

Critical Care Pharmacotherapy: What Do You Need to Know?

Jennifer Mando-Vandrick, PharmD, BCPS
Clinical Pharmacist, Emergency Department
Director, PGY2 Critical Care Pharmacy Residency
Duke University Hospital

Objectives

- Review pertinent pharmacotherapy common to the critically ill patients
- Discuss new developments in the pharmacotherapy of critically ill patients
- Identify relationship between respiratory therapists and pharmacist in the care of critically ill patients

Wh

Daily Awakenings

ECMO

Delirium

Vasopressor Selection

Role of Nutrition Support

Intensive Insulin Therapy

Sleep Cycles

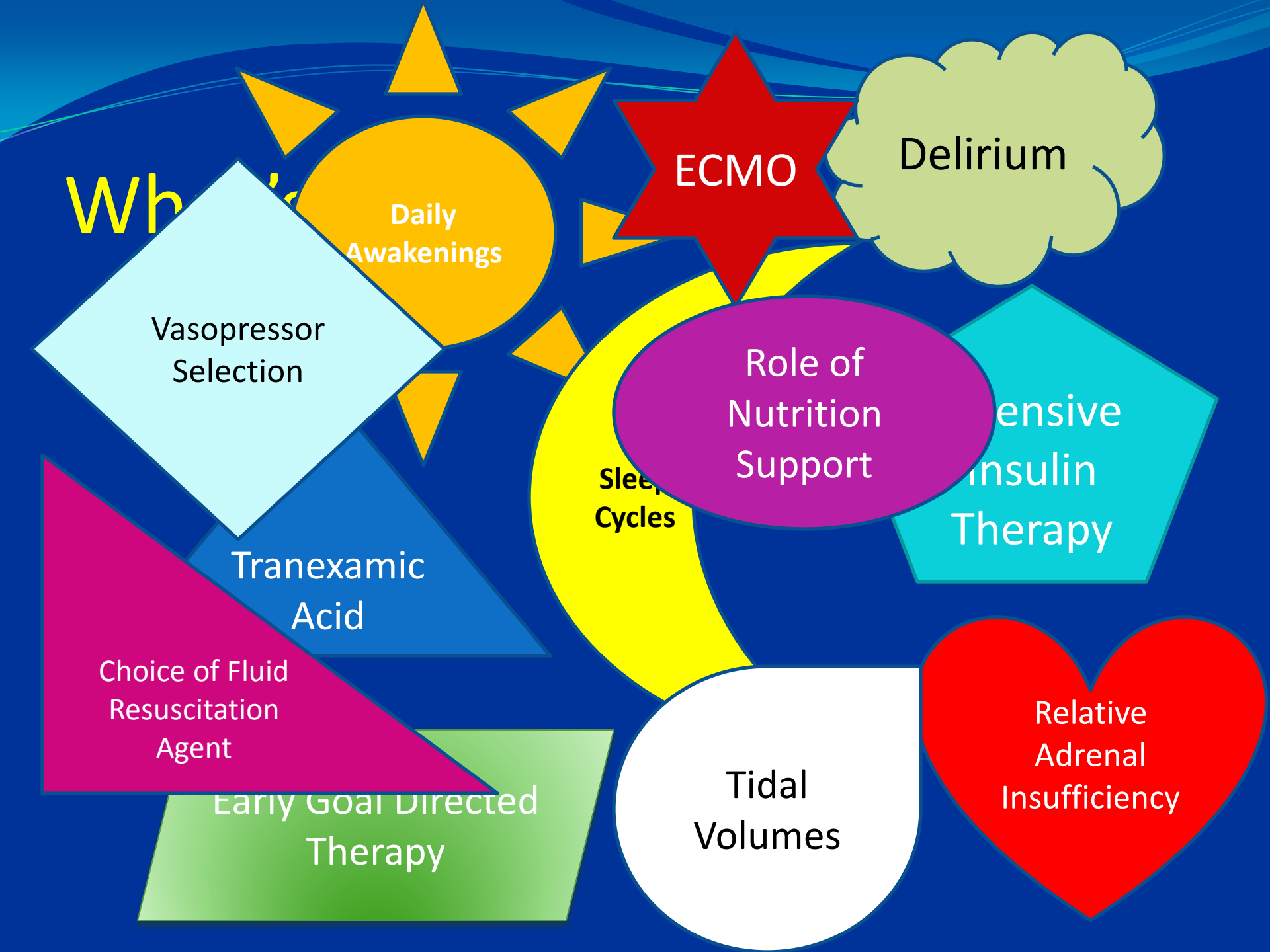
Tranexamic Acid

Choice of Fluid Resuscitation Agent

Early Goal Directed Therapy

Tidal Volumes

Relative Adrenal Insufficiency



2 Key Publications

- Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit
 - Crit Care Med 2013; 41:263-306
 - Update from 2002 guidelines
- Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012
 - Crit Care Med 2013; 41:580-637
 - Update from 2008 guidelines

Pain, Agitation, Delirium Guidelines

- All encompassing for ICU patients
- Greatly effects both of our jobs
- As those with experience know...it is an art...not necessarily a science

Pain

Incidence

- Not readily addressed in 2002 guidelines
- ICU patients routinely experience pain – at rest & with care
- Procedural pain common
- Specified 2 patient populations
 - Cardiac surgery pain is common & poorly treated
 - More pain in female patients undergoing cardiac surgery

Assessment

- Use vital signs to cue further assessment
- Utilize valid scoring systems
 - Behavioral Pain Scale (BPS)
 - Critical-Care Pain Observation Tool (CPOT)

Behavioral Pain Scale

Table 1. The Behavioral Pain Scale (11)

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for the most of time	2
	Fighting ventilator	3
	Unable to control ventilation	4

- Baseline score should be 3 (but studies show it may be 4)
- Scoring increases during painful procedures (6 – 7)

Critical-Care Pain Observation Tool

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
OR			
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			0-8

Pain – Treat It

- Use preemptive analgesia when possible
 - Prior to painful procedures
- Intravenous opioids
 - First line for non-neuropathic pain
 - All are effective if titrated appropriately

Opioid Pharmacology

Opiate	Onset (IV)	Elimination Half-Life	Intermittent Dosing	Infusion Rates	Comments
Fentanyl IV	1-2 m	2-4 h	0.35 – 0.5 mcg/kg q 0.5 -1 h	0.7 – 10 mcg/kg/hr	Less BP ↓ Accumulates in fat Chest wall rigidity
Hydromorphone IV	5-15 m	2-3 h	0.2 – 0.6 mg q 1- 2 h	0.5 – 3 mg/h	Accumulates in renal & liver failure
Morphine IV	5-10m	3-4 h	2 – 4 mg q 1 – 2 h	2 – 30 mg/h	Accumulates in renal & liver failure Histamine release
Methadone IV	1-3d	15-60 h	IV: 2.5 – 40 mg q 6 – 12h	N/A	Unpredictable!
Remifentanil IV	1-3 m	3-10 m	N/A	Load 1.5 mcg/kg then 0.5 – 15 mcg/kg/hr	Watch dosing in obese pts

Non-Opioid Pharmacology

Opiate	Onset (IV)	Elimination Half-Life	Dosing	Comments
Ketamine (IV)	30 – 40 s	2 – 3 h	0.1 – 0.5 mg/kg then 0.05 – 0.4 mg/kg/h	Emergency reactions Hallucinations
Acetaminophen	PO: 30 – 60 m IV: 5 – 10 m	2 – 4 h 2 h	325 – 1000 mg q6h max 4 g/d 1000 mg q 6h max 4 g/d	Caution in liver failure
Ketorolac IV	10 m	2 – 9 h	15 – 30 mg iv q 6h x max of 5 days	Caution in renal failure & bleeding risk
Gabapentin (PO)	25 min	1 – 3 h	Start 100 mg q8h & titrate to 100 – 200 mg q6h (up to 1200 mg/d)	May cause sedation & ataxia

Sedation



- Don't just sedate people...
- Attempt to identify underlying cause of anxiety & agitation
 - Pain
 - Delirium
 - Hypoxemia
 - Hypoglycemia
 - Hypotension
 - Alcohol or drug withdrawal

Sedation

- Depth: Light = good
- Assessments
 - Use Richmond Agitation-Sedation Scale (RASS) or Sedation-Agitation Scale (SAS)
 - Objective measuring techniques (Bispectral Index, etc.)
 - Not recommended as primary method of assessment
 - Adjunctive assessments in paralyzed pts or when subjective assessment is unobtainable
 - Use EEG monitoring for seizing pts

Sedation Pharmacology

Agent	Onset (IV)	Elimination Half-Life	Intermittent or loading doses	Infusion Rates	Adverse Effects
Midazolam	2 – 5 m	3 – 11 h	0.01 – 0.05 mg/kg	0.02 – 0.1 mg/kg/h	Respiratory depression Hypotension
Lorazepam	15 – 20 m	8 – 15 h	0.02 – 0.04 mg/kg load 0.02 – 0.06 mg/kg q 2 – 6 h prn	0.01 – 0.1 mg/kg/h	Respiratory depression Hypotension
Diazepam	2 – 5 m	20 – 120 h	5 – 10 mg load 0.03 – 0.1 mg/kg q 0.5 – 6 h prn	N/A	Respiratory depression Hypotension
Propofol	1 – 2 m	Short term: 3 – 12h Long term: 50 – 70 h	1 mg/kg	5 – 50 mcg/kg/min (or up to 100)	Lots... Hypotension, TG ↑, Acidosis; Pancreatitis.....
Dexmedetomidine	5 – 10 m	1.5 – 3 h	1 mcg/kg over 10 min	0.2 – 0.7 mcg/kg/h	Bradycardia, hypotension, hypertension with loading dose

Benzodiazepines

- Anxiolytic, amnestic, sedating, hypnotic, anticonvulsant effects
- Highly lipid soluble: diazepam & midazolam
 - Quicker onset
 - Larger volume of distribution
- Can hang around forever in certain patients
 - Elderly
 - Liver dysfunction
 - Renal dysfunction

Propofol

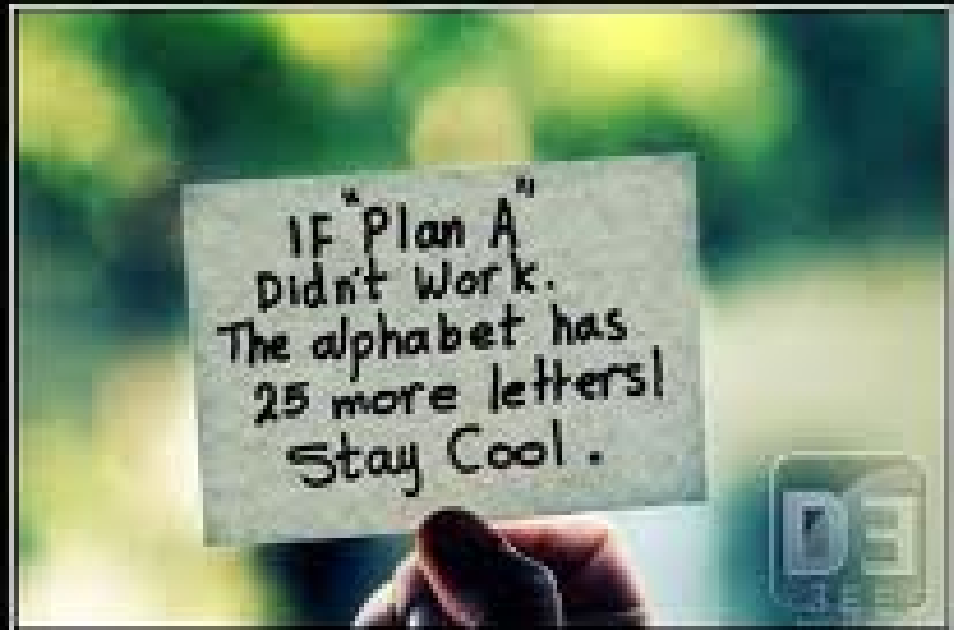
- Sedative, hypnotic, anxiolytic, amnestic, antiemetic, & anticonvulsant effects
- Quick on, quick off...BUT
- Long term use = saturation of peripheral tissues & prolonged effect
- Dose dependent hypotension
- Propofol infusion syndrome
 - Worsening metabolic acidosis, \uparrow TG, \downarrow BP, & arrhythmias
 - Generally associated with prolonged duration of higher dose (> 70 mcg/kg/min)

Dexmedetomidine

- Selective alpha-2 agonist
- Sedative, analgesic/opioid sparing, & sympatholytic properties
- Pts are more easily aroused & minimal respiratory depression
- Often requires higher dosages than general “approved” dose

Sedation Choice

- “We suggest that sedation with a nonbenzodiazepine (either dexmedetomidine or propofol) may improve clinical outcomes in adult ICU patients”
- Class +2B recommendation



It is important

no to panic

Data

Lorazepam vs. Propofol (Carson et al)

- Compared duration of ventilation
- Pts expected to require > 48 hrs ventilation
- Daily awakenings
- N=132 pts
- Lower ventilator days in propofol vs. lorazepam group (5.8 vs. 8.4, $p = 0.04$)

SEDCOM: Dexmedetomidine vs. Midazolam

- Primary endpoint = % time within RASS -2 to +1
- Pts expected to require > 24 hrs ventilation
- N = 366 pts
- No difference in time within RASS goal
- BUT...

SEDCOM Secondary Objectives

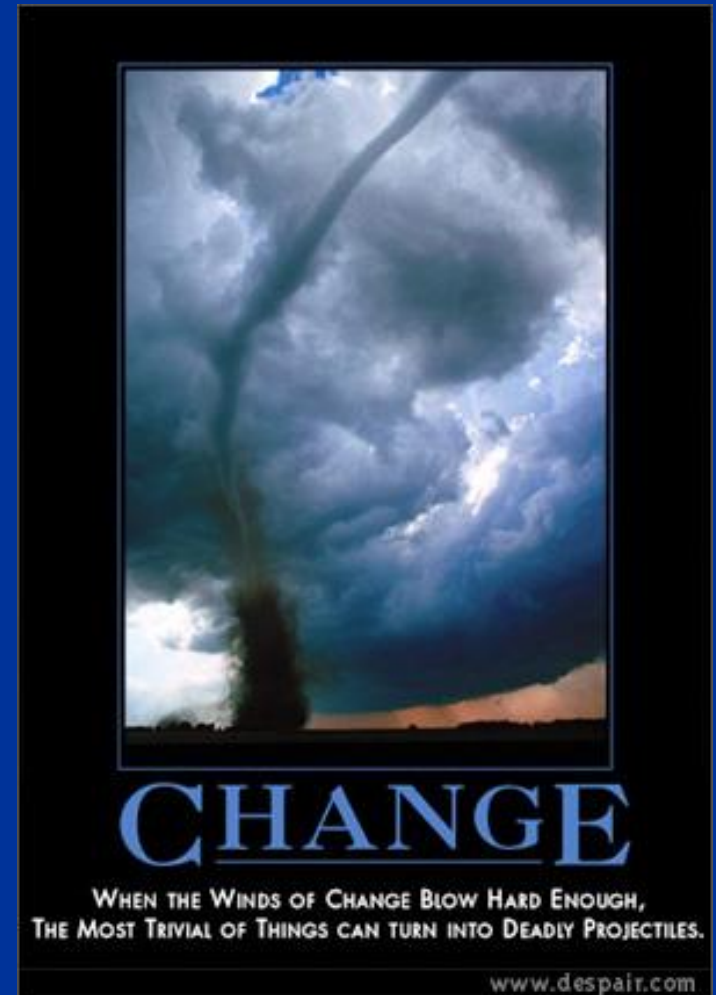
- Decrease in time to extubation with dexmedetomidine group (1.9 day difference)
 - Dexmedetomidine: 3.7 days [95% CI 3.1 – 4.0] vs. Midazolam: 5.6 days [95% CI 4.6 – 5.9]; $p = 0.01$
- Prevalence of delirium in dexmedetomidine (54%) decreased by 22% vs. midazolam (76/6%) $p < 0.001$

Cost Analysis for Dexmedetomidine

- Nested pharmacoeconomic evaluation of SEDCOM
- Prices used: 200 mcg vial of dexmedetomidine = \$58; 5 mg vial of midazolam = \$1.50
- Median total intensive care unit cost savings of \$9679 (CI, \$2314 - \$17,045) with dexmedetomidine compared with midazolam
- Primary cost drivers
 - Reduced cost of ICU stay (median savings \$6584)
 - Reduced costs of mechanical ventilation (median savings \$2958)

Sedation Conclusions

- Guidelines exist
- Most of us don't follow them
- Data are there...but likely need more
- Change is hard...



Delirium

- Syndrome characterized by acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or altered level of consciousness
- Does not require hallucination or delusions
- Pts can fluctuate between 2 types
 - Hyperactive: agitated
 - Hypoactive: calm and lethargic

Delirium Symptoms

- Disturbed level of consciousness (reduced clarity of awareness of surroundings)
- Memory deficit
- Disorientation
- Language disturbance
- Perceptual disturbance like hallucinations or delusions
- Fear
- Anxiety
- Anger
- Depression
- Apathy
- Euphoria

Delirium...So What?

- May affect up to 80% of mechanically ventilated adult ICU pts
- Costs \$ 4 to 16 billion annually in US alone
- Associated with increase in mortality, prolonged ICU & hospital length of stay
- We still really don't understand why and how it happens
- Not great data on how to treat it

Delirium Assessment

- Most important thing...identify it early...before it gets too bad
- Confusion Assessment Method for the ICU (CAM-ICU) Scoring
- Needs to part of standard ICU assessments

Confusion Assessment Method for the ICU (CAM-ICU) Flowsheet

1. Acute Change or Fluctuating Course of Mental Status:

- Is there an acute change from mental status baseline? OR
- Has the patient's mental status fluctuated during the past 24 hours?

NO

CAM-ICU negative
NO DELIRIUM

YES

2. Inattention:

- "Squeeze my hand when I say the letter 'A'."
Read the following sequence of letters: S A V E A H A A R T
ERRORS: No squeeze with 'A' & Squeeze on letter other than 'A'
- If unable to complete Letters → Pictures

0 - 2
Errors

CAM-ICU negative
NO DELIRIUM

> 2 Errors

3. Altered Level of Consciousness Current RASS level

RASS other
than zero

CAM-ICU positive
DELIRIUM Present

RASS = zero

4. Disorganized Thinking:

1. Will a stone float on water?
2. Are there fish in the sea?
3. Does one pound weigh more than two?
4. Can you use a hammer to pound a nail?

Command: "Hold up this many fingers" (Hold up 2 fingers)
"Now do the same thing with the other hand" (Do not demonstrate)
OR "Add one more finger" (If patient unable to move both arms)

> 1 Error

0 - 1
Error

CAM-ICU negative
NO DELIRIUM

Delirium Prophylaxis

- No great data exist to recommend pharmacologic agents to prevent delirium
- Non pharmacologic recommendations
 - Early mobilization & aggressive mobilization

Delirium Treatment

- Vitamin “H” : “no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients”
- Atypical antipsychotics may be of use
 - Small study suggests quetiapine may reduce duration of delirium

Sleep...It's a Good Thing

- “We recommend promoting sleep in adult ICU patients”

Current Events

Expert: Michael Jackson went 60 days without real sleep

By Alan Duke, CNN

updated 11:15 AM EDT, Mon June 24, 2013

Michael Jackson didn't get good night's sleep in two months leading up to 'This Is It' tour: expert

Dr. Charles Czeisler, a Harvard sleep researcher, said Jackson's propofol-induced slumber induced by Conrad Murray wasn't providing the pop star enough REM sleep. He also said that lab rats exposed to the same lack of REM often died after five weeks. Czeisler was testifying during the wrongful-death suit against concert promoter AEG Live, brought on by Jackson's mother, Katherine.

[Comments \(11\)](#)

BY CORKY SIEMASZKO / NEW YORK DAILY NEWS

FRIDAY, JUNE 21, 2013, 5:29 PM

Michael Jackson trial: How long can you survive without sleep?

By Megan Gannon / Published June 24, 2013 / LiveScience

<http://www.nydailynews.com/>

<http://www.foxnews.com>

www.cnn.com

Normal Circadian Rhythm

Wake

- Inhibition of melatonin release
- ↑ orexin, acetylcholine, serotonin, norepinephrine, dopamine, histamine, adenosine

Sleep

- Diurnal secretion of melatonin
- ↓ adenosine

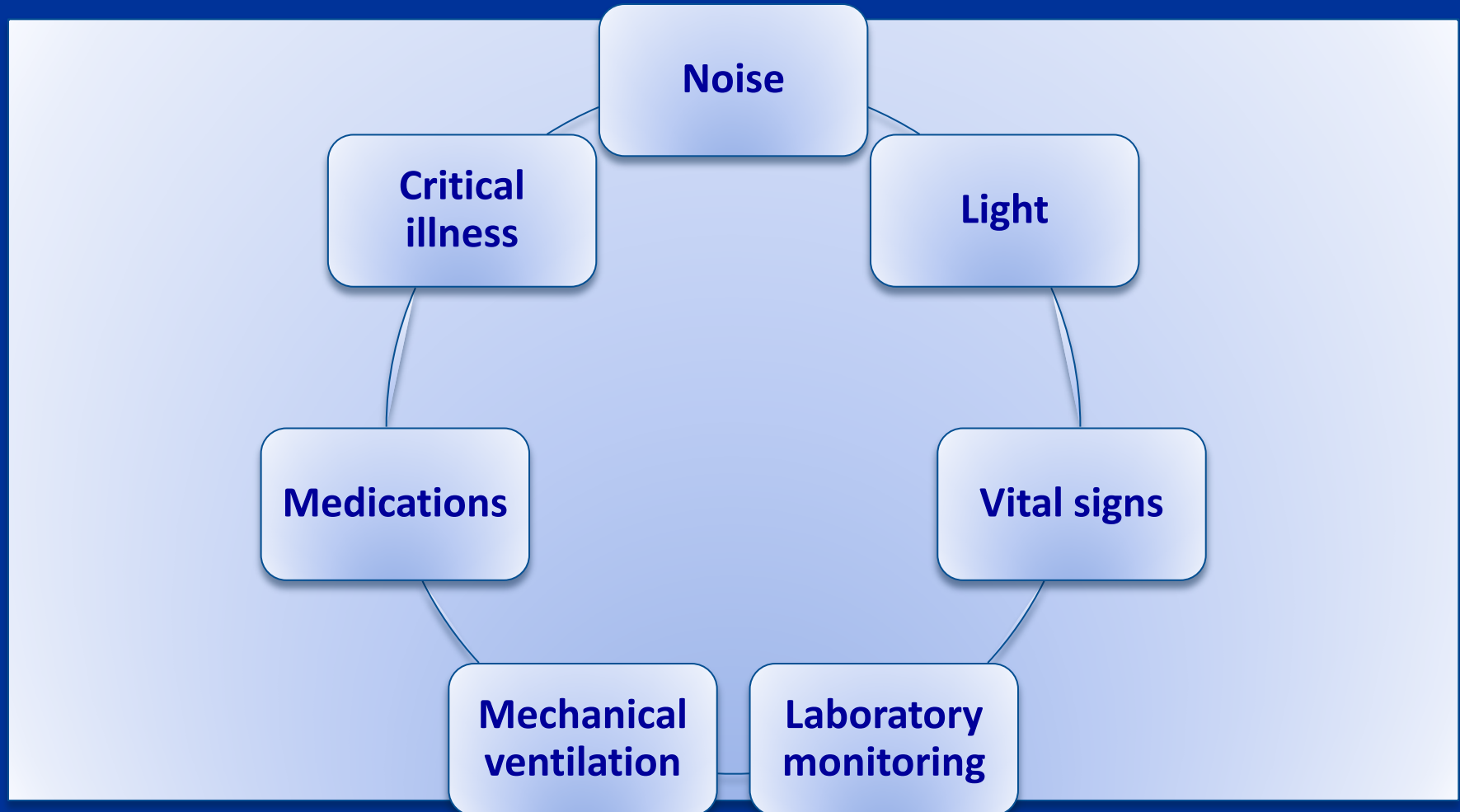
Normal Sleep Architecture

- Normal sleep cycle lasts approximately 90 minutes
- Continuous cycling between Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep stages

Normal Sleep Architecture

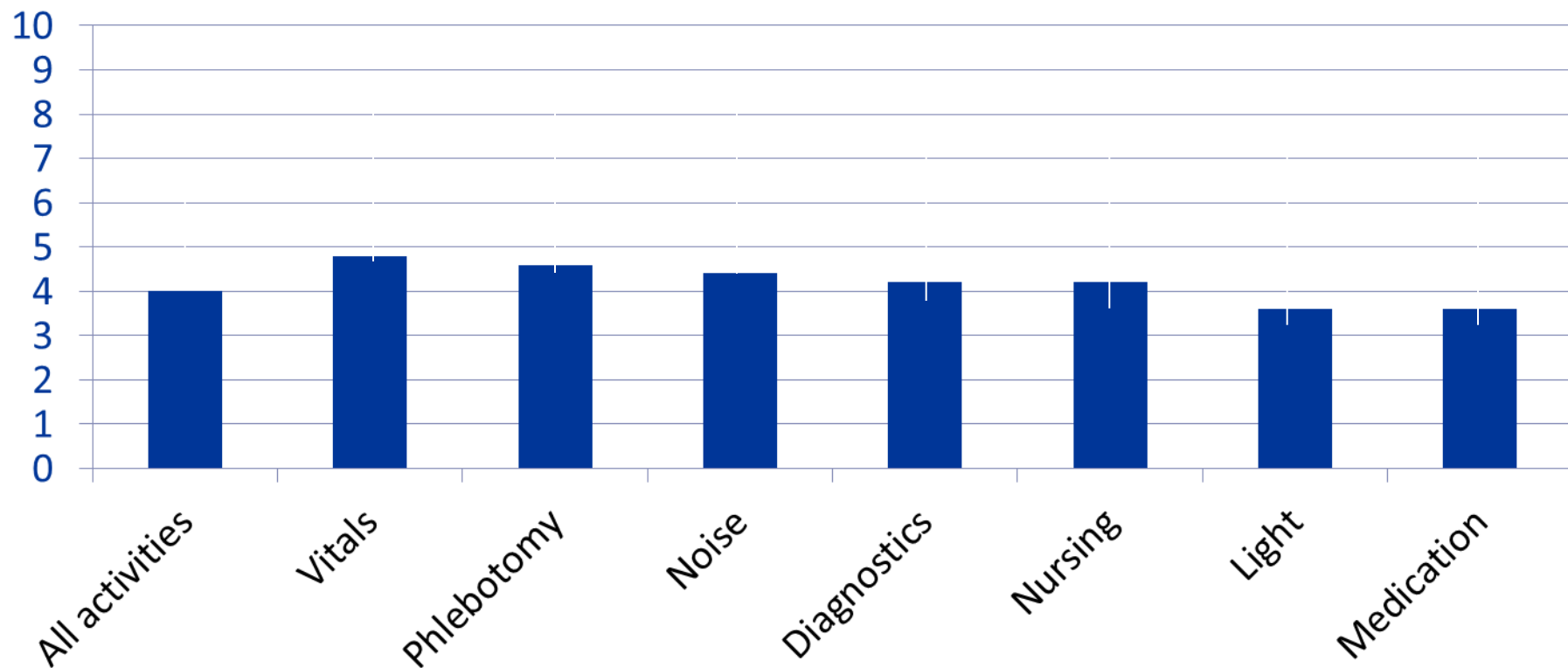
Sleep Stage	Description of Sleep	Percentage of Total Sleep
Stage I (N1)	Light	2-5%
Stage II (N2)	Light	45-55%
Slow wave sleep (SWS)	Deep sleep	15-20%
REM	Deep sleep	20-25%

Sleep Disturbances in the Intensive Care Unit (ICU)



Patient Perception of Sleep Quality in the ICU

Degree of Disruption (Severe:10 to None:0)





Consequences of Sleep Deprivation

- Fatigue, anxiety, impaired cognition and concentration
 - Potential risk factor for development of delirium
- Increased activation of the hypothalamic-pituitary-adrenal axis
 - Tachycardia, hypertension, increased cortisol
- Alterations in nitrogen balance, protein catabolism
 - Increased insulin resistance
- Immune system dysfunction



Mechanical Ventilation and Sleep Quality

- Same alteration of sleep architecture in mechanically-ventilated patients
- Pressure support vs. pressure assist control
 - Less central apneas improved sleep quality
 - Weaning should occur during daytime hours
- Non-invasive ventilation
 - Limited studies

Cooper AB, et al. Chest 2000;117:809-818.

Cabello B, et al. Crit Care Med. 2008;36(6):1749-55.

Alexopoulou C, et al. Intensive Care Med. 2013;39:1040–1047.

Roche-Camp F, et al. Crit Care Med 2013; 41:1637–1644.

Comparison of Sleep and Sedation

Similarities	Differences with Sleep
<ul style="list-style-type: none">• Altered sensorium and mentation• Muscle hypotonia• Temperature dysregulation• Disconjugate eye movements• ↓ respiratory rate	<ul style="list-style-type: none">• Spontaneous• Rhythmic• Essential• Reversible with stimuli

Propofol and Sleep Quality

Study Design

- Randomized, crossover
- Medical ICU (single center)

Inclusion

- Mechanical ventilation (assisted modes) > 48 hours, hemodynamic stability, no concomitant sedation or analgesia

Exclusion

- Glasgow coma scale < 11, APACHE II > 15, presence of delirium, neurologic disease, sleep apnea, sepsis, detectable plasma levels of sedative drugs

Outcomes

- Sleep architecture using PSG

Overnight Intervention (20:00 to 07:00)



Baseline Characteristics

Characteristic	Result
Male sex, %	50
Age (years), median	73
Admission APACHE II, median	23
Mechanical ventilation (days), median	18
Mechanical ventilation mode, %	
Pressure support ventilation	84
Continuous positive pressure airway pressure	8
Proportional assist ventilation +	8
Propofol infusion dose, (mcg/kg/min) median	15

Sleep Architecture Results

Endpoint, median (IQR)	No Propofol	Propofol	p value
TST (min)	214	260	0.37
Sleep efficiency (% TST)	62.6	76.3	0.37
SWS (% TST)	0 (0-0)	0 (0-5.8)	0.75
REM (% TST)	1.4 (0-13)	0 (0-0)	0.04

Influence of Medications on Sleep Quality

Medication	Sleep latency	TST	N1, N2	SWS	REM
Benzodiazepines	↓	↑	↑	↓	↓
Propofol	↓	↑	↑	-	↓
Dexmedetomidine	-	↑	↑	-	-
Dopamine antagonists	↓	↑	-	↑	-
Opioid agonists	-	↓	-	↓	↓
Corticosteroids	↑	-	-	↓	↓
Vasopressors	-	-	-	↓	↓

Treatment of Sleep

- No great pharmacologic options
- Utilize non-pharmacologic techniques
- Ultimately...get 'em out of the unit

The Men & Women Keeping Us All Together



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SHOOT FOR THE MOON

EVEN IF YOU MISS, YOU'LL LAND AMONG THE STARS.

OF COURSE, THEN YOUR EYEBALLS WILL BOIL AND YOUR LUNGS EXPLODE FROM DECOMPRESSION. BUT THAT'S WHAT YOU GET FOR BEING A DAMN SHOWOFF.