Updates in Critical Care Pharmacy: Reviewing Pain, Agitation, and Delirium in the Adult Critically Ill

Chris Oswald, PharmD, BCPS, BCCCP
Clinical Pharmacist
Saint Alphonsus Regional Medical Center (Boise, ID)
Christopher.Oswald@saintalphonsus.org

Disclosures

• I have no disclosures or conflicts of interest
• The following medications will be discussed off-label
  • Lorazepam
  • Dexmedetomidine
  • Haloperidol
  • Atypical antipsychotics

Learning Objectives

• Describe validated screening tools available for both the verbal and non-verbal ICU patients for pain, agitation, and delirium
• Discuss pharmacologic options including pharmacokinetic and pharmacodynamic properties, available for the treatment of pain and agitation in the adult ICU patient
• Identify non-pharmacologic and pharmacologic methods for the prevention and treatment of delirium
• Outline the recommendations on pain, agitation, and delirium for improved outcomes from the 2013 PAD guidelines
Introduction

Background

• 1995: “Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit”
• 2002: “Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult”
• 2013: “Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit”
  • 20-member multidisciplinary, multi-institutional task force
  • Literature review from December 1999 – December 2010
  • Subcommittees: Pain and analgesia, agitation and sedation, delirium, and related ICU outcomes

Background – GRADE Methodology

• Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology used
  • Phrased questions as either descriptive or actionable
  • Quality and strength of evidence (descriptive and actionable)
    • A: high quality, RCTs
    • B: moderate quality, RCTs with significant limitations or high-quality OS
    • C: low quality, OS
  • Strength of recommendation (actionable questions only)
    • Strong (1): “We recommend…”
    • Weak (2): “We suggest…”
    • No recommendation (0)
    • Either for (+) or against (-)
  • Examples: (A), (+1B), (-2C), etc.
2013 PAD Guidelines

- Goal: Improve clinical outcomes in adult ICU patients
- Long and short-term management in both the intubated and nonintubated adult medical, surgical, and trauma ICU patients
- Psychometric aspects of PAD monitoring tools
  - Reliable, viable, and feasible
- Pharmacologic and non-pharmacologic approaches
  - Pain
  - Agitation
  - Delirium
- Preventing, diagnosing, and treating delirium
- Able to adapt to the individual patient and local health care system


Pain – Incidence

- “Adequate pain control is a basic human right”
- Most critically ill patients will likely experience pain sometime during their ICU stay
  - Significant, uncontrolled pain reported in >50% of ICU patients
- Causes of pain
  - Pain at rest
  - Underlying medical conditions (surgery, trauma, cancer, burn, etc)
  - Procedural pain (central line placement, chest tube placement/removal, etc.)

Erstad BL et al. Chest 2009;135:1075-86
Chanques G et al. Anesthesiology 2007;107:858-60

Pain – Consequences

- Short-term
  - Stress response
    - Increased catecholamines, impaired tissue perfusion
  - Hypercatabolic state
    - Hyperglycemia, lipolysis, muscle breakdown
  - Immune suppression
    - Impaired wound healing, reduced neutrophil activity, decrease in T cells
- Long-term
  - Upwards of 80% of patients remember experiencing moderate to severe pain
  - PTSD
  - Chronic pain
  - Lower health-related quality of life

Erstad BL et al. Chest 2009;135:1075-86
Pain – Assessment

• Gold Standard: A patient's self-report of pain

PAD Guideline
• We recommend that pain be routinely monitored in all adult ICU patients (+1B)
• We do not suggest that vital signs be used alone for pain assessment (-2C)
• We suggest that vital signs may be used as a cue to begin further assessment of pain (+2C)
• Pain scores should be documented and readily retrievable to assist in daily pain assessments


Pain – Assessment

Question: What are the most valid and reliable behavioral measures of pain in critically ill adult patients who are unable to self-report?

Answer: The Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) are the most valid and reliable...for monitoring pain in medical, postoperative, or trauma (except for brain injury)...unable to self-report...(+B)

• Rationale: 6 pain scales analyzed
  • Behavioral Pain Scale (BPS)
  • BPS Non-intubated (BPS-NI)
  • Critical-Care Pain Observation Tool (CPOT)
  • Non Verbal Pain Scale (NVPS)
  • Non Verbal Pain Scale revised (NVPS-R)
  • Pain Behavioral Assessment Tool (PBAT)


Pain – Behavioral Pain Scale (BPS)

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial Expression</td>
<td>Relaxed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partially tightened (e.g. brow lowering)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully tightened (e.g. eyelid closing)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Grimacing</td>
<td>4</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>No movement</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partially bent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully bent with finger flexion</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Permanently retracted</td>
<td>4</td>
</tr>
<tr>
<td>Compliance with ventilation</td>
<td>Tolerating movement</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Coughing but tolerating vent most of the time</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fighting ventilator</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Unable to control ventilation</td>
<td>4</td>
</tr>
</tbody>
</table>

• A BPS score >5 indicates significant pain

Payen JF et al. Crit Care Med 2001;29:2258-2263
Pain – Critical-Care Pain Observation Tool (CPOT)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial expression</td>
<td>No muscular tension observed</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Presence of frowning, brow lowering, orbicular tightening, and levator contraction</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>All of the above facial movements plus eyelid tightly closed</td>
<td>2</td>
</tr>
<tr>
<td>Body movements</td>
<td>Does not move at all [does not necessarily mean absence of pain]</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pulling tube, attempting to sit up, moving limbs/thrusting, not following commands, striking at staff, trying to climb out of bed</td>
<td>2</td>
</tr>
<tr>
<td>Muscle tension evaluation by passive flexion and extension of upper extremities</td>
<td>No resistance to passive movements</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Resistance to passive movements</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Strong resistance to passive movements, inability to complete them</td>
<td>2</td>
</tr>
</tbody>
</table>


Pain – Critical-Care Pain Observation Tool (CPOT)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance with ventilator (intubated patients)</td>
<td>Alarms not activated, easy ventilation</td>
<td>0</td>
</tr>
<tr>
<td>OR</td>
<td>Alarms stop spontaneously</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Asynchrony: blocking ventilation, alarms frequently activated</td>
<td>2</td>
</tr>
<tr>
<td>Vocalization (extubated patients)</td>
<td>Talking in normal tone or no sound</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Crying out, sobbing</td>
<td>2</td>
</tr>
</tbody>
</table>


• Total range 0 – 8
• A CPOT score ≥ 3 indicates significant pain

Pain – Treatment

• Preemptive analgesia and/or nonpharmacologic interventions
  • Prior to chest tube removal (+1C)
  • Other types of invasive or potentially painful procedures (+2C)
• IV opioids considered first-line in non-neuropathic pain (+1C)
  • All IV opioids, when titrated to similar endpoints, are equally effective (C)
• Nonopioids may be considered to decrease the amount of opioids administered and to decrease opioid-related side effects (+2C)
• Enteral gabapentin or carbamazepine, in addition to IV opioids, be considered for treatment of neuropathic pain (+1A)
• Thoracic epidural analgesia
  • Post-op abdominal aortic aneurysm surgery (+1B)
  • Traumatic rib fractures (+2B)

Pain – IV Opioids

- Primary choices: Fentanyl, hydromorphone, methadone, morphine, and remifentanil
- Analgesic effect from binding to mu-opioid receptor
- Common adverse effects
  - Constipation, respiratory depression, bradycardia, hypotension, dependence, and altered mental status
- Can be given PRN, scheduled, or by continuous infusion
- Pharmacokinetic and pharmacodynamic properties vary between agents
  - Selection should be based on patient’s needs and comorbidities
  - Use caution when switching between agents


Pain – Fentanyl (IV)

- Usual starting dose
  - Intermittent: 0.35 – 0.5 mcg/kg q1hr
  - Continuous infusion: 12.5 – 25 mcg/hr
  - Onset: 1 – 2 min
- Elimination half-life: 2 – 4 hr
  - Context-sensitive half-life: 200min (6hr infusion) and 300min (12hr infusion)
- Metabolic pathway: CYP3A4/5 substrate
- Notable side effects: Less hypotension than morphine, muscle rigidity, risk of serotonin syndrome when used with other serotonergic agents
- Other information: Accumulation in hepatic impairment, highly lipophilic, high volume of distribution, high protein binding, prolonged infusions may lead to an unpredictable clearance


Pain – Hydromorphone (IV)

- Usual starting dose
  - Intermittent: 0.2 – 0.6 mg q1-2hr
  - Continuous infusion: 0.25 – 0.5 mg/hr
  - Onset: 5 – 15 min
- Elimination half-life: 2 – 3 hr
- Metabolic pathway: Glucuronidation
- Other information: Accumulation in hepatic and renal impairment, low volume of distribution, highly water soluble, low protein binding

### Pain – Morphine (IV)

- **Usual starting dose**
  - Intermittent: 2 – 4 mg q1-2hr
  - Continuous infusion: 1 – 2 mg/hr
- **Onset:** 5 – 10 min
- **Elimination half-life:** 3 – 4 hr
- **Metabolic pathway:** Glucuronidation
- **Notable side effects:** Histamine release
- **Other information:** Accumulation in hepatic/renal impairment, active metabolites (accumulate in renal failure)

### Pain – Other IV Opioids

- **Methadone**
  - Long-acting opiate, can take 3-5 days to reach steady state
  - May be beneficial to those on home methadone
  - **Notable side effects:** QTc prolongation, arrhythmias, risk of serotonin syndrome
  - **Other information:** CYP 3A4/2B6 substrate and 3A4/2D6 inhibitor, multiple drug interactions, and accumulation in hepatic/renal impairment

- **Remifentanil**
  - Very short acting (onset 1-3 min and half-life 3-10 min)
  - Clearance by plasma esterases with no accumulation in organ failure
  - **Notable side effects:** Rebound pain and withdrawal symptoms
  - **Other information:** Mostly studied in Europe, $$$

### Pain – Non-opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (t½)</th>
<th>Metabolic Pathway</th>
<th>Pertinent Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (PO/PR)</td>
<td>PO: 30-60min PR: variable (2-4hr)</td>
<td>Glucuronidation, sulfonation</td>
<td>May be toxic, may require less in hepatic failure</td>
</tr>
<tr>
<td>Acetaminophen (IV)</td>
<td>5 – 15 min</td>
<td>Glucuronidation, sulfonation</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen (PO/IV)</td>
<td>PO: 20-30min (3.8-2.0hr)</td>
<td>Oxidation</td>
<td>Use caution in hepatic/renal dysfunction</td>
</tr>
<tr>
<td>Ketamine (IV)</td>
<td>30 – 40 sec (2-3hr)</td>
<td>N-demethylation</td>
<td>Broad dose range, mild to severe emergence reactions</td>
</tr>
<tr>
<td>Ketorolac (IV/IM)</td>
<td>10 min (2.4-3.7hr)</td>
<td>Hydroxylation, conjugation renal excretion</td>
<td>Use caution in hepatic/renal dysfunction</td>
</tr>
<tr>
<td>Carbamazepine IR (PO)</td>
<td>4 – 5 hr (25-60min/12-17hr)</td>
<td>Oxidation</td>
<td>Neuropathic pain Drug interactions, severe skin reactions</td>
</tr>
<tr>
<td>Gabapentin (PO)</td>
<td>(5-7hr)</td>
<td>Renal excretion</td>
<td>Requires renal adjustment, ODS-effects may be severe</td>
</tr>
</tbody>
</table>
Assessment Question #1

The ICU medical director wants to standardize how mechanically ventilated patients are assessed for pain in the ICU. Which of the following options is best to implement in this patient population?

a) Non-verbal Pain Scale (NVPS) and vital signs
b) Vital signs alone
c) Critical Care Pain Observation Tool (CPOT)
d) Richmond Agitation-Sedation Scale (RASS)

Pain – Discussion

• What tools does your institution use for assessing pain?

• What are your methods for controlling patient’s pain?

Agitation and Sedation

• Prompt identification and treatment of possible underlying cause(s)
  • Pain
  • Delirium
  • Hypoxia
  • Hypoglycemia
  • Hypotension
  • Withdrawal from EtOH or other drugs
Agitation and Sedation

- ICU patient outcomes
- Duration of mechanical ventilation
- ICU LOS
- Hospital LOS
- Incidences of delirium
- Long-term cognitive dysfunction
- Treatment may include:
  - Maintaining patient comfort; adequate analgesia; frequent reorientation; optimizing environment for normal sleep patterns; and/or administering sedatives


Agitation and Sedation – Assessment

**Question:** Which subjective sedation scales are the most valid and reliable in the assessment of depth and quality of sedation in mechanically ventilated adult ICU patients?

**Answer:** The Richmond Agitation-Sedation Scale (RASS) and Sedation-Agitation Scale (SAS) are the most valid and reliable sedation assessment tools... (B)


Agitation and Sedation – Assessment

10 sedation scales reviewed
- 1. Adaptation to the Intensive Care Environment (ATICE)
- 2. Minnesota Sedation Assessment Tool (MSAT)
- 3. Motor Activity Assessment Tool (MAAT)
- 4. New Sheffield Sedation Scale
- 5. Observer's Assessment of Alertness/Sedation Scale (OAA/S)
- 6. Ramsay Sedation Scale
- 7. Richmond Agitation-Sedation Scale (RASS)
- 8. Sedation-Agitation Scale (SAS)
- 9. Sedation Intensive Care Score (SEDIC)
- 10. Vancouver Interaction and Calmness Scale (VICS)

**Agitation and Sedation – RASS**

<table>
<thead>
<tr>
<th>SCORE</th>
<th>TERM</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>Overly combative or violent; immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Pulls on or removes tube(s) or catheter(s) or has aggressive behavior towards staff</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Frequently nonpurposful movement or patient-ventilator dyssynchrony</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious or apprehensive but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td>Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact to voice</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Briefly (less than 10 seconds) awakens with eye contact to voice</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>Any movement (but no eye contact) to voice</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>No response to voice, but any movement to physical stimulation</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

**Agitation and Sedation – SAS**

<table>
<thead>
<tr>
<th>SCORE</th>
<th>TERM</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dangerous agitation</td>
<td>Pulling at ETT, trying to remove catheters, climbing over bedrail, striking as staff, thrashing side to side</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated</td>
<td>Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting ETT</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
<td>Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm and cooperative</td>
<td>Calm, awakens easily, follows commands</td>
</tr>
<tr>
<td>3</td>
<td>Sedated</td>
<td>Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated</td>
<td>Aroused to physical stimuli but does not communicate or follow commands, may move spontaneously</td>
</tr>
<tr>
<td>1</td>
<td>Unarousable</td>
<td>Minimal or no response to noxious stimuli, does not communicate or follow commands</td>
</tr>
</tbody>
</table>

**Agitation and Sedation – Assessment**

Sedation goals may change daily
- May require a deeper level in the first 24-48 hrs
- Address every day
- Daily interruptions with re-titrations of medications
- Assessments should be at least every 4 hours
  - Documented in chart and readily retrievable
Agitation and Sedation – Medication Choices

- Benzodiazepines
  - Midazolam and Lorazepam
- Non-benzodiazepines
  - Propofol and dexmedetomidine
- Choice of agent may depend on
  - Cause of agitation
  - Baseline neurological function
  - Anticipated time on mechanical ventilation
  - Hemodynamic variables
  - Presence of pain
  - Level of sedation required (e.g. light, deep)


Agitation and Sedation – Benzodiazepines

- Bind to GABA<sub>A</sub> receptors in the CNS
  - Sedative, anxiolytic, amnestic, hypnotic, and anticonvulsant effects
  - No analgesic activity
  - Major adverse effects include respiratory depression and systemic hypotension
  - Delayed emergence may result from prolonged administration and tissue saturation, advanced age, and hepatic and/or renal dysfunction


Agitation and Sedation – Benzodiazepines

<table>
<thead>
<tr>
<th></th>
<th>Midazolam</th>
<th>Lorazepam</th>
<th>Diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset (minutes)</td>
<td>2 – 5</td>
<td>5 – 20</td>
<td>2 – 5</td>
</tr>
<tr>
<td>Duration (hours)</td>
<td>1 – 2</td>
<td>4 – 6</td>
<td>2 – 4</td>
</tr>
<tr>
<td>Elimination t½ (hours)</td>
<td>1 – 10</td>
<td>10 – 20</td>
<td>24 – 120</td>
</tr>
<tr>
<td>Active Metabolites</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CYP 3A4 Interactions</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Initial Dosing</td>
<td>1 – 4mg</td>
<td>1 – 4mg</td>
<td>5 – 10mg</td>
</tr>
<tr>
<td>Other Information</td>
<td>Highly lipophilic, prolonged in hepatic and renal failure</td>
<td>Risk of propylene glycol toxicity, use caution in renal failure</td>
<td>Not recommended for continuous infusion</td>
</tr>
</tbody>
</table>

Agitation and Sedation – Propofol

- Anesthetic that binds to multiple receptors, including GABA<sub>A</sub>, glycine, nicotinic, and M<sub>1</sub>. May inhibit NMDA at high doses.
  - Sedative, hypnotic, anxiolytic, amnestic, and anticonvulsant properties
    - Similar to benzodiazepines, no analgesic effects
- Dosing: 5 – 50 mcg/kg/min (titrate every 5 – 10 minutes)
- Onset and Duration: 1 – 2 min and 0.5 – 1 hr (short-term), may be variable in long-term use
- Highly lipophilic, large volume of distribution, metabolized via hepatic conjugation
  - CYP 2B6, 2C9, 2C19, and 3A4 substrate

Propofol Related Infusion Syndrome

- May be due to mitochondrial dysfunction, impaired fatty acid oxidation, metabolite accumulation, changes in metabolism
  - Presents as metabolic acidosis, hypertriglyceridemia, pancreatitis, and PRIS
- Increased risk with high dose and prolonged infusions
  - Discontinue propofol in those with suspected PRIS and provide supportive care


Agitation and Sedation – Dexmedetomidine

- A selective α-2 agonist, inhibiting norepinephrine release
  - Sedative and sympatholytic properties, weak analgesic/opioid sparing properties, and no anticonvulsant activity
- Dosing: Loading dose (optional) 0.5 – 1 mcg/kg over 10 min
  - FDA approved: 0.2 – 0.7 mcg/kg/hr not to exceed 24hrs of infusion
- Onset and Duration: 15 – 20 minutes (w/ loading dose), may be longer without loading dose; 1 – 2 hours duration of action
  - Hepatic glucuronidation and renal excretion, no active metabolites
- Adverse effects: Bradycardia, hypotension; possible tachycardia and hypertension (with loading dose)
  - Avoid in those with acute compensated heart failure or advanced heart block

Agitation and Sedation – Dexmedetomidine

- Going above the FDA-approved dosing recommendations
  - Valitalo et al. Meta analysis of 3 phase III studies (n=527)
    - Doses of up to 1.4mcg/kg/hr for 2 weeks displayed dose-proportional pharmacokinetics
  - Iirola et al. Prolonged infusions of high-dose dexmedetomidine (n=13)
    - Doses up to 2.5mcg/kg/hr for prolonged times (~12 days) maintain linear pharmacokinetics
  - Venn et al. Observational study in MICU patients with a median APACHE II score of 23 (n=12)
    - Doses up to 2.5mcg/kg/hr possible but suggest a reduced loading dose
  - Prolonged infusions (> 7 days) may be associated with withdrawal symptoms (hypertension, anxiety, discomfort)
    - May try dose tapering or clonidine

Iirola et al. Critical Care 2011;15:R257

Agitation and Sedation – Choosing the best agent

**Question:** Should nonbenzodiazepine-based sedation, instead of sedation with benzodiazepines, be used in mechanically ventilated adult ICU patients?

**Answer:** We suggest that sedation strategies using nonbenzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients (+2B)


Agitation and Sedation – Choosing the best agent

Other PAD guideline statements:
- Benzodiazepine use may be a risk factor for the development of delirium (B)
- Insufficient data to determine the relationship between propofol use and the development of delirium (C)
- Dexmedetomidine infusions may be associated with a lower prevalence of delirium compared to benzodiazepines (B)

Agitation and Sedation – MENDS Study, 2007

**Design:** Double-blind, randomized controlled trial comparing the effects of lorazepam and dexmedetomidine at 2 tertiary care centers from August 2004 to April 2006 (n=106)

**Outcome:** Days without delirium or coma and percentage of days spent within 1 RASS point of goal

**Methods:**
- Dexmedetomidine infusion: 0.15 – 1.5 mcg/kg/hr
- Lorazepam infusion: 1 – 10 mg/hr
- Fentanyl boluses for pain and propofol boluses for urgent control of agitation
- Daily interruption or spontaneous breathing trial determined by team


- **Results (Lorazepam vs. Dexmedetomidine)**
  - Prevalence of delirium: 82% vs. 79% (p=0.65)
  - Prevalence of coma (RASS -4 or -5): 92% vs. 63% (p=<0.001)
  - Sedation goal (median dose): 67% [1mg/hr] vs. 80% [0.7mcg/kg/hr] (p=0.04)
  - Days without delirium or coma: 3 vs. 7 (p=0.01)
  - Ventilator-free days: 18 vs. 22 (p=0.22)
  - ICU length of stay (days): 9 vs. 7.5 (p=0.92)

**Conclusions**
- No differences in ventilator-free days or ICU length of stay, but more patients were with 1 RASS point of sedation goal and spent more days delirium or coma free


Agitation and Sedation – SEDCOM Study, 2009

**Design:** Prospective, double-blind, randomized trial comparing dexmedetomidine to midazolam in 68 centers in 5 countries from March 2005 to August 2007

**Primary Outcome:** % at time within target RASS (-2 to +1)
- Secondary: Prevalence and duration of delirium, use of fentanyl and open-label midazolam, and nursing assessments

**Methods:**
- Dexmedetomidine infusion: 0.2 – 1.4 mcg/kg/hr (n=244)
- Midazolam infusions: 0.02 – 0.1 mg/kg/hr (n=122)
- Fentanyl boluses for pain, midazolam boluses for agitation, haloperidol boluses for agitation or delirium, and daily interruption to follow 3 of 4 commands

Agitation and Sedation – SEDCOM Study, 2009

Results (Midazolam vs. Dexmedetomidine)
- % time at target RASS: 75% vs. 77% (p=0.18)
- Prevalence of delirium: 76% vs. 54% (p<0.001)
- Delirium-free days: 1.7 vs. 2.5 (p=0.002)
- Time to extubation (days): 5.6 vs. 3.7 (p=0.01)
- ICU length of stay (days): 7.6 vs. 5.9 (p=0.24)

Conclusions
- No difference in time at targeted sedation goal but the dexmedetomidine group spent less time on the ventilator and experienced less delirium


Agitation and Sedation – BZD vs. Non-BZD Meta-analysis, 2013

“Benzodiazepine versus non-benzodiazepine based sedation for mechanically ventilated, critically ill adults”

- 6 randomized trials reviewed from 1996-2013 (total n=1235)
- Primary Outcomes
  - ICU LOS (n=6): Longer ICU length of stay in the BZD group vs. non-BZD group (mean difference 1.6 days; 95% CI 0.72-2.5; p=0.0005)
  - Days on ventilator (n=4): Longer duration of mechanical ventilation in BZD group (mean difference 1.9 days; 95% CI 1.7-2.09; p=0.0001)
  - Delirium prevalence (n=2): No difference in delirium between BZD and non-BZD (RR 0.83; 95% CI 0.61-1.11; p=0.19)
  - Short-term all-cause mortality (45 days or less, n=4): No difference in risk of death between groups (RR 0.98; 95% CI 0.76-1.2; p=0.88)


Assessment Question #2

J.B. is a 46-y.o. female admitted to the ICU for severe septic shock secondary to pneumonia requiring intubation. Her past medical history includes HTN and anxiety, which she takes lisinopril 10mg daily and lorazepam 1mg as needed prior to dental appointments. She is receiving a fentanyl infusion at 100mcg/hr and vital signs are HR 85 and BP 155/90. During rounds, the nurse reports the patient is “very agitated” and asking for medication to help calm the patient down and maintain ventilator compliance. Which of the following is the most appropriate therapy to initiate?

a) Scheduled quetiapine  
b) Lorazepam infusion  
c) Discontinue fentanyl and start a morphine infusion  
d) Propofol infusion
Agitation and Sedation – Discussion

- What tools does your institution use for assessing agitation?
- What are your methods for controlling a patient’s agitation?
  - Non-pharmacologic?
  - Pharmacologic?

Delirium – Definition

- “Acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered level of consciousness.”
  - A disturbed level of consciousness with a reduced ability to focus, sustain, or shift attention
  - A change in either cognition or the development of a perceptual disturbance
- Subtypes
  - Hyperactive – agitated, hallucinations and delusions
  - Hypoactive – calm or lethargic, confusion and sedation
  - Combination of both

Delirium – Incidence and Outcomes

- Incidence of ICU delirium
  - 60 – 80% of mechanically ventilated patients
  - 20 – 40% of non-ventilated patients
- Delirium is associated with:
  - Increased mortality (A)
  - Prolonged ICU and hospital LOS (A)
  - Development of post-ICU cognitive impairment (B)
Delirium – Risk Factors

- Age
- H/O Dementia*
- H/O Hypertension*
- Emergency surgery
- Trauma
- APACHE II score*
- Mechanical ventilation
- Metabolic acidosis
- Delirium the day prior
- Coma
- Multi organ failure
- Gender was not associated with the development
- Use of dexmedetomidine associated with a lower prevalence of delirium
- Review of studies published between 2001-2013

*Noted in PAD Guidelines as baseline risk factors, also h/o alcoholism (B)

Delirium – Causes

- Disease-induced syndrome
  - e.g. organ dysfunction in severe sepsis
- Iatrogenic
  - e.g. exposure to select medications
- Environmental
  - e.g. prolonged physical restraints, immobilization
- Rule-out drug and/or alcohol withdrawal
  - 15 – 20% of all hospitalized patients have EtOH dependence
    - 8 – 31% of those patients will develop EtOH withdrawal syndrome
  - Chronic illicit or prescription drug use
  - Sedatives or opioids administered during routine ICU care

Delirium – Assessment

PAD Guidelines:

We recommend routine monitoring for delirium in adult ICU patients (+1B)

- At least once per shift for those at moderate to high risk for delirium
- Routine monitoring of delirium in adult ICU patients is feasible in clinical practice (B)
Delirium – Assessment

**Question:** Which instruments available for delirium monitoring have the strongest evidence for validity and reliability in ventilated and non-ventilated medical and surgical ICU patients?

**Answer:** The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable (A).

- 5 Monitoring tools evaluated
  - Cognitive Test for Delirium (CTD)
  - Confusion Assessment Method for the ICU (CAM-ICU)
  - Delirium Detection Score (DDS)
  - Intensive Care Delirium Screening Checklist (ICDSC)
  - Nursing Delirium Screening Scale (Nu-DESC)


- Systematic review and meta-analysis of research from 1966 – 2011
- 16 studies with a total of 1,523 subjects and 5 screening tools included in review
  - CAM-ICU; ICDSC; Nu-DESC; DDS; and Neelon and Champagne Confusion Scale (NEECHAM)
- Only CAM-ICU and ICDSC studies were included in meta-analysis (all other screening tools only had one study)
- Most findings obtained in research settings

<table>
<thead>
<tr>
<th>Screening Tool</th>
<th>% Sensitivity (95% CI)</th>
<th>% Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAM-ICU</td>
<td>75.5 (71.3-79.4)</td>
<td>95.8 (94.9-97.1)</td>
</tr>
<tr>
<td>ICDSC</td>
<td>80.1 (73.4-85.8)</td>
<td>74.6 (69.1-79.5)</td>
</tr>
</tbody>
</table>


Delirium – CAM-ICU

- Feature 1: Acute Onset or Fluctuating Course
  - Is the patient different that his/her baseline mental status or has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale, GCS, or previous delirium assessment?
- Feature 2: Inattention
  - S A V E A H A A R T
  - Directions to Patient: “I’m going to read you a series of 10 letters. Whenever you hear the letter ‘A’, squeeze my hand.”
  - Errors when either no squeeze on ‘A’ or a squeeze on any other letter (>2 errors = feature present)

Delirium – CAM-ICU

- Feature 3: Altered Level of Consciousness
  - Present if actual RASS score anything other than alert and calm (zero)
- Feature 4: Disorganized Thinking
  - A series of Yes/No questions and commands
  - Errors are either incorrect answers or uncomplete commands, >1 errors = present
- Overall CAM-ICU
  - Feature 1 plus Feature 2 and either 3 or 4 = CAM-ICU positive (+)
    - (+) = Delirium Present
    - (-) = No Delirium

Delirium – ICDSC

**Intensive Care Delirium Screening Checklist (ICDSC)**

- Score your patient over the entire shift. Components don’t all need to be present at the same time.
- Components 5 through 8 require a focused bedside patient assessment. This cannot be completed when the patient is deeply sedated or comatose (i.e., SAS = 1 or 2, RASS = -4 or -5).
- Components 5 through 8 are based on observations throughout the entire shift. Information from the prior 24 hours (i.e., from prior 1-2 nursing shifts) should be obtained for components 5 through 8.

1. **Altered level of consciousness**
   - Deep sedation/soma over entire shift [RASS = -2, -3, -4, -5]
   - Agitation [RASS = 5, 6, 7; RASS = -1, -2]
   - Light sedation [RASS = -3, -4, -5] over the entire shift
   - Score = 0 [No assessable], 1 point, 2 points (if recent sedation) 3 points (if recent agitation)
   - No 0 1 Yes

2. **Inattention**
   - Difficulty following instructions or conversation, easily distracted by external stimuli.
   - Will not reliably repeat hands to speller “A S A Y E A H A R T”
   - No 0 1 Yes

3. **Disorientation**
   - In addition to name, place, and date, does the patient recognize ICU caregivers? Does patient know what kind of place they are in? (List examples such as dentist’s office, hunter, walk, hospital)
   - No 0 1 Yes

4. **Hallucinations, delusions, or psychosis**
   - Ask the patient if they are having hallucinations or delusions (e.g., trying to catch an object that isn’t there).
   - Are they afraid of the people or things around them?
   - No 0 1 Yes

5. **Psychomotor agitation or retardation**
   - Either: Hyperactivity requiring the use of sedative drugs or restraints to control potentially dangerous behavior (e.g., pulling iv lines out or hitting staff).
   - OR: Inappropriate or clinically noticeable psychomotor slowing or retardation.
   - No 0 1 Yes

6. **Inappropriate speech or mood**
   - Patient displays inappropriate emotions, disorganized or incoherent speech, sexual or inappropriate interactions, or is agitated or overly demanding.
   - No 0 1 Yes

7. **Sleep-wake cycle disturbance**
   - Either: Frequent awakening/4 hours sleep at night.
   - OR: Insomnia during much of the day.
   - No 0 1 Yes

8. **Symptoms fluctuation**
   - Fluctuation of any of the above symptoms over a 24-hour period.
   - No 0 1 Yes

**Total Shift Score**

(Min 0 - Max 8)

Delirium – Prevention

- Non-pharmacologic interventions
  - PAD Guidelines: We recommend performing early mobilization of adult ICU patients whenever feasible to reduce the incidence and duration of delirium (+1B)
- Pharmacologic interventions
  - No recommendation on using a pharmacologic delirium prevention protocol (0,C)
  - No recommendation on combining non-pharmacologic and pharmacologic interventions for delirium prevention (0,C)
  - Neither haloperidol or atypical antipsychotics are suggested to be given to prevent delirium (-2C)
  - No recommendation on the use of dexmedetomidine to prevent delirium (0,C)

Delirium – Prevention

“Early Mobilization in the Intensive Care Unit: A Systematic Review”

- Objective: Evaluate literature related to mobilization in the critically ill, focusing on functional outcomes and patient safety
- Methods: Sackett’s Levels of Evidence used to rate evidence
- Results: 15 studies met inclusion criteria (levels 1B-4)
  - Functional outcomes: muscle strength, mobility, and quality of life
    - Time to mobility milestones were accomplished earlier but unable to determine improvements seen with muscle strength and QOL
  - Safety: Overall, no serious adverse events that required life saving measures
    - Oxygen desaturation cited as the most common adverse event
- Conclusion: Although limited data, early mobilization is feasible and safe

Delirium – Treatment

PAD Guidelines
- There is no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients (No Evidence)
- Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C)
- We do not recommend administering rivastigmine to reduce the duration of delirium in ICU patients (-1B)
- We do not suggest using antipsychotics in patients at significant risk for torsades de pointes (-2C)
- We suggest that in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, continuous IV infusions of dexmedetomidine rather than benzodiazepine infusions be administered for sedation in order to reduce the duration of delirium (+2B)
Delirium – Treatment

• Correct any underlying cause that may be contributing to the delirium
• Antipsychotic Options
  • 1st Generation (haloperidol)
  • 2nd Generation (atypical antipsychotics)
• If an antipsychotic is started, consider a strategy for discontinuation or follow-up monitoring
  • “Evaluation of discontinuation of atypical antipsychotics prescribed for ICU delirium” (Jasiak 2013)
  • “Implications of atypical antipsychotic prescribing in the intensive care unit” (Kram 2015)

Delirium – Antipsychotics

Haloperidol
  • MOA: Dopamine blockade
  • Usual starting dose: 1-2mg q4-6hrs PRN
  • PO preferred but injectable available
  • Metabolic pathway: Glucuronidation and CYP 3A4/2D6 substrate
  • Adverse effects: sedation, EPS, QTc prolongation (IV route)

Atypical Antipsychotics
  • MOA: Antagonize dopamine, serotonin, serotonin-reuptake, histamine-1, and alpha receptors to varying degrees

Delirium – Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Starting Dose</th>
<th>Peak Plasma (h)</th>
<th>CYP Substrate</th>
<th>Adverse Effects</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>5mg daily</td>
<td>6 hrs</td>
<td>3A2</td>
<td>Sedation, neuromuscular weakness, EPS</td>
<td>Injectable form plasma concentrations may be 5x that of PO</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>50mg 1-3x daily</td>
<td>1.5 hrs</td>
<td>3A4</td>
<td>Sedation, orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25-0.5mg 1-2x daily</td>
<td>1</td>
<td>2D6</td>
<td>Anticholinergic effects, EPS, cardiac abnormalities</td>
<td>Active metabolites, renally cleared.</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20mg PO BID</td>
<td>6hrs</td>
<td>1A2/3A4 (minor)</td>
<td>Somnolence, EPS, dizziness, orthostatic hypotension, QTc prolongation</td>
<td></td>
</tr>
</tbody>
</table>
Delirium – Treatment

- Which agent is best to choose?
  - Current evidence is lacking to support the use of antipsychotics
- Small studies available with limited results, examples below
  - The MIND Trial (Girard 2010)
  - Devlin JW et al, 2010 (Devlin 2010)
  - Michaud CJ et al, 2015 (Michaud 2015)
- Current ongoing research
  - The Modifying the Impact of ICU-Associated Neurological Dysfunction –USA Study (MIND-USA)

MIND-USA Study Available from https://clinicaltrials.gov/ct2/show/NCT01211522

Delirium – Devlin et al, 2011

"Current perceptions and practices surrounding the recognition and treatment of delirium in the intensive care unit: a survey of 250 critical care pharmacists from eight states"

- 457 pharmacists surveyed, 55% responded (n=250)
  - 7% routinely used a delirium screening tool
  - 34% lacked time and 24% believed it was a nursing role
  - 85% believed delirium should be managed with medications
    - Haloperidol, 76%
    - Atypical antipsychotic, 14%
    - Benzodiazepine, 10%
- Conclusion: Despite a lack of evidence to support their use, antipsychotics are frequently recommended by pharmacists. The potential impact of pharmacists on patients' outcomes is unknown.


Delirium – Serafim et al, 2015

"Pharmacologic prevention and treatment of delirium in intensive care patients: A systematic review"

- 15 studies evaluated on prevention
  - Drugs involved: dexmedetomidine, statins, rivastigmine, risperidone, haloperidol, dexamethasone, and clonidine
  - Main outcomes: delirium prevalence, ICU and hospital LOS, and duration of mechanical ventilations
- 7 studies evaluated on treatment
  - Drugs involved: dexmedetomidine, rivastigmine, ziprasidone, quetiapine, olanzapine, and haloperidol
  - Main outcomes: delirium resolution, ICU and hospital LOS, and mortality
- Conclusion: No single pharmacologic intervention to prevent or treat delirium was consistently able to improve survival or hospital LOS

Delirium – Mortality Benefit?

"Randomized ICU trials do not demonstrate an association between interventions that reduce delirium duration and short-term mortality: a systematic review and meta-analysis"

• 17 trials involving 2,849 patients evaluated
  • Pharmacologic Intervention (n=13)
    - Dexmedetomidine, an antipsychotic, rivastigmine, or clonidine
  • Multimodal Intervention (n=2)
    - Spontaneous awakening
  • Non-pharmacologic Intervention (n=2)

• Results:
  - Average delirium duration was lower in intervention groups
  - -0.64 days; 95% CI, -1.15 to -0.13; p=0.01
  - Short-term mortality not reduced
  - RR = 0.90; 95% CI, 0.76 to 1.06; p=0.19

• Conclusion: Current evidence does not show a reduction in short-term mortality despite a reduction in delirium duration


Assessment Question #3

Which of the following therapies may help prevent new-onset delirium in the ICU setting:

a) Utilization of dexmedetomidine prior to extubation
b) Early mobilization
c) Initiation of scheduled low-dose haloperidol on every new admit
d) Maximizing the amount of benzodiazepines a patient can receive

Delirium – Discussion

• What tools does your institution use for assessing delirium?

• What are your methods for addressing delirium?
  • Prevention?
  • Treatment?
    • Short-term vs. Long-term
Improving ICU Outcomes

**PAD Guidelines**

- We recommend either daily sedation interruption or a light target of level of sedation be routinely used in mechanically ventilated patients (+1B)
- We suggest that analgesia-first sedation be used in mechanically ventilated adult ICU patients (+2B)
- We recommend promoting sleep in adult ICU patients by optimizing patients’ environments, using strategies to control light and noise, clustering patient care activities, and decreasing stimuli at night to protect patients’ sleep cycles (+1C)
- We recommend using an interdisciplinary ICU team approach that includes provider education, preprinted and/or computerized protocols and order forms, and quality ICU rounds checklists to facilitate the use of PAD management guidelines or protocols (+1B)


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**Improving Outcomes – Daily Interruptions and Light Sedation**

“Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation”

- Intervention group had sedative/opioid infusions shut off daily until awake (midazolam/propofol and morphine)
- Ventilator days: 4.9 days (active) vs. 7.3 days (control), p=0.0004
- ICU LOS: 6.4 days (active) vs. 9.9 days (control), p=0.02

“Daily sedation interruption versus targeted light sedation strategies in ICU patients”

- With either intervention, trials show benefit in avoiding deep levels of sedation and reductions in benzodiazepine exposure while not showing an increase in psychiatric disturbances or adverse patient outcomes


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**Improving Outcomes – Analgosedation**

“A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomized trial”

- Methods: 140 critically ill requiring ventilation for >24 hrs
  - No sedation (n=70)
  - Sedation as propofol for 48 hrs followed by midazolam thereafter with daily interruptions until awake (n=70, control group)
  - Boluses of morphine (2.5-5mg) in both groups

- Primary outcome: Number of days without mechanical ventilation in a 28-day period
- LOS in ICU and hospital also noted

- Results:
  - 27 either died or were successfully extubated within 48hr and therefore excluded
  - No sedation group had significantly more days without (n=55, mean 13.8 days) compared to sedation group (n=58, mean 9.6 days)
  - Mean difference of 4.2 days (95% CI 0.3-8.1, p=0.0195)
  - No sedation is associated with an increase in days without ventilation

Improving Outcomes – Sleep

- Sleep deprivation is detrimental in humans and common in the ICU
- Impairs tissue repair; cellular immune function; and may affect healing response
- May contribute to the development of delirium and increased levels of physiologic stress
- Opportunities to improve sleep patterns
  - Daytime hours: Lights on and shades open
  - Nighttime (0000-0400): Decrease visitors and alarm volumes (consider ear plugs for patient), turn down lights; avoid unnecessary lab draws, patient turns, routine cares, medication administration if possible


Improving Outcomes – Sleep

“The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU”

- **Design**: Observational, pre-post design in a tertiary U.S. academic hospital
- **Intervention**: “Usual care” as baseline followed by multifaceted sleep-promoting interventions
- **Results**: 634 patient days at baseline and 826 patient days in QI period
  - Incidence of delirium (QI vs. baseline): OR 0.46; 95% CI 0.23-0.89; p=0.02
  - Delirium/coma-free days: OR 1.64; 95% CI 1.04-2.58; p=0.03
- **Conclusion**: Interventions to improve sleep are feasible and associated with significant benefits


The ABCDE Bundle

- **Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility**
- Combining several interventions known to improve outcomes individually into one care bundle may decrease sedative exposure, ventilation time, ICU days, and delirium

  - Conclusion from ABCDE bundle implementation: Patients spent 3 more days without breathing assistance, experiencing less delirium, and more likely to be mobilized during ICU stay

Assessment Question #4

Based on the 2013 PAD Guidelines, which of the following is NOT true:

a) Protocols should include either daily sedative interruption or target a light level of sedation in the mechanically ventilated unless clinically contraindicated.

b) A sedative-first based approach is favored over an analgesia-first approach in the mechanically ventilated.

c) There is insufficient evidence to suggest that the use of haloperidol or atypical antipsychotics be used to prevent delirium in the adult ICU patient.

d) An interdisciplinary ICU team approach should include preprinted and/or computerized protocols and order forms, provider education, and quality ICU rounds checklists

Improving Outcomes–Discussion

- What are some of the strategies your institution has implemented to improve ICU patient outcomes?

- Any pharmacist-driven protocols or pharmacist-led projects?

- Has anything not worked to improve patient care?
References


References

References


