ICU Triad – Pain, Agitation, and Delirium in Mechanically Ventilated Patients

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Objectives

- Recall the treatment options for pain, agitation, and delirium for patients intubated in the ICU
- Recognize the assessment tools available for pain, agitation, and delirium
- Formulate a patient-centered multi-modal analgesic regimen recommendation to providers
- Apply available treatment options to specific patient cases

Mechanical Ventilation in the United States

- An estimated 20-30% of patients admitted to the ICU require mechanical ventilation
- In 2010, estimated national costs of mechanical ventilation were $27 billion and representing 12% of all hospital costs
- Delivery of sedation and analgesic medications to intubated patients is often necessary for patient comfort, tolerance, and improving ventilatory synchrony
- Long-term use of sedative medications can potentially prolong duration of mechanical ventilation and increase overall ICU length of stay

Wunsch H, et al. *Crit Care Med*. 2013;41:2712-2719.
Wunsch H, et al. *Crit Care Med*. 2010 Oct;38(10):1947-53.
Devlin JW, et al. *Crit Care Med*. 2018;46(9):3825-e873.

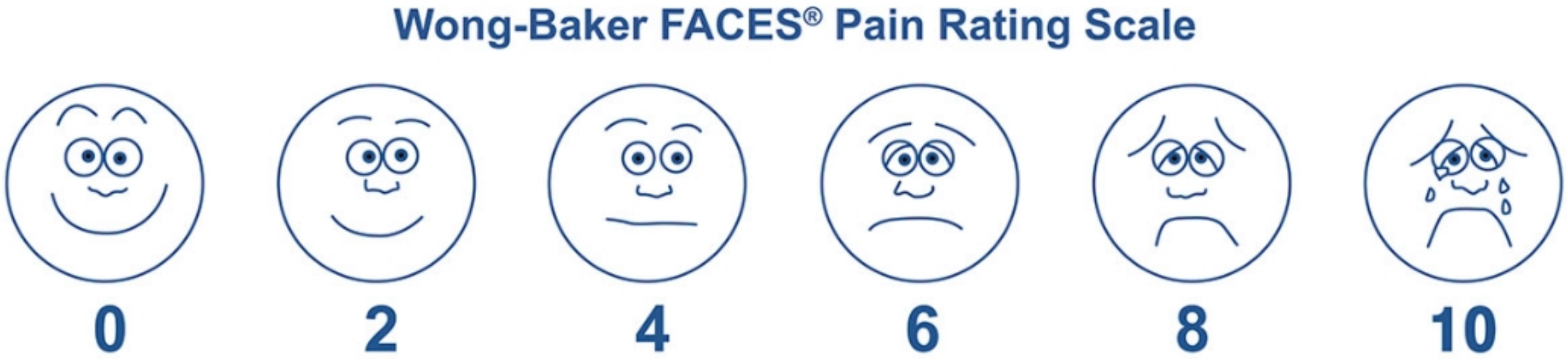
Pain and analgesia

- Pain is defined as an unpleasant sensory and emotional experience
- Individualized pain management

Signs of Pain
Hypertension
Tachycardia
Mydriasis
Pallor
Diaphoresis
Nothing apparent

Types of Pain
Acute pain
Chronic pain
Neuropathic pain
Nociceptive pain
Radicular pain

Pain Scales



https://wongbakerfaces.org/
https://www.healthline.com/health/pain-scale

Pain Scales

Appendix 1: Behavioral Pain Scale (BPS) Tool

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing with movement	2
	Fighting ventilator	3
	Unable to control ventilation	4

https://www.ijnmrjournal.net/article.asp?issn=1735-9066;year=2019;volume=24;issue=2;spage=151;epage=155;aulast=Gomarverdi

Pain Scales – Critical care pain observation tool (CPOT)

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
OR	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
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

https://www.semanticscholar.org/paper/Validation-of-the-critical-care-pain-observation-in

Medications Used for Analgesia

- Opioids
- NSAIDs
- Acetaminophen
- Local Anesthetics
- Antidepressants
- Ketamine
- Anticonvulsants
- Anxiolytics
- Alpha$_2$- agonists

Fentanyl

- Mechanism: synthetic opioid that binds the mu-opioid receptor
- Infusion rate: 25– 200 mcg/hr
  - Bolus: 25 – 100 mcg
- Onset to Peak: 2 – 5 minutes
- Duration: 0.5 - 2 hours

Hydromorphone (Dilaudid)

- Mechanism: Semi-synthetic derivative of morphine binds mu-opioid receptor
- Infusion rate: 0.2 – 3 mg/hr
  - Bolus: IV 0.5-4mg Q2 to 4h prn; PO 1-8mg Q4 to 6h prn
- Onset to peak: 20 – 30 minutes
- Duration: 3 – 4 hours

Morphine

- Mechanism: natural analgesic binds to the mu-receptor
- Infusion rate: 2 – 10 mg/hr
  - Bolus: IV 1-5mg Q1 to 4h prn; PO 10-30mg Q4h prn
- Onset to peak: 20 – 30 minutes
- Duration of action: 3 – 4 hours
- Histamine release

Oxycodone

- Mechanism: Binds mu-opioid receptor
- Dosing: PO 5-15mg every 4-6 hours prn
- Onset: IR 10-15 minutes
- Duration of action: IR 3 to 6 hours; ER $\leq$12hours

Ketorolac (Toradol)

- Mechanism: Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors
- Bolus: 15-30mg Q6h
- Onset: 10min
- Duration: 4 to 6 hours
- Maximum treatment of 5 days

Contraindications:
-CABG surgery
-active peptic ulcer disease, recent GI bleeding or perforation
-intrathecal or epidural administration
-advanced renal impairment
-prophylactic analgesic before any major surgery
-use with other NSAIDs

Acetaminophen (Tylenol)

- Mechanism: inhibits the synthesis of prostaglandins in the CNS
- Dosing: 325-650mg every 6 hours scheduled or as needed
  - Maximum: 4g/day
- Onset: <1 hour
- Duration: IV,PO 4 to 6 hours
- Hepatotoxicity
- Antidote: N-acetylcysteine to restore glutathione

Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: a double blind randomized controlled trial

Cattabriga L, Pacini D, Lamazza G, et al

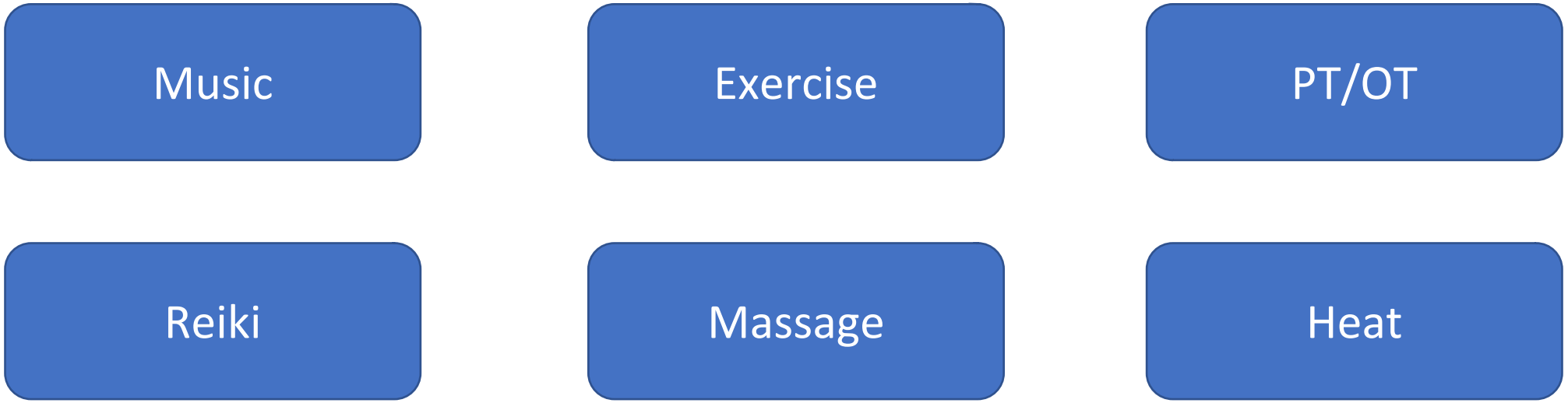
Eur J Cardiothorac Surg. 2007 Sep;32(3):527-31.

Methods	• Single center, placebo-controlled, double-blind, randomized trial • IV acetaminophen 1g vs placebo administered 15 minutes before the end of surgery and every 6 hours for 72 hours • Morphine IV 2 -5mg was administered whenever VAS was greater than 3			
Findings		Intervention group (N=56)	Control group (N=57)	P-value
	Pain at rest 12h postop	1 (0-6)	2 (1-10)	0.0041
	Pain at rest 18h postop	1 (0-5)	2 (0-8)	0.0039
	Pain at rest 24h postop	1 (0-5)	2 (0-8)	0.0044
	Morphine use	48 mg	97 mg	0.274

Other Analgesic Medications

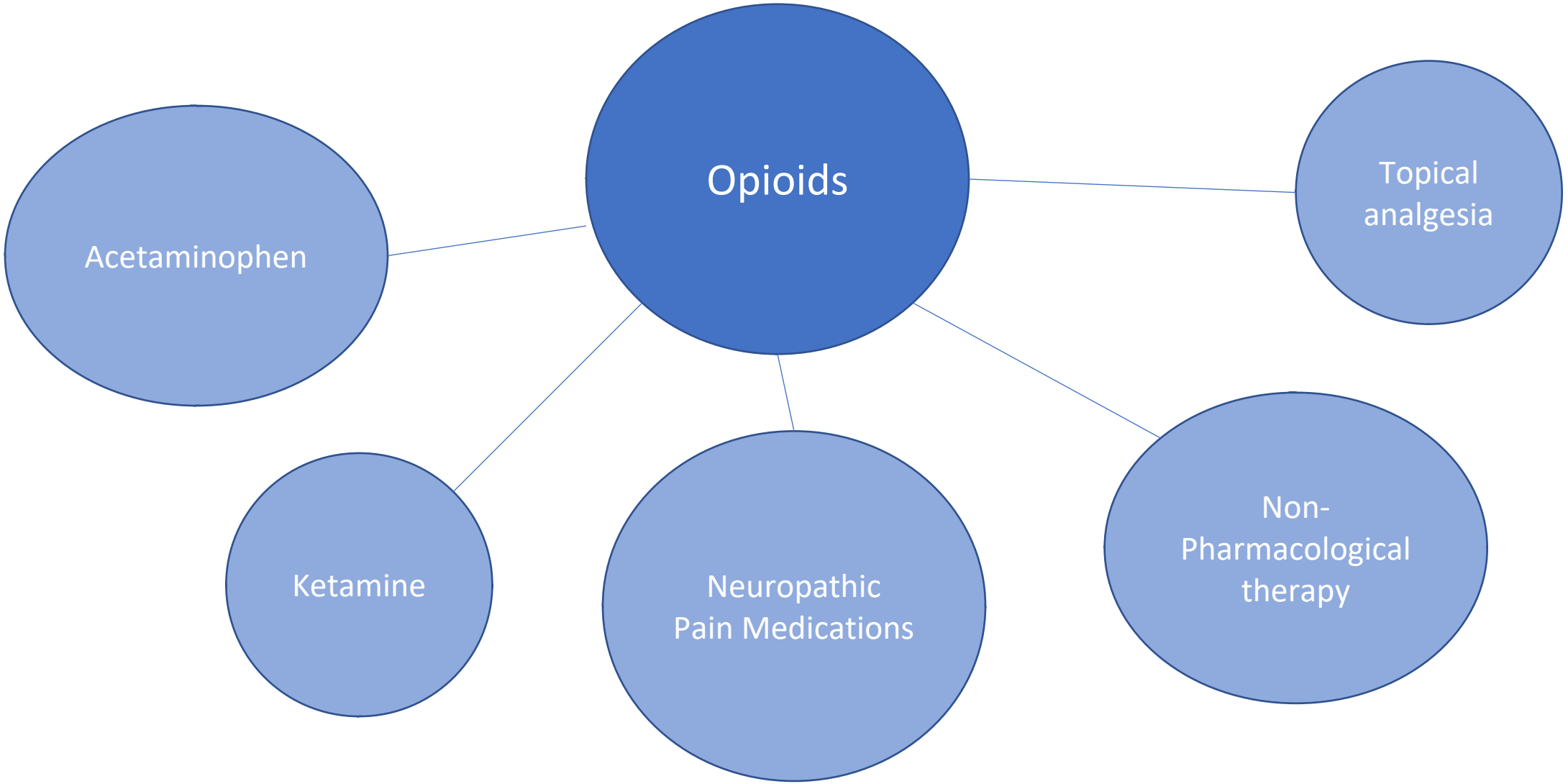
- Lidocaine (Patches, gel, cream, etc)
- Ketamine
- Muscle relaxants: baclofen, cyclobenzaprine, diazepam, methocarbamol
- Neuropathic pain – gabapentin, pregabalin, duloxetine, amitriptyline
- Tramadol

Non-Pharmacological Treatment Options



Relaxation, Distraction, Prevention

Multimodal Pain Treatment



Agitation and Sedation

- Mechanically ventilated patients have an increased risk of experiencing agitation
- May be due to undertreated pain, delirium, withdrawal, etc
- Agitation becomes a barrier to weaning sedation

Tate J, et al. Qual Health Res. 2012 Feb; 22(2): 157-173.

Sedation Assessment Scales

Richmond Agitation and Sedation Scale (RASS)		
Score	Classification	RASS Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior towards staff
+2	Agitated	Frequent non-purposeful movement or patient- ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	**Alert and Calm**	**Spontaneously pays attention to caregiver**
-1	Drowsy	Not fully alert, but has sustained (more than 10 sec) awakening, with eye contact to voice
-2	Light sedation	Briefly (less than 10 sec) awakens with eye contact
-3	Moderate Sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Sedation Assessment Scales

Riker Sedation-Agitation Scale		
Score	Classification	Description
7	Dangerous Agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, trashing side to side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down on verbal instructions
4	Calm, cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Propofol (Diprivan)

- Mechanism: causes global CNS depression, through agonism of $GABA_A$ receptors and reduced glutamatergic activity through NMDA receptor blockade
- Infusion rate: 5 – 80 mcg/kg/min (maximum 60 to 80 mcg/kg/min)
  - bolus 0.03 – 0.15 mg/kg (Max 20mg)
- Onset to peak: 1 - 2 minutes
- Duration of action: < 20 minutes
- Propofol rate infusion syndrome

Midazolam (Versed)

- Mechanism: Stimulate $GABA_A$ receptor
- Infusion rate: 1 - 10 mg/hr
  - Bolus: 1 – 6 mg Q10-15min prn
- Onset to peak: 5 - 10 minutes
- Duration of action: 1.5 - 2 hours

Lorazepam (Ativan)

- Mechanism: Stimulate $GABA_A$ receptor
- Infusion rate: 1 - 5 mg/hr
  - Bolus: 1 – 3 mg
- Onset to peak: 15 – 20 minutes
- Duration of action: 2 - 4 hours

Dexmedetomidine (Precedex)

- Mechanism: alpha$_2$-adrenoceptor agonist
- Infusion Rate: 0.2 – 1.5 mcg/kg/hr
- Onset to peak: 30 min
- Duration of action: 2 - 4 hours

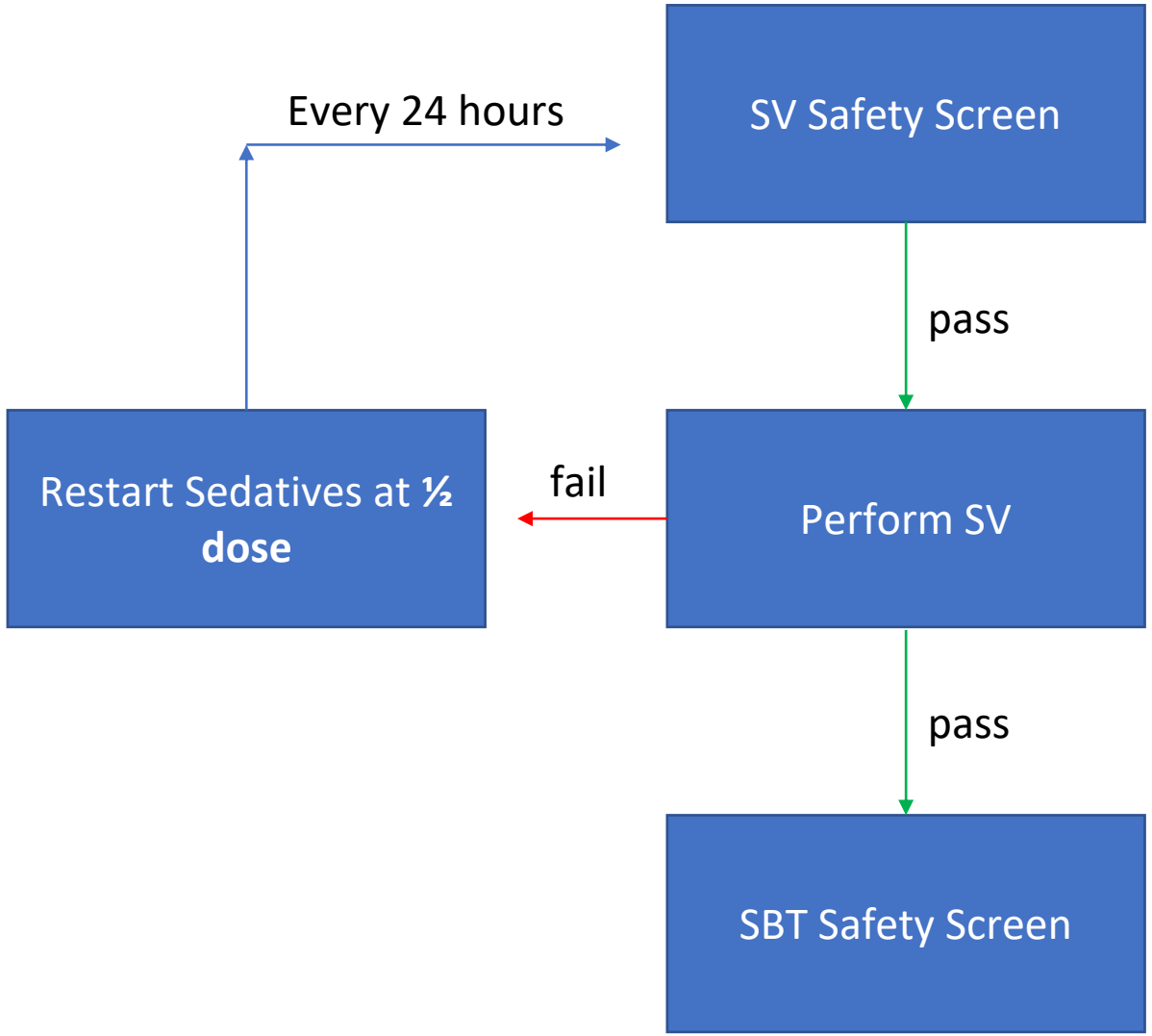
Ketamine

- Mechanism: noncompetitive NMDA receptor antagonist that blocks glutamate
- Infusion rate: 0.5 to 3 mg/kg/hr
  - Bolus: 0.1 – 2 mg/kg Q5 to 10min prn
- Onset to peak: 30 seconds
- Duration of action: 5 – 10 minutes

Daily Sedation Awakening Trials (SAT)

- Daily sedation interruption is a period where a patient's sedative medication is discontinued so patients can wake up and achieve alertness
- Reduce drug accumulation and oversedation
- Reduced ICU LOS, time to extubation, ventilator associated complications

Example Sedation Vacation Protocol



SV Safety Screen
No active seizures
No alcohol withdrawals
No agitation
No paralytics
No myocardial ischemia
Normal intracranial pressure

SV Failure
Anxiety, agitation, or pain
Respiratory rate >35/min
Oxygen saturation <88%
Respiratory distress
Acute cardiac arrhythmia

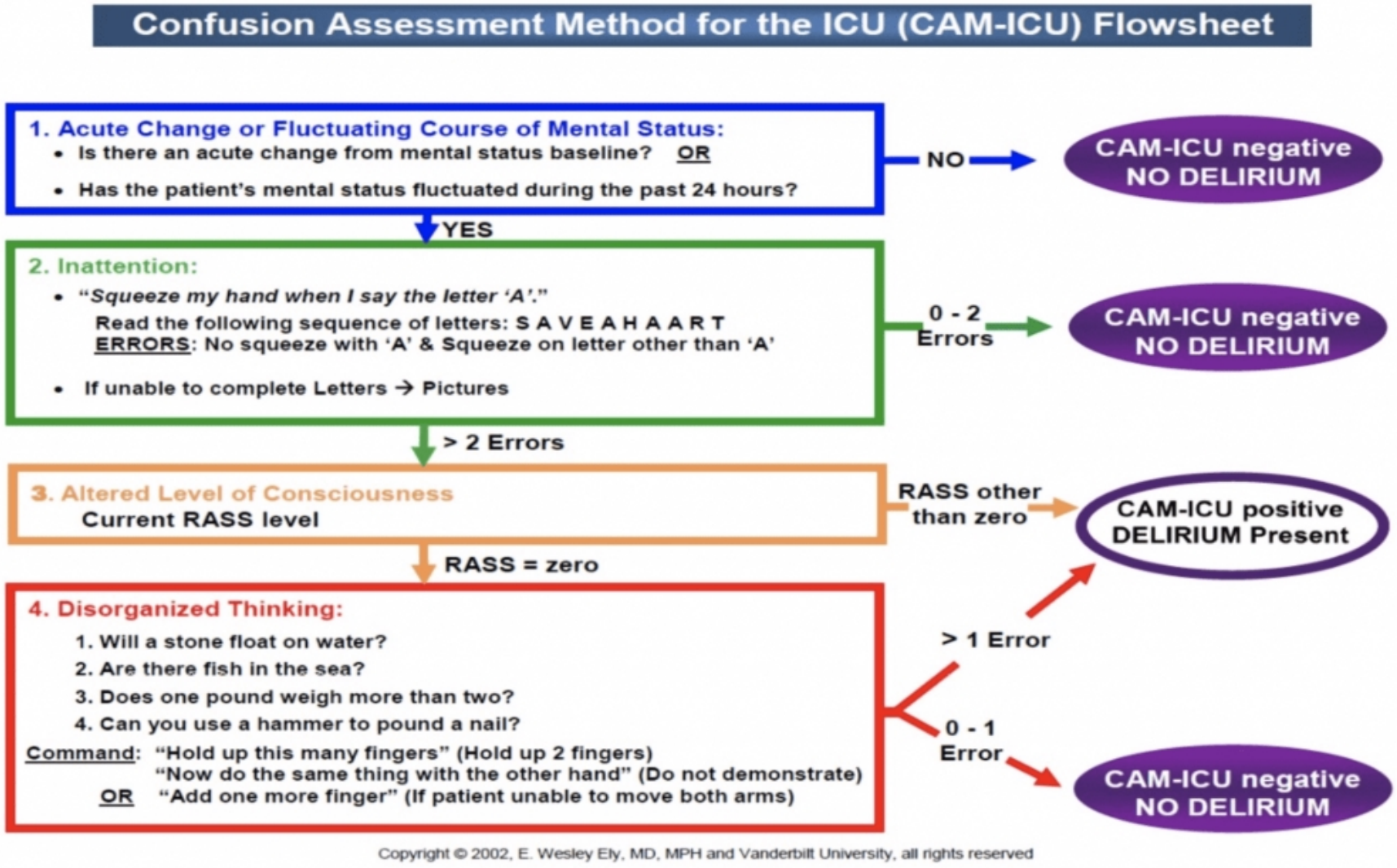
https://www.ahrq.gov/hai/tools/mvp/modules/technical/sat-sbt-protocol.html

Delirium

- Defined as an acute and fluctuating disturbance of consciousness and cognition
- Associated with worse outcomes related to higher ICU and hospital LOS and costs

Delirium Risk Factors	
Modifiable	**Nonmodifiable**
Benzodiazepine use	Increased age
Blood transfusion	Dementia
	Prior coma
	Pre-ICU emergency surgery or trauma

Delirium Assessment



https://www.researchgate.net/figure/Confusion-assessment-method-for-the-ICU-CAM-ICU-Flow-sheet_fig1_303790119

Delirium Treatment

- No routine pharmacological agent is recommended
- To treat symptoms of delirium
  - Haloperidol
  - An atypical antipsychotic (quetiapine, ziprasidone)
- Prevention!
  - Reducing modifiable risk factors for delirium
  - Optimizing sleep cycles
  - Early mobilization
  - Reduce hearing and/or visual impairment

Post COVID-19 ICU

- Transitioning back to standard of care
- Pharmacist education to nursing staff
  - Drip titration
  - Documentation
  - Daily awakening trials
- Pharmacists providing education on rounds

References

- Devlin, JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit care med*. 2018;46(9):e825-e873.
- Marra A, Ely W, Pandharipande P, et al. The ABCDEF Bundle in Critical Care. *Crit Care Clin*. 2017 Apr; 33(2):225-243.
- Lexicomp. Lexicomp Online. Accessed December 12, 2022.

Practice Questions

Q: A patient has been admitted to your ICU overnight due to a motor vehicle accident. They are intubated and sedated on a fentanyl drip and propofol drip. An NG tube has been inserted. What analgesic options would you recommend to the attending?

A. Acetaminophen 650mg PO Q6H
B. Lidocaine topical 5% Patch – apply to rib fracture
C. Non-pharmacological (music, heat/cold, etc)
D. All of the above

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Q: The guidelines recommend targeting a RASS of +1 to -2 or SAS of 3 to 4 for mechanically ventilated patients which correlates to:

A. Deep sedation
B. Light sedation
C. Light agitation
D. Delirium

Q: The guidelines recommend targeting a RASS of +1 to -2 or SAS of 3 to 4 for mechanically ventilated patients which correlates to:

A. Deep sedation
B. Light sedation
C. Light agitation
D. Delirium

True or False: Haloperidol or quetiapine should be recommended as a scheduled medication for the prevention of delirium

A. True
B. False

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A. True
B. False

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