

Sleeping on the Job?

Analgesia and Sedation in the ICU

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2023 ICHP
ANNUAL MEETING



Disclosures and Conflicts of Interest

- None

Learning Objectives

1.

- Assess pain and sedation in the ICU by utilizing a CPOT score and a RASS score.

2.

- Develop a pain management strategy for an ICU patient.

3.

- Create a sedation regimen for an ICU patient.

Definitions



ET tube: Endotracheal tube



NRS: Numeric Rating Scale



BPS: Behavioral Pain Scale



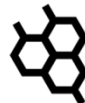
CPOT: Critical-Care
Observation Tool



APAP: Acetaminophen



NSAID: Non-Steroidal Anti-
Inflammatory Drug



MOA: Mechanism of Action



LOS: Length of Stay



MV: Mechanical Ventilation



VAP: Ventilator-Associated
Pneumonia

Why Do I Care?

- Patients experience pain at rest (33%) and during procedures (56%)
- **Appropriate** pain assessment and management can decrease duration of mechanical ventilation and number of infections
- Sedation is frequently utilized to prevent patients from accidentally removing life-saving lines/tubes

What Comes First, The Chicken or the Egg?

"Management of pain for adult ICU patients should be guided by routine pain assessment and pain should be treated before a sedative agent is considered."

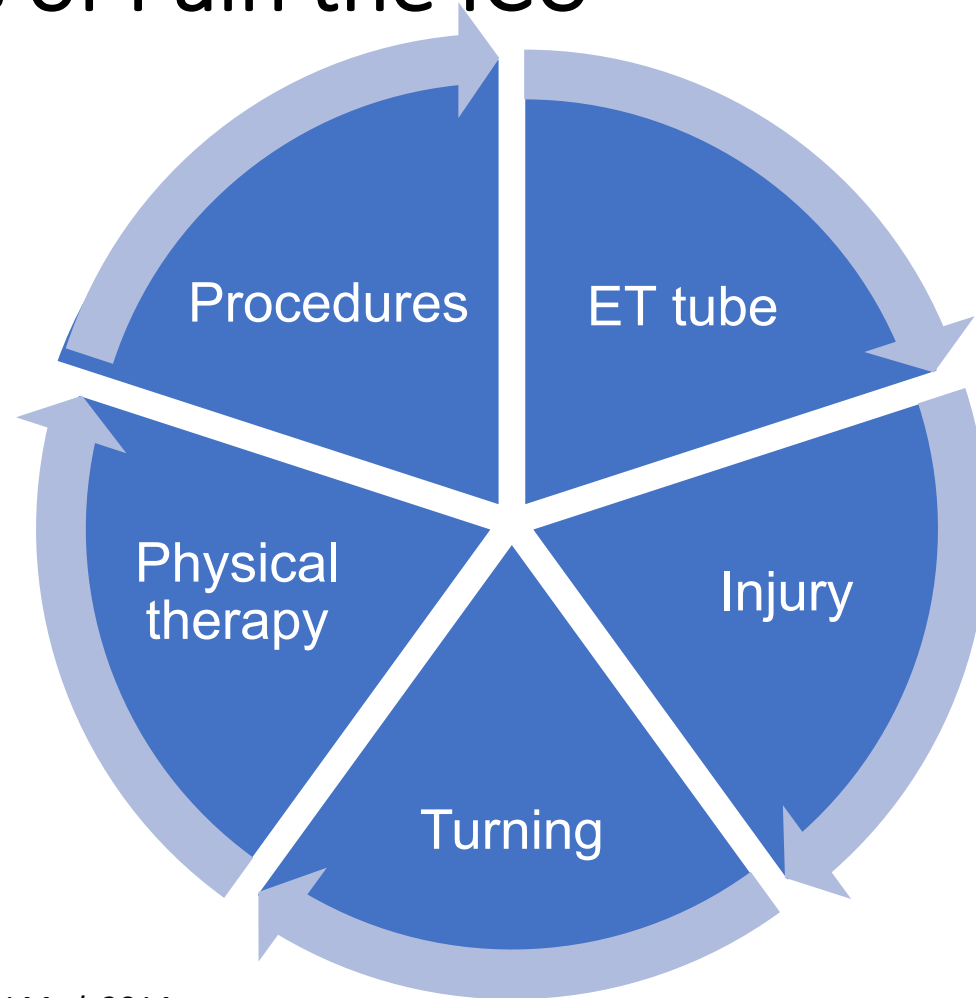


Pain Management in the ICU



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Etiologies of Pain the ICU



Assessing Pain in the ICU

Able to self-report pain

- 0-10 Numeric Rating Scale (NRS)

Unable to self-report pain

- Behavioral Pain Scale (BPS)
- Critical-Care Pain Observation Tool (CPOT)

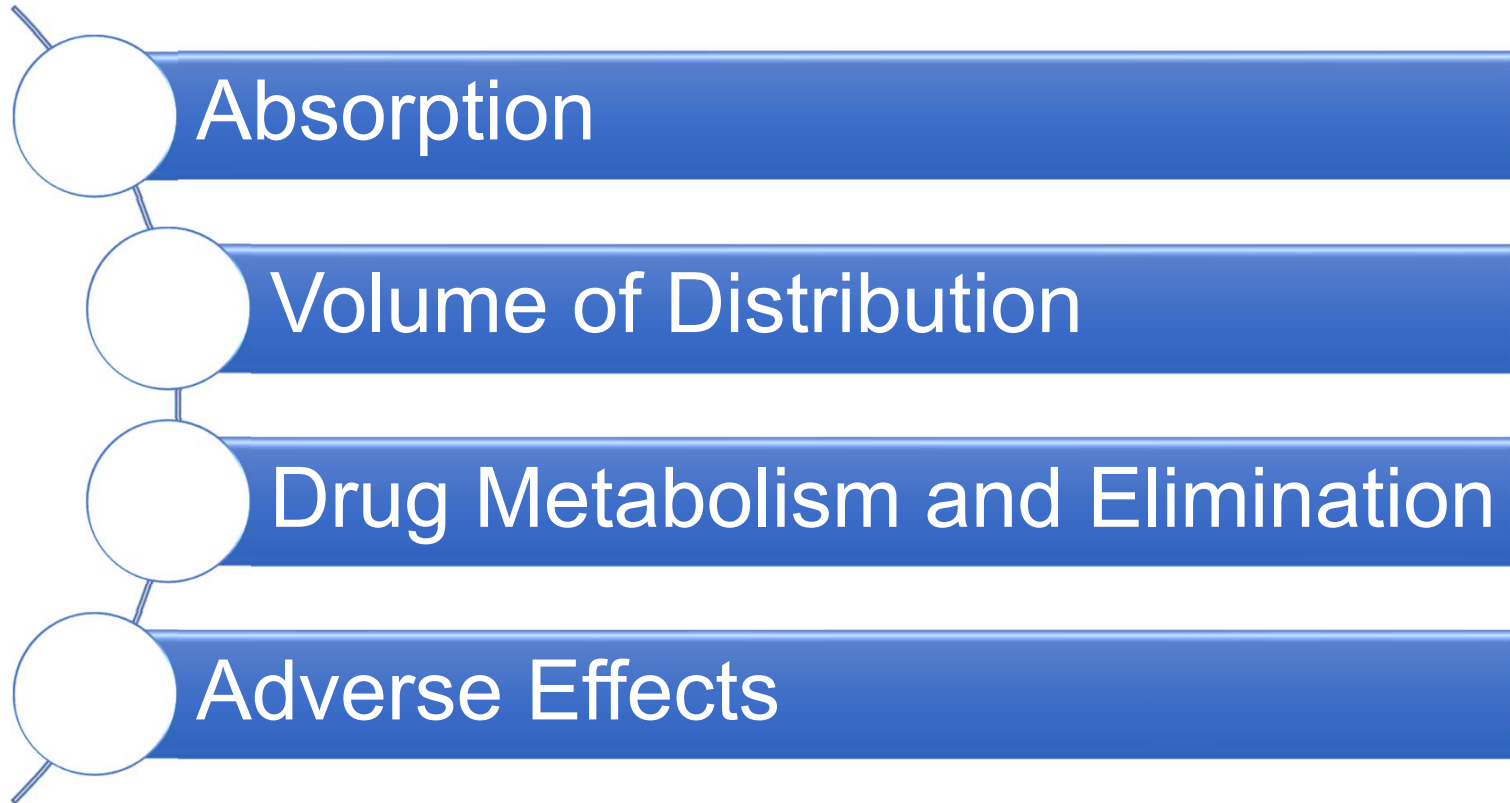
Vital signs should NOT be used

Critical-Care Pain Observation Tool

Indicator	Score	
Facial Expression	Relaxed, neutral	0
	Tense	1
	Grimacing	2
Body Movements	Absence of movements	0
	Protection	1
	Restlessness	2
Muscle Tension	Relaxed	0
	Tense, rigid	1
	Very tense or rigid	2
Compliance with the Ventilator	Tolerating ventilator or movement	0
	Coughing but tolerating	1
	Fighting ventilator	2

CROT Score >2 indicates the presence of pain

Factors that Affect Drug Selection



Modalities for Pain Management in the ICU

Adjuvant Medications

Opioid Therapy

Adjuvant Medications

Adverse Effects of Opioids

Respiratory
depression

Ileus

Immunosuppression

Increased ICU LOS

Increased sedation

Delirium

Acetaminophen

Guidelines recommend the use of acetaminophen as an adjunct to opioid therapy for patients in the ICU.

Study	Key Results
Cattabriga et al	APAP vs Placebo: <ul style="list-style-type: none">• APAP group: less pain at rest (p = 0.0041)• Morphine administration: 48 mg vs 97 mg (p = 0.274)
Memis et al	APAP vs Placebo: <ul style="list-style-type: none">• APAP group: lower BPS scores (p < 0.05)• Meperidine administration: 76.75 ± 18.2 mg vs 198 ± 66.4 mg (p < 0.01)• Extubation time: 64.3 ± 40.6 min vs 204.5 ± 112.7 min (p < 0.01)

NSAIDS

Guidelines do NOT recommend the routine use of NSAIDS in critically ill patients.

Safety Concerns

- Increased risk of bleeding
- Worsening acute kidney injury

NSAIDS

Study	Key Results
Hynninen et al	<ul style="list-style-type: none">• No difference in pain scores• Only patients in the diclofenac group had decreased morphine requirements when compared to placebo (12.4 mg vs 19 mg; p < 0.05)
Oberhofer et al	Patients in the NSAID group had: <ul style="list-style-type: none">• Significantly lower pain scores at 3 (p < 0.01), 6 and 12 hours (p < 0.05)• Significantly lower tramadol usage (p < 0.01)

Novel Pain Management Strategies

Ketamine

Neuropathic pain medications

Lidocaine

Opioid Analgesics

Guidelines suggest the use of a multi-model pain regimen with the goal of using opioids sparingly.

Pros



Minimal bleeding and AKI risk

Numerous studies supporting their use in pain management

Cons



May increase time to extubation

Significant adverse effects

Opioid Analgesics

Study	Key Results
Casey et al	Remifentanil vs placebo: <ul style="list-style-type: none">• Pain score: 1 vs 5 (p = 0.001)• No change in SpO2 between 0.5 mcg/kg group vs placebo
Ahlers et al	Morphine 2.5 mg vs 7.5 mg: <ul style="list-style-type: none">• Unacceptable pain at rest: 14 vs 17% (p = 0.81)• Procedural-related pain: 28 vs 22% (p = 0.53)
Robleda et al	Fentanyl vs placebo: <ul style="list-style-type: none">• AUC for BPS values: 132 vs 147 (p = 0.016)

Fentanyl

Synthetic or Natural?	Synthetic
Onset (IV)	1-2 min
Elimination Half-Life	2-4 hrs
Volume of Distribution	4-6 L/kg
Metabolic Pathway	N-dealkylation CYP3A4/5 substrate
Active Metabolites	None

Hydromorphone

Synthetic or Natural?	Semi-synthetic
Onset (IV)	5-15 min
Elimination Half-Life	2-3 hrs
Volume of Distribution	4 L/kg
Metabolic Pathway	Glucuronidation
Active Metabolites	None

Morphine

Synthetic or Natural?	Natural
Onset (IV)	5-10 min
Elimination Half-Life	3-4 hrs
Volume of Distribution	1-6 L/kg
Metabolic Pathway	Glucuronidation
Active Metabolites	6- and 3-glucuronide metabolite

Remifentanyl

Synthetic or Natural?	Synthetic
Onset (IV)	1-3 min
Elimination Half-Life	3-10 min
Volume of Distribution	Initial: 100 mL/kg; V_{dss} : 350 mL/kg
Metabolic Pathway	Hydrolysis by plasma esterases
Active Metabolites	None

Opioid Analgesics

Intermittent vs Continuous Infusion?

No clear guideline recommendations



Case Study #1

52 y.o.m. presented with SOB. Patient immediately decompensated upon arrival and was intubated. Initial CPOT score after intubation was 4.



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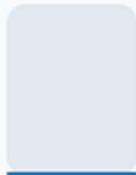


1. Assess the patient's pain based off of the CPOT score of 4.

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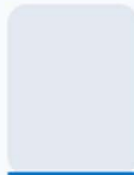
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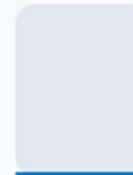
The patient is in pain.

0%



The patient is in moderate pain.

0%



The patient is in severe pain.

0%



The patient is in no pain.



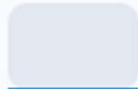
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2. What is an appropriate pain management strategy for this patient?

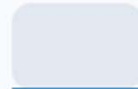
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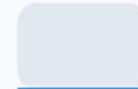
Acetaminophen 650 mg q6h
scheduled plus morphine 2 mg
q6h PRN

0%



Acetaminophen 650 mg q6h
scheduled plus fentanyl 25 mcg
q2h PRN

0%



Fentanyl continuous infusion,
titrated to achieve CPOT score
> 3

0%



Ibuprofen 800
mg q8h PRN

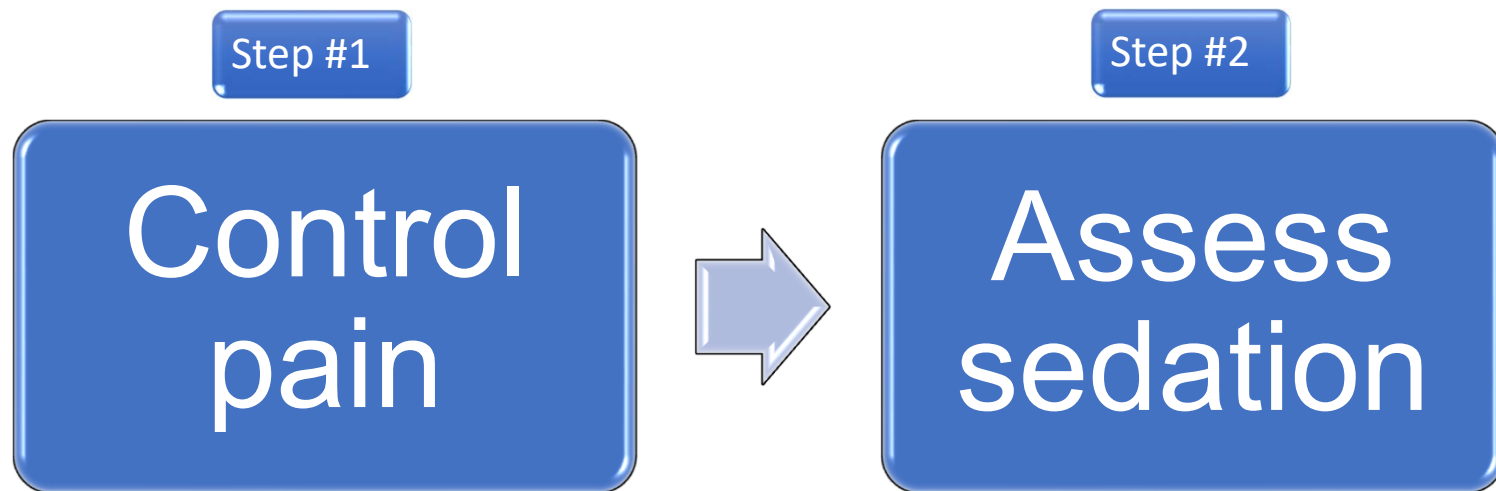


Sedation Management in the ICU



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Assessing the Need for Sedation



- Richmond Agitation Sedation Scale (RASS)
- Sedation-Agitation Scale (SAS)

RASS Scoring

Score	Brief Description
+4	Combative
+3	Very agitated
+2	Agitated
+1	Restless
0	Alert and calm
-1	Drowsy
-2	Light sedation
-3	Moderate sedation
-4	Deep sedation
-5	Unarousable

Light Sedation

Guidelines suggest using light sedation in critically ill, mechanically ventilated patients.

Light sedation is defined as RASS between -2 and +1



Decrease

- **Time to extubation:** MD -0.77 d; (95% CI, -2.04 to -0.50)
- **Rate of tracheostomy:** RR 0.57; (95% CI, 0.41-0.80)

Medications Used for Sedation

Propofol

Dexmedetomidine

Benzodiazepines

Propofol

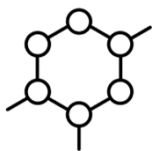
MOA: binds to GABA A receptors, potentiating the inhibitory effects of GABA

Onset of Action	30 seconds
Duration of Action	3-15 minutes
Metabolism	Hepatic to water soluble sulfate and glucuronide conjugates
Adverse Effects	Hypotension, bradycardia, hypertriglyceridemia, pancreatitis, propofol-related infusion syndrome

Propofol Clinical Pearls



Sedative, hypnotic, anxiolytic, amnestic, and anticonvulsant properties



Dissolved in 10% lipid emulsion containing egg lecithin and soybean oil but you **CAN STILL use in patients with egg and soybean allergies**



May rarely cause production of green urine

Dexmedetomidine

MOA: selective alpha2-agonist that results in decreased norepinephrine release

Onset of Action	5-10 minutes*
Duration of Action	60-240 min
Metabolism	Hepatic via N-glucuronidation, N-methylation, and CYP2A6
Adverse Effects	Hypotension, bradycardia

*If IV loading dose is used

Dexmedetomidine Clinical Pearls



Additional analgesic properties

- Inhibits A δ and C fibers
- Decreases release of substance P
- Stimulation of α 2 receptor



Light sedative with minimal risk for respiratory depression

Benzodiazepines

MOA: binds to GABA A receptors, potentiating the inhibitory effects of GABA

	Onset of Action (IV)	Duration of Action (single dose)	Metabolism
Lorazepam IM/IV	15-20 min	6-8 hrs	Glucuronidation
Midazolam IM/IV	1-5 min	2 hrs	CYP3A4 and Hepatic Oxidation
Diazepam IM/IV/rectal	4-5 min	1-2 hrs	CYP3A4, Demethylation, Hydroxylation

Benzodiazepine Clinical Pearls



Anxiolytic, amnestic, sedative, hypnotic, and anticonvulsant effects



Increased risk for ICU-induced delirium



Risk of propylene glycol toxicity with lorazepam

Sedation Literature

Propofol vs Benzodiazepines

Propofol *is preferred* over benzodiazepines

- ↓ • **Reduced** time to light sedation (−7.2 hr; 95% CI, −8.9 to −5.5)
- ↓ • **Decreased** time to extubation (−11.6 hr; 95% CI, −15.6 to −7.6)
- ↓ • **Lower** odds of delirium (OR 1.46; 95% CI, 1.06 – 2.00)

Sedation Literature

Dexmedetomidine vs Benzodiazepines

Dexmedetomidine *is preferred* over benzodiazepines

- ↓ • **Decreased** time to extubation (−1.90 d; 95% CI, −2.32 to −1.48)
- ↓ • **Reduction** in delirium (0.71; 95% CI, 0.61–0.83)

Sedation Literature

Propofol vs Dexmedetomidine

Study	Key Results
Hughes et al	<p>Propofol vs Dexmedetomidine:</p> <ul style="list-style-type: none">• Days alive: 10.7 vs 10.8 days (OR 0.96; 95% CI (0.74-1.26))• Ventilator-free days: 23.7 vs 24 days (OR 0.98; 95% CI, 0.63-1.51)• Death at 90 days: 38% vs 39% (HR 1.06; 95% CI, 0.74-1.52)

Sedation Literature

Propofol vs Dexmedetomidine

Study	Key Results
Pereira et al	Dexmedetomidine was associated with decreased delirium (RR 1.52; 95% CI, 0.85-2.72; p = 0.02)
Heybati et al	No difference in ICU LOS (MD -8.94 hr; 95% CI, -22.4-4.52 hr; p = 0.1603) Dexmedetomidine reduced duration of mechanical ventilation (MD -0.67 hr; 95% CI, -1.31 to -0.03 hr; p = -0.041) and delirium (RR 0.49; 95%, 0.29-0.87; p = 0.019)

Pereira et al. *Eur J Anaesthesiol.* 2020.

Heybati et al. *Brit J Anaesthesia.* 2022.

Sedation Literature

Propofol vs Dexmedetomidine

Study	Key Results
Shin et al	Dexmedetomidine was associated with decreased delirium: 3% vs 6% (OR 0.42; 95% CI 0.201-0.86; p = 0.036)

Sedation Literature

Propofol vs 'Comparator'

Study	Key Results
Kotani et al	Propofol was associated with increased mortality (5.2% vs. 4.3%; RR 1.10; 95% CI (1.01–1.20); p = 0.03)

Sedation Vacations

Daily sedative interruption (DSI) and nursing-protocolized (NP)-targeted sedation can achieve and maintain a light level of sedation.

- DSI = daily **discontinuation** of sedative
 - Goal RASS –1 to +1
- NP-targeted sedation = protocol to manage sedation
 - May determine sedative choice
 - Titrate medications to achieve goals



Case Study #2

52 y.o.m. now has a CPOT < 2 after our previous intervention. The nurse next assesses a RASS score which is currently +2.



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3. What is an appropriate RASS score for this patient?

0

0%



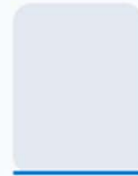
RASS +2

0%



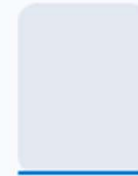
RASS -2

0%



RASS +5

0%



RASS -5



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4. What is the best sedation regimen for this patient?

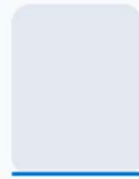


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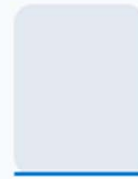
Dexmedetomidine

0%



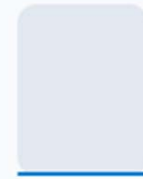
Propofol

0%



Midazolam

0%



No sedation needed



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Questions?

0

Nobody has responded yet.
Hang tight! Responses are coming in.

References

- Payen JF, Chanques G, Mantz J et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology*. 2007;106(4):891-2.
- Reade MC, Finfer S. Sedation and Delirium in the Intensive Care Unit. *N Engl J Med*. 2014;370:444-454.
- Chanques G, Jaber S, Barbotte E, et al. Impact of systematic evaluation of pain and agitation in an intensive care unit. *Crit Care Med*. 2006;34(6):1691-9.
- Chanques G, Sebbane M, Barbotte E, Viel E, Eledjam JJ, Jaber S. A Prospective Study of Pain at Rest: Incidence and Characteristics of an Unrecognized Symptom in Surgical and Trauma versus Medical Intensive Care Unit Patients. *Anesthesiology*. 2007;107:858-60.
- 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):825-73.
- Society of Critical Care Medicine. Critical-Care Pain Observation Tool. Available at: [https://www.sccm.org/getattachment/afd82d09-1a9b-4c8e-9c0e-8575f1721a9d/Critical-Care-Pain-Observation-Tool-\(CPOT\)](https://www.sccm.org/getattachment/afd82d09-1a9b-4c8e-9c0e-8575f1721a9d/Critical-Care-Pain-Observation-Tool-(CPOT)). Accessed May 2, 2022.
- Smith BS, Yagaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. *CHEST*. 2012;141(5):1327-36.
- Cattabriga I, Pacini D, Lamazza G, et al. Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: a double blind randomized controlled trial. *Eur J of Cardio-Thoracic Surg*. 2007;32(3):527-31.

References

- Memis D, Inal MT, Kavalci G, Sezer A, Sut N. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit. *J of Crit Care*. 2010;25(3):458-62.
- Hynninen MS, Cheng DC, Hossain I, et al. Non-steroidal anti-inflammatory drugs in treatment of postoperative pain after cardiac surgery. *Can J Anaesth*. 2000;47(12):1182-7.
- Oberhofer D, Skok J, Neseek-Adam V. Intravenous ketoprofen in postoperative pain treatment after major abdominal surgery. *World J Surg*. 2005;29(4):446-9.
- Casey E, Lane A, Kuriakose D, et al. Bolus remifentanyl for chest drain removal in ICU: a randomized double-blind comparison of three modes of analgesia in post-cardiac surgical patients. *Int Care Med*. 2010;36(8):1390-5.
- Ahlers SJGM, Van Gulik L, Van Dongen EPA, et al. Efficacy of an Intravenous Bolus of Morphine 2.5 versus Morphine 7.5 mg for Procedural Pain Relief in Postoperative Cardiothoracic Patients in the Intensive Care Unit: A Randomised Double-Blind Controlled Trial. *Anaesthesia and Int Care*. 2012;40(3):417-26.
- Robleda G, Roche-Campo F, Sendra MA, et al. Fentanyl as pre-emptive treatment of pain associated with turning mechanically ventilated patients: a randomized controlled feasibility study. *Int Care Med*. 2016;42(2):183-91.
- Barr J, Fraser G, Puntillo K, et al. Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit. *Crit Care Med*. 2013;41(1):263-306.
- Casault C, Soo A, Lee CH, et al. Sedation strategy and ICU delirium: a multicentre, population-based propensity score-matched cohort study. *BMJ Open*. 2021;11:e045087.
- Society of Critical Care Medicine. Richmond Agitation-Sedation Scale. Available at: [https://www.sccm.org/getattachment/41451def-b9f8-404a-8a55-a9aea19c1911/Richmond-Agitation-Sedation-Scale-\(RASS\)](https://www.sccm.org/getattachment/41451def-b9f8-404a-8a55-a9aea19c1911/Richmond-Agitation-Sedation-Scale-(RASS)). Accessed May 2, 2022.

References

- Diprivan [package insert]. Lake Zurich, IL: Fresenius Kabi; 2017.
- Propofol (Lexi-Drugs). Hudson, OH: Lexicomp, 2022. <http://online.lexi.com/lco/action/home>.
- Sahinovic MM, Struys MMR, Absalom AR. Clinical Pharmacokinetics and Pharmacodynamics of Propofol. *Clin Pharmacokinet*. 2018;57(12):139-58.
- Asserhoj LL, Mosbech H, Kroigaard M, Garvey LH. No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut. *Br J Anaesth*. 2016;116(1):77-82.
- Dexmedetomidine (Lexi-Drugs). Hudson, OH: Lexicomp, 2022. <http://online.lexi.com/lco/action/home>.
- Zhao Y, He J, Yu N, Jia C, Wang S. Mechanisms of Dexmedetomidine in Neuropathic Pain. *Front Neurosci*. 2020;14:330.
- Lorazepam; Midazolam; Diazepam (Lexi-Drugs). Hudson, OH: Lexicomp, 2022. <http://online.lexi.com/lco/action/home>.
- Hughes CG, Mailloux PT, Devlin JW et al. Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis. *N Engl J Med*. 2021;384:1424-36.
- Pereira JV, Sanjanwala RM, Mohammed MK, Le ML, Arora RC. Dexmedetomidine versus propofol sedation in reducing delirium among older adults in the ICU: A systematic review and meta-analysis. *Eur J Anaesthesiol*. 2020;37(2):121-31.
- Heybati K, Zhou F, Ali S, et al. Outcomes of dexmedetomidine versus propofol sedation in critically ill adults requiring mechanical ventilation: a systemic review and meta-analysis of randomized controlled trials. *Brit J Anesthesia*. 2022;129(4):515-26.
- Shin H, Nam SW, Kim H, et al. Postoperative Delirium after Dexmedetomidine versus Propofol Sedation in Healthy Older Adults Undergoing Orthopedic Lower Limb Surgery with Spinal Anesthesia: A Randomized Controlled Trial. *Anesthesia*. 2023;138(2):164-71.
- Kotani Y, Pruna A, Turi S, et al. Propofol and survival: an updated meta-analysis of randomized clinical trials. *Critical Care*. 2023;27:139.



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