH, growth hormone; GHRH, growth-hormone-releasing hormone; IκB, inhibitor of NF-κB; IL, interleukin; IL-1R1, type 1 interleukin-1 receptor; LPS, lipopolysaccharide; NF-κB, nuclear factor-κB; TNF, tumour-necrosis factor.

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Impact of Infection on Sleep

Bryant PA et al. Nature Reviews 2004;4:457-67

- Human experiments
  - Influenza virus: reduced sleep during the incubation period, increased during the symptomatic period
  - Rhinovirus: decreased sleep duration during symptomatic period
  - Exposure to high dose LPS:
    - increases body temperature, heart rate, cortisol, some cytokines (e.g. TNF)
    - first decrease, then increase in slow-wave sleep duration with concomitant decrease in REM sleep.
  - Exposure to low dose LPS: increases cytokines but not temperature, heart rate or cortisol level

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Impact of Infection on Sleep

Bryant PA et al. Nature Reviews 2004;4:457-67

- Human clinical infections and sleep
  - Direct CNS infections (e.g. rabies)
  - Human African trypanosomiasis ("sleeping sickness")
  - Asymptomatic HIV infection
  - Sepsis

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Impact of Sepsis on Sleep

Venkateshiah SB, Collop NA. Chest 2012;141:1337-45.

- Increased non-REM sleep
- Decreased REM sleep
  - REM: greatest 02 desaturation/cardiopulmonary variability; ? Protective in pts with borderline hemodynamic status
- Loss of normal circadian melatonin secretion
- Increase in sleep promoting cytokines e.g. TNF, IL-1 β
- Sleep deprivation after septic insult increases mortality in animal models

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Sleep in Hospitalized Patients

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Sleep Disturbances Among Hospitalized Patients

- Common; ~25%-50% of patients on general medicine wards
- Often under-recognized or poorly documented by physicians
  (Meissner HH et al. West J Med 1998;169:146-49)
- Multifactorial including
  - Noise
  - Pain
  - Anxiety
  - Depression
  - Delirium
  - Medications
  - Frequent awakenings for diagnostic testing
  - Underlying illness
  - Others…

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Why study sleep in hospitalized patients with infection?

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Potential Reasons…

- Infectious disease-related conditions (e.g. pneumonia and skin and soft tissue infections) are common among hospitalized patients
- Infections may lead to increased sleep requirement or poor sleep
- Poor sleep may interfere with patients' ability to recover from their infection
- Dearth of data on sleep among patients with infection

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CLINICAL INVESTIGATION

Sleep Quality in Adult Hospitalized Patients With Infection: An Observational Study

Farrin A. Manian, MD, MPH and Cyrus J. Manian, BA

Am J Med Sci 2015;349:56-60

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Sleep Quality In Adult Hospitalized Patients With Infection:
Methods
Manian FA, Manian CJ. Am J Med Sci 2015;349:56-60

- Prospective observational study at 900-bed tertiary care community hospital in St. Louis, Missouri, USA
- Study period: June 26, 2008-December 31, 2011
- Patients: all adult inpatients (≥ 18 y) seen in consultation by an infectious disease physician (FAM)
- Data: Patient were routinely asked about their sleep quality during the previous night primarily as part of their initial encounter

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Sleep Quality In Adult Hospitalized Patients With Infection:
Methods
Manian FA, Manian CJ. Am J Med Sci 2015;349:56-60

- Patient location: all adult hospital wards, including intensive care units (ICUs)
- Patients routinely asked as part of their interview: " *How did you sleep last night*?"
- Categorization of responses
  - "Sound" e.g. "great", "good", "no problem".
  - " Unsound"
    - "Fair" e.g. "Fair", "so-so", "on and off"
    - "Poor" e.g. "terrible", "bad", "none", "not much"

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Sleep Quality In Adult Hospitalized Patients With Infection:
Methods
Manian FA, Manian CJ. Am J Med Sci 2015;349:56-60

- Patients reporting unsound sleep were asked to provide the reason (s) for their poor sleep experience
- No patient was included in the study more than once
- Enquiry was postponed to a later hospital date if the patient's cognitive abilities did not allow for reliable responses, or if the patient had not spent a full night in the hospital wardroom

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Sleep Quality In Adult Hospitalized Patients With Infection:
Methods: Patient Data
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- Age, race, gender
- From 2.26.2008-8.30.2009
  - Ward location (ICU vs. others)
  - Number of days of hospitalization at enquiry
  - Primary infectious disease diagnosis
  - List of potentially sedating and/or hypnotic (S/H) medications administered between 8 PM-12AM night before enquiry

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Sleep Quality In Adult Hospitalized Patients With Infection:
Methods: Patient Diagnosis
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- Based on providing physicians' clinical diagnosis
- No attempt made to distinguish surgical and non-surgical patients
- Abdominal infections included diverticulitis, abscess and postoperative deep organ space infection
- Bloodstream infections included those due to primary (e.g. vascular access-related) and secondary (i.e. extravascular) sources
- "Miscellaneous" infections included diagnoses initially presumed but not necessarily proven to be infectious in origin (e.g. fever of unclear source, encephalopathy, and leukocytosis)

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Sleep Quality In Adult Hospitalized Patients With Infection:
Methods: Sedative/Hypnotics Categories
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- Narcotics
  - Morphine, oxycodone, hydrocodone, fentanyl
- Benzodiazepines
  - Lorazepam, diazepam, temazepam, alprazolam
- Nonbenzodiazepine gamma butyric acid agonists
  - Zolpidem
- Antihistamines
  - Diphenhydramine
- Miscellaneous
  - Quetiapine, tricyclic antidepressants, trazodone, melatonin

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Sleep Quality In Adult Hospitalized Patients With Infection:
Methods:Institutional Review/Statistics
Manian FA, Manian CJ. Am J Med Sci 2015;349:56-60

- Because enquiry into the quality of sleep should be part of the care of all hospitalized patients, patients were not made aware of the conduction of the study
- Study protocol approved by the hospital Institutional Review Board with exemption for patient informed consent granted
- Statistical analysis
  - Chi-square with Yates' correction
  - Fisher's exact test
  - P<0.05 considered statistically significant

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Sleep Quality In Adult Hospitalized Patients With Infection:
Results
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- 1,357 potentially eligible patients
  - 119 (8.8%) excluded because of persistent cognitive limitations
- 1,238 evaluable cases
  - 626 (50.6%) were male; 612 (49.4%) female
  - 1,117 (90.2%) were white; 108 (8.7%) black, 13 (1.1%) other races
  - Sound sleep: 646 (52.2%) patients
  - Unsound sleep:592 (47.8%) patients
    - 183 (14.8%) "fair"; 409 (33.0%) "poor" sleep

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Sleep Quality In Adult Hospitalized Patients With Infection

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TABLE 1. Self-reported sleep quality in hospitalized patients by patient characteristics

Patient characteristic	Sound (N = 1,238), n (%)	Unsound (N = 1,238), n (%)	Total	P
Race				
White	582 (52.1)	535 (47.9)	1,117	0.87
Non-white	64 (52.9)	57 (47.1)	121	
Gender				
Male	330 (52.7)	296 (47.3)	626	0.70
Female	316 (51.6)	296 (48.4)	612	
Age, yr				
<50	157 (42.9)	209 (57.1)	366	
50–79	381 (54.3)	321 (45.7)	702	0.0005[a]
≥80	108 (63.5)	62 (36.5)	170	<0.0001[b]

[a] vs. age group less than 50 years, OR: 1.58 (95% CI: 1.23–2.0), $P = 0.0005$.
[b] vs. age group less than 50 years, OR: 2.32 (95% CI: 1.59–3.38), $P < 0.0001$.

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Top 10 reasons cited for unsound sleep
N=447 (%)

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Staff disruptions	129 (28.9)
Pain	118 (26.4)
Anxiety	43 (9.6)
Noise	30 (6.7)
Fever	20 (4.5)
Roommate	19 (4.3)
IV access	10 (2.2)
Urination	9 (2.0)
Diarrhea	9 (2.0)
Poor sleep at home	9 (2.0)

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Miscellaneous (<2%) reasons cited for unsound sleep by hospitalized patients. N=447

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- Uncomfortable bed
- Sleep during daytime
- Dyspnea
- Cough
- Hospital
- Itching
- No sleeping pill
- Heartburn
- Room cold
- Chill
- Room hot
- Sweating
- Constipation
- Sinus drainage
- Corticosteroids
- Nocturnal profession
- Watch television
- I want my own bed
- Baby in the room
- 10 cups of coffee
- Bi-pap machine
- Nosebleed
- Burping
- Hiccoughs

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Sleep Quality In Adult Hospitalized Patients With Infection

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TABLE 3. Common reasons for unsound sleep by age group, gender and race

Patient characteristic	N = 447	Reason: Staff interruption (%)	Reason: Pain (%)	Reason: Anxiety (%)
Age, yr				
<50	161	45 (28.0)	58 (36.0)[a]	12 (7.4)
50–79	244	69 (28.3)	54 (22.1)	24 (9.8)
≥80	42	15 (35.7)	6 (14.3)	7 (16.7)
Gender				
Male	218	75 (34.4)[b]	59 (27.1)	14 (6.4)
Female	229	54 (23.6)	59 (25.8)	29 (12.7)[c]
Race				
White	404	121 (30.0)	101 (25.0)	40 (9.9)
Non-white	43	8 (18.6)	17 (39.5)	3 (7.0)

[a] Age group less than 50 years vs. 50 to 79 years, OR: 2.0 (95% CI: 1.3–3.1), $P = 0.003$; vs. age group of 80 years or older, OR: 3.4 (95% CI: 1.3–8.5), $P < 0.001$.
[b] Male vs. female, OR: 1.7 (95% CI: 1.1–2.6), $P = 0.01$.
[c] Female vs. male, OR: 2.2 (95% CI: 1.1–4.3), $P = 0.03$.

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Duration of Hospitalization and Sleep Quality In Adult Hospitalized Patients With Infection. N=573

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Days of Hospitalization*	Unsound Sleep (%)
1 d	96/163 (58.9)†
2 d	48/109 (44.0)
≥ 3 d	128/301(42.5)

**Range 1-81 d, mean 5.5 d, median 3.0 d*

†df=2, P=0.002

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Ward Location and Sleep Quality In Adult Hospitalized Patients With Infection. N=610

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Location	Unsound sleep (%)
Non-ICU	260/546 (47.6)
ICU	31/64 (48.4)

P=0.9

- No significant differences in the rates of staff disruptions, pain, anxiety and noise between the 2 groups (data not shown)

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TABLE 4. Self-reported sleep quality by primary infectious disease–related diagnosis

Diagnosis	Total N = 581 (%)[a]	Sound sleep (%)[b]	Unsound sleep (%)[b]
SSTI	196 (33.7)	91 (46.4)	105 (53.6)[c]
RTI	60 (10.3)	32 (53.3)	28 (46.7)
UTI	53 (9.1)	32 (60.4)	21 (39.6)
Abdominal infection	53 (9.1)	33 (62.3)	20 (37.7)[c]
BSI	51 (8.8)	29 (56.9)	22 (43.1)
Osteomyelitis/diskitis	28 (4.8)	14 (50)	14 (50)
CDI	16 (2.8)	9 (56.3)	7 (43.7)
Septic arthritis	12 (2.1)	7 (58.3)	5 (41.7)
CNS infection	10 (1.7)	5 (50.0)	5 (50.0)
Head/neck infection	9 (1.5)	3 (33.3)	6 (66.7)
Miscellaneous[d]	93 (16.0)	42 (45.2)	51 (54.8)

P=0.045

SSTI:skin/soft tissue infection; RTI:respiratory tract infection; UTI: urinary tract infection; BSI: blood stream infection; CDI: *C.difficile* infection

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TABLE 5. Use of sedating/hypnotic (S/H) medications and self-reported sleep quality in hospitalized patients

Medication category	Total N = 540	Sound sleep (%)	Unsound sleep (%)	*P*
Narcotics	229	114 (49.8)	115 (50.2)	0.1
No narcotics	311	177 (56.9)	134 (43.1)	
Narcotics alone	189	94 (49.7)	95 (50.3)	0.1
No S/H drugs	235	137 (58.3)	98 (41.7)	
Benzodiazepines	30	15 (50.0)	15 (50.0)	0.71
No benzodiazepines	510	276 (54.1)	234 (45.9)	
Benzodiazepines alone	21	11 (52.4)	10 (47.6)	0.65
No S/H drugs	235	137 (58.3)	98 (41.7)	
NB-GABA[a] agonists	46	21 (45.7)	25 (54.3)	0.28
No NB-GABA agonists	494	270 (54.7)	224 (45.3)	
NB-GABA agonists alone	29	12 (41.4)	17 (58.6)	0.11
No S/H drugs	235	137 (58.3)	98 (41.7)	
Anti-histamines	13	7 (53.8)	6 (46.2)	1.0
No anti-histamines	527	284 (53.9)	243 (46.1)	
Anti-histamines alone	3	1 (33.3)	2 (66.7)	0.57
Any S/H drug	303	152 (50.7)	151 (49.8)	0.06[b]
No S/H drugs	237	139 (58.7)	98 (41.3)	

[a] Nonbenzodiazepine gamma butyric acid.
[b] OR: 0.71 (95% CI: 0.50–1.00).

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Use of Sedating/Hypnotic Medications and Sleep Quality in Hospitalized Patients. N=540

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Medication	**No. (%)**
Narcotics	229 (42.4)
NBGBAA*	46 (8.5)
Benzodiazepines	30 (5.6)
Antihistamines	13 (2.4)
Miscellaneous	31 (5.7)
Any S/H medication	303 (56.1)

**Nonbenzodiazepine gamma butyric acid agonists*

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Discussion of Selected Aspects and Findings

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Selected Aspects and Findings of The Study

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- Largest study to date of sleep quality in adult hospitalized patients
- Only study to date focusing on the study of sleep in hospitalized patients with infection
- Self-reported sleep quality under "real" conditions based on patients' own words, avoiding potential bias inherent in more formal techniques
  - Reflects patient's perception and ultimately satisfaction
  - If validated, easily adaptable to monitoring of sleep quality before and after intervention in hospitalized patients

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Selected Aspects and Findings of The Study: Prevalence of Unsound Sleep

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- **47.8%** of our patients failed to report sound sleep
  - Similar to 25%-47% rates of sleep difficulties previously reported in patients on general medicine wards
  - For several infections (e.g. skin and soft tissue infections, osteomyelitis/diskitis, CNS infections, and head/neck infections) the rates were 50% or more
    - ? More severe infections
    - ? Patients seen later during their course of their infection

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Selected Aspects and Findings of The Study:
Impact of Age and Gender
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- Patients ≥ 80 y of age were **least** likely to report unsound sleep (36.5%) vs <50 y age group (57.1%) and 50-79 y age group (45.7%)
  - Recent population-based U.S. survey reported improvement in sleep quality over lifetime with the fewest complaints among people in their 80s (Grandner MA et al. SLEEP 2012;35:395-406)
- No significant differences in self-reported sleep quality between men and women (47.3% vs 48.4%, respectively)
  - Women generally considered to have a higher rate of insomnia than men in the general population

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Selected Aspects and Findings of The Study:
Reasons for Unsound Sleep: Staff disruptions
Manian FA, Manian CJ. Am J Med Sci 2015;349:56-60

- Most common cited reason (~30% of patients); consistent with previous reports
- Men more likely to cite as reason for unsound sleep (34.4% vs 23.6%)
- Lower resilience and weaker homeostatic response to sleep disturbing effects of blood drawing among men reported (Vgontzas AN et al. J Clin Endocrinol Metab 2004;89:2119-26.)
- Lab experiments: male mice more sensitive to disturbances by certain environmental stressors and more prone to initial loss of sleep (Koehl M, et al. SLEEP 2006;29:124-31).

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Selected Aspects and Findings of The Study:
Reasons for Unsound Sleep: Pain
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- Second most common cited reason (> 25%)
- Younger age group (<50 y) most likely to report (> 1/3)
- Higher likelihood of significant pain among hospitalized patient ≤ 65 y previously reported on general medical wards (Whelan CT et al. Arch Intern Med 2004;164:175-80)
- Effective control of pain in hospitalized patients often challenging
- Sleep deprivation itself may increase sensitivity to pain (Lautnebader S, et al. Sleep Med Rev 2006;10:357-69)
- Use of narcotics had no impact on sleep quality

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Selected Aspects and Findings of The Study:
Reasons for Unsound Sleep: Anxiety
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- 3rd most commonly cited reason (~10%)
- More frequent among women (12.7% vs 6.4%)
  - Anxiety more common among women in the general population (Pigott TA. Psychiatr Clin North Am 2003;26:621-72)
- Anxiety not uncommon among hospitalized patients (e.g. the elderly, following myocardial infarction) (Kvaal K, et al. Int J Geriatr Psychiatry 2001;16:690-3; Frazier SK, et al. Heart Lung 2002;31:411-20)
- ? Role of "infection anxiety" (e.g. "flesh-eating bacteria", MRSA) due to lay press and media coverage

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Selected Aspects and Findings of The Study:
Hospital Days and Ward Location
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- First full night of hospitalization most likely to be associated with unsound sleep (58.9%) vs 2 d (44%) or ≥ 3d (42%)
  - Previous reports of improved sleep later during hospitalization (Bartick MG, et al. J Hosp Med 2010;5:E20-4; Tranmer JE, et al. Clin Nurs Res 2003;159-73)
- No significant difference in rates of or reasons for unsound sleep between ICU and non-ICU patients
  - ? Infections as "equalizers"

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Selected Aspects and Findings of The Study:
Study Limitations
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- Single center study
- Patients on consultative service only, usually based on data from first visit
- Subjective assessment of sleep quality based on patient self-reporting
  - Should be validated by more objective methodology

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Selected Aspects and Findings of The Study:
Strengths
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- Conducted under "real" conditions during the normal course of patient care, avoiding potential bias and limitations inherent in formal surveys
- Virtually 100% response rate, minimizes possibility of sampling errors
- Easily reproducible methodology

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What can we take away?

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Conclusions

- Self-reported poor quality or unsound sleep is common among hospitalized patients with infection-related diagnoses
- Many patient reported reasons for unsound sleep such as staff disruption, pain, and anxiety may be amenable to intervention
- Given the increasingly recognized potential adverse impact of poor sleep on the immune system, more attention should be directed to improving the sleep experience of hospitalized patients

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Thank You!

Sleep Quality in Hospitalized Patients with Infection: An Observational Study
Prof. Farin Manian, Harvard Medical School
A Webber Training Teleclass

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