Update on the Management of Pain, Agitation, and Delirium

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Disclosures

• None

Objectives

• Describe current guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit.
• Compare the benefits and limitations of available sedatives and analgesics.
• Evaluate validated scales to measure sedation, pain, and delirium in critically ill patients.
• Identify various approaches to sedation in mechanically ventilated patients.
Case Presentation

- DB is a 30-year-old man who presents to the ED with high fevers, chills, and SOB for 3 days
  - PMH: unremarkable
  - Home medications: none
  - SH: law student, non-smoker, social alcohol use

- DB requires endotracheal intubation in the ED for respiratory failure and is immediately transferred to the MICU

- Admitting diagnosis
  - Influenza pneumonia

MICU Course

Days 1-3:
- Mechanically ventilated (MV)
- Hypotensive on vasopressors
- Treated with fentanyl and lorazepam infusions to goal RASS -3/-4

Days 4-7:
- Remains MV
- Develops a Klebsiella ventilator-associated pneumonia (VAP)
- Continued on fentanyl and lorazepam infusions to goal RASS -3/-4

Days 8-12:
- Remains MV
- Sedation and analgesics turned off, but not responsive to pain or stimuli
- EEG and head CT negative

Days 13-16:
- Severe delirium
- Markedly weak
- Trached and transferred to the floor

Were There Missed Opportunities?
Goals for Analgesia and Sedation

Provide comfort / safety and allow for interaction with the environment This IS NOT THE SAME AS COMA

Complications extend beyond hospital discharge
Up to 80% of patients remember pain or discomfort
1-year cognitive impairment = 30%
Post-traumatic stress disorder = 15%

Pain, Agitation, and Delirium

Pain

Assess → Treat → Prevent

Delirium Agitation

Preferred assessment tools:
- Able to self-report → Numerical Rating Scale
- Unable to self-report → Behavioral Pain Scale or Critical Care Pain Observation Tool
Treat pain within 30 minutes then reassess:
• Non-pharmacologic treatment → proper positioning, immobilization of painful area(s), elimination of irritants
• Pharmacologic treatment:
  • Non-neuropathic pain → IV opioids +/- non-opioid analgesics
  • Neuropathic pain → gabapentin or carbamazepine + IV opioids


PAD Guidelines:
Drugs to Use for ICU Pain Relief
• Recommend IV opioids for non-neuropathic pain
  – Choice largely determined by pharmacokinetics/dynamics/side effects

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl</th>
<th>Morphine</th>
<th>Hydromorphone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equianalgesic dose</td>
<td>100 mcg</td>
<td>10 mg</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Lipid Solubility</td>
<td>High</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Onset</td>
<td>1-2 minutes</td>
<td>5-10 minutes</td>
<td>5-15 minutes</td>
</tr>
<tr>
<td>Duration</td>
<td>0.5-1 hours</td>
<td>2 hours</td>
<td>3-5 hours</td>
</tr>
<tr>
<td>Active Metabolites</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Route of Elimination</td>
<td>-</td>
<td>Renal</td>
<td>-</td>
</tr>
</tbody>
</table>


PAD Guidelines:
Drugs to Use for ICU Pain Relief
• Recommend enteral gabapentin or carbamazepine in addition to IV opioids for neuropathic pain

• Suggest non-opioid analgesics (acetaminophen, NSAIDs, ketamine)
  – May result in dose reduction or obviate need for IV opioids
  – May reduce opioid-associated adverse drug events

Pain

Assess  Treat  Prevent

• Administer pre-procedural analgesia and/or non-pharmacologic interventions
• Treat pain first, then sedate


Little Progress With ICU Pain

Mundane/routine aspects of ICU care are the most troublesome for patients

1990
63% remembered moderate to severe pain

2007
50% remembered unmet analgesic needs

Pain Assessment Reduces Sedative Use

<table>
<thead>
<tr>
<th>Day 2 Pain Assessment?</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 631)</td>
<td></td>
</tr>
<tr>
<td>Yes (n = 513)</td>
<td></td>
</tr>
<tr>
<td>Any sedative</td>
<td></td>
</tr>
<tr>
<td>86%</td>
<td>75%</td>
</tr>
<tr>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
</tr>
<tr>
<td>65%</td>
<td>57%</td>
</tr>
<tr>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td></td>
</tr>
<tr>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

Pain Assessment Improves Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Day 2 Pain Assessment?</th>
<th>Unadjusted OR</th>
<th>Adjusted OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Mortality</td>
<td>No: 22% Yes: 19%</td>
<td>0.91</td>
<td>1.06</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>No: 22% Yes: 19%</td>
<td>0.69</td>
<td>1.06</td>
<td>0.71</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>No: 18 d Yes: 13 d</td>
<td>1.70</td>
<td>1.43</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>No: 18 d Yes: 13 d</td>
<td>&lt; 0.01</td>
<td>1.43</td>
<td>0.04</td>
</tr>
<tr>
<td>MV duration</td>
<td>No: 11 d Yes: 8 d</td>
<td>1.87</td>
<td>1.40</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>No: 11 d Yes: 8 d</td>
<td>&lt; 0.01</td>
<td>1.40</td>
<td>0.05</td>
</tr>
<tr>
<td>Ventilator Acquired Pneumonia</td>
<td>No: 24% Yes: 16%</td>
<td>0.61</td>
<td>0.75</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>No: 24% Yes: 16%</td>
<td>&lt; 0.01</td>
<td>0.75</td>
<td>0.21</td>
</tr>
</tbody>
</table>


New Paradigm: Analgesedation

- Analgesic first (A-1), supplement with sedative
- Acknowledges that discomfort may cause agitation
- Inappropriate in:
  - Acute alcohol withdrawal, severe hypoxia
  - Pharmacologic paralysis, increased ICP, severe shock


Analgesedation

- 140 critically ill adults mechanically ventilated
- Randomized, open-label trial

- Primary endpoint:
  - Number of days without mechanical ventilation in a 28-day period

- Other endpoints:
  - Length of stay in ICU (admission to 28 days)
  - Length of stay in hospital (admission to 90 days)

**Analgosedation**

**Results**

- Patients receiving no sedation:
  - More days without ventilation (13.8 vs 9.6 days, \( P = 0.02 \))
  - Shorter stay in ICU (HR 1.86, \( P = 0.03 \))
  - Shorter stay in hospital (HR 3.57, \( P = 0.004 \))
  - More agitated delirium (20% vs 7%, \( P = 0.04 \))

- No differences found in
  - Accidental extubations
  - Need for CT or MRI
  - Ventilator-associated pneumonia

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**Agitation**

**Preferred assessment tools:**
- Richmond Agitation Sedation Scale (RASS) or Sedation Agitation Scale (SAS)

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**Sedation-Agitation Scale (SAS)**

<table>
<thead>
<tr>
<th>Score</th>
<th>State</th>
<th>Behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dangerous Agitation</td>
<td>Pulling at ET tube, climbing over bedrail, striking at staff, thrashing side-to-side</td>
</tr>
<tr>
<td>6</td>
<td>Very Agitated</td>
<td>Does not calm despite frequent verbal reminding, requires physical restraints</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
<td>Anxious or mildly agitated, attempting to sit up, calms with 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, follows 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>

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Richmond Agitation-Sedation Scale (RASS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4</td>
<td>Comatose</td>
<td>Overly combative or violent; immediate danger to staff</td>
</tr>
<tr>
<td>-3</td>
<td>Very agitated</td>
<td>Pulls or removes tube(s) or catheter(s) or has aggressive behavior toward staff</td>
</tr>
<tr>
<td>-2</td>
<td>Agitated</td>
<td>Frequent non-purposeful movement or patient-ventilator dyssynchrony</td>
</tr>
<tr>
<td>1</td>
<td>Restless</td>
<td>Not fully alert, but has sustained (more than 10 seconds) awakening with any contact to voice</td>
</tr>
<tr>
<td>0</td>
<td>Drowsy</td>
<td>Light sedation: barely less than 10 seconds to awaken with any contact to voice</td>
</tr>
<tr>
<td>-1</td>
<td>Sedation</td>
<td>No response to voice, but any movement to physical stimulation</td>
</tr>
<tr>
<td>-2</td>
<td>Unresponsive</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

Targeted sedation:
- Identify sedation goal
- Majority of patients = purposely following commands without agitation
- Choose sedative based on goal, clinical endpoints, and side effects


Pad Guidelines: Depth of Sedation

- Recommend that sedative medications be titrated to maintain a light rather than a deep level of sedation in adult ICU patients, unless clinically contraindicated.
Early Light Sedation Predicts Outcomes

- 251 medical / surgical adult patients mechanically ventilated for > 24 hours
- Receiving intermittent or continuous infusion sedative and/or analgesic


Daily Sedation Interruption Decreases Duration of Mechanical Ventilation

150 Patients

68 Patients (Intervention Group)
60 Patients (Control Group)
37 Patients (Midazolam)
31 Patients (Propofol)
29 Patients (Midazolam)
31 Patients (Propofol)

*All patients received continuous morphine infusion


Daily Sedation Interruption Decreases Duration of Mechanical Ventilation

- Fewer diagnostic tests to assess changes in mental status
- No increase in rate of agitated-related complications or episodes of patient-initiated device removal
- No increase in PTSD or cardiac ischemia

Light Level of Sedation Improves Long Term Outcomes

- 336 patients randomized to spontaneous awakening trial (SAT) plus spontaneous breathing trial (SBT) or SBT with sedation per usual care

<table>
<thead>
<tr>
<th></th>
<th>SBT</th>
<th>SAT + SBT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-free days (median)</td>
<td>12</td>
<td>15</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU discharge, days (median)</td>
<td>13</td>
<td>9</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital discharge, days (median)</td>
<td>19</td>
<td>15</td>
<td>0.04</td>
</tr>
<tr>
<td>Death at 1 year, n (%)</td>
<td>97 (58%)</td>
<td>74 (44%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>


Awakening and Breathing Safety Screens

**Awakening Trial**
- No active seizures
- No active alcohol withdrawal
- No active agitation
- No active paralytic use
- No myocardial ischemia (24 hrs)
- Normal intracranial pressure

**Breathing Trial**
- No active agitation
- Oxygen saturation ≥88%
- FIO₂ ≤50%
- PEEP ≤8 cm H₂O
- No myocardial ischemia (24 hrs)
- Normal intracranial pressure
- No significant vasopressor or inotrope use


PAD Guidelines: Choice of Sedative

- **Suggest** that sedation strategies using nonbenzodiazepine sedatives may be preferred over sedation with benzodiazepines to improve clinical outcomes in mechanically ventilated adult ICU patients.

**Benzodiazepines**

<table>
<thead>
<tr>
<th>Clinical Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sedation</td>
<td>• Accumulation</td>
</tr>
<tr>
<td>• Anxiolysis</td>
<td>• Prolonged recovery</td>
</tr>
<tr>
<td>• Amnesia</td>
<td>• Hypotension (synergy with opiates)</td>
</tr>
<tr>
<td></td>
<td>• Respiratory depression</td>
</tr>
<tr>
<td></td>
<td>• Delirium</td>
</tr>
<tr>
<td></td>
<td>• Withdrawal symptoms</td>
</tr>
</tbody>
</table>


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**Benzodiazepines**

- **Midazolam**
  - Rapid onset of action intravenously
  - May accumulate in liver and/or renal failure
  - Prolonged recovery after long-term use

- **Lorazepam**
  - Slower onset of action than midazolam
  - Commonly used for long-term sedation
  - Renal dysfunction/metallic acidosis


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**Benzodiazepine Use Impacts Outcome**

<table>
<thead>
<tr>
<th>Benzodiazepine Use Impacts Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine use does NOT affect mortality</td>
</tr>
</tbody>
</table>

**Propofol**

<table>
<thead>
<tr>
<th>Clinical Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sedation</td>
<td>• Pain on injection</td>
</tr>
<tr>
<td>• Hypnosis</td>
<td>• Respiratory depression</td>
</tr>
<tr>
<td>• Anxiolysis</td>
<td>• Hypotension</td>
</tr>
<tr>
<td>• Muscle relaxation</td>
<td>• Decreased myocardial contractility</td>
</tr>
<tr>
<td>• Mild bronchodilation</td>
<td>• Increased serum triglycerides</td>
</tr>
<tr>
<td>• Decreased ICP</td>
<td>• Tolerance</td>
</tr>
<tr>
<td>• Decreased cerebral metabolic rate</td>
<td>• Propofol infusion syndrome</td>
</tr>
<tr>
<td>• Antiemetic</td>
<td>• Seizures (rare)</td>
</tr>
</tbody>
</table>


**Dexmedetomidine**

<table>
<thead>
<tr>
<th>Clinical Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sedation</td>
<td>• Hypotension</td>
</tr>
<tr>
<td>• Anxiolysis</td>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Patient arousability</td>
<td>• Nausea</td>
</tr>
<tr>
<td>• Analgesia</td>
<td>• Bradycardia</td>
</tr>
<tr>
<td>• Decreased shivering</td>
<td>• Dry mouth</td>
</tr>
<tr>
<td>• Antihypertensive</td>
<td>• Peripheral vasoconstriction at high doses</td>
</tr>
<tr>
<td>• Potentiate effects of opioids, sedatives, and anesthetics</td>
<td></td>
</tr>
<tr>
<td>• Decreased sympathetic activity</td>
<td></td>
</tr>
</tbody>
</table>


**Dexmedetomidine**

**Competing Concerns**

- Use Dexmedetomidine
  - Less time on the ventilator
  - No interference with respiratory drive
  - Less delirium
  - Sympatholysis can be helpful

- Don't Use Dexmedetomidine
  - Hemodynamic derangement
  - Deep sedation
  - Economic stability

When PP, et al. JAMA 2010; 304:489-90
**Audience Response**

RM is a 46-year-old woman admitted with community acquired pneumonia. She is transferred to the ICU after endotracheal intubation in the ED.

PMH: COPD, DM, HTN

Vitals: temp 101.2°F, BP 150/80 mm Hg, HR 88 bpm, RR 35 breaths/min

What sedation regimen and goal would you choose for RM at this time?

1. Fentanyl 50 mcg IV/P every hour as needed for pain; goal RASS 0 to -2
2. Fentanyl continuous infusion at 100 mcg/hr; goal RASS -2 to -3
3. Lorazepam 2 mg IV/P every hour as needed for agitation; goal RASS -2 to -3
4. Lorazepam continuous infusion at 2 mg/hr; goal RASS 0 to -2
Audience Response

Your sedation strategy works over 2 days, however RM’s respiratory status significantly declines and now has severe respiratory failure requiring neuromuscular blockage.

What sedation regimen and goal would you choose for RM at this time?

1. Initiate fentanyl continuous infusion; goal RASS -0 to -2
2. Initiate lorazepam continuous infusion; goal RASS -2 to -3
3. Initiate both fentanyl and lorazepam continuous infusion; goal RASS -5
4. Initiate dexmedetomidine at 0.5 mcg/kg/hr; goal RASS -4 to -5

Audience Response

SF is a 26-year-old man admitted with traumatic brain injury. He is transferred to the ICU after endotracheal intubation in the ED. PMH: None
Vitals: temp 98.2°F, BP 135/95 mm Hg, HR 88 bpm, RR 30 breaths/min

In addition to a fentanyl infusion, what sedation regimen and goal would you choose for SF at this time?

1. Lorazepam continuous infusion at 1 mg/hr; goal SAS 3-4
2. Propofol continuous infusion at 10 mcg/kg/min; goal SAS 3-4
3. Lorazepam 2 mg IVP every hour as needed for agitation; goal SAS 1
4. Dexmedetomidine 1.5 mcg/kg/hr; goal SAS 1

ICU Delirium

- Develops in ~2/3 of critically ill patients
- 60-80% in mechanically ventilated patients
- Undiagnosed in up to 72% of cases

Subtypes of Delirium

Hypoactive delirium is associated with older age, black race, higher APACHE II, and mechanical ventilation.


Why Care?

**During ICU / Hospital Stay**
- Mortality risk increased 12% per day with delirium
- Longer time to extubation
- Ten additional days in hospital on average
- Higher costs of care

**After Hospital Discharge**
- Two-fold increase in 6-month mortality
- Development of dementia and long-term cognitive impairment
- Requirement for care in chronic care facility
- Decreased functional status at six months


Sedation-related Delirium

- N = 102 with blinded paired CAM-ICU results before and after daily sedation interruption with one year follow-up
- Sedation-related delirium = CAM POS → CAM NEG after 2 hours of sedation interruption

Sedation-related Delirium

Delirium

Assess  Treat  Prevent

Preferred assessment tools:
- Confusion Assessment Method for the ICU (CAM-ICU)
- Intensive Care Delirium Screening Checklist (ICDSC)

Confusion Assessment Method (CAM-ICU)

1. Acute onset of mental status changes or a fluctuating course

and

2. Inattention

and

3. Altered level of consciousness

or

4. Disorganized thinking

= Delirium
Delirium

Assess  Treat  Prevent

- Treat pain as needed
- Reorient
- Pharmacologic treatment (no FDA approved treatment):
  - Benzodiazepines for alcohol or benzodiazepine withdrawal suspected
  - ? antipsychotics


PAD Guidelines: Pharmacologic Interventions for Delirium

- No published evidence that haloperidol reduces the duration of delirium in adult ICU patients
  - No placebo-controlled trials
  - Cannot recommend haloperidol
- Atypical antipsychotics may reduce the duration of delirium in adult ICU patients
- Do not recommend administering rivastigmine to reduce the duration of delirium in ICU patients
- Do not suggest using antipsychotics in patients with a history of or at risk for torsades de pointes


Quetiapine vs. Placebo

<table>
<thead>
<tr>
<th>Delirium + Haloperidol PRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine (n = 18)</td>
</tr>
<tr>
<td>Placebo (n = 18)</td>
</tr>
</tbody>
</table>

- Randomized, double-blind, placebo-controlled
- 36 ICU patients
- Quetiapine dose: 50-200 mg every 12 hours
- Primary outcome: time to first resolution of delirium (ie, first 12-hour period when ICDSC ≤ 3)

Quetiapine added to as-needed haloperidol results in faster delirium resolution, less agitation, and a greater rate of transfer to home or rehabilitation.

Delirium

Identify modifiable delirium risk factors
Mobilize and exercise patients early
Promote sleep
Restart baseline psychiatric medications, if indicated
Avoid benzodiazepine use in patients at increased risk for delirium


Inconsistent Rates of Delirium With Benzodiazepines

- SEDCOM¹
  - 77% (midazolam) vs. 54% (dex); p<0.001

- MENDS²
  - 82% (lorazepam) vs. 79% (dex); p = 0.65


Long-term Cognitive Outcomes

- 826 adult critically ill patients (medical and surgical)
- Mechanical ventilation = 90%
- Delirium 75%

| Table 1: Effect of Delirium, Duration of Care, and Exposure to Sedation in Aged Patients on Global Cognition and Executive Function.¹ |
|---|---|---|---|---|---|---|
| | 24h | 72h | 1 wk | 2 wk | 4 wk | 8 wk |
| Duration of Delirium (days) | 0 | 1 | 2 | 3 | 4 | 5 |
| | 123±54 | 123±54 | 123±54 | 123±54 | 123±54 | 123±54 |
| | 123±54 | 123±54 | 123±54 | 123±54 | 123±54 | 123±54 |
| Duration of Care (days) | 0 | 1 | 2 | 3 | 4 | 5 |
| | 123±54 | 123±54 | 123±54 | 123±54 | 123±54 | 123±54 |
| | 123±54 | 123±54 | 123±54 | 123±54 | 123±54 | 123±54 |

Can ICU Delirium be Prevented?

104 adult patients on mechanical ventilation

P = 0.02  P = 0.02  P = 0.08  P = 0.93


Early Mobilization

Case Presentation

DB is a 30-year-old man intubated in the ED for respiratory failure secondary to influenza pneumonia
What Could Have Been Done Differently?

**Days 1-3:**
- Mechanically ventilated (MV)
- Hypotensive on vaspressors
- Treated with fentanyl and lorazepam infusions to goal RASS -3/-4

**Days 4-7:**
- Remains MV
- Developed *Klebsiella* VAP
- Sedated with fentanyl and lorazepam infusions to goal RASS -3

**Days 4-7:**
- Day 4: CV and respiratory stable; sedation stopped; patient dangled feet over bed at 5 pm
- Day 5: Delirium managed with pm IV haloperidol and quetiapine at night (baseline QTc 430 msec); patient walked one lap around MICU at 10 am and 5 pm
- Day 6: Extubated, delirium resolved
- Day 7: Transferred to floor

Benefits of ABCDE Protocol

[Diagram of ABCDE protocol]

**Implementing ABCDE**

- Multidisciplinary team focused on reducing heavy sedation, using SAT-SBT protocol and increasing MICU staffing to include full-time physical and occupational therapists
- Results:
  - Delirium decreased
  - Sedation use decreased
  - Increased patients mobility
  - Reduced hospital length of stay
  - Increased MICU admissions
Summary

- Sedation in the ICU is common and can be associated with negative sequelae.
- Titrate sedative medications using a validated assessment tool to keep patients comfortable and wakeful if possible.
- Minimize the use of benzodiazepines as they are associated with increased time on the ventilator and in the ICU.
- Early mobility in ICU patients decreases delirium and improves functional outcomes at discharge.
- Use of the ABCDE bundle has led to improved outcomes.