Update on the Management of Pain, Agitation, and Delirium in the ICU

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Disclosures

• Faculty have nothing to disclose.
Objectives

• Describe recent literature on management of pain, agitation, and delirium (PAD) in the intensive care unit (ICU).

• Apply key concepts in the selection of sedatives, analgesics, and antipsychotic agents in critically ill patients.

• Recommend methods to overcome key barriers to optimizing pain, sedation, and delirium pharmacotherapy in critically ill patients.
Case-Based Approach to Pain Management in the ICU

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<table>
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<th>Response</th>
<th>Votes</th>
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<tr>
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Question #1

DT is a 70 yo male w/ COPD, S/P XRT for NSC lung CA, now admitted to the medical ICU for respiratory failure secondary to pneumonia meeting ARDS criteria. Significant home medications include oxycodone sustained release 40mg TID, oxycodone 10-20mg Q4hrs PRN pain, Advair 500/50mcg BID, ASA 81mg QD, and albuterol neb Q4hrs PRN. DT is intubated is currently very agitated (RASS +3), on “ARDS net ventilation settings.”

Which of the following is the best to further assess DT’s agitated state?

A. Serum cortisol
B. Behavioral pain scale (BPS)
C. Urine toxicology screen
D. Confusion Assessment Method ICU (CAM-ICU)
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Etiology of Agitation in Critically Ill Patients

- Gas exchange
  - Hypoxemia
  - Hypercarbia
- Metabolic
  - Hypoglycemia
  - Acidosis
- Ventilator-related
  - Endotracheal tube malposition
  - Tension pneumothorax
- Patient-ventilator dyssynchrony
  - Inadequate flow rates
  - High or low tidal volumes
  - Ventilator Inspiratory/Expiratory times
- Pain
  - Surgical/Trauma/Procedural
  - Baseline pain
  - Routine care/mobilization
- Drug and alcohol related
  - Intoxication
  - Withdrawal
- Infection
  - Central nervous system infection
  - Sepsis
- Ischemia
  - Myocardial
  - Intestinal
  - Cerebral
- Patient positioning in bed
- Fear and Anxiety
  - Inability to communicate
- Sleep deprivation
- Full bladder and or colon
- Drug side effects
  - Anticholinergic
  - Paradoxical response to benzodiazepines

Epidemiology and Outcomes of Pain in the ICU

• Up to 80% of ICU patients experience moderate to severe pain
  – Varies among diverse ICU subgroups (medical, surgical, trauma)
  – At rest, with routine ICU care, and for procedures
• Inadequate pain management is associated with increased morbidity and cost
• Development of chronic pain is reported in up to 50% of ICU survivors
  – Can be as high as 80% after certain surgical procedures

Payen JF et al. Anesthesiology. 2009;111:1308-1316
## “Difficult” analgesia management patients

<table>
<thead>
<tr>
<th>Patient subpopulation</th>
<th>Barriers to management</th>
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</thead>
<tbody>
<tr>
<td>Chronic opioid users</td>
<td>Intrathecal pumps&lt;br&gt;Buprenorphine – requires switch to full agonist&lt;br&gt;Tolerance, sensitization, and hyperalgesia</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation (ECMO)</td>
<td>Altered pharmacokinetics&lt;br&gt;Mobilization requirements for lung transplant</td>
</tr>
<tr>
<td>Severe burns</td>
<td>Altered pharmacokinetics&lt;br&gt;Complex pain physiology</td>
</tr>
<tr>
<td>Severe brain injury (trauma, anoxic)</td>
<td>Assessment of pain symptoms</td>
</tr>
<tr>
<td>Obesity</td>
<td>Altered pharmacokinetics</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>Respiratory depression susceptibility</td>
</tr>
<tr>
<td>Dementia/Cognitive impairment</td>
<td>Assessment of pain symptoms</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>Altered pharmacokinetics&lt;br&gt;Assessment of pain symptoms</td>
</tr>
</tbody>
</table>
Consensus Guidelines in Adults

• **American College of Critical Care Medicine (ACCM) Pain, Agitation, Delirium Guidelines**
  - Pain should be routinely monitored in all adult ICU patients (LOE +1B)
    - Use of validated pain assessment tools
    - Vital signs
      - Should not be used alone for pain assessment in adult ICU patients (LOE –2C)
      - Can serve as cue for further assessment of pain (LOE +2C)
    - Behavioral pain scales in non-communicative patients
      - Medical, postoperative, or trauma (except for brain injury) adult ICU patients who are unable to self-report and in whom motor function is intact and behaviors are observable.

• **American Society of Anesthesiologists (ASA) Perioperative Pain Guidelines**
  - Use standardized, validated instruments to facilitate the regular evaluation and documentation of pain intensity, the effects of pain therapy, and side effects caused by the therapy

LOE = level of evidence

Hierarchy of Pain Assessment

1. Self-reporting is preferred
2. Search for Potential Causes of Pain
3. Observe Patient Behaviors
4. Proxy Reporting (family members, parents, unlicensed caregivers, professional caregivers) of Pain and Behavior/Activity Changes
5. Attempt an Analgesic Trial

Pain Assessment Scales: Self-Reporting Patient

• Able to communicate and self reporting
  – Numerical rating scales (NRS or NRS 11)
  – Visual analogue scales (VAS)

• Thresholds/Acceptable pain
  – Typically < 3 to 5 (scale 1-10)
  – Not all pain is avoidable, making individualized goal-oriented therapy vital

• Limitations
  – Patient unable to communicate

Pain Assessment Scales: Unable to Communicate

- Behavioral pain assessment tools
  - Facial expression, movement, ventilator interaction
- Consensus Guideline- recommended scales
  - Critical-Care Pain Observation Tool (CPOT) (Range 0-8)
    - Score > 2
  - Behavioral Pain Scale (BPS) (Range 3-12)
    - Score > 5
- Limitations:
  - Validation still needed:
    - Diverse languages/cultures
    - Traumatic brain Injury
  - Paralysis

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D. Confusion Assessment Method ICU (CAM-ICU)
Impact of pain assessment on outcomes in the ICU

• A higher degree of pain assessment with a validated tool via protocol or education is associated with:
  - Improved pain scores
  - Reductions in length of ventilation and stay
  - Reduced mortality
  - ↑↓ prescription and consumption of opioids
  - Reduced consumption of sedatives
  - Reduced need for bolus analgesic in non communicative
  - Increased use of nonopioid analgesics
  - Opioid related adverse drug events (ORADE) neutral

Payen JF et al. Anesthesiology. 2009;111:1308-1316
Key Concepts of ICU Pain Assessment

• Pain should be routinely assessed **AND** documented using validated pain assessment tools
• Self-reporting and non communicative scales are essential
• Therapeutic goal of analgesia is established and is patient-specific
  – Thresholds for treatment established as raw value or delta value
• Pain assessment tools have limitations
• Analgesic trial may be an effective form of assessment
Question #2

DT is on propofol @ 5mg/kg/hr due to agitation (RASS +2) and ventilator dyssynchrony. DT is on assist control ventilation with tidal volumes ~6ml/kg, positive-end expiratory pressure of EEP 12 cmH₂O, FiO₂ 0.8 and is tachycardic (heart rate 110 beats/minute). DT currently has a RASS fluctuating from (+2 to -3), CAM-ICU is unable to assess, and CPOT of 6.

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Mechanisms of pain and analgesics: Not all about opioids

Tissue trauma causing release of inflammatory mediators (bradykinins, leukotrienes, prostaglandins, substance P, and histamine)

Local anesthetics
- Opioids
- α2 agonists
- NMDA antagonists
- Gabapentinoids

Epidural or intrathecal local anesthetics

Acetaminophen
- Opioids
- α2 agonists
- NMDA antagonists
- Gabapentinoids

Tissue

Epidural Opioids
- α2 agonists

Descending modulation tract

Spinothalamic tracts

Spinal cord

Peripheral nerve fibers
- Aβ, Aδ, C fibers

Surgery/Trauma
- Burns
- Malignancy
- Infection
- Tubes/lines/drains

Local anesthetics
- NSAIDS
- COX-2 inhibitors

Tissue trauma causing release of inflammatory mediators (bradykinins, leukotrienes, prostaglandins, substance P, and histamine)
Patient-Specific Factors for Selection of Analgesic Regimens

- Pain physiology/severity/duration
  - Surgical site/type, malignancy, neuropathic
- Age
- Body habitus: Obesity and cachexia (Volume of distribution)
- Allergies and “sensitivities”
- Medication administration access (IV, IM, enteral)
- Chronic pain: medication tolerance and pain sensitization/hyperalgesia mechanisms
- Organ function/clearance mechanisms (Renal, hepatic, plasma esterase, drug Interactions)
- Hemodynamic status (stable vs. unstable)
- Respiratory status (Obstructive sleep apnea, mechanically ventilated)
- Coagulopathy/hematological derangements
- Institutional resources
ACCM Pain, Agitation, Delirium Guidelines in Adults

- IV opioids are the first-line treatment for non-neuropathic pain (LOE +1C)
  - All available IV opioids, when titrated to similar pain intensity endpoints, are equally effective (LOE C)
- Analgesia-first sedation should be used in mechanically ventilated ICU patients (LOE +2B)
- Preemptive analgesic therapy and/or nonpharmacologic therapy for invasive and potentially painful procedures (+2C), chest tube removal (+1C)

Opioid Pharmacology

Four Opioid Subclasses
- Phenanthrenes
- Benzomorphans
- Phenylpiperidines
- Diphenylheptanes

Clinical Effects
- Analgesia
- Sedation
- Respiratory depression/anti dyspnea
- Anti-shivering

Fentanyl

Morphine

Remifentanil

Guiding Principles for Opioid Selection in the ICU

- **Route (IV often needed)**
  - Onset for procedure/routine care
- **Use in hemodynamic instability**
  - Sedation +/- histamine release
- **Duration of therapy & volume of distribution**
  - Accumulation capacity
- **Dosing/efficacy**
  - Chronic tolerance
  - Acute tolerance and sensitization mechanisms
    - Acute opioid tolerance (AOT) or OIH opioid-induced hyperalgesia
- **Clearance mechanisms/organ function**
- **Tolerance to side effects**
  - Hypotension, pruritus, CV effects
# Pharmacology of “The Big Four” Opioid Analgesics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fentanyl</th>
<th>Hydromorphone</th>
<th>Morphine</th>
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<td>5-10</td>
<td>5-10</td>
<td>1-3</td>
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<tr>
<td>Elimination T 1/2</td>
<td>2-4 hr*</td>
<td>2-3 hr</td>
<td>3-4 hr</td>
<td>3 - 10 min</td>
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<tr>
<td>Organ failure prolongation</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Renal/Hep</td>
<td>None</td>
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<tr>
<td>Metabolic pathway</td>
<td>N-dealkylation</td>
<td>Glucuronidation</td>
<td>Glucuronidation</td>
<td>Plasma esterases</td>
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<tr>
<td></td>
<td>CYP3A4/5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Metabolite</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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</table>

*Context-sensitive half-life

Non workhorse and transition opioids in the ICU

• Methadone
  – Antihyperalgesic profile (NMDA antagonist)
  – Potential for transition from short-acting agents to facilitate weaning from the ventilator
  – Caution with initiation/transition

• Oxycodone
  – Limited to oral route

• Meperidine
  – Weak analgesic with a high frequency and severe ADR profile*
    – Delirium, serotonin syndrome, seizures
    – Neurotoxic normeperidine metabolite → Accumulation in elderly/renal dysfunction
  – Use should be limited to low dose for rigors/shivering

Opioid adverse drug effects

- **Class effects**
  - Respiratory depression
  - Constipation
  - N/V
  - Pruritus
  - Withdrawal
  - Myoclonus
  - Hypotension
  - Delirium
  - Post traumatic stress disorder
  - Immunomodulation

- **Specific agents**
  - Fentanyl
    - Chest wall rigidity
    - Transdermal toxicity
  - Morphine
    - Cholecystitis
  - Remifentanil
    - ↑ ammonia levels
  - Meperidine
    - Tremors/seizures
  - Methadone
    - QTC prolongation

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Riker RR, Fraser GL. *Pharmacotherapy*. 2005 May;25(5 Pt 2):8S-18S.
Key Concepts in Opioid therapy for Pain in the ICU

- Choice of agent, route, dosing, and monitoring is often patient-specific
- Acute/Chronic opioid tolerance or suspected hyperalgesia
  - Opioid rotation, multimodal, anti-hyperalgesia agents
- Institutional level
  - Institutional guidelines
    - Opioid equianalgesic dosing tables
  - Information systems and smart pumps
  - Specialist consultation for patients with complex chronic pain or opioid withdrawal

Question #2

DT is on propofol @ 5mg/kg/hr due to agitation (RASS +2) and ventilator dyssynchrony. DT is on assist control ventilation with tidal volumes ~6ml/kg, positive-end expiratory pressure of 12 cmH₂O, FiO₂ 0.8 and is tachycardic (heart rate 110 beats/minute). DT currently has a RASS fluctuating from (+2 to -3), CAM-ICU is unable to assess, and CPOT of 6.

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PS is 55 yo male s/p ex lap with whipple procedure. PS is admitted to the SICU postoperatively due to intraoperative bleeding and respiratory failure secondary to transfusion related acute lung injury (TRALI). PS is on assist control ventilation with TV ~6ml/kg, positive end expiratory pressure 10 cmH₂O, FiO₂ 0.6 and is tachycardic (heart rate 100 beats/minute). PS currently has a RASS fluctuating from +1 to -1 and CPOT of 6.

Which of the following interventions would you make to initiate PS’s PAD regimen?

A. Ibuprofen 400mg IV Q6hrs
B. Dexmedetomidine IV infusion 0.2-0.7mcg/kg/hr titrated to RASS +2 to -3 & CPOT < 2
C. Fentanyl IV infusion 0-200 mcg/hr and Fentanyl 25-50mcg every 20mins PRN titrated to Goal RASS and CPOT
D. Ketamine IV infusion 0.3mg/kg/hr titrated to Goal RASS and CPOT
Question #3

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“Analgesedation”

- Also known as analgesia-based or analgesia-first sedation
- Principles based on findings that pain and discomfort may cause agitation
- Address pain and discomfort first, and then add a hypnotic agent if necessary
- Fairly extensive research on the concept going back over a decade, mostly European data
- Typically opioid-based sedation therapy with short-acting agents, however case for dexmedetomidine-based therapy could be made
Key Concepts of Analgosedation

• Takes advantage of certain opioid properties
  – Reduces/eliminates sedative requirements and their associated ADRs
  – Improves sedation-agitation scores
  – Dyspnea & respiratory depressant properties
• Can accentuate opioid-related ADR’s
  – Gastric dysmotility, delirium, hypotension, myoclonus, chest wall rigidity
• May not be appropriate in patients with GABA agonist/sedative needs:
  – Alcohol/drug withdrawal & drug intoxication
  – Neuromuscular blockade
  – Elevated intracranial pressure & status epilepticus

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Analgesic administration: Technique is as important as agent selection

- Preemptive analgesia
  - Initiated before and is operational during procedures in-order to reduce the physiological consequences of nociceptive pain transmission
  - More effective than the same treatment administered during or after the procedure to reduce pain and analgesic needs
  - Pharmacologic & Non pharmacologic
  - Upgraded in the surgical realm to the concepts of preventative and protective analgesia

Enteral gabapentin or carbamazepine in addition to IV opioids should be considered for treatment of neuropathic pain (LOE +1A)

Nonopioid analgesics should be used to decrease the amount of opioids administered (or to eliminate the need for IV opioids altogether) and to decrease opioid-related side effects (LOE +2C)

Neuraxial techniques:
- Thoracic epidural anesthesia/analgesia should be considered for abdominal aortic aneurysm surgery, (LOE +1B) traumatic rib fractures (LOE +2B)
- No recommendation
  - Lumbar epidural over parenteral opioids for postoperative abdominal aortic aneurysm surgery
  - Intrathoracic or nonvascular abdominal surgical procedures
  - Medical ICU patients (0, No Evidence)
Multimodal Analgesia

- **Definition**
  - Combining different analgesics that act by different mechanisms and at different sites in the nervous system, resulting in additive or synergistic analgesia with lowered adverse effects compared to sole administration of individual analgesics

- Also known as “balanced analgesia”

- Established 1993

- Recommended by consensus guidelines

- Limited focused ICU literature

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Multimodal Agents: A LOT to choose from but not much ICU data

“Workhorse agents”
- Anti-inflammatory
  - Acetaminophen
  - NSAIDs
  - Cox-2 inhibitors
- Opioids/mu-receptor agonists
- Local Anesthetics
  - Regional & local techniques

“Secondary agents”
- NMDA receptor antagonists
  - Ketamine
- α-2 agonists
  - Clonidine & Dexmedetomidine
- Anticonvulsants
  - Gabapentin/Pregabalin
- Corticosteroids
- TRPV1 agonist: Capsaicin
- Cannabinoids

Choice of agent, route, dosing, and monitoring is often patient specific and limited by resources available

Improved Outcomes Associated with Pain Assessment in the ICU

Post-hoc analysis of the DOLOREA prospective, observational analysis in 14 European ICUs from January 2004 to January 2005. 1,144 patients were divided into those assessed for pain on day 2 (n=513) and those not assessed for pain on day 2 (n=631). Various pain scales were used among different institutions.

Single center, prospective, Two phase, controlled study of 230 ICU patients requiring > 24hr stay before (n = 100) and after (n = 130) implementation of a pain and sedation at Montpellier University hospital in France. Education and encouragement of use of pain scale and sedation assessment tools.

Acetaminophen & NSAIDs: Often forgotten

• Surgical populations: Basal +/- preemptive acetaminophen and NSAIDs
  – Improved pain control
  – Reduced opioid utilization and opioid-related ADRs
  – Potential for reduced LOS

• Cons
  – Platelet dysfunction and bleeding risk (NSAIDS)
    – Black box in cardiac surgery
  – Organ dysfunction (Renal: NSAIDS, Hepatic: Acetaminophen)
  – Fever suppression
  – Cost of certain agents

# Local Anesthetics: It’s about technique

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regional Neuraxial</th>
<th>Regional peripheral continuous/ single shot</th>
<th>Local/ Wound Infiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td>• Potent analgesia \n• Can combine with opioid/α-2 agonist</td>
<td>• Potent analgesia \n• Opioid sparing</td>
<td>• Ease of Admin \n• No specialist \n• Can discharge patient</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>• Antithrombotic therapy \n• Coagulopathy/thrombocytopenia \n• Specialist needed \n• ADRs/Toxicity</td>
<td>• Specialist needed \n• Reduced limitations/ADR’s compared to neuraxial</td>
<td>• Technology limits on duration of effect \n• $$$</td>
</tr>
</tbody>
</table>

Evolving role of local anesthetic analgesia in the ICU

• Advancement in the efficacy and safety of single shot and nerve catheter placement
  – Peripheral nerve catheters for continuous infusion
  – Local/wound infiltration analgesia
    – Thoracotomy/sternotomy, major abdominal, plastics, orthopedic

• Fast track surgical protocols using multimodal analgesia with local anesthetic backbones
  – Improved pain control
  – Reduced opioid consumption and ADR’s
  – Reduced rehabilitation time
  – Reduced length of stay
  – Reduced mortality (thoracics)

Ketty and DExCLoN: Adjuncts not backbones of multimodal regimen

Ketamine

• Primary analgesic mechanism: NMDA antagonism
  – Anti sensitization
  – Opioid sparing
• Dose related analgesia effects → Low dose
• Combo with opioids/Locals
  – Burn dressing changes
  – Hyperalgesia/AOT
• Cons
  – Slow recovery time
  – ADR’s
  – Specialist often required

Dexmedetomidine & Clonidine

• Primary analgesic mechanism: $\alpha$-2 agonism descending pain modulating
  – +/- Opioid consumption
• Multimodal with opioids
  • Hyperalgesia/AOT
• Cons
  • CV ADR’s
  • Bolus can be dangerous
  • $$


Analgesia and Early Mobilization

- Pain, agitation, and delirium are key barriers to mobilization in the ICU
- Pharmacotherapy selection may be limited by adverse effects
  - Local anesthetics (by administration location)
  - Opioids
  - α 2 agonists
  - Ketamine
- Multimodal therapy
  - Acetaminophen/NSAIDs
  - Local infiltration analgesia (LIA) in selected surgical populations
Local Protocols and guidelines for PAD in the ICU

- Predominantly multicomponent analysis with interventions for pain, agitation, and delirium
- Address core components of management
  - Assessment tool and goal directed
  - Multimodal pharmacotherapy
  - Order sets/Algorithms/Information systems implementation
- Impact on outcomes
  - ↑Adherence to best practices
  - Improved pain control
  - Reduced morbidities and adverse effects
  - Cost savings

Key Takeaways

1. Perform and document pain assessments
   – Communicative and non-communicative

2. Structured patient-focused management strategy
   – Incorporate key patient considerations into drug therapy
   – Goal directed multimodal approach

3. Systematic ICU/Institutional approach
   – Guideline or protocol
   – Educational, specialist resources
   – IS implementation
Adult ICU Sedation

Gilles Fraser, Pharm.D., MCCM
Clinical Pharmacist in Critical Care
Maine Medical Center
Portland, Maine
ICU Agitation

• Frequent (up to 86%) and complex
• Management is context/patient specific
  – Probable reason(s) for agitation
    – Pain, substance withdrawal, anxiety, delirium, ventilator asynchrony
  – Other modifiers
    – Intubated vs. not, hemodynamic stability, short vs. long-term sedation, light vs. deep sedation, organ dysfunction
    – Potential econotoxicity
• Caregiver responsibilities
  – Appreciate the short- AND long-term ICU patient consequences of therapeutic choice and method of administration

What We’ve Learned:
Goals for Our ICU Patients

• **THEN**: Survival and discharge

• **NOW**: Don’t fix patients and break them at the same time
  
  – **Short-term issues** = pain, anxiety, fear, coma, prolonged mechanical ventilation and ICU stay, delirium, delusions, trauma, disruption of anastomotic sutures, and medical device removal
  
  – **Complications after hospital discharge**
    
    – Persistent delirium = 10%
    
    – Long-term cognitive impairment ≈ 30% at one year
      
      – Similar to traumatic brain injury or Alzheimer's disease
      
      – New unemployment ~50%
      
      – Posttraumatic stress disorder (PTSD) ≈ 7–15%

• **FUTURE**: Modifiable risk factors?


Question #4

The ACCM PAD guidelines suggest that comfort and wakefulness should be sedation goals for most ICU patients. This is represented by:

A. RASS -2 (opens eyes and tracks for <10 seconds)
B. Sedation Agitation Score (SAS) 3 to 4 (obeys commands)
C. Arousal with any stimulus
D. Arousal with verbal stimulus
Your poll will show here

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Goal: Titrate Sedatives to **Wakefulness**

“respond to commands (i.e., a combination of any three of the following actions upon request: open eyes, maintain eye contact, squeeze hand, stick out tongue, and wiggle toes). This degree of responsiveness and awareness goes beyond patients being merely “sleepy but arousable” and is essential for the evaluation of pain through patient self-report, for assessing patients’ readiness to wean and extubate, for performing delirium assessments, and for implementing early mobility efforts.”

Validated Tools for Sedation/Agitation Assessment

- Sedation Agitation Scale (SAS)
  - Please note word order
- Richmond Agitation Sedation Scale (RASS)
## Sedation-Agitation Scale (SAS) 1994

<table>
<thead>
<tr>
<th>Score</th>
<th>State</th>
<th>Behaviors</th>
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<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 down to verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm and Cooperative</td>
<td>Calm, awakens easily, follows commands</td>
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<tr>
<td>3</td>
<td>Sedated</td>
<td>Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off, follows commands</td>
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<tr>
<td>2</td>
<td>Very Sedated</td>
<td>Aroused to physical stimuli but does not communicate or follow commands</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>

Richmond Agitation-Sedation Scale (RASS)

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

Very agitated

Question #4
The ACCM PAD guidelines suggest that comfort and wakefulness should be sedation goals for most ICU patients. This is represented by:

A. RASS -2 (opens eyes and tracks for <10 seconds)
B. SAS 3 to 4 (obeys commands)
C. Arousal with any stimulus
D. Arousal with verbal stimulus
Question #5

Patient has been kept at a RASS of -3 as a sedation goal (moves to verbal stimulus). Can delirium be evaluated?

A. Yes, because that is what icudelirium.org suggests
B. Yes, because the level of sedation does not influence delirium assessment
C. No, because icudelirium.org suggests that patients should be able to respond to queries
D. No, because RASS -3 can influence delirium assessments
Your poll will show here

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Does RASS -3 = Moderate Sedation?

• Any movement but no eye contact to verbal stimuli

• Vanderbilt authors and others
  – Coma
  – Severe brain dysfunction
  – Deep sedation

• And why is this important?

We All Agree---Avoid Sedation-Induced Coma for Most Patients

- Reduces
  - Mechanical ventilation time (28-57%)
  - ICU length of stay (30-47%)
  - Neurodiagnostic testing (67%)
- Limits the post-intensive care syndrome (PICS)?
  - Delirium?
  - PTSD?
  - Long-term cognitive impairment?
RASS and CAM-ICU ASSESSMENTS
N = 12,875

<table>
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<tr>
<th>Study</th>
<th>RASS -2 to -3</th>
<th>RASS 0 to -1</th>
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<td># Assessments</td>
<td># CAM ICU positive</td>
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<td>4</td>
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<td>212</td>
</tr>
<tr>
<td>Total</td>
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<td>729</td>
</tr>
</tbody>
</table>

Timing of CAM-ICU vs Sedation Depth

Should I do a CAM-ICU assessment before, during, or after a Spontaneous Awakening Trial (SAT)?

“The best picture of the patient’s mental status will come from assessing delirium serially throughout the day. Thus, we recommend that you assess patients for delirium both before and after daily sedative interruption (SAT).”

icudelirium.org accessed 8.15.16

“Drug induced sedation does not, in our opinion, constitute delirium” Ouimet ICM 2007
Question #5

Patient has been kept at a RASS of -3 as a sedation goal (moves to verbal stimulus). Can delirium be evaluated?

A. Yes, because that is what icudelirium.org suggests
B. Yes, because the level of sedation does not influence delirium assessment
C. No, because icudelirium.org suggests that patients should be able to respond to queries
D. No, because RASS -3 can influence delirium assessments
Sedation Management

• Light sedation for most patients (B)
  – Allow wakefulness: respond purposefully to at least three commands
  – RASS and SAS for sedation assessment

• Use protocol with daily sedation interruption (SAT) or that targets light level of sedation (1B)

Question #6

Which of the following is true regarding protocolization of sedation using SAT or titration to wakefulness?

A. SAT is best since there are mortality benefits
B. Titration is best since patients experience less time on mechanical ventilation
C. Either SAT or titration is fine since they result in shorter ICU stays
D. Either SAT or titration is fine since they have associated mortality benefits
Your poll will show here

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Daily Sedation Interruption (SAT) vs Light Sedation Titration
Lumpers Versus Splitters

  - No apparent advantage of one approach over the other
- No advantage of sedation interruption when patients are also receiving light sedation

Ouellette D. *CHEST.* 2016 (in press).
Protocolized Sedation and Clinical Outcomes in Ventilated ICU Patients

ACCP/ATS 2016 (in press)

- **Duration of ventilation**
  - Shortened by 1 day ($p = 0.11$)
  - $I^2 = 63\%$
- **ICU LOS**
  - Shortened by 1.8 days ($p = 0.03$)
  - $I^2 = 71\%$
- **Mortality (hospital)**
  - Relative risk = 0.88 ($p = 0.3$)
  - $I^2 = 0\%$

Meta-analysis 2015 Mayo Clin Proc

- **Duration of ventilation**
  - Shortened by 1 day ($p = 0.18$)
  - $I^2 = 74\%$
- **ICU LOS**
  - Shortened by 1.7 days ($p = 0.03$)
  - $I^2 = 60\%$
- **Mortality (hospital)**
  - Relative risk = 0.89 ($p = 0.27$)
  - $I^2 = 0\%$
Protocolized PAD Management Seems Worthwhile!

- Decreases time in the ICU and perhaps requiring mechanical ventilation
- Facilitates Early Mobility, which decreases delirium burden and allows independent functioning
- Perceived vs. Actual Practice
  - Survey 85 ICUs = 24-hr practice snapshot
  - Sedation protocols used in 50% ICUs
  - Sedation interruption reported in 66% ICUs
    - Performed in 36% patients
  - Delirium monitoring reported in 25% ICUs
    - Performed in 10% of patients

Question #6

Which of the following is true regarding protocolization of sedation using SAT or titration to wakefulness?

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B. Titration is best since patients experience less time on mechanical ventilation.
C. Either SAT or titration is fine since they result in shorter ICU stays.
D. Either SAT or titration is fine since they have associated mortality benefits.
Make It Easy To Do The Right Thing!

Orders Set:

- Intermittent Agitation/Discomfort
- Sustained Agitation/Discomfort with a Goal of Light Sedation in a Mechanically Ventilated Patient
- Sustained Agitation/Discomfort with Goal of Light Sedation in Mechanically Ventilated Patients Requiring High Dose Vasopressors
- Sustained Agitation/Discomfort with a Goal of Light Sedation in a Patient Without Mechanical Ventilator Requirements
- Delirium (not related to substance withdrawal)
- Deep Sedation in Patients Receiving Mechanical Ventilation

Additional Orders:

- Chemistry - Other
  - Based on the selection of some medications, certain laboratory tests should also be ordered:
    - If Propranolol is ordered, also select Triglyceride lab orders.
    - If Valproate Sodium or Valproic acid is ordered, also select the Ammonia lab order.
    - Ammonia
    - Lipid Panel Non-Fasting
    - Lipid Panel
Sedating agents

• “Analgesedation”
• Benzodiazepines
  – Selected patients
• Propofol
• Dexmedetomidine
Introducing Analgesia-Based “Sedation,” a Tough Sell!

• Analgosedation or analgesia-first (A-1) sedation
• Discomfort is a common cause of agitation
• Any opioid useful... typically rapid onset and offset
• ~ 50% will require additional sedative agents

Clinical Practice Pearl: This is one way to limit avoidable serious adverse reactions from sedatives (death, delirium, immunomodulation, metabolic acidosis, hemodynamic derangement, etc).

Finding the Balance with Analgosedation

- Pain and discomfort are common causes for agitation
- Avoid potential sedative-related adverse events:
  - Immunomodulation
  - Death (e.g., PRIS)
  - Delirium
  - Metabolic acidosis
  - Hemodynamic derangement

- ICU LOS, ventilator time, delirium, VAP, mortality, and cost of care NOT consistently reduced
- May interfere with respiratory drive, gastric motility, nutrition
- Potential for withdrawal
- Rigorously evaluated mostly in European ICUs

Potential Benefits

PRIS = propofol related infusion syndrome

Potential Limitations
Benzodiazepines: Good and Bad

- Useful for
  - GABA agonist withdrawal
  - Anxiety
  - Intermittent agitation
  - Agitation in the setting of hemodynamic instability?
  - Seizures
  - Deep sedation and when amnesia is beneficial

- And sometimes they are indeed the devil’s handiwork
Sedation Management:
Benzodiazepines NOT Optimal

• Sedation strategies with non-benzodiazepines may be preferred because they are associated with improved clinical outcomes (2B)
  – Ventilator time
  – ICU time
  – Delirium?
• No effect on mortality

Barr  *Crit Care Med.* 2013; 41:263.
Comparative Hypotensive Effects

• Midazolam = Dexmedetomidine (27%)
  – SEDCOM Riker RR. JAMA 2009; 301:489-99

• Midazolam (12%) < Dexmedetomidine (21%)
  – MIDEX Trial Jakob SM. JAMA 2012;307:1151-60

• Propofol = Dexmedetomidine
  – PRODEX trial (13% each) Jacob SM. JAMA 2012;307:1151-60
  – Neurocritical Care Patients; ~25% each Erdman MJ. Crit Care Med 2014; 42:1696-702
Propofol: Indications and Pharmacodynamics

- Pharmacology: GABA agonist
- Preferred over the benzodiazepines (2B)
- Benefits
  - Rapid onset & offset
    - Allows easy dose titration to goal and facilitates daily sedation evaluation
    - Shorter time on mechanical ventilation and in the ICU vs benzodiazepines
      
      Carson SS. *Crit Care Med.* 2006; 34:1326-32

- Has not been linked to delirium
Propofol: Concerns

• Not reliably amnestic, especially at low doses
• NO analgesia!
• Hypotension, hypertriglyceridemia, respiratory depression
  – Limits patient throughput to non-ICU setting
• Propofol Infusion Syndrome (PRIS)--rare, but often fatal
Dexmedetomidine

• Pharmacology: α-2 agonist
  – Has sedating, anxiolytic, and opiate-sparing properties
  – Permits patient awareness and responsiveness on stimulation
• Comparative data vs propofol are few
Dexmedetomidine

Competing Concerns

Use Dex
- Less time on the ventilator (2B)
- No interference with respiratory drive
- Less delirium (2B)
- Sympatholysis can be helpful

Don’t Use Dex
- Econotoxicity; need ICU for administration
- Hemodynamic derangement
- Not for deep sedation
  - No amnestic properties

Helpful Hints
- If you wouldn’t treat a patient with a beta-blocker, don’t use dex
- Withdrawal tachycardia and hypertension unusual

Pearls For The Use of Dexmedetomidine

• Do not use loading dose
• Expand dosing range to 1.4mcg/kg/hr
• Expand permissible treatment duration >24hr
• Combination with other sedatives or analgesics OK
• Transition to clonidine (may facilitate transfer to non-ICU setting)
Alternative Agents

- Clonidine
- Ketamine
- Valproate
- Quetiapine (for its sedative effects)
- Phenobarbital
- Volatile anesthetics
Key Takeaways

- Sedation goal = comfort and wakefulness for most
  - Example: When RASS is used, offer additional evaluations to include assessments of wakefulness.

- Protocolization of sedation shortens ICU stay by about 2 days
  - Either daily SAT or simple titration to wakefulness may be used

- Analgesedation is effective and often avoids the need for standard sedatives
  - Example: Start with an opioid for those patients requiring sedation
Always remember….

“Caution should be exercised, however, when guiding patients in selecting their music.

Chaotic music, such as hip-hop and heavy metal, is not healing to human cells.”

!!!!!!!!!!

Courtesy of Lauren Payne, Pharm.D.

Chlan. JAMA 2013; 309:2335.
Updates on Delirium in Critically ill Patients

Paul M. Szumita, Pharm.D., BCCCP, BCPS, FCCM
Clinical Pharmacy Practice Manager
Brigham and Women’s Hospital
Boston, Massachusetts
2013 ACCM Guidelines: Delirium in Adult ICU Patients

• Outcomes associated with delirium
  – Delirium is associated with increased mortality and increased ICU and hospital LOS: (LOE A)
  – Delirium is associated with the development of post-ICU cognitive impairment in adult ICU patients: (LOE B)

Associated outcomes from ICU delirium

• During ICU and hospitalization
  – Increased mortality
  – Increased re-intubation rates
  – Increased length of stay
  – Higher cost of care
  – Increased need for tracheotomy
  – Increase restraint use
• Post hospital discharge
  – Increased mortality
  – Decreased functional status at 6 months
  – Increased risk of long-term cognitive impairment
  – Increased risk of dementia
  – Increase reliance on chronic care facilities

• Key Term – “Associated” = Not implying causation
• Is medication-related delirium = to toxic-metabolic delirium?

Question #7
Compared to persistent delirium, rapidly reversible delirium (sedation related) is associated with:

A. Increased mortality
B. Decreased mortality
C. The same mortality
D. Increase discharge to hospice
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Rapidly Reversible, Sedation-Related Delirium

Single center, prospective, cohort of 102 intubated adult medical ICU patients at the University of Chicago. CAM-ICU assessed before and after SAT daily. Rapidly reversible delirium defined by CAM-ICU assessment abated within 2 hours of an SAT.

Question #7
Compared to persistent delirium, rapidly reversible delirium (sedation related) is associated with:

A. Increased mortality
B. Decreased mortality
C. The same mortality
D. Increase discharge to hospice
Delirium Outcomes Summary

• Avoiding delirium would be best
• Likely different classification of delirium based on cause (beyond the classic hypoactive, hyperactive, mixed)
  – Toxic metabolic
• Different classifications of delirium based on cause probably are associated with different outcomes (prime area for research)
  – e.g., Delirium from liver failure likely is not the same as delirium from hypoxia
2013 ACCM Guidelines: Delirium in Adult ICU Patients

• Detecting and monitoring delirium
  – Routine monitoring of delirium is recommended in adult ICU patients (LOE +1B)
  – Confusion Assessment Method- ICU (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) are most reliable (LOE A)
  – Delirium monitoring is feasible in clinical practice (LOE B)

What is the prevalence/Incidence of delirium?

• 3%?
• 15%?
• 50%?
• 80%?
• Highly dependent on:
  – Systematic screening (all patients every shift?)
    – Underestimating if not done (if you’re not looking you, won’t find it)
  – Frequency of assessment (and adherence)
  – Assessment tool
  – Surgical/medical
  – Type of surgery
  – Study design
  – Metric
  – Mechanically vented

Evaluation of unable-to-assess CAM-ICU documentation

• Convenience sample of 3 months in MICU and SICU at a single center
  – 116 unable to assess (UTA)
  – 103 positive
  – 220 negative

• UTA 36 % of all assessments
  – Inappropriate UTA documentations ~30%

• Rates of inappropriate UTA assessments may be higher than previously reported in literature

• Additional research may be warranted to identify acceptable rates of inappropriate UTA CAM-ICU assessments

### MICU-3C Unit Safety Dashboard

<table>
<thead>
<tr>
<th>Vent</th>
<th>Sedation Mgmt</th>
<th>Early Mobility</th>
<th>Family Mix</th>
<th>Glucose Control</th>
<th>Nutrition</th>
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<tr>
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</tbody>
</table>

- **Guideline Compliant**: Green
- **Risky State**: Yellow
- **Action Needed**: Red

---

**Sedation**
- RN has had the opportunity to provide input to team from patient and family regarding goals and plan of care.
  - Yes  
  - No

**Coordination of Sedation**
- RASS: Current 24-hr Average: 0

**Delirium Management**
- CAM-ICU-(M)
  - CAM results in last 24h:
    - 9/20 08:00 Negative
    - 9/20 04:00 Negative
    - 9/20 08:00 Negative
  - Last QTc: 449 msec (9/19/16 15:42)
  - Antipsychotics: [Details]
  - We have discussed a plan to optimize delirium management.
    - Yes  
    - No

**Mobility**
- Pressure Ulcers: Braden Score: 15 (high risk)  
  - Pressure Ulcer: [Details]
  - We have discussed the patient’s pressure ulcer prophylaxis and passive mobilization.
    - Yes  
    - No

- Active Mobilization: Consult Placed: 9/10/16 5:54
  - It is appropriate for the patient to participate in active mobility efforts:
    - Yes
    - No, due to the following reason:
      - Hemodynamic instability (frequent titration of pressors)
      - Unsafe to perform SAT
      - Paralysis
      - Post-surgical concerns
      - Comfort measures only status

- The patient has a new mobility or strength impairment requiring a PT consult.
  - Yes  
  - No
Detection and Monitoring Summary

- Prevalence is highly patient population dependent

- CAM-ICU or ICDSC should routinely be used

- Each institution should have a standard and quality improvement method
Question #8

According to the 2013 ACCM PAD Guidelines, what are the baseline risk factors significantly associated with the development of delirium in the ICU in addition to preexisting dementia and high severity of illness?

A. Benzodiazepine consumption and history of alcoholism
B. History of hypertension and history of alcoholism
C. Hyperglycemia and history of diabetes
D. Preexisting pain, history of opioid dependence
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2013 SCCM Guidelines: Delirium in Adult ICU Patients

- Delirium risk factors
  - Four baseline risk factors are positively and significantly associated with the development of delirium in the ICU: preexisting dementia, history of hypertension and/or alcoholism, and a high severity of illness at admission (B)
  - Coma is an independent risk factor for the development of delirium in ICU patients (B)
  - Conflicting data surround the relationship between opioid use and the development of delirium in adult ICU patients (B)
  - Benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients (B)
  - There are insufficient data to determine the relationship between propofol use and the development of delirium (C)
  - In mechanically ventilated adult ICU patients at risk of developing delirium, dexmedetomidine infusions administered for sedation may be associated with a lower prevalence of delirium compared to benzodiazepine infusions (B).

Question #8

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- A. Benzodiazepine consumption and history of alcoholism
- B. History of hypertension and history of alcoholism
- C. Hyperglycemia and history of diabetes
- D. Preexisting pain, history of opioid dependence
Pathophysiology of Delirium in Critically ill Patients

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<th>Subtype</th>
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<td>Hypoxia</td>
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<td>Encephalopathies</td>
<td>Organ failure: Liver, renal, heart</td>
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<td>Elevated BUN</td>
<td>Toxin Ingestion</td>
</tr>
<tr>
<td></td>
<td>Hyperthermia</td>
<td>Intoxification of alcohols (ethanol, ethylene glycol, methanol)</td>
</tr>
<tr>
<td></td>
<td>Electrolyte abnormalities</td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Toxin mediated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infection/Inflammation</td>
<td></td>
</tr>
<tr>
<td>Alteration of neurotransmitters</td>
<td>GABA and Glutamate</td>
<td>Ethanol abuse</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>Excessive or inappropriate tapering of benzodiazepines/barbiturates/opioids</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine</td>
<td>Sleep deprivation and circadian rhythm alteration</td>
</tr>
<tr>
<td></td>
<td>Serotonin</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>NMDA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetylcholine</td>
<td></td>
</tr>
</tbody>
</table>

Most cases are multifactorial!! = Treatment is multimodal!!

Question #9

JM currently is receiving IV norepinephrine 20 mcg/min, vasopressin 0.04 units/min, epinephrine 5 mg/min, and propofol 75 mcg/kg/min, with fentanyl IV bolus doses prn. JM is noted to have a MAP = 66 mmHg, HR = 91 bpm, CPOT 0, RASS -3, CAM-ICU positive. Which of the following would be the best initial management recommendation based on assessments, current medication therapy, hemodynamics and vital signs?

A. Replace propofol with a dexmedetomidine infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU

B. Replace propofol with a midazolam infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU

C. Continue propofol to achieve a goal RASS of 0 to-1 and negative CAM-ICU

D. Add quetiapine 50 mg NG every 12 hr to achieve a goal of negative CAM-ICU
question #9

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Effect of Sedation Level on the Prevalence of Delirium

Single center in Switzerland, prospective, double-blind trial of 104 mixed medical/surgical ICU. 80 patients enrolled (467 patient days) and delirium assessed via the ICDSC and CAM-ICU during SAT.

Systematic Review of Risk Factors for Delirium in Critically Ill Adults

- Strong evidence
  - ↑Age
  - Dementia
  - Hypertension
  - Pre-ICU surgery or trauma
  - ↑APACHE II score
  - Mechanical ventilation
  - Metabolic acidosis
  - Delirium on the prior day
  - Sedation-associated coma

Probability of Transitioning to Delirium in Mechanically Ventilated Patients

- 198 mechanically ventilated patients admitted to the MICU or CCU at Vanderbilt University Medical Center from February 2000 to May 2001
- APACHE II: 25.7±8.4
- Sepsis/ARDS: 47%

Question #9

JM currently is receiving IV norepinephrine 20 mcg/min, vasopressin 0.04 units/min, epinephrine 5 mg/min, and propofol 75 mcg/kg/min, with fentanyl IV bolus doses prn. JM is noted to have a MAP = 66 mmHg, HR = 91 bpm, CPOT 0, RASS -3, CAM-ICU positive. Which of the following would be the best initial management recommendation based on assessments, current medication therapy, hemodynamics and vital signs?

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B. Replace propofol with a midazolam infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU
C. **Continue propofol to achieve a goal RASS of 0 to -1 and negative CAM-ICU**
D. Add quetiapine 50 mg NG every 12 hr to achieve a goal of negative CAM-ICU
Extremely controversial question

• Is it the sedative drug or the level of sedation?
  – Glass of wine or a bottle of tequila

Risk Factors Summary

• Many risk factors
  – Often non-modifiable

• Modify as many of the risk factors as possible in a systematic way
2013 ACCM Guidelines: Delirium in Adult ICU Patients

• Delirium prevention
  – Early mobilization to prevent delirium is recommended (LOE +1B)
  – Conflicting data surround the relationship between opioid use and delirium in adult ICU patients (LOE B).
  – Benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients (LOE B).
  – Inconclusive relationship between propofol use and delirium in adult ICU patients (LOE C)
  – In mechanically ventilated adult ICU patients at risk of developing delirium, dexmedetomidine infusions administered for sedation may be associated with a lower prevalence of delirium compared with benzodiazepine infusions (LOE B)
  – Antipsychotics should not be given to prevent delirium (LOE -2C)
  – No recommendation for the use of dexmedetomidine to prevent delirium in adult ICU patients (LOE 0,C)

Preventive Strategies

• Largely nonpharmacologic and involves multidisciplinary action
  - Correct any known precipitating cause
    - Toxic metabolic, hypoxia, infection, organ dysfunction, shock
  - Early mobilization
  - Use of scheduled pain management protocols and pain scales
  - Target awake and alert via the use of sedation scales
  - Provide light, signs, calendars, clocks
  - Reorient, hearing aids, eyeglasses
  - Encourage family visits
  - Timely removal of catheters and restraints
  - Bowel, hydration, nutrition issues
  - Minimizing unnecessary stimuli
  - Adjusting ventilator settings
  - Promote sleep-wake pattern
  - Medication review

Caution

• Dot phrase world
  – Early mobilization
  – Minimize deep sedation
  – Maximize day/night cycle
  – Frequent orientation
  – Post reminders of friends and family - Photos
Collaborative Approach

- Clinicians, Educators, Administrators, Programmers, Physicians
  - Pharmacists
  - Licensed independent Providers
  - Nurses
  - Information systems personnel
  - Respiratory Therapists
  - Physical Therapists
  - Occupational Therapists
  - Care coordinators
Two-center trial of 104 adult patients on mechanical ventilation for less than 72 hr, randomized to early exercise and mobilization (PT and OT) during periods of daily interruption of sedation or to daily interruption (DSI) of sedation with therapy as ordered by the primary care team.

Question #10

JM currently is receiving IV norepinephrine 20 mcg/min, vasopressin 0.04 units/min, amiodarone 0.5 mg/min, and propofol 20 mcg/kg/min. JM is noted to have a MAP = 66 mmHg, HR = 91 bpm, CPOT 4, RASS +1, CAM-ICU positive. Which of the following would be the best initial management recommendation based on assessments, current medication therapy, hemodynamics and vitals?

A. Replace propofol with a dexmedetomidine infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU

B. Replace propofol with a midazolam infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU

C. Add fentanyl bolus 25-50 mcg PRN CPOT >2 to achieve a goal CPOT < 3, goal RASS of 0 to -1 and negative CAM-ICU

D. Add quetiapine 50 mg NG every 12 hr to achieve a goal of negative CAM-ICU
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Impact of Pain-Sedation-Delirium Protocol on Subsyndromal Delirium


Significant patient characteristics/metrics/outcomes

<table>
<thead>
<tr>
<th></th>
<th>Protocol</th>
<th>PRE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium†</td>
<td>(34.2)</td>
<td>(34.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Subsyndromal Delirium†</td>
<td>(24.6)</td>
<td>(33)</td>
<td>0.009</td>
</tr>
<tr>
<td>Lorazepam equivalents, mg*</td>
<td>2.75 ± 7.94</td>
<td>5.79 ± 31.78</td>
<td>0.02</td>
</tr>
<tr>
<td>MSO4 equivalents, mg*</td>
<td>22.3 ± 40.1</td>
<td>103.5 ± 239.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Data presented as mean  †Data presented as n (%)  
Subsyndromal delirium; max ICDSC 1-2 in ICU

Single center, observational trial of 1,133 adult ICU patients requiring > 24hr of ICU care before (PRE) (n = 572) and after (n = 561) implementation of a protocol for pain, sedation, and delirium management at Hospital Maisonneuve-Rosemont from 8/03 to 11/05. Protocol used goal oriented sedation to target RASS and numeric rating scale (NRS).
Single center, before/after evaluation of ICU delirium prevention protocol carried out in 476 critically ill patients at high risk for delirium in mixed (primarily medical/surgical) 33 bed ICU in the Netherlands. High-risk patients, defined as having predicted delirium risk > 50% using PREDELIRIC scoring, diagnosis of dementia or alcohol abuse, were prophylactically dosed with haloperidol 1mg IV every 8 hr from ICU admission to 24 hours after ICU admission. Patients screened for delirium using CAM-ICU.

Preventing ICU subsyndromal delirium conversion to delirium with low-dose IV haloperidol

- Double-blinded, placebo controlled pilot study. 68 mixed medical/surgical ICU received 1 mg every 6 hours until delirium occurred:
  - 34 patients in each arm
  - Developed delirium = no difference
  - Haloperidol reduced time agitated
Melatonin Receptor Agonists

• Help promote sleep
  – Very little evidence in ICU patients

• One small Japanese study (67 patients – of which 24 were in ICU)
  – prevalence of delirium 3% in ramelteon group vs 32% placebo in medically ill patients

• Much more literature is needed to support routine use of ramelteon in the ICU

Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomized, double-blind, placebo-controlled trial

• Randomized, double blinded, placebo-controlled RCT at 2 medical centers is in Beijing, China
• Dexmedetomidine 0.1 mcg/kg/hr or placebo
• APACHE II score ~ 10; surgical ICUs (non-CV surg)
• Primary endpoint incidence of delirium during the first 7 postoperative days
  – Dex 32/350 (9%), placebo 79/350 (23%), p<0.0001

Prevention Summary

• Clearly would like to eliminate delirium
  – Not feasible

• Non-pharmacologic interventions in all patients when feasible
  – Early mobilization best evidence
  – Goal awake and alert

• Pharmacologic prophylaxis
  – Often not helpful and potentially harmful
  – Needs further research
Question #10

JM currently is receiving IV norepinephrine 20 mcg/min, vasopressin 0.04 units/min, amiodarone 0.5 mg/min, and propofol 20 mcg/kg/min. JM is noted to have a MAP = 66 mmHg, HR = 91 bpm, CPOT 4, RASS +1, CAM-ICU positive. Which of the following would be the best initial management recommendation based on assessments, current medication therapy, hemodynamics and vitals?

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D. Add quetiapine 50 mg NG every 12 hr to achieve a goal of negative CAM-ICU
2013 SCCM Guidelines: Delirium in Adult ICU Patients

• Delirium treatment
  – Haloperidol treatment of delirium (no recommendation)
  – Atypical antipsychotics may reduce duration of delirium (LOE C)
  – We do not recommend administering rivastigmine to reduce the duration of delirium in ICU patients (LOE –1B).
  – We do not suggest using antipsychotics in patients at significant risk for torsades de pointes (i.e., patients with baseline prolongation of QTc interval, patients receiving concomitant medications known to prolong the QTc interval, or patients with a history of this arrhythmia) (LOE –2C)
  – In ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, continuous IV infusions of dexmedetomidine rather than benzodiazepine infusions may be preferred for sedation to reduce the duration of delirium (LOE +2B)
Single center, randomized, double-blind, placebo controlled trial in mixed medical/surgical ICU. Early treatment of critically ill MV patients with IV haloperidol for duration of ICU stay or until delirium-free and coma-free for 48 hours. Patients were included if mechanically ventilated within 72 hr of ICU admission. Patients in intervention arm were administered haloperidol 2.5 mg IV q 8hr within 72 hours of ICU admission to the ICU regardless of their delirium or coma status.
Randomized, double-blind, placebo-controlled trial. Six centers in USA. 101 Mechanically ventilated mixed medical/surgical ICU patients with delirium diagnosed by positive CAM-ICU. Haloperidol, ziprasidone or placebo every 6 hours for up to 14 days. Number of days alive without delirium or coma at day 21 primary endpoint.

Olanzapine vs. Haloperidol for the Treatment of Delirium in SICU Patients

Single center, prospective, open label trial of 73 mixed medical/surgical ICU patients with delirium via ICDSC scale tolerating tube feeds, randomized to olanzapine 5mg QD or haloperidol 2.5–5 mg every 8hr “titrated per response,” with rescue haloperidol. Patients > 60 yr received a lower initial dosage (haloperidol 0.5–1 mg, or olanzapine 2.5 mg).

Mean olanzapine dose: 4.5mg/day
Mean haloperidol dose: 6.5mg/day

Quetiapine for the Treatment of Delirium in Mixed ICU Patients

Three center, prospective, double-blind trial of 36 mixed medical/surgical ICU patients with delirium via ICDSC scale and tolerating tube feeds, randomized to quetiapine 50mg BID (titrated up to 200mg BID) or placebo with open label IV haloperidol in both groups. 258 screened, 36 enrolled.

Quetiapine for the Treatment of Hypoactive Delirium

Two center, retrospective study of 113 mixed medical/surgical ICU patients with hypoactive delirium diagnosed by positive CAM-ICU and RASS scores between 0 and -3. Resolution of delirium defined as first 24-hour period of consecutive negative CAM-ICU screenings.

<table>
<thead>
<tr>
<th></th>
<th>Quetiapine (n=52)</th>
<th>No AP^ (n=61)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to delirium *</td>
<td>4</td>
<td>4</td>
<td>0.55</td>
</tr>
<tr>
<td>Duration of delirium *</td>
<td>1.5</td>
<td>2</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of MV *</td>
<td>7</td>
<td>7.5</td>
<td>0.88</td>
</tr>
<tr>
<td>Duration MV after CAM+</td>
<td>3</td>
<td>5</td>
<td>0.07</td>
</tr>
<tr>
<td>DEX †</td>
<td>14 (27)</td>
<td>14 (23)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

^ Antipsychotic medication
*Data presented in median
†Data presented as n (%)

Quetiapine effect on QTc interval

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (CI)</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>1.12 (0.92 – 1.35)</td>
<td>0.24</td>
</tr>
<tr>
<td>CHF</td>
<td>0.92 (0.69 – 1.21)</td>
<td>0.53</td>
</tr>
<tr>
<td>Baseline QTc &gt; 400 msec</td>
<td>0.84 (0.65-1.09)</td>
<td>0.19</td>
</tr>
<tr>
<td>Baseline QTc &gt; 450 msec</td>
<td>0.88 (0.76 – 1.00)</td>
<td>0.055</td>
</tr>
<tr>
<td>TDD &gt; 50 mg</td>
<td>1.09 (0.91 – 1.30)</td>
<td>0.37</td>
</tr>
<tr>
<td>TDD &gt; 100 mg</td>
<td>0.87 (0.68 – 1.13)</td>
<td>0.30</td>
</tr>
<tr>
<td>TDD &gt; 150 mg</td>
<td>1.22 (0.92 – 1.60)</td>
<td>0.16</td>
</tr>
<tr>
<td>1 or more concomitant meds</td>
<td>1.15 (1.00-1.32)</td>
<td><strong>0.046</strong></td>
</tr>
</tbody>
</table>
# Dexmedetomidine vs Lorazepam: MENDS TRIAL

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine (n = 52)</th>
<th>Lorazepam (n = 51)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium, No. (%)</td>
<td>41 (79)</td>
<td>42 (82)</td>
<td>p = 0.65</td>
</tr>
<tr>
<td>Duration of Delirium, days</td>
<td>2.5 (1-5)</td>
<td>4 (1-5)</td>
<td>p = 0.71</td>
</tr>
<tr>
<td>Ventilator-free, days</td>
<td>22 (0-24)</td>
<td>18 (0-23)</td>
<td>p = 0.22</td>
</tr>
<tr>
<td>ICU LOS, days</td>
<td>7.5 (5-19)</td>
<td>9 (6-15)</td>
<td>p = 0.92</td>
</tr>
<tr>
<td>28 day all-cause mortality, No. (%)</td>
<td>9 (17)</td>
<td>14 (27)</td>
<td>p = 0.18</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dexmedetomidine vs Midazolam: SEDCOM TRIAL

Dexmedetomidine versus Midazolam, \( P < 0.001 \)

Blinded

Dexmedetomidine vs Propofol/Midaz for long-term sedation in ICU (PRODEX MIDEX Pilot Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine (n = 41)</th>
<th>Midaz/Prop (n = 44)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in target sedation range* (hr)</td>
<td>64</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>CAM ICU Positive</td>
<td><strong>43.9</strong></td>
<td><strong>25.0</strong></td>
<td><em>p = 0.04</em></td>
</tr>
<tr>
<td>Extubation time, hr*</td>
<td>77.2 (17.5–338.8)</td>
<td>110.6 (20.1–675.0)</td>
<td><em>p = 0.11</em></td>
</tr>
<tr>
<td>ICU LOS from admit*</td>
<td>6.6 (2.2–20.7)</td>
<td>6.8 (2.6–30.8)</td>
<td><em>p = 0.28</em></td>
</tr>
<tr>
<td>ICU LOS from randomization*</td>
<td>5.5 (1.7–19.5)</td>
<td>5.7 (1.7–29.0)</td>
<td><em>p = 0.82</em></td>
</tr>
<tr>
<td>ICU LOS MICU*</td>
<td>5.0 (1.7 –19.5)</td>
<td>4.9 (1.8 –29.0)</td>
<td><em>p = 0.43</em></td>
</tr>
<tr>
<td>ICU LOS SICU*</td>
<td>5.7 (2.0 –16.7)</td>
<td>5.9 (1.7–16.8)</td>
<td><em>p = 0.06</em></td>
</tr>
</tbody>
</table>

*Value expressed as median (IQR)

Trial stopped early

Dexmedetomidine vs Midazolam or Propofol:
MIDEX PRODEX; Key Critiques

- RASS awake and alert
  - 0 to -3
  - (4 to -5)
- Dose equivalence
  - Six dose levels of each study drug covered the full dose range
    - dexmedetomidine, 0.2-1.4 mcg/kg per hour;
    - midazolam, 0.03-0.2 mg/kg per hour;
    - propofol, 0.3-4.0 mg/kg per hour
- Blinded continuous infusion
- No antipsychotic use data

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine</th>
<th>Midaz/Prop</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRODEX CAM ICU Positive:</td>
<td>22 (9.6)</td>
<td>31 (13.7)</td>
<td>0.231</td>
</tr>
<tr>
<td>n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIDEX CAM ICU Positive:</td>
<td>28 (11.9)</td>
<td>33 (13.9)</td>
<td>0.396</td>
</tr>
<tr>
<td>n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dexmedetomidine for the Treatment of Hyperactive Delirium Refractory to Haloperidol in Nonintubated ICU Patients: A Nonrandomized Controlled Trial

- Nonrandomized, controlled, single center in Barcelona, Spain
- Agitated delirium
- Dexmedetomidine added for non-responders to haloperidol (n = 47) vs. responders haloperidol (n = 86)
  - Dexmedetomidine patients had a higher percentage of time at satisfactory sedation level 92.7% vs. 59.3% p = 0.0001
- Dexmedetomidine may be useful as a rescue drug for treating agitation due to delirium in patients who fail to respond to haloperidol

Effect of Dexmedetomidine Added to Standard Care for Agitated Delirium

Multicenter RCT in New Zealand and Australia in mixed medical/surgical ICUs. Dex (39) or placebo (32) added to standard of care in agitated delirious patients.

Other Metrics

<table>
<thead>
<tr>
<th>Metric</th>
<th>Dex n=39</th>
<th>Placebo n=32</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any day antipsychotic %</td>
<td>36.8</td>
<td>65.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Study day with any antipsychotic %</td>
<td>26.3</td>
<td>40</td>
<td>0.08</td>
</tr>
<tr>
<td>Underwent tracheostomy %</td>
<td>17.9</td>
<td>6.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Time to tracheostomy Median hours</td>
<td>41.9</td>
<td>71.1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Any day Propofol Median (mg)</td>
<td>980</td>
<td>5390</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Treatment Summary

- Very little evidence that any specific medication will provide better outcome than alternatives
- More research is needed
- Patient-specific personalized regimen is important
- Atypical antipsychotics may be helpful in certain patients
- Dexmedetomidine has a role, but needs further investigation
Key Takeaways

• Key Takeaway #1
  – ICU delirium is common and is often associated with poor outcomes

• Key Takeaway #2
  – Preventive strategies are mostly non-pharmacologic
  – Collaborative approach is necessary

• Key Takeaway #3
  – Treatment
    – Atypical antipsychotics may have a role
    – Dexmedetomidine may be effective, probably by avoiding the adverse effects from the alternative agents
Questions?
References and Recommended Readings

Guidelines

General Reviews
References and Recommended Readings

General Reviews (Cont)

Epidemiology and outcomes
References and Recommended Readings

Epidemiology and outcomes (Cont)


Assessment

References and Recommended Readings

Assessment (Cont)


Pain Physiology

References and Recommended Readings

Clinical pharmacology/Pharmacotherapy

- Riker RR, Fraser GL. Adverse events associated with sedatives, analgesics, and other drugs that provide patient comfort in the intensive care unit. Pharmacotherapy. 2005 May;25(5 Pt 2):8S-18S.
References and Recommended Readings

Clinical pharmacology/Pharmacotherapy (Cont)

References and Recommended Readings

Clinical pharmacology/Pharmacotherapy (Cont)

References and Recommended Readings

Sedation interruption

Analgesedation
References and Recommended Readings

Analgesedation (Cont)


References and Recommended Readings

Protocols and Guidelines


• Morris PE, Munro CL. All ICUs are not created equal: evaluating pilot studies performed in different environments. *AJCC* 2009;18(4):294-7.


Implementation strategies
