Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in ICU Patients

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2013 PAD Guidelines Methods

- GRADE Methodology: (www.gradeworkinggroup.org)
  - Transparent process for statements, recommendations
  - Strength of recommendations based on evidence and relative risks, benefits
- Professional librarian
  - MeSH terms, standardized searches
  - Internet database (Refworks™) > 18,000 references
- Anonymous online voting (E-survey™) by Task Force
  - Standard voting thresholds to achieve consensus
  - Recused if conflict-of-interest
- Expanded from the 2002 Guidelines
  - 53 statements and recommendations (28 in 2002)
  - 36 S/R in the 2008 Sepsis Guidelines

We recommend that pain be routinely monitored in all adult ICU patients (+1B)

An 0–10 NRS scale was the most valid and feasible

The Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT) are the most valid and reliable behavioral pain assessment tools

We do not suggest that vital signs (or observational pain scales that include vital signs) be used alone for pain assessment in adult ICU patients (-2C), but as a cue to further assess pain (+1C)
Behavioral Pain Scale (BPS) 3-12

<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 (eg, brow lowering)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully tightened (eg, 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 ventilation for 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>


Critical Care Pain Observation Tool

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial expression</td>
<td>Relaxed, neutral</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Tear</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Grim must, episodes of crying</td>
<td>2</td>
</tr>
<tr>
<td>Body movements</td>
<td>No resistance, episodes of crying</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Resistance to passive movements</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Resistance to passive movements, inability to complete three tasks</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>To cough but tolerating ventilator</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Coughing but tolerating ventilator</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>
</tbody>
</table>


Assessing Pain Associated With Improved Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Day 2 Pain Assessment?</th>
<th>Unadjusted OR</th>
<th>P</th>
<th>Adjusted OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Mortality</td>
<td>No Yes</td>
<td>22% 19%</td>
<td>0.91 0.69</td>
<td>1.06 0.71</td>
<td></td>
</tr>
<tr>
<td>ICU LOS</td>
<td>18 d 13 d</td>
<td>1.70 &lt; 0.01</td>
<td>1.43 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV duration</td>
<td>11 d 8 d</td>
<td>1.87 &lt; 0.01</td>
<td>1.40 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator-Acquired Pneumonia</td>
<td>24% 16%</td>
<td>0.61 &lt; 0.01</td>
<td>0.75 0.21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


PAD Guidelines: 2013

- We recommend IV opioids as first-line drug to treat non-neuropathic pain (+1C). All IV opioids, when titrated to similar pain intensity endpoints, are equally effective (C)
- RECOMMEND = enteral gabapentin or carbamazepine in addition to IV opioid for neuropathic pain
- SUGGEST = Non-opioid analgesics [acetaminophen, NSAID, ketamine] - may reduce dose or need for IV opioids


Sedation-Agitation Scale (SAS)

7 Dangerous agitation
6 Very agitated
5 Agitated
4 Calm and Cooperative
3 Sedated
2 Very Sedated
1 Unarousable

Richmond Agitation Sedation Scale (RASS)

+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

Processed EEG Monitors

- Bispectral Index or BIS most studied
  - Translates raw EEG via fast fourier transformation
  - Power Spectral Analysis
  - Bispectral analysis
  - Numeric value 0-100
- Other monitors - Sedline (PSI), Narcotrend, Entropy, Cerebral State Monitor, ...
- The clinical events associated with the 0-100 values for these monitors are NOT interchangeable between monitors
  - eg, PSI of 60 not the same as BIS of 60

Theoretical SAS-BIS Agreement

Actual SAS-BIS Agreement

PAD Guidelines: 2013

- We suggest that analgesia-first sedation be used in adult ICU patients who are mechanically ventilated (+2B)
- Maintaining light levels of sedation is associated with improved clinical outcomes (eg, shorter mechanical ventilation and a shorter ICU LOS) (B)
- We recommend that sedative medications be titrated to maintain a light rather than a deep level of sedation in adult ICU patients, unless clinically contraindicated (+1B)
- We recommend either daily sedation interruption or a light target level of sedation be routinely used in mechanically ventilated adult ICU patients (+1B)

Analgesia-First (A1st) “Sedation”

- 105 patients randomized remifentanil (initial dose 6-9 μg/kg/h) before addition of midazolam for sedation (A1st) VS midazolam sedation regimen + pm fentanyl or morphine
- Patients sedated to Sedation–Agitation Scale (SAS) score of 3-4 and a pain intensity (PI) score of 1 or 2
- A1st reduced ventilation by 54 hours ($P = 0.033$) and time from start of weaning to extubation by 27 hours ($P < 0.001$)
- 26% A1st patients received no midazolam
  - Total dose of midazolam required was reduced the in rest (M4x, F9x)
**Sedation-Agitation Scale (SAS)**

- 7 Dangerous agitation
- 6 Very agitated
- 5 Agitated
- 4 Calm and Cooperative
- 3 Sedated
- 2 Very Sedated
- 1 Unarousable

**Richmond Agitation Sedation Scale (RASS)**

- +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

**Patients with RASS -3**

Awake vs Not Awake, n = 38

- 9 (24%) SAS 1-2
- 20 (76%) SAS 3+

**Lighter Level of Sedation**

- Protocol vs non-protocol-directed sedation
  - Similar rate continuous infusion (40.7% vs 41.5%) but shorter duration (3.5 vs 5.6 days, $P = 0.003$)
  - Median duration of MV: 55.9 vs 117.0 hrs, $P = 0.008$
  - ICU LOS: 5.7 vs 7.5 days, $P = 0.013$
  - Hospital LOS: 14.0 vs 19.9; $P < 0.001$
  - Lower tracheostomy rate: 6.2% vs 13.2%, $P = 0.038$
  - Lighter sedation – better outcome

- 128 adults continuous infusion sedation drugs
- Daily wake-up versus standard care
- Daily wake-up shortened:
  - duration ventilation: 4.9 vs 7.3 days, $P = 0.004$
  - median ICU LOS: 6.4 vs 9.9 d, $P = 0.02$
  - diagnostic testing: 9% vs 27%, $P = 0.02$
- % days patients were awake while receiving a sedative infusion: 86% vs 9%, $P < 0.001$
- Lighter sedation – better outcome

**Lighter Level of Sedation**

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### Lighter Level of Sedation


- 129 adult mechanical ventilation patients - single center
- Randomized, semi-open label trial (blinded outcome)

- Light (n = 65): Modified Ramsay 1 (awake but tranquil and cooperative) or 2 (asleep - can open eyes to surroundings)
- Deep (n = 64): Modified Ramsay 3 (asleep - can open eyes to name) or 4 (asleep - can open eyes to physical stimulus)

Morphine for analgesia in both

- Midazolam for sedation to target

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### Light vs Deep Sedation


- At ICU Discharge, deep sedation had:
  - Longer ventilation 5.5 vs 2.9 days, \( P = 0.02 \)
  - Longer ICU LOS 5.5 vs 4.0, \( P = 0.03 \)
  - More depression 19% vs 5%, \( P = 0.02 \)

- At 4-wk follow-up, deep sedation had:
  - Inability to complete questionnaire 6% vs 0%, \( P = 0.04 \)
  - Higher PTSD scores 56 vs 46, \( P = 0.07 \)
  - Trouble remembering ICU 37% vs 14%; \( P = 0.01 \)
  - Disturbing ICU memories 18% vs 4%; \( P = 0.05 \)

- Lighter sedation – Better outcome

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### SLEAP

**RCT 430 ventilated adults: protocol sedation (Brook) (n = 209) vs protocol + DSI (Kress) (n = 214)**

- Benzos/opioids titrated to SAS 3-4 or RASS -3 to 0
- DSI nurses resumed infusions at half previous dose
- T2Ext 7 d, ICU LOS 10 d, Hosp LOS 20 d in both
- DSI higher daily doses midazolam (102 vs 82 mg/d; \( P = 0.04 \)) and fentanyl (550 vs 260; \( P < 0.001 \))
- More daily benzo boluses (0.25 vs 0.18; \( P = 0.007 \)) and opiates (2.18 vs 1.79; \( P < 0.001 \))
- If patients titrated to light sedation, DSI adds no benefit, but increases nurse workload and drug requirements

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### Early Deep Sedation = Worse Survival

Early Deep Sedation = Worse Survival


- We suggest sedation using non-benzodiazepine sedatives (propofol or dexmedetomidine) over benzodiazepines (midazolam/orazepam) to improve clinical outcomes in mechanically ventilated ICU patients (+2B)


- Delirium is associated with increased mortality (A), prolonged ICU and hospital lengths of stay (A), and post-ICU cognitive impairment (B) in adult ICU patients
- We recommend routine monitoring for delirium with the CAM-ICU or the Intensive Care Delirium Screening Checklist (ICDSC), the most valid and reliable delirium monitoring tools in adult ICU patients (A)
- Coma is an independent risk factor for delirium in ICU patients. Benzodiazepines may be a risk factor for the delirium in adult ICU patients (B). There are insufficient data to determine the relationship between propofol and delirium in adult ICU patients (C)


ICU Delirium Screening Checklist

- 8 items based on DSM criteria
- Normal = 0, 1-3 = subsyndromal delirium, ≥ 4 = delirium

- Altered LOC 1
- Inattention 1
- Disorientation 0
- Hallucination, delusion, psychosis 0
- Agitation or psychomotor retardation 1
- Inappropriate speech or mood 0
- Sleep/wake cycle disturbance 1
- Symptom fluctuation 1
- Total score (0 – 8) 4/8


Subsyndromal Delirium - ICDSC

<table>
<thead>
<tr>
<th></th>
<th>No Delirium (ND)</th>
<th>Subsyndromal (SD)</th>
<th>Delirium (D)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Mort</td>
<td>2.4%</td>
<td>10.6%</td>
<td>15.9%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>2.5 d</td>
<td>5.2 d</td>
<td>10.8 d</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hosp LOS</td>
<td>31.7 d</td>
<td>40.9 d</td>
<td>36.4 d</td>
<td>ND vs SD, = 0.002</td>
</tr>
<tr>
<td>Severity of illness APACHE II</td>
<td>12.9</td>
<td>16.7</td>
<td>18.6</td>
<td>ND vs SD, = 0.001 SD vs D, &lt; 0.016</td>
</tr>
</tbody>
</table>


CAM-ICU

In mechanically-ventilated ICU patients, dexmedetomidine may be associated with a lower prevalence of delirium compared to benzodiazepine infusions (B).

We provide no recommendation for:
- The use of dexmedetomidine to prevent delirium
  - Pharmacological or nonpharmacological delirium prevention
- We do not suggest that haloperidol or atypical antipsychotics be administered to prevent delirium in ICU patients (-2C)
- We recommend that early mobilization be performed to reduce the incidence and duration of delirium (+1B)

There is no published evidence that treatment with haloperidol reduces delirium in adult ICU patients.

Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C). We do not suggest using antipsychotics in patients at risk for torsades de pointes
  - Baseline prolongation of QT interval
  - Concomitant medications known to prolong QT interval
  - History of this arrhythmia
- We do not recommend rivastigmine (-1B)

For delirium not related to alcohol or benzodiazepine withdrawal, we suggest dexmedetomidine rather than benzodiazepine infusions in order to reduce the duration of delirium (+2B)

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**Early Mobilization**


**MIND Trial Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Haloperidol n = 35</th>
<th>Ziprasidone n = 30</th>
<th>Placebo n = 36</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium/coma-free days</td>
<td>14.0</td>
<td>15.0</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Delirium days</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Delirium resolution on drug, n(%)</td>
<td>24(69)</td>
<td>23(77)</td>
<td>21(58)</td>
<td>0.28</td>
</tr>
<tr>
<td>Coma days</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>7.8</td>
<td>12.0</td>
<td>12.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>11.7</td>
<td>9.6</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>13.8</td>
<td>13.5</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>21-day mortality, n (%)</td>
<td>4(11)</td>
<td>4(13)</td>
<td>6(17)</td>
<td></td>
</tr>
<tr>
<td>Brain dysfunction 1st day, n(%)</td>
<td>12(35)</td>
<td>9(32)</td>
<td>14(40)</td>
<td></td>
</tr>
<tr>
<td>Delirium/coma-free days</td>
<td>16(47)</td>
<td>15(54)</td>
<td>17(49)</td>
<td></td>
</tr>
</tbody>
</table>

**Olanzapine ~ Haloperidol for ICU Delirium**


- First RCT antipsychotic RX of ICU delirium
- 73 medical - surgical patients
- Oral haloperidol 2.5–5 mg q 8 h
- Oral olanzapine 5 mg daily with dose titration
- IV haloperidol/benzodiazepines allowed
- No differences except less EPS with olanzapine

**Quetiapine Faster Resolution of Delirium**


- 457 patients non-cardiac surgery (70% cancer surgery, APACHE-II = 8.7)
- 31% midazolam, 55% propofol, 63% fentanyl, 27% steroids
- Haloperidol (0.5 mg IV + 0.1 mg/h x 12 hrs) vs placebo
- Median ICU LOS 21.3 hrs H vs 23.0 hrs P, P = 0.024
- Delirium incidence first 7 days 15.3% H vs 23.2% P, P = 0.03
- Mean time onset delirium 6.2 days H vs 5.7 days P, P = 0.02
- Mean delirium-free days 6.8 days H vs 6.7 days P, P = 0.027
- All-cause 28-day mortality 0.9% H vs 2.6% P, P = 0.18
- No drug-related side effects were documented

Haloperidol Prophylaxis in Critically Ill Patients with a High Risk for Delirium

- Before/after evaluation of delirium prevention in selected patients at high risk for delirium (≥ 50% prediction, dementia, ETOH abuse)
- Complex delirium monitoring program
- Haloperidol 0.5-1mg q8 hrs in 177 patients
- Haloperidol reduced delirium (65% vs 75%, P = 0.01), increased delirium-free-days (20 [8-27] vs 13 [3-27] days, P = 0.003), reduced Cox HR for 28-day mortality (Asepsis) 0.80 (0.66-0.98), ICU re-admit (11% vs 18%, P = 0.03) and unplanned removal of tubes/lines (12% vs. 19%, P = 0.02).


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Rivastigmine Decreased ICU Survival

- Median duration delirium 5.0 days R vs 3.0 days P, P = 0.06


Delirium During Study Drug Administration

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine</th>
<th>Midazolam</th>
<th>Diff</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium at baseline</td>
<td>90/131 (68.7%)</td>
<td>63/66 (95.5%)</td>
<td>26.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No Delirium at baseline</td>
<td>2576 (32.9%)</td>
<td>22/40 (55.0%)</td>
<td>22.1%</td>
<td>0.03</td>
</tr>
</tbody>
</table>


PAD Guidelines: 2013

- YES/MAY
  - NRS-BPS-CPOT, opiates for pain
  - SAS-RASS, sedation interruption OR titration
  - Analgesia first
  - Light target sedation
  - Non-benzodiazepine sedation
  - ICDS or CAM-ICU
  - Early mobilization
  - Atypical antipsychotics (not with torsade risk)
  - Dexmedetomidine if not WD (benzos-ETOH)


Thank You