

Sleeping on the Job?

Analgesia and Sedation in the ICU

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Disclosures and Conflicts of Interest

- None











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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.

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Definitions

- | | |
|---|--|
|  ET tube: Endotracheal tube |  NSAID: Non-Steroidal Anti-Inflammatory Drug |
|  NRS: Numeric Rating Scale |  MOA: Mechanism of Action |
|  BPS: Behavioral Pain Scale |  LOS: Length of Stay |
|  CPOT: Critical-Care Observation Tool |  MV: Mechanical Ventilation |
|  APAP: Acetaminophen |  VAP: Ventilator-Associated Pneumonia |

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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

Payen et al. *N Engl J Med.* 2014. Chanques et al. *Crit Care Med.* 2006.
Reade et al. *N Engl J Med.* 2014. Chanques et al. *Anesthesiology.* 2007.

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What Comes First, The Chicken or the Egg?

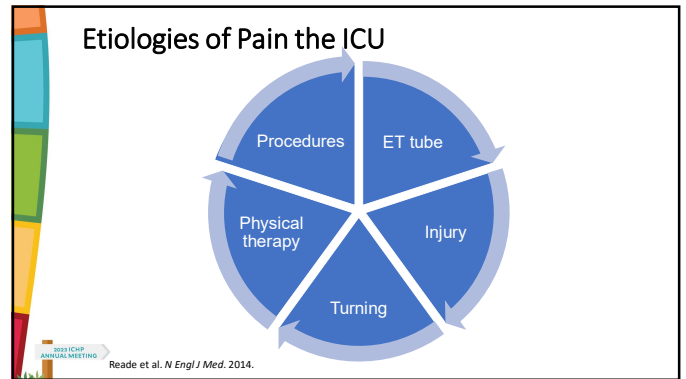
"Management of pain for adult ICU patients should be guided by routine pain assessment and pain should be treated before a sedative agent is considered."

Devlin et al. *Crit Care Med.* 2018.

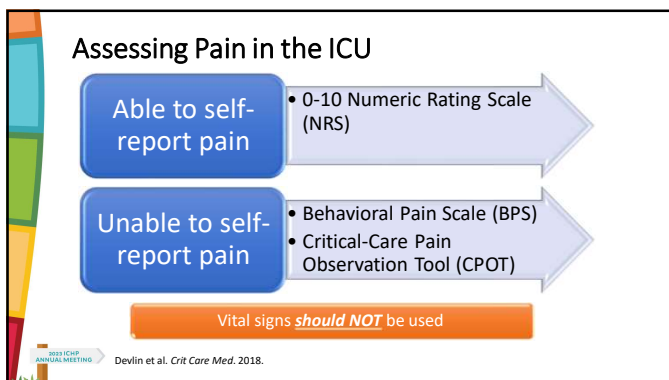
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Pain Management in the ICU

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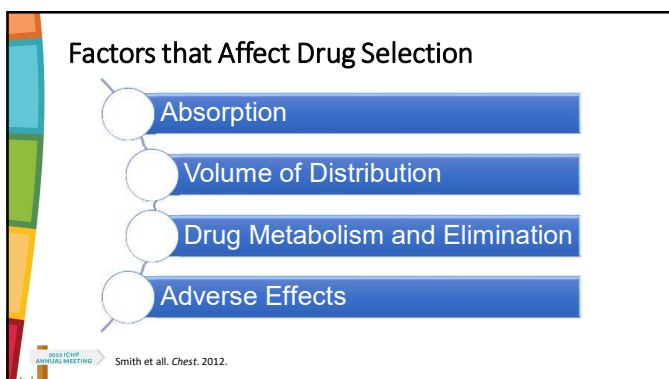
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Critical-Care Pain Observation Tool

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

CPOT Score >2 indicates the presence of pain

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Adjuvant Medications

Adverse Effects of Opioids

Respiratory depression	Ileus	Immunosuppression
Increased ICU LOS	Increased sedation	Delirium

2023 ICSP ANNUAL MEETING Reade et al. *N Engl J Med.* 2014.

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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 ($p < 0.01$)

2023 ICSP ANNUAL MEETING Cattabriga et al. *Eur J Cardio-Thoracic Surg.* 2007. Memis et al. *J of Crit Care.* 2010.

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NSAIDs

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

Safety Concerns

- Increased risk of bleeding
- Worsening acute kidney injury

2023 ICSP ANNUAL MEETING Devlin et al. *Crit Care Med.* 2018.

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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 ($p < 0.01$)

2023 ICSP ANNUAL MEETING Ninenen et al. *Can J Anaesth.* 2000. Oberhofer et al. *World J Surg.* 2005.

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Novel Pain Management Strategies

- Ketamine
- Neuropathic pain medications
- Lidocaine

2023 ICSP ANNUAL MEETING Devlin et al. *Crit Care Med.* 2018.

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Opioid Analgesics

Guidelines suggest the use of a multi-modal 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

2023 ICSP ANNUAL MEETING Devlin et al. *Crit Care Med.* 2018.

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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 ($p = 0.016$)

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Casey et al. *Int Care Med.* 2010.
Ahlers et al. *Anesthesia and Int Care.* 2012.Robleda et al. *Int Care Med.* 2016.

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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

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Barr et al. *Crit Care Med.* 2013.

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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

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Barr et al. *Crit Care Med.* 2013.

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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

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Barr et al. *Crit Care Med.* 2013.

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Remifentanil

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

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Barr et al. *Crit Care Med.* 2013.

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Opioid Analgesics

Intermittent vs Continuous Infusion?

No clear guideline recommendations

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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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Self-Assessment Question #1

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

- The patient is in pain.
- The patient is in *moderate* pain.
- The patient is in *severe* pain.
- The patient is in *no* pain.



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Self-Assessment Question #2

What is an appropriate pain management strategy for this patient?

- Acetaminophen 650 mg q6h scheduled *plus* morphine 2 mg q6h PRN
- Acetaminophen 650 mg q6h scheduled *plus* fentanyl 25 mcg q2h PRN
- Fentanyl continuous infusion, titrated to achieve CPOT score > 3
- Ibuprofen 800 mg q8h PRN



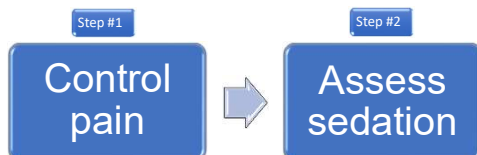
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Sedation Management in the ICU



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Assessing the Need for Sedation



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



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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



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Society of Critical Care Medicine. Richmond Agitation-Sedation Scale. Accessed May 2, 2022.

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)

2023 CUP ANNUAL MEETING Devlin et al. Crit Care Med. 2018.

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Medications Used for Sedation

Propofol

Dexmedetomidine

Benzodiazepines

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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

2023 CUP ANNUAL MEETING Diprivan [package insert], Lake Zurich, IL: Fresenius Kabi; 2017. Reade et al. N Engl J Med. 2014. Propofol (Lexi-Drugs), Hudson, OH: Lexicomp, 2022. Barr et al. Crit Care Med. 2013.

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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

2023 CUP ANNUAL MEETING Reade et al. N Engl J Med. 2014. Sahinovic et al. Clin Pharmacokinet. 2018. Barr et al. Crit Care Med. 2013. Aserhøj et al. Br J Anaesth. 2016.

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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

2023 CUP ANNUAL MEETING Dexmedetomidine (Lexi-Drugs), Hudson, OH: Lexicomp, 2022.

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Dexmedetomidine Clinical Pearls

- Additional analgesic properties
 - Inhibits Aδ and C fibers
 - Decreases release of substance P
 - Stimulation of α2 receptor
- Light sedative with minimal risk for respiratory depression

2023 CUP ANNUAL MEETING Zhao et al. Front Neurosci. 2020.

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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

2023 ICSP ANNUAL MEETING | Reade et al. *N Engl J Med.* 2014.
Lorazepam; Midazolam; Diazepam (Lexi-Drugs). Hudson, OH: Lexicomp, 2022.

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Benzodiazepine Clinical Pearls

- Anxiolytic, amnestic, sedative, hypnotic, and anticonvulsant effects
- Increased risk for ICU-induced delirium
- Risk of propylene glycol toxicity with lorazepam

2023 ICSP ANNUAL MEETING | Barr et al. *Crit Care Med.* 2013.

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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)

2023 ICSP ANNUAL MEETING | Devlin et al. *Crit Care Med.* 2018.
Casault et al. *BMJ Open.* 2021.

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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)

2023 ICSP ANNUAL MEETING | Devlin et al. *Crit Care Med.* 2018.

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Sedation Literature

Propofol vs Dexmedetomidine

Study	Key Results
Hughes et al	Propofol vs Dexmedetomidine: <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)

2023 ICSP ANNUAL MEETING | Hughes et al. *NEJM.* 2021.

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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% CI, 0.29-0.87; p = 0.019)

2023 ICSP ANNUAL MEETING | Pereira et al. *Eur J Anaesthesiol.* 2020.
Heybati et al. *Brit J Anaesthesia.* 2022.

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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; $p = 0.036$)

2023 ICSP ANNUAL MEETING Shin et al. *Anesthesiology*. 2023.

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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); $p = 0.03$)

2023 ICSP ANNUAL MEETING Kotani et al. *Critical Care*. 2023.

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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

2023 ICSP ANNUAL MEETING Devlin et al. *Crit Care Med*. 2018.

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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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Self-Assessment Question #3

What is an appropriate RASS score for this patient?

- RASS +2
- RASS -2
- RASS +5
- RASS -5

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Self-Assessment Question #4

What is the best sedation regimen for this patient?

- Dexmedetomidine
- Propofol
- Midazolam
- No sedation needed

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Analgesia and Sedation in the ICU

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