Analgesia, Sedation and Neuromuscular Blockade - Critically Ill COVID19 Patients

This document should be used in conjunction with the guidelines listed below and applies to mechanically ventilated patients only.

Adult Continuous Infusion: Standard Concentrations and Nursing Titration Guidelines: [LINK]

Pain, Agitation, Delirium Guideline for Mechanically Ventilated Patients: [LINK]

ICU Sedation with Propofol for Mechanically Ventilated Patients: [LINK]

Neuromuscular Blockade Therapy Guidelines: [LINK]

Methadone Formulary Guidance [LINK]

Goal: Due to the COVID-19 pandemic, medications commonly used for analgesia, sedation, and neuromuscular blockade have become difficult to obtain. The goal of these guidelines is to promote early use of enteral therapies and minimize intravenous agents when possible.

<table>
<thead>
<tr>
<th>Aspects of Care</th>
<th>Considerations</th>
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<tbody>
<tr>
<td><strong>Global</strong></td>
<td>All patients should be assessed for pain and sedation in a manner consistent with the UPHS Pain, Agitation, Delirium Pathway for Mechanically Ventilated Patients. A goal RASS and BPS for each patient should be established and documented. <strong>Patients with ARDS resulting in ventilator asynchrony despite ventilator adjustments may require lower RASS goals of -2 to -3.</strong> If ventilator asynchrony persists despite RASS goal of -2 to -3, a RASS goal of -4 to -5 should be attempted. If ventilator asynchrony persists, consider neuromuscular blockage with a RASS goal of -4 to -5. Dosing and monitoring of neuromuscular blockade should be done in accordance with the UPHS Guideline for Use of Neuromuscular Blocking Agents in the ICU.</td>
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<td>Daily evaluation of analgesia and sedation as well as the need for neuromuscular blockade is imperative. Minimization of medications should be considered where possible to conserve supply.</td>
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<td>In general, patients on vasopressors <strong>WITHOUT</strong> adequate volume resuscitation should not receive oral therapies. Once volume resuscitated, oral therapy should be initiated. Medications should be scheduled together to assist the bedside nurse with bundled care.</td>
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<td>When implementing the therapies below, consider patient specific factors such as history of substance abuse, age, or body weight.</td>
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<td>Please note selection of agent may be impacted by availability at each institution.</td>
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<td><strong>Analgesia</strong></td>
<td>Analgesic therapy should not be used with a goal of achieving a determined RASS goal. <strong>If a patient has a BPS&lt;6, but higher than desired RASS, a sedative medication should be initiated.</strong></td>
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<td>1. Intermittent IV analgesia: Use of intermittent IV analgesia to achieve goal BPS or RASS is recommended as first line.</td>
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<td>2. <strong>In patients tolerant of RASS 0 to -1/2, consider initiation of oral analgesic therapy prior to continuous infusion.</strong></td>
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<td>3. If goal RASS is not achieved or BPS remains &gt;6 with the above measures, refer to the UPHS PAD guidelines for initiation of IV continuous infusion therapy.</td>
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<td>In mechanically ventilated patients that require continuous infusion analgesia that do <strong>NOT</strong> require frequent neurologic assessment, the following algorithm should be applied:</td>
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4. Continuous infusion analgesia:
   a. Fentanyl is the preferred analgesic for continuous infusion. Hydromorphone is an alternative analgesic for continuous infusion.
   b. Morphine is an alternative analgesic for continuous infusion, but not preferred in ICU patients. Patients with renal dysfunction may require lower doses due to accumulation. Monitor for hypotension upon initiation.

5. Oral analgesic therapy (Mechanical ventilation expected >24hrs): Following initiation of continuous infusion therapy, oral analgesic therapy should be initiated as described below:
   - Oxycodone 10-20 mg q6h standing (May titrate)
   - Hydromorphone 4-6 mg Q4-6h standing (May titrate)
   - Methadone tablet 5 mg Q8h OR Methadone 2.5 mg IV Q8H (if available)
     o This is a fixed dose and SHOULD NOT be increased
     o Methadone WILL NOT require approval for use from APS or Palliative Care, but should be discussed with a clinical pharmacist
     o Prior to initiation of methadone patients should be assessed for:
       - Drug interactions that may alter drug levels
       - Prolonged QTc: Obtain a baseline, pre-treatment, corrected QT interval (QTc) using a standard 12-lead ECG
         o An ECG recording from Telemetry or a mobile ECG device (e.g. *KardiaMobile 6L provides a 6 lead ECG) can also be used as a reasonable screening tool but will be less accurate for borderline cases.
         o Refer to institution guidelines for specific initiation and monitoring parameters. See: Considerations at the Time of Initiation of Medications for COVID-19 that Can Affect the QT Interval Guidance.
       - Acetaminophen may be considered in patients following consideration of antipyretic effect and masking of fever. Adjust dose consistent with organ function. Oral route is preferred see Penn Medicine Formulary for IV restrictions.

Sedation

Sedation should be initiated in patients unable to achieve goal RASS despite achievement of BPS <6.

In mechanically ventilated patients that require continuous sedation for agitation or ventilator synchrony, not requiring frequent neurologic assessment the following algorithm should be applied:

1. Propofol continuous infusion is the sedative of choice
   - Patients should be evaluated for baseline triglyceride (TG) monitoring and Q48 hours
   - If patients exceed 300 mg/dL switch to q24h monitoring
   - If triglycerides exceed 800 mg/dL, discontinue propofol and initiate an alternate agent
   - If above 800 mg/dL, obtain lipase and amylase to evaluate for pancreatitis

2. Intermittent Benzodiazepines
   a. Intermittent bolus doses of intravenous benzodiazepines are preferred to achieve goal RASS if non-benzodiazepines are contraindicated or ineffective.
   b. Consider the below therapies if propofol is contraindicated or ineffective and/or intermittent benzodiazepines are unsuccessful, or anticipated to be unsuccessful, in achieving goal sedation.
3. Consider the below therapies if propofol or intermittent benzodiazepines are contraindicated or ineffective.
   a. Phenobarbital (IV or PO)
      i. Loading Dose: 130 mg IV x 1
      ii. Maintenance Dose: 64.8 – 97.2 mg Via Gastric Tube Q8h
         1. Titrate to sedation goal while not exceeding a level of 50mg/L
         2. In patients unable to tolerate orals, IV therapy with 65 – 130 mg Q8h may be used

   OR

   b. Continuous Benzodiazepines
      i. Midazolam or lorazepam are the preferred continuous infusion benzodiazepines (Institutional preference or availability)

4. Following initiation of continuous infusion sedation (propofol or benzodiazepine), begin oral benzodiazepine therapy with one of the agents below to minimize intravenous therapy. These agents may be titrated to achieve desired sedation goal.
   - Clonazepam 1-2 mg Q8h
   - Lorazepam 1-2 mg Q6h
   - Oxazepam 10 - 30 mg Q8h

5. Other adjunctive medications (consult with clinical pharmacy)
   - Quetiapine or alternative antipsychotic. Exercise caution in patients on other QTc prolonging medications such as hydroxychloroquine or methadone.
   - Gabapentin
   - Valproic acid

Dexmedetomidine achieves light sedation (RASS -1/-2). This agent should be used consistent with current UPHS guidelines and should NOT be used in patients requiring deep sedation (RASS -3 to -5) and/or neuromuscular blockade. Caution should be used in patients displaying signs of reduced ventricular function, bradycardia or heart block.

If a patient has a RASS of -4/-5, but continues to demonstrate ventilator asynchrony, despite appropriate ventilator manipulation, therapy with a paralytic agent should be initiated. Additional use of sedation with a low RASS WILL NOT aid in increased ventilator synchrony and will lead to inappropriate overdosing of patients and waste of drug.

<table>
<thead>
<tr>
<th>Neuromuscular blockade</th>
<th>Neuromuscular blockade is only required in the presence of ventilator dyssynchrony and deep sedation (RASS -4 to -5)</th>
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<tr>
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<td>Ensure adequate sedation and analgesia are achieved prior to neuromuscular blockade as evidenced by RASS -4 to -5 and BPS &lt;6. If BIS is not available, do not titrate analgesia or sedation once neuromuscular blockade has been established. If BIS is available, titrate to 40-60.</td>
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<td>Intermittent dosing may be preferred over continuous infusion</td>
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<td>Dose optimization of paralytic agents should be used based upon individual patient characteristics, such as renal or hepatic function, paralytic requirements, etc.</td>
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<td>Paralytic requirement should be evaluated daily to limit use</td>
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<tr>
<td>1. Intermittent dosing:</td>
<td>Vecuronium is the preferred agent for intermittent dosing (Alternative: Rocuronium)</td>
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<td>Dosing: 0.1 – 0.2 mg/kg every 4-6 hours</td>
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Dose and frequency will vary based on organ dysfunction; Patients with significant organ dysfunction may require smaller and less frequent dosing
- If initial dosing of intermittent vecuronium or rocuronium does not achieve desired ventilator synchrony and/or TOF 1-2/4, increase dose or frequency as appropriate
- If patient goals are not achieved or requires more than Q4h dosing, begin continuous infusion neuromuscular blocking agent

2. Continuous infusion:
   - Vecuronium is the preferred NMBA for patients without renal/liver dysfunction
   - Cisatracurium is permitted for patients with significant organ dysfunction
   - Rocuronium is an alternative NMBA to the above strategies
     - Dosing strategy will vary based on organ function

Appendix 1: Opioid Conversion

When converting continuous opioid therapy, the following should be considered:
1. Current analgesic assessment and control
2. The presence of organ dysfunction as certain medications may require decreased doses in these patients
3. Previous opioid exposure including oral therapy
4. Dose reduction for incomplete cross tolerance
5. Evaluation of possible fentanyl tachyphylaxis

Equianalgesic Dosing of Intravenous Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Equianalgesic IV Dose</th>
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<tbody>
<tr>
<td>Fentanyl</td>
<td>200 mcg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3 mg</td>
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<tr>
<td>Morphine</td>
<td>20 mg</td>
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Patients transitioning between agents should be bolused with an equianalgesic dose of the new medication and started on an appropriate dose of continuous infusion. Prior intravenous therapy should then be discontinued.