Management of Pain, Agitation, Delirium, and Neuromuscular Blockade in Adult Intensive Care Unit Patients

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Learning Objectives

1. Develop a management strategy for the prevention and treatment of pain, agitation, and delirium (PAD) in an intensive care unit (ICU) patient with various comorbidities.
2. Discuss relevant pharmacokinetic and pharmacodynamic considerations of PAD medications as they pertain to disturbances in critical care physiology.
3. Identify relevant adverse effects, drug interaction, and drug withdrawal syndromes in the management of PAD.
4. Evaluate patients in the ICU for PAD using a validated screening tool.
5. Construct a plan for the management of delirium.
6. Recognize the long-term effects of critical illness in adult ICU patients.
7. Create a management strategy for PAD-related medications that are continued beyond ICU discharge.
8. Describe a treatment and monitoring plan for critically ill patients receiving neuromuscular blockade.

Abbreviations in This Chapter

- ARDS: Acute respiratory distress syndrome
- BPS: Behavioral Pain Scale
- CAM-ICU: Confusion assessment method for the intensive care unit
- CPOT: Critical-Care Pain Observation Tool
- GABA: γ-Aminobutyric acid
- ICDSC: Intensive Care Delirium Screening Checklist
- ICP: Intracranial pressure
- ICU: Intensive care unit
- NMBA: Neuromuscular blocking agent
- PAD: Pain, agitation, and delirium
- PRIS: Propofol-related infusion syndrome
- RASS: Richmond Agitation Sedation Scale
- SAS: Sedation-Agitation Scale
- SAT: Spontaneous awakening trial
- SBT: Spontaneous breathing trial
- SCCM: Society of Critical Care Medicine
- TOF: Train of four

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. PJ. has been receiving propofol 50–60 mcg/kg/minute and fentanyl 75–100 mcg/hour for 4 days. She has no significant medical history. Laboratory results today show that liver function tests have increased to 5 times baseline, lactate is increased to 5 mmol/L, and triglyceride concentration is 450 mg/dL. No new medications have been added. Given these laboratory values, which complication would be most appropriate to address?
   - B. Critical illness-induced polyneuropathy.
   - C. Intensive care unit (ICU) delirium.
   - D. Propofol-related infusion syndrome (PRIS).

2. T.I. is a 35-year-old man admitted to the ICU for severe alcohol withdrawal. His medical history is otherwise unknown. Laboratory values are within normal limits on admission. He has been receiving a lorazepam infusion 6–8 mg/hour for active alcohol withdrawal. On day 4, his blood pressure is 130/75 mm Hg, oxygen saturation is 98% on 2 L of oxygen, blood urea nitrogen (BUN) is 50 mg/dL, and serum creatinine (SCr) is 2.0 mg/dL; he has a new anion gap of 20 mEq/L, an osmolar gap of 18 mmol/L H₂O, and a fractional excretion of sodium of 0.2. Which is the most likely cause for his clinical presentation?
   - A. Acute respiratory distress syndrome (ARDS).
   - B. Propylene glycol toxicity.
   - C. Delirium tremens.
   - D. Acute tubular necrosis.

3. R.B. is a 25-year-old man admitted to the ICU for acute pancreatitis and sepsis. He is intermittently agitated on hydromorphone 2 mg/hour and midazolam 6 mg/hour (Richmond Agitation-Sedation Scale [RASS] score of -1 to +2) and is not oxygenating adequately after adjustments on the ventilator. The physician would like to initiate therapeutic paralysis. Which is the next best step in the treatment of this patient?
A. Spontaneous awakening and breathing trials.  
B. Cisatracurium infusion.  
C. Intermittent vecuronium.  
D. Sedate the patient to a “deeply sedated” clinical state.

4. P.V. is a 70-year-old woman (weight 50 kg, decreased from 60 kg 2 months ago) admitted to the ICU in ARDS. She has a history of cirrhosis and is currently fluid overloaded (net positive 5 L). She has been on a continuous infusion of fentanyl and propofol for 5 days. Which pharmacologic factor would best be considered with respect to her analgesics or sedatives?  
A. Risk of PRIS in patients with ARDS.  
B. Unpredictable clearance of fentanyl.  
C. Enzymatic induction of fentanyl by propofol.  
D. Hypocalcaemia secondary to extended use of propofol.

5. L.B. is a 38-year-old woman intubated in the neurosurgery ICU for 72 hours receiving propofol. The nurse is requesting medications for “severe agitation and hallucinations.” Her heart rate and blood pressure have steadily increased since admission, and a chart review reveals years of chronic pain while receiving oxycodone and tramadol at home. Her laboratory values are normal, but she is not tolerating enteral route medications. Which is the most appropriate recommendation at this time?  
A. Quetiapine as needed for agitation.  
B. Fentanyl infusion.  
C. Lorazepam as needed for agitation.  
D. Hydromorphone patient-controlled analgesia.

6. S.P. has just been intubated in the ICU and is in severe alcohol withdrawal. He has a frequent history of delirium tremens and alcohol withdrawal seizures. Which medication is most appropriate to begin initial management of pain, agitation, and delirium (PAD) in this patient?  
A. Dexmedetomidine.  
B. Phenytoin.  
C. Fentanyl.  
D. Midazolam.

7. H.F., a 65-year-old man admitted to the ICU from home for aspiration pneumonia requiring intubation, is initiated on levofloxacin and metronidazole. Other medications include fentanyl and dexmedetomidine infusions as well as amiodarone and quetiapine given enterally, which are home medications. His last RASS was -2), and he has intermittent agitation. Vital signs and laboratory values are normal, and corrected QT (QTc) is 500 milliseconds. The team has implemented nonpharmacologic delirium management measures. Which is the most appropriate recommendation at this time?  
A. Increase quetiapine for agitation and monitor QTc.  
B. Change levofloxacin and metronidazole to piperacillin-tazobactam.  
C. Discontinue amiodarone and quetiapine because of his prolonged QTc.  
D. Give lorazepam as needed for agitation.

8. S.V., a 70-year-old woman with a history of hypertension, is transferred from the floor to the ICU for worsening pneumonia and new-onset hypoactive delirium. She has been nil per os (NPO) since admission 3 days prior. She remains febrile (temperature 102°F) with decreased urine output; other vital signs and laboratory values are within normal limits. Her medications include ceftriaxone, heparin, and hydrochlorothiazide. Which best represents the most important set of considerations regarding her delirium?  
A. Dementia and sleep disorder.  
B. Undetected alcohol withdrawal.  
C. Adrenal insufficiency.  
D. Dehydration and untreated infection.
I. PAIN, AGITATION, AND DELIRIUM IN THE INTENSIVE CARE UNIT

A. Background

1. The Society of Critical Care Medicine (SCCM) published updated guidelines for the management of PAD in adult ICU patients in 2013. These guidelines, together with recently published research, help guide ICU clinicians in the challenging task of optimizing patient comfort and outcomes while avoiding the complications of under- or oversedation. The PAD guidelines were written by a 20-member multidisciplinary, multi-institutional task force, each member of which with extensive expertise in the overall management and associated outcomes of PAD. Rigorous research has developed our understanding of the assessment tools and medications used for PAD, the prevention and treatment methods used for PAD, and the long-term effects of the ICU environment on patients and caregivers. Recommendations for specific ICU populations such as burn, neurologic, neurosurgical (including traumatic brain injury), and cardiac populations may need specialized consideration.

2. Specific management concepts to highlight within the updated PAD guidelines:
   a. A renewed focus on the assessment, prevention, and control of pain in the ICU. Patients continue to report inadequate pain control as their primary concern during their ICU stay.
   b. Target a lighter level of sedation or implement a strategy of daily interruption of sedation.
   c. Assess a level of wakefulness as assessed by the patient’s ability to follow commands.
   d. Routine assessment for delirium and recommendations for methods of delirium prevention

3. The 2013 PAD guidelines used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method to develop each recommendation for both descriptive and actionable questions. Only important or critical outcomes were considered when reviewing the evidence, and only critical outcomes were assessed for each recommendation.
   a. Each guideline statement and recommendation was ranked according to the quality and strength of the evidence and was denoted “A” (high quality; randomized controlled trials), “B” (moderate-quality; randomized controlled trials with significant limitations or high-quality observational studies), or “C” (low quality; observational studies).
   b. A strong recommendation is worded as “we recommend” and is denoted with a “1,” showing that most task force members believed the benefits of the intervention significantly outweighed the risks and would likely pursue the action.
   c. A weak recommendation is worded as “we suggest” and is denoted with a “2,” showing that most task force members believed the benefits of the intervention likely outweighed the risks, but the task members were not confident about the tradeoff.
   d. A no recommendation could also be stated because of either lack of evidence or lack of consensus among the reviewers and would be denoted with a zero.

B. Pharmacy Intervention – Pharmacists provide unique and valuable insight into the management of PAD in the ICU. Much of the management for PAD involves medications with complex pharmacologic profiles, allowing many opportunities for pharmacy expertise on the critical care team. As the management of PAD in the ICU continues to evolve, pharmacists should seek avenues for contributing to the critical care community through development of hospital protocols and assessing for quality improvement; providing education for medical, pharmacy, and nursing colleagues; and/or doing research on pertinent questions surrounding the management of PAD in the ICU.
II. PAIN IN THE INTENSIVE CARE UNIT

A. Introduction
1. More than half of ICU survivors report severe pain as the most traumatic memory of their ICU stay. Both short- and long-term negative sequelae are related to uncontrolled pain in the ICU.
2. Assessing pain in the ICU is challenging, particularly in patients who cannot effectively communicate. If patients cannot adequately communicate their degree of pain but retain motor activity, medications should be titrated according to validated behavioral pain scales.

B. Incidence and Causes of Pain: Pain may occur in any type of ICU patient, and considerations for pain management often require an individualized approach to optimize treatment. The interdisciplinary team should complete a comprehensive review of all variables such as acute and chronic pain, routine nursing care that may cause discomfort, and procedural-based pain. Recent data show that 50%–80% of ICU patients report pain as “uncontrolled” during their ICU stay, similar to research from 2 decades ago.
1. Common causes of pain in the ICU include, but are not limited to, acute trauma, injury or burns, postoperative pain, exacerbation of chronic pain, heart disease, ischemia, acute or chronic underlying disease state pain such as cancer pain, pancreatitis, or other abdominal pathology.
2. Less discernible causes of pain may include those from either routine nursing care or the provision of life-sustaining measures: presence of an endotracheal tube and endotracheal tube suctioning, wound care, tube or Foley insertion, immobility, bed repositioning, bathing, medication administration, and physical and occupational therapy. Other examples of painful invasive procedures include intravenous line placement, scoping procedures, chest tube placement or removal, paracentesis, lumbar puncture, biopsies, and fracture reductions.

C. Short- and Long-term Consequences of Pain in the ICU
1. Acute pain can invoke a stress response, resulting in a hypercatabolic state, decreased tissue perfusion, and impaired wound healing. Uncontrolled pain decreases a patient’s immune response to infection by suppressing natural killer cell activity and neutrophil function.
2. Long-term studies (12 months post-ICU stay) report detrimental physiologic and psychological function in patients who recall significant pain during their hospitalization, particularly in patients admitted with a traumatic injury.
   a. Health-related quality of life is decreased in up to 20% of patients.
   b. Chronic pain is reported in up to 40% of patients.
   c. Posttraumatic stress disorder is reported in 5%–20% of patients.

D. Assessment of Pain
1. The gold standard for assessing pain remains the patient’s self-report of pain. Several scenarios in the ICU make the self-reporting of pain challenging for clinicians (e.g., mechanical ventilation, presence of sedation and/or delirium). SCCM currently recommends two validated behavioral pain scales to be done in a repetitive and routine manner: the Behavioral Pain Scale (BPS) (Table 1) and the Critical-Care Pain Observation Tool (CPOT) (Table 2).
   a. Assessment scales should be used routinely in all ICU patients (+1B recommendation). Most nursing protocols assess pain every 4–6 hours while the patient is awake. In addition, it is important to reassess the degree of pain within approximately 30 minutes to 1 hour after administering an “as-needed” pain medication to determine the appropriateness of the pain medication or dose.
   b. Pain scores should be documented in the medical chart and then used to help formulate daily titrations in pain medications.
   c. The PAD guidelines recommend that patients be treated within 30 minutes of a “significant pain” score (e.g., BPS greater than 5; CPOT score of 3 or greater).
2. Using vital signs alone is not recommended for assessing pain in the ICU patient. Abnormal vital signs such as tachycardia and hypertension are appropriate for use as a prompt to further investigate the need for pain control.

3. Further research is needed to determine the effectiveness of a preprocedural pain assessment tool and the ways in which this assessment will affect analgesic administration. A recent study by Puntillo et al. in 2014 found the procedures most likely to double the patient’s pain intensity score (from preprocedure to during-procedure scoring) were chest tube removal, wound drain removal, and arterial line insertion. This study found that higher-intensity pain and pain distress before the procedure were associated with a high risk of increased pain during the procedure (Am J Respir Crit Care Med 2014;189:39-47).

**Table 1. Behavioral Pain Scale**

<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>Partly tightened (e.g., brow lowering)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully tightened (e.g., eyelid closing)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Grimacing</td>
<td>4</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>No movement</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partly 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 most of the time</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fighting ventilator</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Unable to control ventilation</td>
<td>4</td>
</tr>
</tbody>
</table>

*A BPS score > 5 indicates significant pain.


**Table 2. Critical-Care Pain Observation Tool (CPOT)**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial expression</td>
<td>No muscular tension observed Relaxed, neutral</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Presence of frowning, brow lowering, orbit tightening, and levator contraction</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>All of the above facial movements plus eyelids tightly closed</td>
<td>2</td>
</tr>
<tr>
<td>Body movements</td>
<td>Does not move at all (does not necessarily mean absence of pain)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Slow, cautious movements; touching or rubbing the pain site; seeking attention through movements</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pulling tube, trying to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed</td>
<td>2</td>
</tr>
</tbody>
</table>
### Table 2. Critical-Care Pain Observation Tool (CPOT)\(^a\) (continued)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle tension Evaluation by passive flexion and extension of upper extremities</td>
<td>No resistance to passive movements</td>
<td>Relaxed</td>
</tr>
<tr>
<td></td>
<td>Resistance to passive movements</td>
<td>Tense, rigid</td>
</tr>
<tr>
<td></td>
<td>Strong resistance to passive movements, inability to complete them</td>
<td>Very tense or rigid</td>
</tr>
<tr>
<td>Compliance with the ventilator (intubated patients)</td>
<td>Alarms not activated, easy ventilation</td>
<td>Tolerating ventilator or movement</td>
</tr>
<tr>
<td></td>
<td>Alarms stop spontaneously</td>
<td>Coughing but tolerating</td>
</tr>
<tr>
<td></td>
<td>Asynchrony: Blocking ventilation, alarms frequently activated</td>
<td>Fighting ventilator</td>
</tr>
<tr>
<td>OR Vocalization (extubated patients)</td>
<td>Talking in normal tone or no sound</td>
<td>Talking in normal tone or no sound</td>
</tr>
<tr>
<td></td>
<td>Sighing, moaning</td>
<td>Sighing, moaning</td>
</tr>
<tr>
<td></td>
<td>Crying out, sobbing</td>
<td>Crying out, sobbing</td>
</tr>
<tr>
<td><strong>Total, range</strong></td>
<td>0–8</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)A CPOT score ≥ 3 indicates significant pain.


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### E. Treatment of Pain in the ICU

1. In a patient whose pain is inadequately controlled in the ICU, intravenous opioids are considered first-line treatment for nonneuropathic pain (+1C recommendation). Non-opioids should be considered for mild-moderate pain or used in conjunction with opioids to reduce opioid dosing requirements.

2. Preprocedural pain management should be considered in all ICU patients. One study reported that up to 60% of patients did not receive preprocedural systemic pain medication for common procedures and wound care in the ICU, although 89% of patients received a topical anesthetic for central venous catheter placement (Am J Crit Care 2002;11:415-29).

   a. Preprocedural pain management with both nonpharmacologic and pharmacologic therapies is recommended for procedures that may cause pain (+2C recommendation). If a medication is deemed necessary, the timing of administration should be in accordance with the onset of the specific analgesic medication. The American Society for Pain Management Nursing (ASPMN) published recommendations for preprocedural pain management in 2011. The ASPMN recognizes both the psychological and the physical elements of procedural pain and agrees with combining nonpharmacologic and pharmacologic methods. Examples of nonpharmacologic options recommended by ASPMN include relaxation and breathing techniques, imagery, massage, music, thermal measures, and positioning (Pain Management Nursing June 2011(12):95-111).

   b. Preemptive analgesia for chest tube removal is a “strong” recommendation by SCCM, together with nonpharmacologic relaxation techniques (+1C recommendation).

3. Postoperative thoracic epidural anesthesia/analgesia is recommended for patients undergoing abdominal aortic aneurysm treatment. Thoracic epidural anesthesia is “suggested” for traumatic rib fractures in the ICU.

4. Pharmacotherapy for pain

   a. Intravenous opioids on an as-needed, scheduled, or continuous infusion basis are recommended to treat pain in the ICU. The pharmacokinetics of different opioids may vary; thus, opioids should be chosen according to patient comorbidities and individual needs (Table 3). Fentanyl is the most commonly used intravenous opiate in American adult ICUs.
Table 3. Opiates Commonly Used in the ICU

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolic/Drug Interaction Considerations</th>
<th>Usual CI Starting Dose</th>
<th>Drug-Specific Adverse Effects</th>
<th>Drug Accumulation Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>3A4 major substrate</td>
<td>12.5–25 mcg/hr; 0.35–0.5 mcg/kg</td>
<td>Muscle rigidity</td>
<td>Hepatic failure; high volume of distribution; high lipophilicity; unpredictable clearance (long context-sensitive half-time) with prolonged infusion</td>
</tr>
<tr>
<td>Morphine</td>
<td>Glucuronidation</td>
<td>1–2 mg/hr</td>
<td>Hypotension, bradycardia from histamine release</td>
<td>Hepatic failure; active metabolite (3-morphine glucuronide) accumulates in renal failure</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Glucuronidation</td>
<td>0.25–0.5 mg/hr</td>
<td>Overdose effects from dosing errors (high-potency opiate)</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Methadone</td>
<td>3A4 and 2B6 major substrates</td>
<td>Loading dose: 1.5 mcg/kg CI: 0.5–15 mcg/kg/hr</td>
<td>QTc prolongation, serotonin syndrome</td>
<td>Long half-life; hepatic and renal failure will delay clearance</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Blood and tissue esterases</td>
<td>Loading dose: 1.5 mcg/kg CI: 0.5–15 mcg/kg/hr</td>
<td>Chest wall rigidity; rebound pain on discontinuation</td>
<td></td>
</tr>
</tbody>
</table>

aUsual starting dose in the ICU for pain management in an opiate-naive patient.

bOther common significant adverse effects for all opiates to be considered: Constipation, respiratory depression, bradycardia, hypotension, altered mental status.

CI = continuous infusion.

i. General mechanism of action of opiates: Bind to mu-opioid receptors in the central nervous system (CNS)

ii. Commonly used intravenous opioids in the ICU: Fentanyl, morphine, hydromorphone, remifentanil, and methadone

iii. Tolerance: May quickly develop to all opiates, particularly when given as a continuous infusion. On switching to a different intravenous or oral opiate, equianalgesic dosing may be difficult to estimate, and low starting doses should be considered.

iv. Significant adverse effects: Decreased respiratory drive: This may be a desired effect in some ICU scenarios; however, a depressed respiratory drive is a critical negative implication during the ventilator weaning process; decreased blood pressure and heart rate, constipation, gastrointestinal (GI) intolerance, altered sensorium

v. GI intolerance and constipation: A bowel regimen should be initiated on day 1 unless contraindicated, with assessment for efficacy every 24–48 hours. GI intolerance in the ICU can result in increased time on mechanical ventilation, delayed time to attaining nutritional goals, and prolonged ICU stay. Constipation may also contribute to agitation.

vi. Altered mental status: Opiates may induce a sedative effect as well as an altered sensorium in some patients. Unless contraindicated, clinicians should consider tapering the opiate dose in an altered patient who has adequate pain control.

vii. Patient-controlled analgesia: In alert and clinically stable patients, use of patient-controlled analgesia may be considered to titrate to the patient’s perceived level of pain. Patient-controlled analgesia may also be useful on discontinuation of continuous infusion opiates.
b. Fentanyl
   i. Pharmacokinetics: Hepatic metabolism, cytochrome P450 (CYP) 3A4 substrate. Quick onset and short duration of action; lacks a pharmacologically active metabolite. Highly lipophilic, high volume of distribution and protein binding; maintains a three-compartment model; continuous infusion dosing may lead to prolonged and unpredictable clearance (prolonged context-sensitive half-time)
   ii. Many dosage forms: Injectable (intravenous, intramuscular, intrathecal, epidural), transdermal, transmucosal, nasal spray. Different dosage forms should not be converted on a 1:1 mcg basis; use specific manufacturer recommendations if converting. Injectable form of fentanyl is most commonly used in the ICU setting. The fentanyl patch is not generally appropriate for use in the ICU because of its latent onset (about 12 hours) and erratic/increased absorption in a febrile patient.
   iii. Adverse effects: Respiratory depression, bradycardia, hypotension, CNS depression, constipation, ileus, risk of serotonin syndrome when used with other serotonergic agents

c. Morphine
   i. Pharmacokinetics: Hepatic metabolism by glucuronidation to two major active metabolites, morphine-3-glucuronide (45%–55%) and morphine-6-glucuronide (10%–15%). The glucuronide metabolites of morphine are both renally eliminated; accumulation can occur with the chronic use of morphine or in patients with decreased renal function. Morphine-3-glucuronide does not have analgesic activity, but adverse effects may include seizure activity or agitation. Morphine-6-glucuronide does have analgesic activity by the mu-receptor and may cause additive sedation and respiratory depression if accumulation occurs. Continuous morphine infusions are rarely used for analgesia in the ICU setting because of the concerns with the active metabolites.
   ii. Dosage forms: Injectable (intravenous, subcutaneous, intrathecal, epidural) and oral. Intravenous-to-oral conversion is not a 1:1 mcg ratio.
   iii. Adverse effects: Histamine release may cause hypotension; bradycardia, respiratory depression, CNS depression, constipation, ileus

d. Hydromorphone (Dilaudid)
   i. Pharmacokinetics: Hepatic metabolism by glucuronidation to an inactive, but potentially neurotoxic metabolite. Low volume of distribution, highly water soluble, and relatively low protein binding
   ii. Dosage forms: Injectable (intravenous, subcutaneous) and oral; intravenous-to-oral conversion is not a 1:1 mg ratio
   iii. Adverse effects: CNS alterations (e.g., abnormal dreams, aggressive behavior, altered thinking), respiratory depression, hypotension, constipation

e. Remifentanil (Ultiva)
   i. Research primarily done in Europe; limited reported use in U.S. adult ICUs for ongoing analgesic use
   ii. Dosage form: Injectable only
   iii. Pharmacokinetics: Clearance by blood and tissue esterase; clearance not dependent on organ function. Fast onset and short duration of action with little to no accumulation. High volume of distribution, high protein binding
   iv. Adverse effects: Respiratory depression, hypotension, bradycardia, constipation
   v. Rebound pain: Quick offset (5–10 minutes) may lead to rebound pain and withdrawal symptoms, and additional pain medication may be needed if remifentanil is interrupted or discontinued.
   vi. Benefit in adult ICUs: Decreased time on mechanical ventilation with short-term use (72 hours or less)
   vii. Cost (AWP): 1 mg = $55.16; 5 mg = $234.74.
f. Methadone
   i. Pharmacokinetics: Phase I hepatic metabolism to inactive metabolites. Many drug interactions: major substrate of CYP 34A, 2B6. Moderate inhibitor of CYP2D6, weak inhibitor of CYP3A4. Longer-acting opiate with variable duration of action (12–48 hours); may accumulate quickly in patients with hepatic failure or patients receiving hemodialysis. Animal studies have found that the d-isomer of methadone works as both a partial mu-agonist and an N-methyl-d-aspartate receptor antagonist (the l-isomer is a full mu-agonist). These properties of the d-isomer are thought to decrease the tolerance effect to other opioids. Methadone is currently marketed as the racemic mixture. On initiating oral methadone, steady state and peak analgesic effect may not be reached for 3–5 days; oversedation and respiratory depression may occur if titrated too quickly.
   ii. Dosage forms: Injectable (intravenous, intramuscular, subcutaneous) and oral. Not a milligram-per-milligram conversion
   iii. Adverse effects: Dose-dependent QTc prolongation, altered mental status, respiratory depression, confusion, dizziness, arrhythmias, constipation, risk of serotonin syndrome when used with other serotonergic agents

5. Non-opioid adjunctive pain medications should be considered in combination with opioids to reduce opioid requirements. Clinically stable patients may tolerate a conversion from opiates to non-opiate medications.
   a. Local and regional anesthetics such as bupivacaine
   b. Acetaminophen (Tylenol)
      i. Total daily acetaminophen doses should be considered from all acetaminophen combination products, with a maximum total daily dose of 4 g. Decreased total daily dosing should be considered in patients with significant liver disease.
      ii. Intravenous acetaminophen: Dose reduction recommended if the creatinine clearance (CrCl) is 30 mL/minute/1.73 m² or less or with continuous renal replacement therapy (every 8 hours); contraindicated in severe hepatic disease. The cost of the intravenous formulation of acetaminophen is considerably higher than that of the oral or rectal formulations.
   c. Intravenous or oral nonsteroidal anti-inflammatory medications: Ibuprofen, ketorolac. Use with caution in critically ill patients with renal or hepatic dysfunction. May increase the risk of acute renal failure, bleeding, or GI adverse effects
   d. Ketamine (Ketalar) has been used for analgesia and sedation in the ICU, primarily in the pediatric population. Published data for the use of ketamine in adults for analgesia and/or sedation are limited to case reviews, and long-term cognitive effects of ketamine are not known. Data from animal studies suggest a significant decline in cognitive function after continued use of ketamine.
      i. Called a “dissociative anesthetic,” providing analgesic activity at subanesthetic doses. It is a schedule III controlled substance and works primarily as an N-methyl-d-aspartate receptor antagonist. Ketamine is void of the constipation, respiratory depression, and hypotensive effects which plagues the opiate class.
      ii. May decrease dose requirements of concurrently administered opioids
      iii. Other uses include rapid sequence intubation, refractory pain syndromes, cancer pain, neuropathic pain, asthma (bronchodilatory effects), refractory seizure activity, and depression.
      iv. Dosing range is varied; usual starting dose for analgesia or sedation is 0.1 mg/kg/hour. Reviews of ketamine use in adult ICUs report a dosing range of 0.1–2.5 mg/kg/hour and a range in duration of 3 hours to 9 days.
      v. Significant adverse effects: Mild to severe emergence reactions (e.g., confusion, excitement, irrational behavior, hallucinations, delirium) in around 12% of patients, enhanced skeletal muscle tone, tachycardia, hypertension, hypotension
6. Anticonvulsants are recommended in the PAD guidelines together with opioids for confirmed neuropathic pain. Anticonvulsants have not been studied extensively in the ICU population. There is a potential for significant adverse effects and drug interactions, requiring close monitoring and follow-up. If the patient is discharged home on an anticonvulsant for neuropathic pain, follow-up should be documented and the primary care provider notified.
   a. Gabapentin (Neurontin)
      i. Suggested starting dose range: 300–600 mg/day divided two or three times daily; requires renal adjustment
      ii. Pharmacokinetics: Renally excreted, dose adjusted for reduced CrCl
      iii. Adverse effects: May be severe, including CNS depression, paresthesias, and asthenias
   b. Carbamazepine (Tegretol)
      i. Suggested starting dose range: 50–100 mg twice daily; use with caution in patients with hepatic impairment, and adjust for a CrCl less than 10 ml/minute/1.73 m² or with hemodialysis
      iii. Adverse effects: Somnolence, severe skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis), pancytopenia, syndrome of inappropriate antidiuretic hormone

F. Analgosedation Method in the ICU: This method of sedation advocates the use of opiate medications before prescribing an anxiolytic/hypnotic medication to provide patient comfort in the ICU unless anxiolytics are otherwise indicated. The PAD guidelines give the analgosedation method of sedation a +2B level of recommendation. Providing pain relief early in the ICU stay may decrease the agitation associated with pain and/or general discomfort while minimizing the use of alternative medications commonly used for agitation (e.g., benzodiazepines). The guidelines recognize that current data using analgosedation are primarily limited to open-label trials, using remifentanil as the analgesic, and mostly conducted in Europe, where critical care staffing and management practices differ from those in the United States. Despite these limitations, it remains notable that studies using the analgosedation method found a significant decrease in benzodiazepine dosage requirements when opiates were the primary medications used for discomfort and agitation. This is a positive step in decreasing the untoward adverse effects of the benzodiazepine class of sedatives. There is a potential for high cumulative doses of opiates with the analgosedation method, necessitating daily monitoring of their adverse effects (e.g., respiratory depression, altered mental status, GI slowing).

Patient Case

Questions 1 and 2 pertain to the following case.
T.O. is a 70-year-old man just admitted to the ICU with multiple fractures after a motor vehicle accident. His medical history includes hypertension. He is now agitated after intubation. His laboratory values are normal, and his vital signs include blood pressure 175/95 mm Hg and heart rate 110 beats/minute.

1. Which grouping of initial sedatives most appropriate at this time?
   A. Fentanyl infusion and midazolam infusion.
   B. Propofol infusion and fentanyl as needed.
   C. Midazolam as needed and fentanyl as needed.
   D. Fentanyl infusion and propofol infusion.
**Patient Case (continued)**

2. After 2 weeks in the ICU, T.O. is being prepared for chest tube removal. He is currently receiving a fentanyl drip with adequate pain control. Which is the best pain management regimen for chest tube removal?
   - A. Give intravenous acetaminophen 15 minutes before chest tube removal.
   - B. Make no change in pain treatment because his current pain regimen is adequate.
   - C. Increase his pain medication infusion dose by 50% the morning of his chest tube removal.
   - D. Give fentanyl 50 mcg injectable 15 minutes before chest tube removal.

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**III. AGITATION IN THE INTENSIVE CARE UNIT**

A. Agitation in the ICU – Maintaining patient comfort for the duration of an ICU stay can be extremely challenging, requiring significant resources and daily discipline from the nursing, medical, and pharmacy team. Ongoing research has improved our understanding of the consequences of either under- or overtreating agitation in the ICU, and clinicians should continue to apply this knowledge to their daily selection and titration of medications. Treatment of a patient who presents with agitation must always begin with attempts to identify and correct the etiology of the agitation. Common causes of agitation in the ICU include pain, delirium, hypoxia, hypoglycemia, dehydration, and drug or alcohol withdrawal. Close inspection of significant patient variables will also help determine the appropriate sedative:

1. Pain control
2. Substance abuse and smoking history
3. Neurologic function: Baseline and acute mental status, history of seizure activity, dementia, psychiatric history
4. Clinical variables: Blood pressure, heart rate, respiratory rate
5. Comorbidities (baseline and acute): Cardiac, renal, hepatic, gastric, pulmonary, pancreatic
6. Home medication use: Any medication from which a patient could withdraw: Benzodiazepines, opioids, antidepressants, other γ-aminobutyric acid (GABA) receptor agonists

B. Primary Medications for the Treatment of Agitation – Include propofol, dexmedetomidine, and benzodiazepines (usually lorazepam and midazolam) (Table 4). Benzodiazepines are first-line agents for status epilepticus, alcohol withdrawal, benzodiazepine dependence or withdrawal, and need for deep sedation or amnesia and with the use of neuromuscular blockade. Other indications for benzodiazepines may exist, which must be scrutinized throughout the ICU stay.
Table 4. Sedatives for Patients on Mechanical Ventilation in the ICU

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset and Duration</th>
<th>Precautions for Use</th>
<th>CYP Substrate (major)</th>
<th>Usual Dose</th>
<th>Significant Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>Onset: 1 min</td>
<td>Hypotension, bradycardia, hepatic/renal failure, pancreatitis</td>
<td>2B6</td>
<td>5–50 mcg/kg/min; 0.3–3 mg/kg/hr</td>
<td>Hypotension, respiratory depression, bradycardia, PRIS</td>
</tr>
<tr>
<td></td>
<td>Duration: short term: 0.5–1 hr; long term &gt; 7 days; variable; 25–50 hr has been observed (depends on depth and time on sedation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Onset: 5–10 min (with LD) 1–2 hr (without LD) 1–2 hr (without LD) Duration: 1–2 hr</td>
<td>Hepatic failure; symptomatic bradycardia</td>
<td>2A6</td>
<td>LD: 0.5–1 mcg/kg (optional) MD: 0.2–0.7 mcg/kg/hr</td>
<td>Hypo/hypertension, bradycardia</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Onset: 5–20 min Duration: 4–8 hr; prolonged with CI</td>
<td>Delirium, renal failure</td>
<td>N/A</td>
<td>Intermittent: 1–4 mg IV every 4–6 hr</td>
<td>Oversedation, propylene glycol toxicity</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Onset: 3–5 min Duration: 2–6 hr, prolonged with CI</td>
<td>Hepatic failure, end-stage renal failure or dialysis, delirium</td>
<td>3A4 (active metabolite)</td>
<td>0.02–0.1 mg/kg/hr</td>
<td>Oversedation</td>
</tr>
</tbody>
</table>

CI = continuous infusion; IV = intravenously; LD = loading dose; MD = maintenance dose; N/A = not applicable; PRIS = propofol-related infusion syndrome.

C. SCCM provides the following statement in the PAD guidelines regarding sedation in the ICU: “We suggest that sedation strategies using non-benzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred to sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients” (+2B recommendation).” SCCM further states that “benzodiazepine use may be a risk factor for the development of delirium in adult ICU patient” (level B quality of evidence). Two randomized studies evaluated the differences in clinical outcomes while adult ICU patients were receiving sedation with either a benzodiazepine or a non-benzodiazepine strategy. Heterogeneity occurred among the findings of these two studies (see No. 1 and No. 2 below), which may be partly because of differences in study method.

1. The MENDS study compared the sedative effects of lorazepam and dexmedetomidine in medical and surgical adult ICU patients (n=103). The prevalence of “delirium without coma” was not different in the lorazepam group (82%) from the dexmedetomidine group (79%), p=0.65, and there was no difference in duration of delirium (lorazepam 4 days; dexmedetomidine 2.5 days, p=0.71). Dexmedetomidine had more “delirium-free + coma-free” days than lorazepam (7 vs. 3 days, p=0.01), and the prevalence of “delirium or coma” was lower in the dexmedetomidine group (87 vs. 98%, p=0.03). There was no difference in mechanical ventilator–free days, ICU length of stay, or 28-day mortality; more patients were within 1 point of their RASS goal with dexmedetomidine (67%) than with lorazepam (55%), p=0.008 (JAMA 2007;298:2644-53).
2. The SEDCOM study compared the sedative effects of midazolam with those of dexmedetomidine in medical and surgical adult ICU patients (n=366). The prevalence of delirium was lower in the dexmedetomidine group (54%) than in the midazolam group (76.6%), p<0.001. Median time to extubation was shorter in the dexmedetomidine group (3.7 days) than in the midazolam group (5.6 days), p<0.01; however, the times in target sedation range, ICU length of stay, and mortality were no different between the two groups (JAMA 2009;301:489-99).

D. Clinical Outcome Differences Among Sedative Agents in Medical and Surgical ICU Patients: A recent meta-analysis, “Benzodiazepine versus Nonbenzodiazepine-Based Sedation for Mechanically Ventilated Critically Ill Adults,” reviewed trials from 1996 to 2013 (Crit Care Med 2013;41:S30-8):
1. Studies from this review contained the following criteria: (1) randomized controlled parallel-group design; (2) medical and surgical adult ICU patients on mechanical ventilation receiving intravenous sedation; (3) patients receiving a non-benzodiazepine (propofol 1% or dexmedetomidine) compared with a benzodiazepine (lorazepam or midazolam); and (4) patients having predefined outcomes. Excluded cardiac surgery and obstetric patients
2. Four primary outcomes from six randomized trials were reported in the review (1235 patients):
   a. ICU length of stay (all six studies reported): ICU length of stay was longer in a benzodiazepine strategy than in a non–benzodiazepine-based strategy (mean difference 1.6 days; 95% confidence interval [CI], 0.72–2.5; p=0.0005).
   b. Duration of mechanical ventilation (four studies reported): Longer duration of mechanical ventilation in a benzodiazepine-based strategy than in a non–benzodiazepine-based strategy (mean difference 1.9 days; 95% CI, 1.7–2.09; p=0.0001)
   c. Delirium prevalence (two studies reported): No difference in delirium prevalence between a benzodiazepine and a non–benzodiazepine-based strategy (relative risk [RR] 0.98; 95% CI, 0.76–1.27; p=0.94)
   d. Short-term (45 days or less) all-cause mortality (four studies reported): No difference in risk of death between a benzodiazepine and a non–benzodiazepine-based strategy (RR 0.98; 95% CI, 0.76–1.27, p=0.94)

E. Propofol (Diprivan)
1. SCCM suggests using a non-benzodiazepine (propofol or dexmedetomidine) for sedation to improve clinical outcomes in mechanically ventilated patients (+2B recommendation). Over the last decade propofol has been increasingly used world-wide for sedation in the ICU. Propofol’s short duration of action, lack of accumulation, and relatively clean adverse effect profile at low to moderate doses makes it an appealing alternative.
2. Mechanism of action: General anesthetic by potentiation of the GABA\textsubscript{A} receptor; may inhibit N-methyl-D-aspartate receptor activity at high doses. Propofol decreases cardiac \(\beta\)-adrenergic responsiveness and attenuates \(\beta\)-adrenergic signal transduction in cardiac myocytes, resulting in direct cardiac depressive effects.
3. Pharmacokinetics: Hepatic conjugation; clearance may be prolonged (from minutes to hours) in patients with severe hepatic impairment or cirrhosis or with long-term infusions as it redistributes from fat and muscle to plasma. Highly lipophilic pharmacokinetics and a large volume of distribution lead to extensive tissue distribution. Propofol maintains a three-compartment linear model: plasma, rapidly equilibrating tissues (e.g., major organs), slowly equilibrating tissues (e.g., fat deposits). Substrate of CYP 2B6, 2C9, 2C19, and 3A4; pharmacokinetic studies of healthy volunteers show a 25% increase in propofol plasma concentrations when given with midazolam, a weak CYP 3A4 and 2C9 inhibitor
4. Lipid formulation considerations: Standard propofol is a 1% (10 mg/mL) lipid emulsion containing 1.1 kcal/mL (0.1 g of fat per 1 mL of propofol); this should be accounted for when calculating nutritional intake (e.g., propofol at 50 mcg/kg/minute in a 70-kg patient would provide around 500 calories per
day contributed by fat). Propofol contains 0.005% disodium edetate (EDTA) to decrease the rate of microorganism growth, which is known to chelate trace metals, including zinc. Zinc supplementation should be considered in patients at high risk of zinc deficiency (sepsis, burns, large-volume diarrhea) if propofol is used for more than 5 days. Strict aseptic technique must be followed when handling propofol; manufacturers recommend discarding propofol bottles and changing intravenous tubing every 12 hours to decrease the risk of contamination.

5. Dosing range for ICU sedation: Usual starting dose 5–10 mcg/kg/minute, titrated every 5–10 minutes to goal sedative effect. Abrupt discontinuation of propofol is not recommended because of its rapid clearance (5–10 minutes).

6. Data: In a multicenter European trial (PRODEX), Jakob et al. compared propofol (n=249) with dexmedetomidine (n=251) for sedation in prolonged mechanical ventilation. Patients in both groups were treated with daily sedation interruption trials and spontaneous breathing trials (SBTs), and pain was treated with fentanyl boluses. Proportion of time in target RASS (0, -3) without rescue therapy was the same in the propofol group (65%) as in the dexmedetomidine group (65%). There was no difference in median time on mechanical ventilation in propofol (5 days) versus dexmedetomidine (4 days), p=0.24. Patients’ ability to communicate discomfort was better in the dexmedetomidine group. Rates of hypotension and bradycardia were similar between the two groups. Critical illness polyneuropathy was more common in the propofol group (n=11) than in the dexmedetomidine group (n=2), p<0.02 (JAMA 2012;307:1151-60).

7. Adverse effects: Bradycardia and hypotension (may be more common or severe in patients with cardiac dysfunction, intravascular volume depletion, or low systemic vascular resistance); respiratory depression, hypertriglyceridemia, pancreatitis with or without hypertriglyceridemia, PRIS

8. PRIS: This is a rare but life-threatening complication of propofol, usually occurring at doses greater than 50 mcg/kg/minute for 48 hours or more. The mechanism of PRIS may include alterations in the liver metabolism of the lipid emulsion, leading to an accumulation of ketone bodies and lactate and/or disruptions in the mitochondrial respiratory chain and inhibition of oxidative phosphorylation. Patients with urea cycle disorders may experience alterations in propofol metabolism within 24–48 hours of propofol use. Consider avoiding in patients with acute liver failure, or pancreatitis, because the symptoms of PRIS may be difficult to distinguish from the underlying disease state abnormalities. PRIS carries a high mortality rate, and propofol should be discontinued immediately if symptoms are present.
   a. Clinical characteristics of PRIS: Metabolic acidosis, acute renal failure, cardiovascular collapse, cardiac arrhythmias including Brugada-like syndrome, rhabdomyolysis, myoglobinemia, myoglobinuria, hyperkalemia, hypertriglyceridemia, elevated creatine kinase concentrations
   b. Risk factors for PRIS or other adverse effects of propofol: Neurologic injury, sepsis, use of vasoactive medications, high-dose propofol, acute liver failure

F. Dexmedetomidine (Precedex)
   1. SCCM suggests that in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, dexmedetomidine infusions rather than benzodiazepine infusions should be administered for sedation to reduce the duration of delirium (+2B recommendation). Dexmedetomidine is a considered a weak sedative with opiate sparing analgesic properties. Although ICU surveys report low use of dexmedetomidine compared to other sedatives, clinical outcomes research of dexmedetomidine has shown favorable results.
   2. Mechanism of action: Highly selective and dose-dependent 2α-adrenoceptor agonist in the CNS. Dexmedetomidine provides a hypnotic and sedative effect by inhibition of norepinephrine release from the locus coeruleus; dexmedetomidine also produces a weak antinociceptive effect via inhibition of neuronal transmission through presynaptic C-fibers and release of substance P, and hyperpolarization of postsynaptic α receptors in the dorsal horn of the spinal column. Dexmedetomidine does not directly affect respiratory drive; therefore, intubation is not required with use. Dexmedetomidine is considered
a weak sedative and would not be appropriate for use when deep sedation is required (e.g., in a patient requiring neuromuscular blockade). Both anterograde amnesia and retrograde amnesia have been described in a small proportion of patients (20%–50%) in adult and pediatric studies. A benzodiazepine may be required if full amnesia is desired because of the clinical scenario.

3. Pharmacokinetics: Hepatic by glucuronidation and renal excretion. Onset with loading dose 15–20 minutes; onset without loading dose greater than 20 minutes to 1 hour; terminal half-life = 3 hours (may be significantly prolonged in hepatic impairment). Highly protein bound 94%

4. Clinical effects: Sedation and opiate-sparing antinociceptive effects

5. Dosing for ICU sedation: Optional loading dose 0.5–1 mcg/kg intravenously over 10 minutes, followed by 0.2–0.7 mcg/kg/hour. The loading dose may initially cause severe tachycardia and hypertension, but it can then quickly lead to significant bradycardia and/or hypotension secondary to receptor saturation. Because of these untoward hemodynamic effects, the loading dose is rarely administered in clinical ICU practice on initiation of dexmedetomidine, and the drip is usually initiated at 0.2–0.4 mcg/kg/hour. If a loading dose is desired, a reduced infusion rate should be considered. For the maintenance infusion dose, randomized trials have safely used dexmedetomidine at higher than manufacturer-recommended doses, up to 1.5 mcg/kg/hour. Clinical efficacy with doses greater than 1.5 mcg/kg/hour remains unclear. Other routes of administration have been described for dexmedetomidine, including intramuscular, subcutaneous, epidural, and intranasal.

6. Duration of use: Although the package insert recommends a therapy of 24 hours or less, randomized trials have used dexmedetomidine for up to 5–7 days; thus, ICU clinicians often administer dexmedetomidine for longer than 24 hours. Safety beyond 7 days of use has not been well established.

7. Adverse effects: Tachycardia, bradycardia, hypertension, hypotension, dry mouth. Should generally be avoided in patients with acute decompensated heart failure or advanced heart block

8. Other potential uses in the ICU: Procedural sedation, palliative care pain and anxiety control, adjunct to opiates for sickle cell crisis, adjunct to benzodiazepines or propofol for alcohol withdrawal, bridge to extubation while tapering off longer-acting sedatives and/or opiates, to provide sedation and anxiolysis during noninvasive mechanical ventilation

G. Lorazepam (Ativan)

1. Pharmacokinetics: Benzodiazepine that binds to the postsynaptic GABA\textsubscript{A} receptor, undergoes hepatic clearance by conjugation to inactive compounds; moderate to high volume of distribution and high protein binding. Onset of action is 15–30 minutes, slower than more lipophilic benzodiazepines (e.g., midazolam). Duration of action of intermittent dosing is 4–8 hours. As a continuous infusion, clearance of lorazepam decreases in an unpredictable fashion, and prolonged sedation may occur.

2. Effects: Anxiolysis/sedation, anticonvulsant, muscle relaxant. Maintains anterograde amnesia properties; however, studies report that patients who received benzodiazepines in the ICU may maintain delusional versus factual memories

3. Dosing range: 1–4 mg every 4–6 hours intermittent dosing is recommended before using continuous infusion; accumulation and prolonged awakening times with continuous infusion of lorazepam may occur because of prolonged duration of action.

4. Data: Carson et al. studied the number of days on mechanical ventilation in medical ICU patients receiving intermittent lorazepam (n=64) compared with continuous infusion propofol (n=68); each group underwent daily interruption of sedation if the fraction of inspired oxygen (F\text{\textsubscript{IO}}\text{\textsubscript{2}}) was less than 80%. Median time on mechanical ventilation was 9 days in the lorazepam group versus 4.4 days in the propofol group, p=0.006; ICU length of stay was 12.7 days in the lorazepam group versus 8.6 days in the propofol group (p=0.05); no difference in hospital mortality. Delirium was not assessed in this study (Crit Care Med 2006;34:1326-32).

5. Propylene glycol toxicity: Because of its insolubility, injectable lorazepam is diluted in propylene glycol. Propylene glycol toxicity can occur with lorazepam infusions for more than 48 hours, particularly at doses
of 6–8 mg/hour or greater, and can manifest as new-onset renal failure, respiratory failure, metabolic acidosis, and altered mental status. Most hospitals can not measure quantitative levels of propylene glycol, therefore surrogate markers of propylene glycol toxicity such as an elevated osmolar gap (>10) and elevated anion gap with new metabolic acidosis are recommended for monitoring. If these metabolic abnormalities are present while on a lorazepam infusion, the lorazepam should be discontinued.

6. Other adverse effects: Paradoxical agitation, confusion, prolonged duration of sedative action, respiratory depression, hypotension, bradycardia

H. Midazolam (Versed)

1. Pharmacokinetics: Benzodiazepine that binds to the postsynaptic GABA<sub>A</sub> receptor; undergoes phase I hepatic metabolism to an active glucuronidated metabolite, α1-hydroxymidazolam, which is then renally excreted. A short- to medium-acting benzodiazepine in patients with normal renal and hepatic function. CYP3A4 substrate. Midazolam is highly lipophilic, has a large volume of distribution, and is highly protein-bound.

2. Clearance: Clearance of midazolam or its metabolite is significantly altered if either hepatic (primary drug accumulation) or renal (active metabolite α-hydroxymidazolam accumulation) functions are significantly impaired. Continuous renal replacement therapy partly clears the active metabolite but does not effectively clear the parent compound and is therefore not recommended as a method for definitive midazolam clearance (Am J Kidney Dis 2005;45:360-71). High lipophilicity and a large volume of distribution may lead to significant drug accumulation and a depot effect in the ICU patient. In general, clearances of midazolam infusions have wide interpatient variability in the ICU, and emergence times may be significantly prolonged.

3. Effects: Anxiolysis/sedation, anticonvulsant, muscle relaxant. Maintains anterograde amnesia properties

4. Dosing range: 1–4 mg every 2–4 hours intermittently or as needed should be considered before initiating continuous infusion. Older adult patients may tolerate only 1–2 mg per dose.

5. Data: In a multicenter European trial (MIDEX), Jakob et al. compared midazolam (n=251) with dexmedetomidine (n=249) for sedation in prolonged mechanical ventilation. Patients in both groups were treated with daily sedation interruption trials and SBTs, and pain was treated with fentanyl boluses. There was no difference in the primary outcome: proportion of time in target RASS (0, -3) without rescue therapy in the midazolam group (56%) versus the dexmedetomidine group (60%). Median time on mechanical ventilation was lower in the dexmedetomidine group (5 days) than in the midazolam group (6.8 days), p=0.03. Patients in the dexmedetomidine group were more arousable, more cooperative, and better able to communicate discomfort or pain to clinical staff than were patients in the midazolam group. Hypotension occurred more often in the dexmedetomidine group (20.6%) than in the midazolam group (11.6%; p=0.007); and bradycardia was more common in the dexmedetomidine group (14.2%) than in the midazolam group (5.2%; p<0.001). The two treatment groups showed no difference in neurocognitive adverse events after 48 hours of follow-up, including agitation, anxiety, and delirium (JAMA 2012;307:1151-60).

6. Adverse effects: Paradoxical agitation and prolonged duration of sedative action, respiratory depression, hypotension, bradycardia

I. Amnestic Effects of Sedatives: Lorazepam, midazolam, and propofol all produce anterograde amnesia. This may be a beneficial effect of these drugs in certain ICU settings.

J. Sedation Protocols: Titration of Sedation in the ICU

1. Titration of medications using a sedation protocol to a goal level of sedation is arguably one of the most salient clinical practice standards within ICU care. This titration practice has consistently been shown to decrease time on mechanical ventilation, decrease ICU length of stay, and decrease rates of tracheostomy, which may all result in faster physical and cognitive rehabilitation time.
management of pain, agitation, delirium, and neuromuscular blockade in adult intensive care unit patients

K. SAT Paired with SBT: The daily coordination of a SAT completed before an SBT is a method of weaning sedation before attempts at breathing trials in order to maximize a patient’s chances of weaning from mechanical ventilation. This pairing of a SAT before an SBT is becoming recognized as an important component to ICU care and management of sedation. Important safety screens are incorporated into the daily SAT because studies have shown that the SAT is not appropriate for all ICU patients. If a patient does not pass the safety screen and does not undergo the SAT, this should not preclude the appropriate titration of sedatives to a goal level of sedation throughout the remainder of the day:

1. SAT safety screen (criteria may vary, published trial protocols have had variations): If any are present, discontinue the protocol and repeat in 12–24 hours or according to hospital protocol:
   a. Current RASS greater than 2; or goal for deeper sedation (e.g., RASS -3 to -5)
   b. Active seizures
   c. Active alcohol withdrawal
   d. FiO2 of 60% or greater (these criteria are not consistently present among published trial protocols)
   e. Neuromuscular blockade
   f. Myocardial ischemia in previous 24 hours or ongoing myocardial ischemia
   g. Intracranial pressure (ICP) more than 20 mm Hg or need for control of ICP

2. If pass SAT safety screen, begin SAT: Hold continuous benzodiazepine infusions and/or sedative boluses; for shorter-acting agents (e.g., propofol), gradually decrease dose every 20–30 minutes to point of awareness. Bolus opioids allowed for breakthrough pain. Continuous opioid infusions allowed if presence of active pain. If the patient “passes” the SAT, continue to the SBT safety screen.

3. SAT failure (if any are present, discontinue the protocol, and repeat in 12–24 hours or according to hospital protocol):
   a. Anxiety/agitation/pain present (e.g., RASS greater than +1 for 5 minutes or more)
   b. Respiratory rate greater than 35 breaths/minute for 5 minutes or more
   c. Oxygen saturation less than 88% for 5 minutes or more
   d. ICP greater than 20 mm Hg
   e. Acute cardiac ischemia or arrhythmia
   f. Respiratory or cardiac distress (e.g., heart rate increase of 20 beats/minute or greater, heart rate less than 55 beats/minute, use of accessory muscles, abdominal paradox, diaphoresis, or dyspnea)
4. If SAT fails: Reinitiate sedation, if necessary, at half the previous dose and titrate to goal. Determine the reasons for SAT failure. Repeat SAT steps in 12–24 hours or according to hospital protocol.

5. SBT safety screen (if any are present, discontinue the protocol, and reinitiate the previous sedative dose; repeat in 12–24 hours or according to hospital protocol):
   a. Agitation
   b. Oxygen saturation less than 88%, \( \text{Fi}_2 \text{O}_2 \) greater than 50%
   c. PEEP (positive end expiratory pressure) greater than 7.0 cm H\(_2\)O
   d. Myocardial ischemia in previous 24 hours
   e. Increasing vasopressor requirements
   f. Lack of inspiratory efforts

6. SBT: If a patient tolerates the SBT for more than 2 hours, consider extubation.

7. SBT failure:
   a. Respiratory rate greater than 35 breaths/minute (for more than 5 minutes) or less than 8 breaths/minute
   b. Oxygen saturation less than 88% for more than 5 minutes
   c. ICP greater than 20 mm Hg, mental status change
   d. Acute cardiac ischemia or arrhythmia
   e. Respiratory distress (use of accessory muscles, abdominal paradox, diaphoresis, and dyspnea)

8. If SBT fails: Reinitiate sedation, if necessary, at half the previous dose and titrate to goal. Repeat bundle in 12–24 hours or according to hospital protocol.

L. Sedation Protocol Compared with the Paired SAT-SBT Protocol: Studies comparing a standard sedation protocol to daily pairing of a SAT with SBT, have shown decreased days on mechanical ventilation, days in the ICU, and decreased rates of delirium when the SAT is paired with the SBT.

1. The ABC (Awakening and Breathing Controlled) trial included 336 mechanically ventilated patients from four tertiary care hospitals. Patients were randomized to patient-targeted sedation protocol plus the SBT (“usual care” control group) or to daily SAT paired with the SBT (intervention group). Both groups were deeply sedated on enrollment (RASS -4), and both groups had been admitted for 2.2 days before enrollment. In the intervention group, patients who passed the safety screen underwent a SAT: sedatives and analgesics used for sedation were discontinued, and analgesics used for active pain were continued. Patients “passed” their SAT if they opened their eyes to command or tolerated being off sedation for at least 4 hours without meeting failure criteria. The mean ventilator-free days was 11.6 days in the usual care control group versus 14.7 days in the SAT plus SBT group (p=0.02). The time to discharge was 12.9 days in the control group versus 9.1 days in the intervention group (p=0.01). Self-extubations were higher in the intervention group, but there was no difference in self-extubations requiring reintubation between groups. Rates of delirium assessed by the confusion assessment method for the intensive care unit (CAM-ICU) were no different between groups (74% vs. 71%).

2. The ABCDE (Awakening and Breathing Coordination, Delirium Monitoring/Management, and Early Mobility) trial compared clinical outcomes in patients before (n=146) and after (n=150) bundle-protocol implementation; 187 patients were on mechanical ventilation. The bundle protocol consisted of a daily-paired SAT/SBT, delirium screening with the CAM-ICU every 8 hours, and an early mobility protocol. The “before” bundle patients were enrolled from February to October 2011; the “after” bundle patients were enrolled from October 2011 to April 2012. There were some differences in patient type on admission, including more elective admissions in the post-bundle group (39 vs. 30), more cardiothoracic surgery patients in the post-bundle group (20 vs. 6), more surgical patients in the pre-bundle group (21 vs. 11), and more patients coming from an outside hospital in the pre-bundle group (9 vs. 1). The post-bundle group had more median ventilator-free days (24 vs. 21 days, p=0.04), less delirium at any time (49 vs. 62%, p=0.03), and less percentage of ICU days with delirium (33.3 vs. 50 %, p=0.003).
3. The SLEAP investigators from the Canadian Critical Care Trials Group studied the outcomes of patients receiving a daily sedation protocol alone versus patients receiving a daily sedation protocol plus a daily sedation interruption (Crit Care Med 2015;43:557-66; Crit Care Med 2015;43:2180-90; JAMA 2012;308:1985-92). From January 2008 to July 2011, 430 patients were enrolled from 16 tertiary care medical and surgical ICUs. Only opiate and benzodiazepine infusions were allowed in the study. According to the sedation-alone protocol, the RASS goal was -3 to 0, and the Sedation-Agitation Scale (SAS) goal was 3 or 4. Nurses assessed sedation levels on an hourly basis and titrated medications every 15–30 minutes to achieve sedation goals. If patients were oversedated in either group (SAS 1 or 2; RASS -4 or -5), infusions were discontinued. According to the sedation protocol with daily sedation interruption, nurses stopped benzodiazepine and opiate infusions once a day and assessed hourly for wakefulness (e.g., a light SAS or RASS score, plus ability to follow at least three commands).

a. Clinical outcomes (published 2012): There was no difference in the primary outcome of time to successful extubation between the two groups (7 days in both groups). There was a significant difference in time to extubation in the prespecified surgical/trauma group between sedation protocol with daily sedation interruption and sedation protocol alone (6 vs. 13 days; hazard ratio [HR] 2.55; 95% CI, 1.40–5.44). No difference in time to extubation was detected between groups among medical ICU patients (9 vs. 8 days; HR 0.92; 95% CI, 0.72–1.18). Lower daily doses of both benzodiazepines and opiates were used in the sedation protocol–alone group than in the sedation protocol plus interruption group.

b. Delirium outcomes (published 2015): Delirium by the Intensive Care Delirium Screening Checklist (ICDSC) was diagnosed in 53.8% of patients in the study; there was no difference in delirium in the sedation protocol–alone group versus the protocol plus daily sedation interruption group. Patients who had delirium had a longer duration of mechanical ventilation, longer ICU and hospital stay, longer use of restraints, higher rates of tracheostomy, and higher incidence of unintentional device removal. Patients with delirium received almost the twice the mean dose of midazolam equivalents/patient/day (104 mg vs. 57 mg), higher fentanyl equivalents/patient/day (1497 mcg vs. 1150 mcg), more frequent use of anticholinergics (18 vs. 8.6%), and more frequent use of trazadone or zopiclone (17.7 vs. 9.8%), than did patients who were not delirious. Patients who developed delirium had a higher incidence of alcohol and cigarette use than did patients who did not develop delirium.

c. Recall in ICU survivors (published 2015): The SLEAP investigator study did patient interviews on days 3, 28, and 90 post-ICU discharge to determine differences in recall between the sedation-alone protocol group and the protocol plus daily sedation interruption group. There were no differences in type of recall between the sedation strategies. Delusional memories were common at day 28 (70% of patients) but were unrelated to the presence of delirium or the total dose of benzodiazepines or opiates. Patients with no recall had received lower total doses of benzodiazepines than had patients with recall. Emotional memories such as panic and confusion declined over time.

M. The PAD guidelines suggest using objective measures of brain function (e.g., auditory evoked potentials, Bispectral index) as an adjunct to subjective sedation assessments in adult ICU patients concomitantly receiving a NMBA (+2B); the guidelines also recommend that “electroencephalogram monitoring be used to monitor nonconvulsive seizure activity in adult ICU patients with either known or suspected seizures or to titrate electrosuppressivemedication to achieve burst suppression in adult ICU patients with elevated intracranial pressure (+1A).”
Table 5. 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>Overtly combative or violent; immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Pulls on or removes tube(s) or has aggressive behavior toward staff</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Frequently nonpurposeful movement or patient-ventilator dyssynchrony</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious or apprehensive, but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Not fully alert but has sustained (&gt; 10 s) awakening, with eye contact, to voice</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>Briefly (&lt; 10 s) awakens with eye contact to voice</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>Any movement (but no eye contact) to voice</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>No response to voice, but any movement to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

Procedure
1. Observe patient. Is patient alert and calm (score 0)? Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under Description)?
2. If patient is not alert, in a loud speaking voice, state the patient’s name and direct the patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker. Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score -1). Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score -2). Patient has any movement in response to voice, excluding eye contact (score -3).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder. Patient has any movement to physical stimulation (score -4). Patient has no response to voice or physical stimulation (score -5).


Table 6. Riker Sedation-Agitation Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dangerous agitation</td>
<td>Pulling at ETT, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated</td>
<td>Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting ETT</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
<td>Anxious or mildly agitated, trying to sit up, calms down to verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm and cooperative</td>
<td>Calm, awakens easily, follows commands</td>
</tr>
<tr>
<td>3</td>
<td>Sedated</td>
<td>Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated</td>
<td>Arouses 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>

ETT = endotracheal tube

N. Acute Withdrawal Syndrome of Long-term Analgesia and/or Sedation in the ICU
1. Patients who have been receiving high doses of continuous infusion sedation and/or analgesia in the ICU for an extended period may be at risk of sedative or analgesia withdrawal as dose tapering begins. In a retrospective review of adult trauma/surgical ICU patients, 32% of patients experienced either sedative or opiate withdrawal soon after discontinuing these medications. The patients in this study had been in the ICU for 20 days or more and were receiving higher mean daily analgesic and sedative doses than were the non-withdrawal patients (fentanyl 6.4 mg vs. 1.4 mg; lorazepam 38 mg vs. 11 mg). The withdrawal patients in this study were also more likely to have received a NMBA (Crit Care Med 1998;26:676-84).
2. The risk factors and incidence of sedation or analgesia withdrawal in adult ICU patients have not been well characterized; however, these are important considerations in the long-term ICU patient receiving high doses of these medications. Use of longer-acting agents given orally or by feeding tube has been described to assist in the transition off long-term continuous infusions. The medical indication and dosing plan for using oral medications to taper off continuous infusions should be clearly documented in the medical chart on patient discharge from the ICU.

### Patient Cases

3. A 48-year-old man with cirrhosis and now hepatorenal syndrome was intubated for respiratory distress. He has been receiving midazolam 1 mg/hour and fentanyl 75 mcg/hour for 2 days; his RASS (-4 to -5) and pain score have been negative for 24 hours. Oxygen requirements have decreased, and vital signs are normal. Which is the most appropriate change in his medications?
   A. Discontinue midazolam; give as-needed lorazepam for agitated RASS score.
   B. Decrease midazolam; give as needed fentanyl for agitated RASS score.
   C. Discontinue midazolam; initiate propofol drip.
   D. Change midazolam to dexmedetomidine drip.

4. T.L. is a 55-year-old woman intubated for respiratory distress for severe pneumonia. She is receiving fentanyl 50 mcg/hour and dexmedetomidine 1.0 mcg/kg/hour. Her home medications are confirmed to include esomeprazole 20 mg daily, lorazepam 1 mg three times daily, and citalopram 10 mg daily. The nurse reports intermittent agitation with tachycardia and a negative pain score. Which is the most appropriate recommendation?
   A. Increase fentanyl drip for agitated RASS score.
   B. Reinitiate lorazepam and citalopram.
   C. Give fentanyl boluses as needed for agitation.
   D. Increase dexmedetomidine.

### IV. DELIRIUM IN THE INTENSIVE CARE UNIT

A. Delirium is an acute and fluctuating disturbance in consciousness resulting in the inability to receive, process, store, or recall information. In the ICU, delirium may present as hyperactive (agitated and restless), hypoactive (flat affect, apathy, lethargy, decreased responsiveness), or mixed hyper/hypoactive states. Most common in the ICU are mixed and hypoactive states of delirium. Two screening tools are currently recommended by the PAD guidelines: (1) the CAM-ICU and (2) the ICDSC. Both the CAM-ICU and the ICDSC require a RASS (-3) or a SAS (3) or more alert, to be completed.
1. The CAM-ICU assesses four features: (1) acute change or fluctuation in mental status from baseline, (2) inattention, (3) altered level of consciousness, and (4) disorganized thinking. If features 1 and 2 plus feature 3 or 4 are present, the patient is considered positive for delirium. Detailed training is available at www.icudelirium.org.

2. The ICDSC consists of eight items, evaluated over an 8- to 24-hour period. The eight symptoms are level of consciousness, inattention, disorientation, hallucinations-delusions-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep-wake cycle disturbances, and symptom fluctuation. A point is given for any symptom that is present during the previous 24 hours; a score of 4 or higher indicates the presence of delirium.

B. Background – 30%–80% of ICU patients reportedly develop delirium, depending on the severity of illness and the diagnostic method, yet assessment for delirium is still not routine in most U.S. ICUs. During a patient’s hospitalization, the presence of delirium is associated with difficulty in weaning mechanical ventilation and longer duration of mechanical ventilation, increased use of physical and chemical restraints, longer duration of ICU stay, and additional stress to family and friends who may not understand the course of delirium. Delirium is also associated with up to a 3-fold increase in mortality, increase in cognitive decline, delay in cognitive recovery, and increased likelihood of being discharged to a nursing home. Two studies found that a longer duration of delirium was independently associated with worse activity of daily living scores and worse cognitive impairment scores at 3 and 12 months post-ICU discharge (Crit Care Med 2014;42:369-77; N Engl J Med 2013;369:1306-16). A recent retrospective study reported increased difficulty in the weaning of mechanical ventilation when delirium was detected in patients during the first spontaneous weaning trial compared with in patients who did not have delirium (Respirology Nov 2015;1-8).

1. The underlying pathophysiology of delirium is not well understood; however, it may involve a complex set of factors:
   a. Cerebral hypoperfusion and alterations in cerebral blood flow
   b. Degradation of the blood-brain barrier, causing influx of inflammatory cytokines and microvascular thrombosis
   c. Depletion in central neurotransmitters (e.g., dopamine, norepinephrine, serotonin)
   d. Depletion in acetylcholine
   e. Medication withdrawal

2. Risk factors for delirium: A recent systematic review of studies from 2001 to 2013 described 11 variables identified as risk factors for developing delirium in the ICU, extracting from only a strong or moderate level of evidence (Crit Care Med 2015;43:40-7):
   a. Age
   b. Preexisting dementia
   c. History of baseline hypertension
   d. Sedative-associated coma
   e. APACHE II (Acute Physiology and Chronic Health Evaluation II) score
   f. Delirium on the previous day
   g. Emergency surgery
   h. Mechanical ventilation
   i. Organ failure
   j. (Poly)trauma
   k. Metabolic acidosis

3. Other reported risk factors or precipitants:
   a. Infection
   b. Dehydration or malnutrition
   c. Sleep deprivation
   d. Centrally acting medications (benzodiazepines, opiates, anticholinergics)
Management of Pain, Agitation, Delirium, and Neuromuscular Blockade in Adult Intensive Care Unit Patients

4. Medication-induced altered mental status – Although the development of delirium is considered multifactorial, any patient who presents with a change in mental status should have his or her medications and medication doses immediately scrutinized as part of the initial workup for delirium. Several classes of medications have long been recognized for their effects on mental status and cognitive function, in or out of the ICU. These medications have the potential to affect a patient’s level of consciousness or course of delirium at any point in the patient’s hospital stay. Anticholinergics, benzodiazepines, opiates, antipsychotics, antispasmodics, anticonvulsants, corticosteroids, and others should be used with caution in a hospitalized patient, with close monitoring of the patient’s cognitive adverse effects. Because renal and hepatic function may fluctuate throughout an ICU stay and affect the clearance of these medications, doses must be thoughtfully titrated. Research on the degree of impact these medications have on the overall course of sedation and delirium in the ICU is difficult to characterize, and research is undergoing. Given the multifactorial nature of delirium in the ICU, clinicians should be leery of solely assigning blame to medications, but should remain vigilant when assessing the need and doses of the aforementioned medications.

a. Benzodiazepines: The PAD guidelines state “benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients (B).” Of interest, research directed at finding an independent association between the use of benzodiazepines and the development of delirium in the ICU has yielded mixed results. Reports including a recent meta-analysis, systematic review, and randomized trial found no direct relationship between benzodiazepines and delirium in the ICU (Crit Care Med 2015;43:40-7; Crit Care Med 2015;43:557-66; Crit Care Med 2013;41:S30-8). Most recently, investigators used more appropriate statistical analysis for a fluctuating illness such as delirium (e.g., Markov modeling) to examine the use of benzodiazepines and the transition from an awake state without delirium to delirium, or from coma to delirium by the next day (Intensive Care Med 2015;41:2130-7). The mean age was 60 years and included medical and surgical patients. This study found that a midazolam equivalent dose of just 5 mg/day increased the odds of developing delirium the next day by 4%, and the use of benzodiazepine infusions was an independent risk factor for the transition to delirium in the study population. As the data evolve, the scrutiny of benzodiazepine use should persist for ICU clinicians. Routine strategies to discontinue benzodiazepine infusions when appropriate, or to transition from an infusion to intermittent dosing or to a non-benzodiazepine sedative (e.g., propofol or dexmedetomidine), should be considered.

b. Anticholinergics: These medications are known for their sedating and altering effects on mentation and should be avoided or used with extreme caution in the ICU setting. One proposed mechanism for delirium is a decline in acetylcholine concentrations; therefore, any medication that may further inhibit the activity of acetylcholine could worsen the patient’s mental status.

c. Systemic corticosteroids: The neuropsychiatric effects of systemic steroids in various clinical settings have been described for more than 50 years. Common symptoms include mania, depression, mood lability, anxiety, insomnia, delirium, and psychosis. The incidence of these symptoms varies greatly depending on the clinical setting, dose of steroid, and patient’s underlying medical history. Reported risk factors for neuropsychiatric effects secondary to steroids include a daily prednisone dose equivalent to 40 mg or greater, hypoalbuminemia, underlying psychiatric disorder, and blood-brain barrier damage (Curr Opin Organ Transplant 2014;19:201-8). Although steroids are commonly used in the ICU for various indications and at various doses, significant research directed at the neuropsychiatric effects of steroids in the critically ill population is lacking. In a secondary analysis of a multicenter observational study of adult medical and surgical ICU patients with acute lung injury (n=330), Schreiber et al. found a significant and independent association between the use of...
systemic corticosteroids and the transition to delirium from a non-comatose, non-delirious state within 24 hours of corticosteroid administration (odds ratio [OR] 1.52 [1.05–2.21], p=0.03). Delirium was documented on one or more days in 83% of patients, with a median duration of 7 days. There was no significant association in prednisone-equivalent dose and transition to delirium. Schreiber et al. recognize that a direct causal relationship could not be determined between corticosteroid use and delirium from this observational study; however, they believe that the study adds valuable data toward our understanding of risk factors for delirium in the ICU (Crit Care Med 2014;42:1480–6). A second study that investigated steroids and transition to delirium in a mixed medical and surgical ICU population (n=1112) found no association between steroid use and a transition to delirium. The median prednisone equivalent dose was 50 mg (Crit Care Med 2015;43:e585–8).

5. Outcomes of sedation-related versus illness-related delirium: Research is ongoing to investigate differences in outcomes between sedation-related delirium and non–sedation-related or persistent delirium (e.g., delirium related to an underlying illness). A single-center study using propofol and fentanyl timed its CAM-ICU assessments before and after a daily sedation interruption protocol. Patients were 10.5 times more likely to screen positive for delirium when assessed before daily interruption of sedation than after daily interruption of sedation. Patients who had “no delirium” or “reversible sedation-related delirium” had significantly shorter days on mechanical ventilation, ICU days, hospital days, and decreased 1-year mortality than the “persistent delirium” group. The authors of that study suggest that the timing of delirium assessment with sedation interruption is crucial to better defining the type of ICU delirium and that patients with “reversible sedation-related delirium” have better outcomes than those with “non-sedation-related persistent delirium” (Am J Respir Crit Care Med 2014;189:658–65). Patients can have both sedation-related and illness-related delirium, and additional research in this area is needed to clarify the differences in short- and long-term outcomes.

C. Monitoring for Delirium: SCCM provides a grade 1B strong recommendation for routine monitoring in all ICU patients for delirium, using either the CAM-ICU or the ICDSC. The PAD guidelines summarized their review of five delirium assessment scales used for adult ICU patients. The two scales with the highest psychometric (e.g., validity and reliability) scores were the CAM-ICU and the ICDSC. Both scales were designed for patients in the ICU either on or off mechanical ventilation, and both showed high sensitivity and specificity when tested against the American Psychiatric Association’s criteria for delirium.

1. Delirium should be assessed every 8–12 hours and documented in the medical chart; results should be discussed with the medical team. Because these assessment scales cannot distinguish between sedation-related and disease-related causes of delirium, delirium assessments should ideally be timed after a decrease or interruption in sedative doses, with appropriate time allowed for drug clearance (www.icudelirium.org, Am J Respir Crit Care Med 2014;189:658–65). If this timing is not feasible and a patient screens positive for delirium while receiving ongoing analgesia or sedation, an effort to decrease the doses of these medications should be considered to assist in ruling out a medication-induced cause of delirium.

2. If a patient’s delirium score is positive, the medical team should correct possible etiologies (e.g., decrease sedative doses, if safe), decrease ongoing risk factors, address inciting factors (e.g., metabolic derangements, infection, withdrawal), and try nonpharmacologic treatment and preventive measures when appropriate.

D. Prevention of Delirium: With a lack of data supporting the use of pharmacologic agents to prevent delirium, the PAD guidelines focus their recommendations on nonpharmacologic prevention methods when feasible, particularly for patients at high risk of delirium. Preventive efforts may help avert 30%–40% of new-onset delirium cases, particularly in older adults. Recommended nonpharmacologic strategies include:

1. Early mobilization (+1B recommendation)
2. Decreasing nighttime disturbances to optimize a sleep environment: Cluster patient care activities and medication administration to daytime and evening to help normalize sleep patterns; control light and noise; consider earplugs at night in patients without delirium (+1C recommendation).

3. Decrease the use of benzodiazepines and anticholinergics in patients at risk of delirium; use the lowest effective doses of any sedating medication (e.g., opiates, antipsychotics).

E. Sleep in the ICU: Uninterrupted sleep (ideally 4 hours or more) is vital for an adequate immune response to illness, to maintain normal metabolic and hormonal balance, and to help decrease delirium and/or agitation. Disturbances in the ICU such as multiple alarms and frequent physical interruptions (e.g., examination, turning, laboratory tests, medication administration) make it challenging for patients to maintain the slow-wave sleep cycle needed for optimal immune function. Sleep research in the ICU is ongoing, and more information will be forthcoming regarding its effects in the critically ill patient. Currently, the PAD guidelines strongly recommend promoting sleep in adult ICU patients by optimizing patients’ sleep environments (+1C recommendation):
1. To avoid waking patients at night, pharmacists should ensure that medications are scheduled during the daytime and evening hours, if possible—particularly orally or subcutaneously administered medications.
2. Sleep protocols should seek to cluster patient care activities (e.g., vital sign checks, radiology tests, laboratory checks, sedation assessments) around nighttime sleeping hours unless clinically indicated in a specific patient population.

F. Treatment of Delirium: The cause of delirium may be multifactorial, and identifying and correcting the underlying etiology is the first step in management. Patients can also progress to alcohol withdrawal or withdrawal from other chronic medications/substances and present with hyperactive delirium. The PAD guidelines state that “There is no published evidence that haloperidol reduces the duration of delirium (no evidence)” and that “atypical antipsychotics may reduce the duration of delirium in adult ICU patients” (grade C level of evidence). More data are needed to determine clinical outcomes with the use of antipsychotics for the treatment of delirium. If an antipsychotic is initiated, low starting doses should be considered, and daily review of drug interactions, adverse effects, dosing titration, and need for the antipsychotic should be completed. Additionally, a strategy for discontinuation or outpatient follow-up should be documented to help avoid inadvertent continuation beyond the hospital environment (Table 7). Serious adverse effects are associated with the use of any antipsychotic; effects such as arrhythmias, serotonin syndrome, neuroleptic malignant syndrome, extrapyramidal symptoms, and oversedation should be closely monitored on a daily basis. Dose ranges for atypical antipsychotics for ICU delirium are not well described. The American Geriatrics Society 2015 Beers Criteria for medication use in older adults includes the following recommendation: “Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options have failed or are not possible AND the older adult is threatening substantial harm to self or others.” If the ICU team decides to use antipsychotics in older adults, lower starting doses should be considered, along with daily review of drug interactions and adverse effects.

G. Inadvertent Continuation of Antipsychotics Beyond ICU Discharge: The PAD guidelines discuss the use of adjunctive medications for ICU patients (e.g., antipsychotics, gabapentin, carbamazepine). Although their use in the ICU may be appropriate, there is a potential for inadvertent continuation of these medications on hospital discharge if a treatment plan is not clear in the medical record. This has been a well-documented problem with other medications initiated in the ICU (e.g., histamine receptor blockers, proton pump inhibitors), and recent studies have been published describing the continuation of newly prescribed antipsychotics from the ICU and hospital, even when an indication for continuation was not documented (J Crit Care 2015;30:814-6). Continued use of these medications beyond the hospital stay could lead to serious adverse effects, drug interactions, and significant drug cost as well as a presumption of a psychiatric or neuromuscular disorder associated with these drugs. Communication to the next direct patient care provider is crucial to appropriately direct the next steps in medication reconciliation.
Table 7. Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP Substrate (major)</th>
<th>Usual Starting Dose</th>
<th>Significant Adverse Effects</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>3A4, 2D6</td>
<td>1–2 mg older adults; 2–4 mg if history of psychiatric disorders</td>
<td>Anticholinergic: * Sedation: * EPS: ** NMS: *</td>
<td>PO, IM, IV (non-FDA approved)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1A2</td>
<td>5 mg</td>
<td>Anticholinergic: ** Sedation: ** EPS: * NMS: * Neuromuscular weakness</td>
<td>PO, disintegrating tablet, IM</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3A4</td>
<td>12.5–25 mg</td>
<td>Anticholinergic: ** Sedation: ** NMS: * Orthostatic hypotension: **</td>
<td>PO</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2D6</td>
<td>0.5–1 mg</td>
<td>Anticholinergic: * Sedation * EPS: ** NMS: * Orthostatic hypotension: ** Cardiac conduction abnormalities</td>
<td>PO, disintegrating tablet</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1A2 (minor) 3A4 (minor)</td>
<td>20 mg PO; 10 mg IM</td>
<td>Anticholinergic: * Sedation: * EPS: * NMS: *</td>
<td>Oral, IM</td>
</tr>
</tbody>
</table>

NOTE: * = lower risk; ** = medium-higher risk.

*aNot all medications listed are FDA label approved for use in delirium; not all are recommended by SCCM for the treatment of delirium in the ICU.

*bAdverse effects other than QTc prolongation. Documented QTc prolongation incidence: IV haloperidol = ziprasidone > risperidone > olanzapine = quetiapine. EPS = extrapyramidal symptoms; IM = intramuscular(ly); IV = intravenous(ly); NMS = neuroleptic malignant syndrome; PO = oral(ly).

1. Quetiapine (Seroquel): A randomized, placebo-controlled pilot trial compared the efficacy and safety of scheduled quetiapine with placebo for the treatment of delirium in ICU patients during a 10-day study (Crit Care Med 2010;38:419-27). Significant exclusions were as follows: patients with end-stage liver disease, those with alcohol withdrawal, those with a QTc greater than 500, and those receiving concomitant QTc-prolonging agents. This small pilot study (n=36), in which the placebo group was administered as-needed intravenous haloperidol, found that quetiapine was associated with a shorter time to first resolution of delirium, reduced duration of delirium, and less agitation than placebo. Mortality and ICU length of stay were not different from placebo. Another more recent retrospective study reported outcomes of 113 adult medical-surgical ICU patients with hypoactive delirium. Clinical outcomes were compared in patients who received quetiapine (n=52) with no quetiapine (n=61). Hypoactive delirium was defined as a positive CAM-ICU score and a RASS score of 0 to -3, with no RASS scores of +1 to +4 documented throughout the disease course. SATs and SBTs were performed in all patients. Quetiapine use was associated with a shorter median duration of hypoactive delirium than was no quetiapine use (1.5 vs. 2.0 days; p=0.04) and a reduced probability of delirium persisting in the subsequent 24 hours (p=0.007). There was no difference in time on mechanical ventilation or length of ICU or hospital stay.
there was no reported difference in the amount or type of sedatives used 48 hours before the first positive delirium screen. In a predefined subgroup analysis, patients who had delirium for 2 days or less (n=32) received quetiapine sooner than patients who had greater than 2 days of delirium (n=20). Patients who had delirium for 2 days or less spent less time on mechanical ventilation (4.5 vs. 13.5 days, \( p=0.001 \)), with reduced ICU length of stay (9 vs. 12.5 days, \( p=0.03 \)) compared with patients with delirium for greater than 2 days.

a. Pharmacokinetics: Hepatically metabolized to one active and two inactive metabolites. Metabolites renally cleared. Many drug interactions, CYP3A4 (major) and CYP2D6 (minor) substrates. Peak plasma concentrations for oral about 1½ hours (immediate release)

b. Initial dose range for ICU delirium: 50 mg one to three times daily. Consider lower starting doses for older adult patients because of sedating effects. The Devlin study initiated 50 mg every 12 hours and titrated to a maximum dose of 200 mg every 12 hours.

c. Adverse effects (early onset): Sedation, orthostatic hypotension, extrapyramidal symptoms, QTc prolongation

2. Olanzapine (Zyprexa): Available in oral, orally disintegrating, and intramuscular (immediate and extended release) dosage forms. Intramuscular administration may result in plasma concentrations 5 times those of oral administration. The U.S. Food and Drug Administration (FDA) warns that the use of intramuscular olanzapine has resulted in unexplained deaths; use of intramuscular olanzapine with benzodiazepines may result in significant oxygen desaturation.

a. Pharmacokinetics: Metabolized by glucuronidation and CYP 1A2, 2D6 oxidation. Clearance is significantly increased (around 40%) in smokers and decreased in females (around 30%). Many drug interactions, CYP1A2 (major) and CYP2D6 (minor) substrates. Weak inhibitor of several CYP isoenzymes. Peak plasma concentrations for oral: About 6 hours

b. Suggested starting dose for ICU delirium: 5 mg orally once daily

c. Adverse effects (early onset): Drowsiness, extrapyramidal symptoms, neuromuscular weakness, serotonin syndrome. High doses may cause cardiac arrhythmias, cardiopulmonary arrest, and extreme sedation to coma-like states.

3. Risperidone (Risperdal): Available in oral and oral dispersible tablets (M-tabs) and intramuscular injection dosage forms

a. Pharmacokinetics: Hepatically metabolized to active metabolites, renally cleared. Many drug interactions, CYP2D6 (major) and CYP3A4 (minor) substrates and P-glycoprotein. Peak plasma concentrations for oral about 1 hour

b. Suggested starting dose for ICU delirium: 0.25–0.5 mg once or twice daily

c. Adverse effects (early onset): Cardiac arrhythmias, anticholinergic effects, extrapyramidal symptoms

4. Ziprasidone (Geodon): Studied in a multicenter, randomized, placebo-controlled pilot trial of mechanically ventilated patients to test the hypothesis that antipsychotics would improve days alive without delirium or coma in the ICU (MIND trial). Medical and surgical adult ICU patients (n=101) from six tertiary care centers in the United States on mechanical ventilation who had an abnormal level of consciousness or were receiving analgesia/sedative medications were randomly assigned to receive haloperidol, ziprasidone, or placebo every 6 hours for up to 14 days during a 21-day study. During the study, no difference was found in median days alive without delirium or coma between the haloperidol (14 days), ziprasidone (15 days), and placebo (12.5 days) groups, \( p=0.66 \). The study also found no difference in ventilator-free days, hospital length of stay, or mortality among the three groups (Crit Care Med 2010;38:428-37). Ziprasidone is available in oral and intramuscular dosage forms.

a. Pharmacokinetics: Hepatic by glutathione and aldehyde oxidase. Minor substrates of CYP 1A2, 3A4. Peak plasma concentrations for oral about 6 hours; intramuscular about 1 hour

b. Suggested starting dose for ICU delirium: 20 mg twice daily (oral)

c. Adverse effects (early onset): Somnolence, extrapyramidal symptoms, dizziness, orthostatic hypotension
V. ABCDEF BUNDLE

A. Incorporating multiple concomitant patient care interventions into one consolidated bundle may be an effective strategy to improve clinical outcomes in critically ill patients. SCCM recommends implementing the “ABCDEF” bundle to reduce sedative doses, possibly prevent or decrease the duration of delirium, and decrease time on mechanical ventilation. The bundle may require modification to best fit a specific ICU environment and requires a multidisciplinary approach (e.g., physician, nursing, pharmacy, respiratory therapy, physical and occupational therapy). Challenges with the bundle have been recognized and published, notably the lack of adequate staff to fully perform all steps in the bundle on a daily basis (e.g., one respiratory therapist for 8–10 patients; lack of physical therapists and nursing care partners) and nursing concerns with having two patients undergoing an awakening or breathing trial at the same time. The following practice principles are applied to the bundle:
1. A: Assess, prevent, and manage pain
2. B: Both SATs and SBTs
3. C: Choice of sedation
4. D: Delirium: Assess, prevent, and manage
5. E: Early mobility and exercise
6. F: Family engagement and empowerment

B. Daily coordination of the SAT with the SBT, versus usual care with the SBT, has been shown to significantly decrease the time on mechanical ventilation and ICU length of stay in randomized studies. This was reviewed earlier in the chapter in the Agitation section.

C. Choice of Sedation (“C” of the bundle): Use a multidisciplinary approach, including focused pharmacy input, to choose a sedative according to individual patient needs, hemodynamic stability, and organ function (e.g., hepatic, renal, cardiac, pulmonary, pancreatic).

D. Delirium Assessment, Prevention, and Management (“D” of the bundle): Monitor sedation to titrate toward a daily goal, and regularly assess for delirium using the CAM-ICU or the ICDSC when patients are wakeful (every 8–12 hours). Use delirium preventive measures in all patients when safe to do so.

E. Early Mobility (“E” of the bundle): Perform a mobility safety screen, and implement a daily mobility protocol.

Patient Cases

5. T.L. (from question 4) was extubated 24 hours ago, is currently receiving dexmedetomidine 0.2 mcg/kg/hour, and has received two doses of fentanyl 25 mcg over 24 hours for pain. She is alert and calm with intermittent periods of agitation. Her pain score is now negative, and she is newly positive for delirium by CAM-ICU. Her laboratory values and vital signs are normal. Which would best be recommended for the management of delirium?
   A. Continue dexmedetomidine, and start quetiapine for delirium.
   B. Discontinue dexmedetomidine, and increase maintenance fluids for dehydration.
   C. Discontinue dexmedetomidine, and order patient mobility as tolerated.
   D. Continue dexmedetomidine, and schedule oxycodone sustained release every 12 hours.
Patient Cases (continued)

6. P.V. is a 70-year-old woman intubated for severe respiratory failure ($\text{FiO}_2$ 80%) and refractory shock from methicillin-resistant *Staphylococcus aureus* pneumonia, for which she was administered antibiotics, vasopressors, and steroids. She is day 5 of mechanical ventilation ($\text{FiO}_2$ 50%) and has been off vasopressors for 48 hours. The nurse describes PAD, but the patient denies pain. Medications include vancomycin 1000 mg daily, heparin 5000 units subcutaneously every 12 hours, hydrocortisone 50 mg every 6 hours, and fentanyl 75 mcg/hour. Which is the most appropriate recommendation at this time?

A. Increase fentanyl and add midazolam for agitation.
B. Decrease fentanyl and discontinue hydrocortisone.
C. Decrease fentanyl and add haloperidol for delirium.
D. Increase fentanyl and change vancomycin to linezolid.

VI. NEUROMUSCULAR BLOCKADE IN THE INTENSIVE CARE UNIT

A. The most recent SCCM guidelines for the sustained use of neuromuscular blockade in the ICU were published in 2002. Surveys have reported a dramatic decrease in the use of NMBAs during the past 20 years, from around 80% to 15% in patients on mechanical ventilation. This change in practice may be secondary to a better understanding of the serious adverse effects of prolonged paralysis, together with accepted standards of care for modes of mechanical ventilation in patients with ARDS.

B. Clinical Scenarios for the Use of NMBAs in the ICU May Include:
   1. Rapid sequence intubation
   2. ARDS
   3. Status asthmaticus
   4. Elevated ICP
   5. Elevated intra-abdominal pressure
   6. Therapeutic hypothermia after cardiac arrest

C. Acute Respiratory Distress Syndrome
   1. Cisatracurium has been the most-studied NMBA for ARDS since 2000, primarily as short-term treatment and in severe cases of ARDS. In 2010, a randomized placebo-controlled trial (n=340) found that short-term fixed-dose cisatracurium (48 hours) significantly improved 90-day survival, increased ventilator-free days, increased organ dysfunction–free days, and decreased barotrauma in patients with severe ARDS ($\text{PaO}_2/\text{FiO}_2$ less than 120 mm Hg). The investigators found no difference in neuromuscular weakness compared with placebo. Other cisatracurium studies have shown improvements in oxygenation and a reduction in inflammatory mediators.
   2. In retrospective studies, the use of NMBAs in ARDS was associated with a prolonged duration of mechanical ventilation, prolonged ICU length of stay, and increased mortality.
   3. Protective mechanisms of NMBAs in severe ARDS: Researchers have proposed mechanisms by which a NMBA may protect the lung against further injury in severe ARDS. These mechanisms are not completely understood, but they may help explain the beneficial effects of NMBAs in early, severe ARDS:
      a. Provide improved adaptation to the ventilator through increased thoracopulmonary compliance
      b. Increase functional residual capacity and decrease intrapulmonary shunt
c. Provide uniform distribution of pulmonary perfusion and pressures, favoring the perfusion of ventilated areas
d. Limit over-distension of high-compliance lung regions and recruits areas of smaller compliance
e. Decrease muscular oxygen consumption by decreasing ventilator asynchrony
f. Decrease production of proinflammatory cytokines in lung and blood
g. Provide protective role against ventilator-induced trauma, including decreased incidence of pneumothoraces

4. Use of NMBAs in ARDS remains controversial. Short-term use of cisatracurium (48 hours or less) when used early may be beneficial for severe ARDS (Pao₂/Fio₂ less than 120 mm Hg). It is imperative to understand that the use of NMBAs in ARDS is still considered a last resort and that they are used only after aggressive sedation and appropriate ventilatory adjustments have been tried.

D. Therapeutic Hypothermia After Cardiac Arrest

1. The American Heart Association guidelines for “post-cardiac arrest care” (Circulation 2010;122:S768) provide the following summary statements regarding therapeutic hypothermia: “We recommend that comatose (e.g., lack of meaningful response to verbal commands) adult patients with return of spontaneous circulation (ROSC) after out-of-hospital ventricular fibrillation cardiac arrest should be cooled to 32°C–34°C for 12–24 hours (class I, level of evidence B). Induced hypothermia also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electrical activity or asystole (class IIb, level of evidence B).”

2. NMBAs have been used to prevent or treat shivering during therapeutic hypothermia.

3. The optimal combination and dosing of sedatives and paralytics have not been well established because the metabolism of these drugs is significantly slowed during hypothermia, and potency may be decreased. NMBAs have been used in both a bolus and a continuous infusion fashion during therapeutic hypothermia.

E. Sedation During NMBA: It is critical that patients be in a sedated, non-agitated, and pain-free state before initiating a NMBA. Once the patient becomes paralyzed from the NMBA, the ability to accurately assess mental status or pain is ostensibly challenging and often unattainable. The deeper the degree of paralysis, the higher the risk of drug accumulation because nurses cannot routinely complete sedation interruption or taper to a lighter level of sedation. Common scenarios that slow the clearance of sedatives (e.g., hepatic and renal failure or a hypothermic state) can add to the likelihood of increased drug exposure and delayed awakening times once the paralytic and sedatives are discontinued. This risk of drug accumulation underscores the importance of a daily assessment for need of paralysis and frequent tapering of NMBA dosing once it is safe for the patient.

F. Two Classes of NMBAs According to Mechanism of Action: Depolarizing and nondepolarizing:

1. Depolarizing NMBA: Bind and activate acetylcholine receptors, causing persistent depolarization, which then renders muscle fibers resistant to further cholinergic stimulation. Succinylcholine is the only available depolarizing NMBA. Because of its quick onset and short duration, it is commonly the drug of choice for urgent or emergency intubation.
   a. Pharmacokinetics: Hydrolyzed by plasma pseudocholinesterase
   b. Usual dose: 0.10–1.5 mg/kg intravenously or intramuscularly
   c. Onset intravenously: 30–60 seconds; intramuscularly: 2–3 minutes
   d. Duration intravenously: 4–6 minutes; intramuscularly: 10–30 minutes
   e. Should not be used in patients with a history of malignant hyperthermia, hyperkalemia, stroke, paralysis, glaucoma, penetrating eye injuries, or spinal, crush, or burn injuries after 24 hours
   f. Adverse effects: Arrhythmias, bradycardia or tachycardia, hyperkalemia, rhabdomyolysis
2. Nondepolarizing NMBAs: Nicotinic receptor antagonists (competitive), blocking the action of acetylcholine at the neuromuscular junction. Divided into aminosteroid group (pancuronium, vecuronium, and rocuronium) and benzyl isoquinolinium group (atracurium, cisatracurium, doxacurium, and mivacurium)
   a. Pancuronium: Long-acting aminosteroid; intermittent or scheduled bolus may be preferred to continuous infusion because of accumulation and variable clearance. Older NMBAs, not used much in the United States
      i. Pharmacokinetics: Hepatically metabolized (30%–50%) and renally cleared as unchanged drug (50%–70%). Accumulation and prolonged duration of paralysis will occur with varying degrees of hepatic and/or renal dysfunction. Duration about 60–120 minutes
      ii. Adverse effects: Vagolytic activity, sympathetic stimulation, bradycardia, prolonged effect
   b. Vecuronium (Norcuron): Intermediate-acting aminosteroid; often used as a continuous infusion
      i. Pharmacokinetics: Hepatically metabolized (30%–50%); cleared renally (20%–30%), with fecal excretion. Has an active metabolite, around half the activity of parent compound. Duration 30 minutes after bolus intubation dose
      ii. Adverse effects: Vagolytic activity at higher doses, prolonged weakness
   c. Rocuronium (Zemuron): An intermediate-acting aminosteroid; considered a suitable alternative to succinylycholine for rapid sequence intubation (dose: 0.6–1.0 mg/kg) because of its rapid onset of action (60–90 seconds). Duration 30–40 minutes
      i. Pharmacokinetics: Primarily hepatically metabolized, minimal renal excretion. No active metabolite. Prolonged effects have been observed in patients with hepatic or renal failure.
      ii. Adverse effects: Vagolytic activity at higher doses, bradycardia
   d. Atracurium: Intermediate-acting benzyl isoquinolinium; a mixture of 10 stereoisomers (contains 15% cisatracurium)
      i. Pharmacokinetics: Undergoes Hofmann elimination to form the toxic metabolite laudanosine at high levels. Laudanosine is a cerebral stimulant that may precipitate seizure activity, clearance dependent on liver and kidney function. Duration of atracurium 20–40 minutes
      ii. Adverse effects: Histamine release may cause cardiovascular adverse effects and bronchospasm; laudanosine accumulation may cause seizure activity.
   e. Cisatracurium (Nimbex): An intermediate-acting benzyl isoquinolinium. Differences compared with atracurium: It is only one isomer, has a slower onset at normal bolus doses, no histamine release
      i. Pharmacokinetics: Undergoes Hofmann elimination, forms laudanosine but at much lower levels than atracurium. Renal and hepatic dysfunction do not alter cisatracurium clearance. Duration 30–60 minutes
      ii. Adverse effects: Prolonged weakness with continued use

G. Drug Interactions with NMBAs: Certain medications may decrease the activity of NMBAs, whereas others can enhance or prolong the paralytic action.
   1. Drugs decreasing the activity of NMBAs:
      a. Calcium: Antagonizes the effect of magnesium on neuromuscular blockade
      b. Carbamazepine: Competitor of acetylcholine receptor
      c. Phenytoin: Depressed postsynaptic response to acetylcholine
      d. Ranitidine: Unknown mechanism
      e. Theophylline: Unknown mechanism
   2. Drugs prolonging the activity of NMBAs:
      a. Antibiotics: Aminoglycosides, clindamycin, tetracyclines, vancomycin. Decreases prejunctional acetylcholine release with decreased postjunctional acetylcholine receptor sensitivity; blocks acetylcholine receptor
b. Cardiac medications: β-Blockers, calcium channel blockers, procainamide, quinidine, and furosemide. Decreases prejunctional acetylcholine release

c. Immunosuppressants: Steroids (decrease end plate sensitivity to acetylcholine), cyclosporine (inhibits metabolism of certain NMBAs)

H. Choice of NMA: Intermediate- to longer-acting agents such as vecuronium may be tried in bolus fashion initially before continuous infusion, particularly if organ dysfunction is present. The duration of paralysis for NMBAs cleared by Hofmann degradation may be more reliable when used as a continuous infusion because their clearance is not dependent on renal or hepatic function.

I. Train-of-Four (TOF) Monitoring and Dose Titration

1. Typically, the goal of using a NMA is to improve patient-ventilator synchrony and increase oxygenation. This may be achieved with varying degrees of paralysis and may not necessitate 100% block.

2. Monitoring the depth of neuromuscular blockade by peripheral nerve stimulators (e.g., TOF), together with measured oxygenation parameters, helps find the “lowest effective paralytic dose” and allows quicker recovery of spontaneous neuromuscular transmission once the NMA is discontinued. Some clinicians do not believe that TOF monitoring is necessary and believe that using the clinical values alone is sufficient to determine NMA dosing.

3. TOF delivers four supramaximal electrical impulses every 0.5 seconds to the ulnar, facial, or posterior tibial nerve. Response to the impulse is then measured by muscle twitches visualized from the associated innervated muscles (thumb or eye). Goals of paralysis can usually be reached with 2 or 3 of 4 twitches; 0 of 4 twitches indicates complete neuromuscular blockade, usually necessitating a decrease in NMA dose. Oxygenation goals may be reached even with 4 of 4 twitches, indicating that the NMA dose is effective and an increase is not warranted.

4. A baseline electrical current should be established before initiating a NMA to determine how much electrical current is needed to produce a twitch. Usually 10–20 mA (amperage) is sufficient. The conduction of the electrical impulse may be dampened because of peripheral edema, loss of electrode adhesion, incorrect electrode placement, and hypothermia, which can lead to inaccurate readings. These factors should be reassessed with each use of the TOF.

J. Complications of NMBAs

1. Prolonged weakness: Several case reports associate the use of NMBAs and prolonged weakness, which could include myopathy, polyneuropathy, or neuromyopathy. Other risk factors may include concomitant use of corticosteroids, persistent hyperglycemia, and type of NMA used. However, data are inconsistent and not controlled, and further studies are needed to clarify specific risk factors for prolonged weakness associated with NMBAs. Following a trend in creatine kinase concentration every 48–72 hours may help assess the presence of myopathy secondary to paralysis and prolonged immobilization. A creatine kinase concentration should not be solely relied on for the presence of myopathy, and daily determination of the need for the NMA should still be considered, even with a normal creatine kinase.

2. Corneal abrasions: Paralysis eliminates the ability of the eyes to close and blink, increasing the risk of corneal ulcerations and infection. Prophylactic eye protection must be used in all patients on NMBAs (e.g., lubricating eye ointments or eye covers).

3. Thrombosis: Caused partly by immobility, patients receiving a NMA may be up to 8 times more likely to have a DVT than those not on a NMA. Prophylaxis for a DVT must be provided for all patients on a NMA.

4. Awareness: Recent case reports document patient awareness during paralysis in the ICU. These patients report weird dreams, fear, resistance of restraints, thoughts of life and death, and pain. It is critical that patients be deeply sedated before initiating a NMA.
5. Resistance to paralysis and/or potentiation: Certain disease states may produce an up-regulation in acetylcholine skeletal muscle receptors, leading to higher-than-normal doses of the NMBA (e.g., muscle trauma, muscle atrophy, burns). Acid-base disorders, electrolyte imbalances, and adrenal insufficiency may also cause unpredictable alterations in dosing requirements.

6. Anaphylaxis: Allergic reactions can occur after the first dose of a NMBA because the ammonium ions in NMBAs are commonly found in the household environment and in household products. If an allergic reaction is suspected, skin prick testing for the NMBA against a control can be done within 6 weeks of the reaction.

Patient Cases

7. A 55-year-old man intubated for severe ARDS (PaO₂/FIO₂ ratio less than 100) is receiving fentanyl 200 mcg/hour, midazolam 8 mg/hour, and propofol 40 mcg/kg/minute. He is deeply sedated but remains hypoxic and dyssynchronous with the ventilator after several changes in mechanical ventilation settings. Which is the most appropriate consideration at this time?
   A. Start scheduled lorazepam every 6 hours.
   B. Add quetiapine 50 mg every 8 hours.
   C. Change propofol to dexmedetomidine.
   D. Start a cisatracurium infusion.

8. A 70-year-old who is day 2 in the ICU is receiving a neuromuscular blocking agent (NMBA) and is sedated for severe ARDS. The TOF over 24 hours is 2 of 4 twitches at an amplitude of 10 mA. Arterial blood gas is pH 7.38, Pco₂ 40, Po₂ 91, and bicarbonate 24 mEq/L on 50% inspired oxygen and 10 cm PEEP; the patient is synchronous with the ventilator, and other clinical markers are stable. Which changes in management would be best to recommend?
   A. Decrease stimulator amplitude to decrease pain from excessive electrical current.
   B. Increase stimulator amplitude to test for more frequent twitches.
   C. Decrease the NMDA dose because the patient is clinically stable.
   D. Increase the NMDA dose until the TOF induces fewer twitches.

VII. POST–INTENSIVE CARE SYNDROME

Post-intensive care syndrome has become a recognized set of medical complications that can start in the ICU and continue for weeks to months after ICU discharge. SCCM has taken progressive steps to help clinicians recognize the prolonged post–ICU complications, which may significantly affect patients and their families over the long term. The SCCM website includes information for providers and families as well as other supportive care websites and video links to educate all involved.

   A. ICU-Acquired Weakness: Muscle weakness that begins to develop during the ICU stay because of prolonged immobility and critical illness. Protracted weakness affects normal daily activity levels and hinders the ability to return to a working environment.

   B. Cognitive Dysfunction: Problems with recall, problem solving, organizational skills, and attention deficits
C. Mental Health: Anxiety, depression, and posttraumatic stress disorder have been well described in the post-ICU recovery period. Patients may need long-term psychological follow-up and medications, depending on the severity of compromise.

D. Family Involvement: The importance of family involvement in care is crucial in the recovery of patients. Providers should educate families and make them well aware of the potential challenges in front of them and the resources that are available, as well as stress the importance of caregiver health hygiene. If the family is physically and emotionally strong, the patient’s recovery is likely to be a faster and more successful process. Researchers have identified core elements essential to clear communication between providers and patients or family:
   1. Use simplified speech: Avoid or minimize complex medical jargon.
   2. Be concrete: Keep explanations or instructions direct and to the point.
   3. Take your time: Do not make the patient or family member feel rushed; rapid speech or communication often prevents full comprehension.
Pain
1. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306. The most updated guidelines from SCCM, the American College of Critical Care Medicine, and the American Society of Health-System Pharmacists. This was a multidisciplinary effort coordinating all three areas of management (pain, agitation, and delirium).
Agitation

1. Balas MC, Vaselevskis EE, Olsen KM, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med 2014;42:1024-36. Known as the ABCDE trial, this was the second study to coordinate the efforts of SATs and SBTs. The investigators added delirium monitoring and management as well as an early mobility protocol to this study; medical or surgical ICU population, n=296. Primary outcome was median time breathing without mechanical ventilator assistance during the 28-day study period. This study used safety screens for the SAT, SBT, and mobility protocols. The intervention group had 3 more days of breathing without mechanical ventilator assistance than did the standard care group (median 24 vs. 21 days; p=0.04). The intervention group was almost half as likely to develop delirium (OR 0.55; p=0.03) and had an increased odds of getting out of bed at least once during the ICU stay (p=0.003) compared with the standard care group.


7. Carson SC, Kress JP, Rodgers J, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Crit Care Med 2006;34:1326-32. Nice study from two large university hospitals, medical ICU population (n=546). Primary outcome was median days on mechanical ventilation, which was lower in the propofol daily interruption group (propofol = 5.8 days; intermittent lorazepam = 8.4 days; p=0.04). Hospital mortality was no different between the two groups.


9. de Wit M, Gennings C, Jenvey W, et al. Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients. Crit Care 2008;12:1-9. Pivotal study terminated early because of complications in patients randomized to the daily interruption of sedation group. The authors concluded that daily interruption is not appropriate in all medical ICU patients. A patient safety screen is now recommended for all patients as part of any daily interruption or SAT.


and Breathe, or ABC, trial, this was the first study to coordinate SATs with SBTs. The study was from four tertiary care hospitals (n=336), and primary outcome was time breathing without assistance during a 28-day study period. This study used a safety screen for both the SAT and the SBT protocols. The intervention group spent more time breathing without assistance than did the standard care group (median 14.7 vs. 11.6 days; p=0.02).


15. Honiden S, Siegel M. Analytic reviews: managing the agitated patient in the ICU: sedation, analgesia, and neuromuscular blockade. J Intensive Care Med 2010;25:187-204. Succinct review of the primary issues in sedation management. This was published before the 2013 PAD guidelines, but it contains a very good discussion.


17. Hughes CG, Girard TD, Pandharipande P. Daily sedation interruption versus targeted light sedation strategies in ICU patients. Crit Care Med 2013;41:S39-45. This review finds that it is still unclear whether one sedation strategy is better than the other, that using the two strategies together may offer more benefit than either alone, and that coordinating either strategy with SBT should be considered.

18. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine versus midazolam or propofol for sedation during prolonged mechanical ventilation. JAMA 2012;307:1151-60. This article reported on two trials; the “MIDEX” trial compared midazolam with dexmedetomidine, and the “PRODEX” trial compared propofol with dexmedetomidine. Only fentanyl boluses were used for pain management. Primary outcomes were time at target sedation level and duration of mechanical ventilation. The time at target sedation level was the same between groups from both studies; the only difference in median time on mechanical ventilation was between midazolam and dexmedetomidine (164 hours vs. 123 hours; p=0.03).


21. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol. JAMA 2012;308:1985-92. This study (for the SLEAP study investigators and Canadian critical care trials group) compared daily sedation interruption with a standard sedation protocol targeting lighter sedation scores (e.g., RASS 0 to -3; SAS 3 or 4). The study found no difference between the two groups in their end points of time on mechanical ventilation or duration of ICU stay.


24. Riker R, Shahabi Y, Bokesch P, et al. Dexmedetomidine versus midazolam for sedation of critically ill patients. A randomized trial: SEDCOM. JAMA 2009;301:489-99. This study investigated differences in time at targeted sedation level between dexmedetomidine and midazolam. The investigators found no difference in efficacy of sedation; the prevalence of delirium was lower in the dexmedetomidine group, and the median time to extubation was shorter in the dexmedetomidine group.


Delirium


10. Kamdar BB, King LM, Collop NA, et al. The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. Crit Care Med 2013;41:800-9. This study investigated the effects of a sleep protocol before and after implementation. Study investigators found that implementation of a sleep protocol is feasible in an adult ICU, decreases perceived level of noise, and may decrease the incidence of delirium. Very good study that moves forward the discussion regarding the importance of adequate sleep in the ICU and for future research in this area.


14. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306-16. This trial is from the BRAIN-ICU investigators group, which studied the risk factors for and incidence of cognitive impairment 3 and 12 months from ICU discharge to a medical or surgical ICU. The found that 74% of patients developed delirium during their ICU stay, and a longer duration of delirium was associated with worse global cognition and executive function scores at 3 and 12 months after discharge. Use of sedative and analgesic medications was not associated with
cognitive impairment in this study at 3 and 12 months.
18. Vanderbilt University Medical Center. ABCDEFs of Prevention and Safety. Available at www.icudelirium.org. Accessed December 9, 2014. Vanderbilt website containing extensive educational materials about delirium in the ICU for medical professionals, patients, and families. This website uses several modalities for education, including references, training manuals, Vanderbilt’s protocols, and videos, to assist medical professionals in assessing and managing delirium in their ICU.

Neuromuscular Blocking Agents
1. Greenburg SB, Vender J. The use of neuromuscular blocking agents in the ICU: where are we now? Crit Care Med 2013;41:1332-44. Very good review and discussion of NMDAs, including indications, pharmacology, TOF monitoring, and complications of prolonged paralysis.
5. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16. Large multicenter, double-blind trial completed in France (n=340); studied the effects of cisatracurium in patients with early and severe ARDS. Primary end point was 90-day mortality. Investigators found that a fixed dose of cisatracurium for 48 hours decreased mortality in patients with severe ARDS (Pao2/Fio2 less than 120).
ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**  
This patient has a clear indication for intravenous pain medication from his recent trauma and multiple fractures. An “as-needed” opiate would likely not keep up with his pain control needs (Answers B and C are incorrect). His age and history of hypertension place him at risk of delirium; therefore, a benzodiazepine is not the best initial choice for this patient. A propofol infusion would be the most appropriate sedative (Answer A is incorrect; Answer D is correct).

2. **Answer: D**  
Chest tube removal is specifically cited in the PAD guidelines as an indication for both preemptive analgesia and nonpharmacologic relaxation techniques. This is given a “strong” recommendation, determining that the benefits outweigh the risks of preemptive therapy (Answer D is correct). Acetaminophen given just before the procedure will most likely not adequately treat pain associated with chest tube removal (Answer A is incorrect). Increasing an opiate infusion several hours before a bedside procedure can expose the patient to substantially higher amounts of drug than needed and cause delayed awakening times or other significant adverse effects from opiates (Answer C is incorrect). Extensive studies of appropriate preemptive analgesia for chest tube removal have not been completed; however, administering an opiate appropriately timed before manipulation of a chest tube is an accepted standard of therapy (Answer B is incorrect).

3. **Answer: A**  
This patient has end-stage liver failure and acute renal failure; he will therefore not predictably clear midazolam or fentanyl infusions. With a RASS of -4 to -5, indicating no meaningful responsiveness to stimuli, all sedatives should be held if the patient is otherwise clinically stable to allow time for clearance of medications (Answer A is correct). A decrease in sedative dose, or changing to a different sedative is not needed at this time based on the deeply sedated RASS score, and would only further delay awakening time.

4. **Answer: B**  
Withdrawal from certain home medications may occur if these medications are not reinitiated within a few days of admission. The onset of withdrawal symptoms will vary depending on the half-life of each medication. Symptoms may include agitation, anxiety, psychosis, insomnia, hypertension, and tachycardia and can occur with medications such as opiates, GABA receptor agonists, antiepileptics, antidepressants, and antipsychotics. A pharmacist can assist the medical team by obtaining a thorough medication history and assessment of home medication adherence to help identify drug withdrawal symptoms. Reinitiating these medications can be considered, unless contraindicated because of the clinical scenario (e.g., drug-drug interactions, drug-disease state interactions). The Agitation and Sedation section of the PAD guidelines discusses identifying and treating the etiology of agitation before adding other medications; reinitiating the benzodiazepine and antidepressant to treat withdrawal symptoms is the most appropriate answer (Answer B is correct). Neither fentanyl nor dexmedetomidine would treat withdrawal from a benzodiazepine or antidepressant (Answers A, C, and D are incorrect).

5. **Answer: C**  
The PAD guidelines stress using nonpharmacologic means to manage delirium when it is safe for the patient. Strong evidence for using medications such as antipsychotics and dexmedetomidine to treat delirium is still not available. This patient’s presentation of “alert and calm with intermittent periods of agitation” is a common scenario, and initial therapy should focus on reorienting and getting the patient interactive and mobile (Answers A and D are incorrect; Answer C is correct). Dehydration is a common cause of agitation, and it should be addressed; however, with normal laboratory values and vital signs, this patient is unlikely dehydrated at this time (Answer B is incorrect).

6. **Answer: B**  
In the general population, systemic corticosteroids are known to cause many neuropsychiatric events, including hyperactivity and agitation; in a recent study of adult ICU patients with acute lung injury, only age and use of systemic corticosteroids in the preceding 24 hours were independently associated with the transition to delirium from a non-delirious state (Answer B is correct). Benzodiazepines have a sedating effect and may calm
an acutely agitated patient; however, they would not be recommended in this patient because they could worsen her confusion or delirium (Answer A is incorrect). The PAD guidelines state that no evidence supports the use of haloperidol to reduce the duration of delirium (Answer C is incorrect). Vancomycin is not currently recognized as a cause of delirium; therefore, changing to linezolid is not indicated (Answer D is incorrect).

7. **Answer: D**

The midazolam dose is high, and the patient is “deeply sedated”; therefore, adding another benzodiazepine will likely not improve this patient’s clinical status. Quetiapine has no indication for general sedation in a critically ill patient, and it should not be a consideration for sedation in this patient with severe ARDS. Dexmedetomidine is considered a weak sedative with no effect on respiratory drive; therefore, it would likely not improve this patient’s ventilator dyssynchrony and hypoxia (Answers A–C are incorrect). At this stage in the patient’s clinical course, it is reasonable to consider an NMMA. In a 2010 study of cisatracurium versus placebo for 48 hours in early ARDS, the cisatracurium group had more days free of mechanical ventilation and decreased mortality (30% vs. 44%) at 90 days for the subgroup of patients with severe ARDS (Pao2/Fio2 ratio less than 120). The incidence of pneumothorax was lower in the cisatracurium group than in the placebo group (4% vs. 11%). There were more days free of organ failure (non-lung) in the cisatracurium group than in the placebo group (15.8 vs. 12.2 days) in the first 28 days. A recent meta-analysis concluded that using short-term cisatracurium in patients with severe ARDS decreases mortality and time on mechanical ventilation compared with placebo. The risk of prolonged neuromuscular weakness was not found in these studies; however, use beyond 48 hours may increase this risk (Answer D is correct).

8. **Answer: C**

The TOF method of assessment is primarily used to help determine the degree of neuromuscular blockade and should not be used to titrate the dose of the NMBA. The patient’s clinical status and laboratory values are the true determinants for dose adjustment of the NMBA. Patients may be at their clinical goal with a TOF of 2 or 3 twitches of 4. This is the ideal scenario, and it will predict a faster reversal of neuromuscular blockade (Answer C is correct). A TOF of 0 or 1 of 4 twitches predicts a significantly slower neuromuscular recovery time, and clinicians should try to decrease the NMBA as soon as the patient is clinically stable by laboratory values and ventilator management (Answer D is incorrect). A baseline electrical current intensity (amperage) should be established before the onset of neuromuscular blockade and should not be changed during paralysis unless a new baseline is indicated (Answer A is incorrect). As the electrical intensity (amperage) is established, an increase in the amperage is not indicated during infusion of the NMBA in order to increase the number of twitches. A decrease in the dose of NMBA would be indicated if an increase in the number of twitches were the clinical goal (Answer B is incorrect).
1. **Answer: D**
   Propofol infusion syndrome is a well-documented and complex set of adverse events, potentially resulting in multiorgan failure. An elevation in lactate, creatine kinase, transaminases, SCr, and triglycerides and the presence of a metabolic acidosis are some of the abnormalities that should concern the critical care provider for the presence of PRIS (Answer D is correct). Both DVT and critical illness polyneuropathy are serious concerns in the ICU patient; however, the abnormalities in the case are not representative of these complications (Answers A and B are incorrect). There are currently no known abnormal laboratory values to help determine whether delirium is present in an ICU patient (Answer C is incorrect).

2. **Answer: B**
   This patient is at risk of propylene glycol toxicity after receiving a lorazepam drip for more than 48 hours. Lorazepam is dissolved in propylene glycol, an alcohol that can induce an osmolar gap and metabolic lactic acidosis, particularly in patients with significant hepatic or renal failure. Quantitative propylene glycol levels may be unavailable; therefore, surrogate markers such as an abnormal osmolar gap (greater than 10 mmol) and metabolic acidosis may indicate propylene glycol toxicity and a need to discontinue lorazepam. Although lorazepam drips are not routinely used for general sedation in adult ICUs, they may be used for other indications (e.g., severe EtOH [ethyl alcohol] or benzodiazepine withdrawal), and clinicians should remain aware of this serious complication (Answer B is correct). With an oxygen saturation of 98% on 2 L of oxygen, this patient does not meet the predefined criteria of ARDS (Answer A is incorrect). Encephalopathy will not cause a metabolic acidosis; therefore, an ammonia concentration would not be helpful at this stage (Answer C is incorrect). With a low fractional excretion of sodium and a high BUN/SCr ratio, the patient’s laboratory values are indicative of a pre-renal concern versus acute tubular necrosis (Answer D is incorrect).

3. **Answer: D**
   It is inappropriate to initiate a NMBA in a patient who has a sedation score indicating “agitation.” This implies that the patient may potentially detect pain or discomfort while paralyzed (Answers B and C are incorrect). The goal should be to achieve a deeply sedated and/or non-agitated state before initiating a NMBA in an effort to avoid any patient discomfort that may be undetected during paralysis (Answer D is correct). The SAT would be inappropriate in someone who is rated “agitated” on the sedation scale or in a patient requiring escalating doses of sedation (Answer A is incorrect).

4. **Answer: B**
   The pharmacokinetics/dynamics of prolonged fentanyl infusions have not been well described in the adult ICU population. Most data for fentanyl are derived from short-term infusions or boluses in healthy volunteers and in animal models. Fentanyl is hepatically metabolized primarily by the CYP3A4 enzyme, and decreased clearance of fentanyl has been described in patients with significant liver disease. Other properties of fentanyl (e.g., high volume of distribution, high protein binding, and high lipophilicity) may contribute to unpredictable clearance and a prolonged context-sensitive half-time for patients in acute renal failure or in patients who have inadequate nutritional status (Answer B is correct). Propofol is a CYP3A4 inhibitor; therefore, it should not induce the metabolism of fentanyl (Answer C is incorrect). Propofol is known to chelate trace elements and increase urinary loss of zinc when used for more than 5 days; propofol has not been shown to cause hypocalcemia (Answer D is incorrect). Disease states identified as risk factors for PRIS may include sepsis, acute liver failure, and history of pancreatitis; ARDS is not currently a documented risk factor (Answer A is incorrect).

5. **Answer: B**
   Withdrawal from certain home medications may occur if these medications are not reintiated within a few days of admission. The onset of withdrawal symptoms will vary depending on the half-life of each medication. Symptoms may include agitation, anxiety, psychosis, insomnia, hypertension, and tachycardia and can occur with medications such as opiates, GABA receptor agonists, antiepileptics, antidepressants, and antipsychotics. A pharmacist can assist the medical team by obtaining a thorough medication history and assessment of home medication compliance to help identify drug withdrawal.
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symptoms. Reinitiating these medications can be considered unless contraindicated because of the clinical scenario (e.g., drug-drug interactions, drug-disease state interactions). The Agitation and Sedation section of the PAD guidelines discusses identifying and treating the etiology of agitation before adding other medications; fentanyl should treat this patient’s chronic pain and treat opiate/tramadol withdrawal (Answer B is correct). Adding quetiapine or lorazepam for agitation would not address or treat the underlying etiology of potential opiate/tramadol withdrawal (Answers A and C are incorrect). Patient-controlled analgesia with an opiate would help treat opiate withdrawal; however, this patient is not alert enough to use it (Answer D is incorrect).

6. Answer: D
Up to 30%–60% of ICU patients may go through alcohol withdrawal on cessation of alcohol use. The presence of alcohol withdrawal in ICU patients may prolong their ICU stay, increase hospital costs significantly, and lead to other complications during the hospital stay. Early and aggressive symptom-triggered management with a benzodiazepine, particularly in a patient with a history of alcohol withdrawal, is a key element in management. There is no otherwise published protocol for alcohol withdrawal in ICU patients. In this case, although dexmedetomidine has been shown useful as an adjunctive agent to help decrease sympathetic storm and agitation secondary to alcohol withdrawal, it is not currently recommended for use as a single agent for alcohol withdrawal (Answer A is incorrect). Opiates do not treat alcohol withdrawal (Answer C is incorrect). Phenytoin is a known antiepileptic for use in epilepsy; however, it has not been shown to be effective in preventing or treating alcohol withdrawal (Answer B is incorrect). Benzodiazepines are the drugs of choice for alcohol withdrawal seizures; therefore, midazolam is the most appropriate drug for this patient, whose medical history is significant for recurrent alcohol withdrawal seizures (Answer D is correct).

7. Answer: B
Giving several medications that carry a risk of QTc prolongation is a common scenario in the ICU. Clinicians should seek to find alternatives to decrease this risk, if possible, particularly if the QTc is already high (e.g., QTc of 500 or greater is considered high risk of cardiac arrhythmias, including torsades de pointes). Switching levofoxacin to piperacillin-tazobactam is an acceptable alternative to treat an aspiration pneumonia and would decrease the risk of increasing the QTc interval further (Answer B is correct). This patient is at risk of delirium given the patient’s age and being critically ill in the ICU. Avoiding medications that may cause or worsen delirium, such as benzodiazepines, is a strong recommendation in the PAD guidelines (Answer D is incorrect). With a QTc of 500 milliseconds, increasing the quetiapine dose for agitation could further increase the QTc and put this patient at high risk of cardiac arrhythmias (Answer A is incorrect). Amiodarone and quetiapine are home medications for this patient, and they should be continued, if safe. Alternative methods for decreasing the risk of QTc prolongation should be considered before discontinuing chronic medications (Answer C is incorrect).

8. Answer: D
Dementia is a progressive and chronic state of cognitive impairment that worsens over weeks to months; this differs from the acute onset characteristic of ICU delirium (Answer A is incorrect). Alcohol withdrawal should always be a consideration for patients who become altered or agitated in the ICU. This patient’s vital signs are normal, and she is presenting in a hypoactive state; these findings are not typical for acute alcohol withdrawal, and alternative causes for her decline in mental status need to be considered (Answer B is incorrect). Adrenal insufficiency in the ICU usually presents with abnormal laboratory values and/or hemodynamic instability. This patient’s laboratory values and hemodynamics are reported as normal; therefore, adrenal insufficiency is unlikely (Answer C is incorrect). Both iatrogenic and non-iatrogenic causes for delirium are well documented in the literature. Dehydration and infection are common causes of delirium, particularly in the older adult population. This patient has several reasons for being dehydrated in the hospital: NPO status, persistent fevers, and taking hydrochlorothiazide. Untreated infection or lack of source control is also a concern with the presence of persistent fever, even while the patient is taking antibiotics (Answer D is correct).