

**Protocolized Sedation vs Usual Care in Pediatric Patients
Mechanically Ventilated for Acute Respiratory Failure**

Supplement 2 – Table of Contents

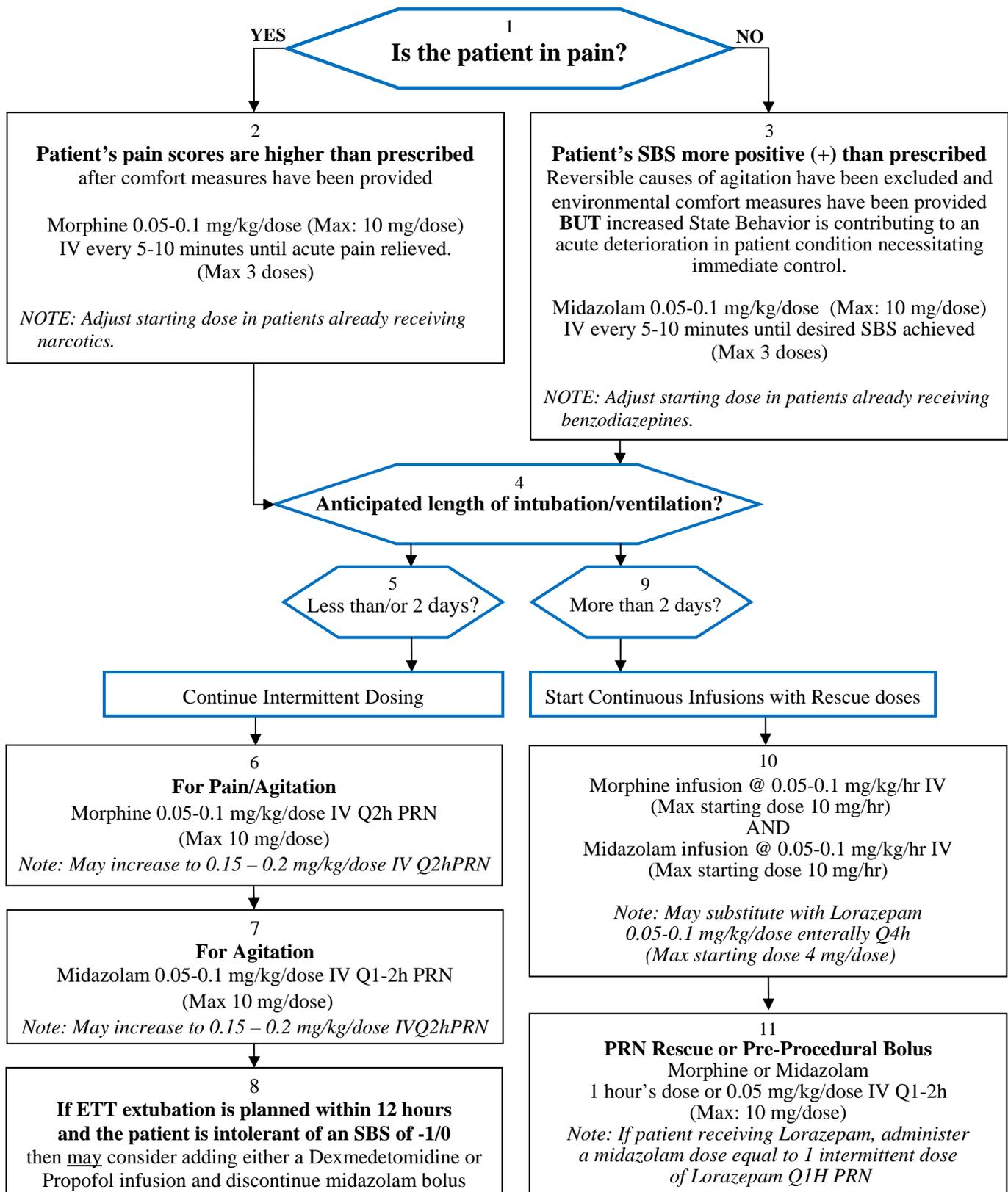
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RESTORE

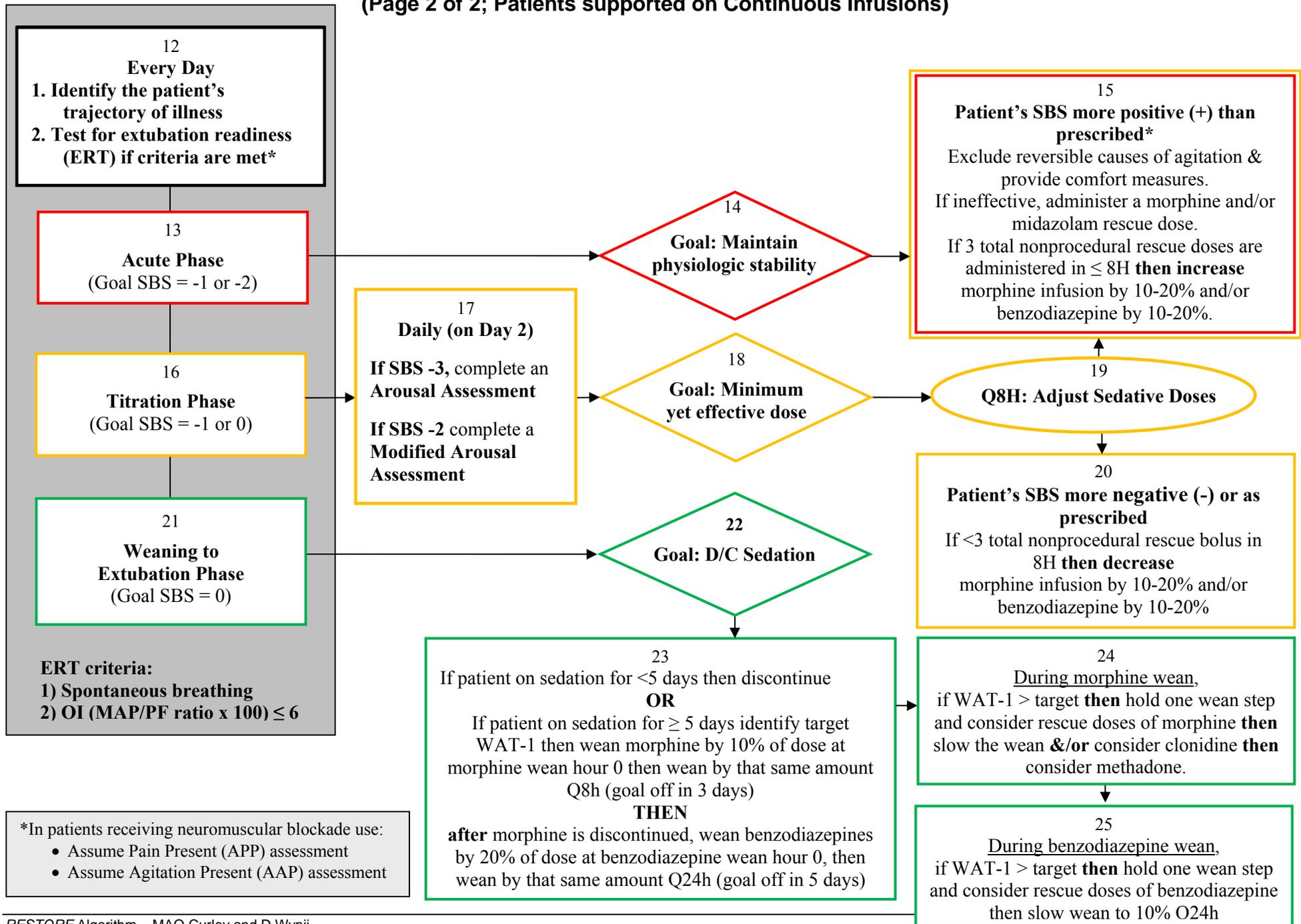
Nurse-Implemented Goal-Directed Comfort Algorithm

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RESTORE

Nurse-Implemented Goal-Directed Comfort Algorithm (Page 2 of 2; Patients supported on Continuous Infusions)



RESTORE Nurse-Implemented Goal-Directed Comfort Algorithm

These guidelines are designed to provide clinicians with an analytical framework for the evaluation and management of pain and agitation in intubated infants and children supported on mechanical ventilation. These guidelines are not intended to establish a protocol for **all** patients supported on mechanical ventilation nor are they intended to replace a clinician's clinical judgment. If a patient does not achieve an acceptable level of comfort and/or safety with the following recommendations, then the multidisciplinary care team is encouraged to re-evaluate the patient and alter the management plan accordingly.

The following assumptions apply:

1. The comfort algorithm is used to manage pain and agitation in intubated patients supported on mechanical ventilation. Comfort is defined as an acceptable level of analgesia and sedation for an individual patient.
2. Pain and SBS assessments are completed at least every four hours and after each intervention using the "AIR" cycle: **Assessment-Intervention-Reassessment**. The rationale for each intervention is documented in the medical record.
3. The patient's pain and SBS scores are evaluated during routine care. Similar to the Glasgow coma scale, the SBS requires the use of a progressive stimulus to quantify the minimal stimulus necessary to elicit a patient's response. First, observe the patient undisturbed. Second, provide progressive stimuli, as necessary, to elicit the patient's response. Specifically, speak the patient's name using a calm voice. If there is no response, then speak the patient's name and gently touch the patient's body. If there is still no response, assess the patient's response to a planned noxious stimulus, such as endotracheal suctioning. Third, console the patient for at least 2 minutes. If a patient is unresponsive to usual cares, including ETT suctioning and assessment of an SBS score is critical then, and only then, provide a painful stimulus. Using a pencil/pen, provide <5 seconds of direct pressure to the patient's nail bed. If there is still no response after painful stimulus, it can be concluded that the patient is "unresponsive."
4. Clinicians should adjust the recommended morphine and midazolam starting doses based upon the patient's individual needs. For example, patients with a history of opioid or benzodiazepine exposure will generally require higher starting doses than patients who are opioid/benzodiazepine naïve.
5. In general, drug dosing is based on actual body weight. Consider using an adjusted dosing weight if the patient is >130% of ideal body weight. Normalization to adult dosing is considered in patients whose weight is >70 kg (average adult body weight).
6. Any correctable environmental and/or physical factor causing discomfort is addressed before the introduction of pharmacological agents: Family presence, day-night cycling, and sleep are encouraged. Attention is paid to the provision of feeding and hydration, appropriate lighting, minimization of environmental noise, and the temporal orientation of patients.
7. Pharmacologic agents to manage sleep and/or delirium may be used.
8. Patients can enter the algorithm at Box 1 immediately after intubation. Box 4 helps to determine progression to either Box 5 (intermittent sedatives) or Box 9 (continuous infusion of sedatives) depending on anticipated length of intubation. If the patient is already intubated and the length of intubation is clear, proceed directly to Box 5 or Box 9 as appropriate. Transition plans are discussed during multidisciplinary rounds. The Pharmacist Coinvestigator or unit-based *RESTORE* Champions are available for consultation.

RESTORE Algorithm (Page 1)

Box 1	<p>Is the patient in pain?</p> <p><i>Rationale: It is important to identify the source of a patient's discomfort so that appropriate management can be initiated. If a patient is in pain, opioids should be administered. Agitation in the ICU patient may result from inadequate pain relief. If however, the patient does not appear to have a pain source and is scoring lighter than the prescribed SBS, non-pharmacologic comfort measures should be tried, and if unsuccessful, a benzodiazepine should be administered.</i></p>
Box 2	<p>Patient's pain scores are higher than prescribed after comfort measures have been provided.</p> <p>If YES (patient in pain): Administer morphine 0.05-0.1 mg/kg/dose (max 10 mg/dose) IV every 5-10 minutes until acute pain relieved. Administer a maximum of 3 doses.¹</p> <p>NOTE: Adjust starting dose in patients already receiving opioids.</p> <p><i>Rationale: Priority is to relieve the patient's pain as quickly as possible. Starting doses should be adjusted in patients already receiving opioids.</i></p> <p><i>Patients with a history of opioid exposure will generally require higher starting doses than those who are opioid naïve.</i></p>
Box 3	<p>If NO (patient not in pain): Patient's SBS more positive (+) than prescribed</p> <p>Reversible causes of agitation have been excluded and environmental comfort measures have been provided BUT increased State Behavior is contributing to an acute deterioration in patient condition necessitating immediate control.</p> <p>Administer midazolam 0.05-0.1 mg/kg/dose (max 10 mg/dose) IV every 5-10 minutes until desired SBS state achieved. Administer a maximum of 3 doses.²</p> <p>NOTE: Adjust starting dose in patients already receiving benzodiazepines.</p> <p><i>Rationale: The priority is to help the patient achieve a safe and comfortable state as quickly as possible. Intubated patients who appear uncomfortable should be assessed for the adequacy of oxygenation and ventilation and other potentially reversible causes of agitation (e.g. urinary retention, infiltrated intravenous lines, etc.). All intubated patients should receive developmentally or age-appropriate environmental and non-pharmacologic interventions to optimize comfort measures (e.g. patient reassurance/communication, light/noise control, swaddling/repositioning, therapeutic use of music, and parental comfort). After pain and reversible causes of agitation have been excluded and environmental comfort measures have failed, the priority is to achieve the desired SBS as quickly as possible.</i></p> <p><i>Patients with a history of benzodiazepine exposure will generally require higher starting doses than those who are benzodiazepine naïve.</i></p>

¹ morphine: peak analgesic effect in 20 minutes; duration of action approximately 2 hours.

² midazolam: peak sedation effect in 5–10 minutes; duration of action approximately 30-120 minutes.

<p>Box 4</p>	<p>Anticipated length of intubation/ventilation?³</p> <p><i>Rationale: Anticipating the total length of intubation and mechanical ventilation helps to determine the best approach to patient management. Continuous IV analgesia and/or sedation have been identified as an independent predictor of a longer duration of mechanical ventilation and longer ICU and hospital LOS.⁴ Tolerance⁵ may develop more rapidly with continuous rather than intermittent opioid or benzodiazepine dosing.⁶ A threshold of two days anticipated total intubation is used to determine whether or not to begin continuous infusions.</i></p>
<p>Box 5</p>	<p>Length of intubation/ventilation anticipated to be ≤ 2 days – <u>Continue Intermittent Doses</u></p> <p>Patients with an anticipated length of intubation/mechanical ventilation of <2 days and who are not chemically paralyzed. Examples: The patient with a plan to remain intubated overnight or the patient who is intubated for transient respiratory depression.</p> <p><i>Goal: Maintain comfort and safety; prescribe SBS depending on the individual needs of the patient; extubate within 2 days.</i></p> <p><i>Rationale: If the anticipated length of intubation is less than 2 days, avoid continuous infusions. Scheduled intermittent and rescue doses of opioids and benzodiazepines are prescribed. If a patient’s clinical trajectory changes and extubation is no longer anticipated within 2 days then start continuous infusions (Box 10).</i></p>
<p>Box 6</p>	<p>For Pain/Agitation: morphine 0.05-0.1 mg/kg/dose (max 10 mg/dose) IV Q2h PRN pain/agitation</p> <p>Note: If the patient fails to respond to the starting dose, may increase morphine to 0.15 – 0.2 mg/kg/dose (max 10 mg/dose) IV Q2h PRN pain</p> <p><i>Rationale: morphine is the preferred opioid analgesic because, compared with fentanyl, it has a longer duration of action and has some sedative properties. Consider using the higher end of dose range for opioids if pain is expected (eg: post-operative patient).</i></p>
<p>Box 7</p>	<p>For Agitation: midazolam 0.05-0.1 mg/kg/dose (max 10 mg/dose) IV Q1-2h PRN pain</p> <p>May substitute with lorazepam 0.05-0.1 mg/kg/dose enterally Q4h if IV access is a problem or if the patient is tolerating enteral feedings</p> <p>Note: If the patient fails to respond to the starting dose, may increase midazolam to 0.15 – 0.2 mg/kg/dose (max 10 mg/dose) IV Q2h PRN agitation</p> <p><i>If SBS score remains more positive than prescribed after increasing the bolus dose of either morphine or midazolam then increase the bolus dose of the other agent.</i></p> <p><i>Rationale: Compared with midazolam, lorazepam has a longer duration of action⁷ and flexibility regarding route of administration (i.e. the same dose may be used intravenously or enterally).</i></p>

³Changes in the patient’s anticipated illness trajectory may require a change in strategy.

⁴ Kollef et al. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. Chest 1998;14 :347-373.

⁵ Tolerance is operationally defined as decreasing pharmacologic effects of a drug after repeated administration or as requirements for larger doses of the same drug to achieve the same clinical effect. Tobias JD. CCM 2000; 28:2122-2132.

⁶ Arnold et al. Changes in the pharmacodynamic response to fentanyl in neonates. J Pediatr 1991;119:639-643.

⁷ Enteral lorazepam: onset 60 minutes; duration approximately 12 hours

<p>Box 8</p>	<p>If ETT extubation is planned within 12 hours and the patient is intolerant of an SBS of -1/0 then may consider adding either a dexmedetomidine or propofol infusion and discontinue midazolam bolus doses.</p> <ul style="list-style-type: none"> <i>Dexmedetomidine infusion (max duration <24 hours) is titrated to achieve desired SBS score in patients over 2 months of age and/or in infants weighing more than 5 kg. The usual continuous infusion dosage is 0.2 – 0.5 mcg/kg/hr. NOTE: Whereas adequate sedation and analgesia is typically achieved with dosing of 0.5 mcg/kg/hr and current labeling includes continuous infusion doses up to 0.7 mcg/kg/hr, infusions as high as 2 mcg/kg/hr have been reported as necessary to achieve sedation goals. When ready for extubation, discontinue dexmedetomidine and then extubate patient when SBS 0.⁸</i> <i>Propofol infusion (max duration <12 hours): Usual starting dose is 12.5–25 mcg/kg/min, titrated to achieve desired SBS score, up to a usual maximum of 150 mcg/kg/min. When ready for extubation, discontinue propofol, and then extubate when SBS 0.⁹</i> <i>Patients receiving either agent may still receive morphine bolus doses for pain, but midazolam bolus doses are discontinued. Duplication of sedative therapy is typically unnecessary for a short term intubation.</i>
<p>Box 9</p>	<p>Length of intubation/ventilation anticipated to be more than 2 days – <u>Start Continuous Infusions with Rescue doses</u></p> <p><i>Rationale: If the anticipated length of intubation is more than 2 days, continuous infusions are started and intermittent rescue doses are prescribed as PRN for procedures or SBS >target.</i></p>
<p>Box 10</p>	<p>Morphine infusion 0.05-0.1 mg/kg/hr IV (max starting dose 10 mg/hr) AND midazolam infusion 0.05-0.1 mg/kg/hr IV (max starting dose 10 mg/hr)¹⁰</p> <p>May substitute midazolam with lorazepam 0.05-0.1 mg/kg/dose enterally Q4h (max starting dose 4 mg/dose)</p> <p><i>Rationale: The analgesic of choice for continuous infusion is morphine and the sedative of choice for continuous infusion is midazolam.¹¹ Patients on fentanyl infusions are reported to develop tolerance more quickly.¹² Fentanyl may be used in patients with profound hypotension, unremitting reactive airways disease or intolerance to morphine. If used, fentanyl is titrated and weaned with the same strategy as morphine in this protocol.</i></p>

⁸ dexmedetomidine: onset immediate; duration approximately < 6 minutes

⁹ propofol: onset 30-50 seconds; duration approximately 3-10 minutes

¹⁰ midazolam: When given by continuous intravenous infusion, the duration of action is significantly longer and, after prolonged administration, sedative effects may persist for 48 hours after discontinuation of the agent.

¹¹ When switching to a morphine infusion use the following conversions. 1 mg of intravenous morphine sulfate: 15 micrograms intravenous fentanyl citrate OR 0.15 mg intravenous hydromorphone hydrochloride OR 0.15-0.3 mg intravenous/enteral methadone hydrochloride. Also acceptable as a conversion rate is fentanyl 1 mcg/kg/hr = morphine 0.075 mg/kg/hr. Note that the fentanyl to morphine switch is not considered a wean but a quasi-equivalent transition.

When converting to morphine, the morphine should be titrated as necessary to keep the patient's SBS as prescribed. During this transition the dose should be manipulated to reach the goal range then titrated Q8h per protocol. The usual starting range for morphine when not transitioning from another agent is 0.05-0.1 mg/kg/hr and the higher end of the dose range should be used when the patient is in pain.

¹² Katz et al. CCM 1994;22:763-767.

	<p><i>Midazolam offers several advantages over lorazepam when used as a continuous infusion including ease of titration, greater stability, and fewer side effects associated with accumulation of the excipient in lorazepam.¹³</i></p> <p><i>Enteral lorazepam may be used if IV access is problematic or if the patient is tolerating enteral feedings. Compared with midazolam, lorazepam has a longer duration of action and flexibility regarding route of administration (i.e. the same dose may be used intravenously or enterally).</i></p>
Box 11	<p>PRN Rescue or Pre-Procedural bolus: morphine or midazolam one hour's dose or 0.05 mg/kg/dose IV Q1-2h PRN¹⁴ pain/agitation</p> <p>If patient is receiving lorazepam, administer a midazolam dose equal to one intermittent enteral dose of lorazepam Q1h PRN procedures or pain/agitation. (Example: if a patient is receiving enteral lorazepam 4 mg Q4h, the rescue bolus medication and dose is midazolam 4 mg IV Q1h PRN agitation)</p> <p><i>Rationale: If patient is in acute pain or SBS >target then administer rescue bolus doses of morphine and/or midazolam. The medications that are used as continuous infusions are also used to provide pre-procedural and PRN doses of analgesics and sedatives should they be necessary. A dose that is equivalent to one hour's worth of infusion is used to pre-treat the patient prior to noxious procedures and/or for episodes of agitation. The rationale for each bolus dose is documented in the medical record.</i></p>

¹³ When switching from a midazolam infusion use the following conversions. 1 mg intravenous midazolam: 2 mg intravenous diazepam, 0.15-0.3 mg intravenous or enteral lorazepam. Lorazepam doses are typically 1/4–1/6 of the total daily midazolam dose. For example, if a patient is on midazolam 1 mg/hr IV infusion (24 mg/day) that would convert to lorazepam 4 to 6 mg/day. This can be administered as either 1 mg IV/enteral Q4h (6 mg/day = 1/4th total daily midazolam dose); 1 mg IV/enteral Q6h (4 mg/day = 1/6th total daily midazolam dose); or 0.7 mg IV/enteral Q4h (4.2 mg/day = roughly 1/6th total daily midazolam dose). Typically, the 3rd option is used when the amount per dose causes undesired somnolence.

¹⁴ Per local practice, rescue boluses may be delivered off an infusion pump to avoid repetitive breaks into a central line. This practice is sometimes referred to as “nurse-controlled analgesia” (NCA).

RESTORE Algorithm (Page 2 - Patients supported on Continuous Infusions)

Box 12	<p>Every day:</p> <ol style="list-style-type: none"> 1. Identify the patient’s trajectory of illness 2. Test for extubation readiness if criteria are met*: <p style="text-align: center;">Criteria include: Spontaneous breathing and an Oxgenation Index ≤ 6 [Oxygenation Index (OI) = MAP/PF ratio x 100; MAP is the mean airway pressure and the PF ratio is $\text{PaO}_2/\text{FiO}_2$¹⁵]</p> <p><i>Rationale: The patient’s ability to tolerate the burden of intensive care varies over their course of illness. Daily identification of the patient’s phase of illness (acute, titration, or weaning to extubation) allows the multidisciplinary team to target and, as a team, reach agreement on a management goal for the day.</i></p> <p>If extubation readiness criteria are met, an extubation readiness test (ERT) is performed before multidisciplinary rounds. (see Appendix B). ERT results help situate and drive where in the algorithm the patient’s care should be focused.</p> <p><i>Rationale: Knowledge of the patient’s capacity to meet ERT criteria and ERT results can be helpful in directing the plan for the day. Specifically, patients in the acute phase seldom qualify for ERT testing; patients in the titration phase may qualify but not pass an ERT; patients in the weaning phase typically qualify and pass an ERT(if not too sedated).</i></p> <p>NOTE: <i>If the patient fails an ERT because of sedation-related hypoventilation then a modified daily arousal assessment (see Box 17) is completed and an ERT is repeated before 4 pm.</i></p>
Box 13	<p>Acute Phase: Desired SBS -1 or -2</p> <p><i>Rationale: The acute phase of illness describes a time in which the patient is considered to be critically ill and/or unstable with interventions escalating, vasopressors and/or inotropes increasing, possible need for neuromuscular blockade to facilitate mechanical ventilation, and/or physiologic intolerance of pain/PICU stress. <u>Rapid control of agitation is warranted</u>. During this phase the desired SBS is –1 or less.</i></p> <p><i>In the patient receiving neuromuscular blockade, Assume Pain Present (APP) or Assume Agitation Present (AAP) should be the assessed score when the patient’s vital signs increase >20% with stimulation. The clinician’s clinical judgment is used to differentiate pain from agitation. In general, discomfort is assumed to be present in all chemically paralyzed patients who demonstrate a significant physiologic response to routine care, and the patient is empirically managed with morphine for APP and benzodiazepines for AAP.</i></p>
Box 14	<p>Goal: Maintain physiologic stability</p> <p><i>Rationale: During the acute phase the goal is to maintain physiologic stability and unburden the patient from added PICU stress.</i></p>

¹⁵ Use the “SpO2 - Estimated PaO2 Conversion Table” to estimate the PaO2 in patients without an arterial line.

Box 15**Patient's SBS more positive (+) than prescribed**

Exclude reversible causes of agitation and provide comfort measures.

If non-pharmacologic measures are ineffective, administer a morphine and/or midazolam rescue dose.

If 3 total non-procedural rescue doses are administered in ≤ 8 hours then increase morphine infusion by 10-20%¹⁶ and/or benzodiazepine by 10-20%¹⁷ of the current dose.

Rationale: During the acute phase, patients will remain on the same or higher doses of comfort medications. Infusions are not decreased unless the patient's neurologic status requires assessment. Patients receiving prolonged administration of opioids may develop tolerance and require escalating doses over time.

Patients in the acute phase who score more positive than prescribed are first assessed for an evolving clinical state that may precipitate agitation; specifically, inadequate ventilatory support or an uncomfortable position. In these cases, non-pharmacologic interventions are reattempted first.

*After reversible causes of agitation/discomfort have been excluded and environmental comfort measures have been provided, the patient can be bolused with the equivalent of one hour's worth of either morphine and/or midazolam infusion. If a patient is assessed to be in pain, morphine is administered. If however, the patient does not appear to be in pain, midazolam is administered. Clinicians should use their clinical judgment when selecting which agent to adjust, when to repeat a rescue bolus, and when to increase the sedative infusion(s). The goal in the acute phase is **physiologic stability**. Factors taken into consideration include the patient's previous response and the synergistic effect of each sedative.*

At a minimum, morphine infusion for pain and/or midazolam infusion for agitation (separately or together), are increased by 10-20% if the patient received 3 total non-procedural rescue doses (of either morphine and/or midazolam) in the previous 8 hours or less time; if not, infusions are held constant during the acute phase. Titrate opioid and/or benzodiazepine infusion based on which type of rescue bolus (morphine or benzodiazepine) that has been more effective or in tandem to optimize their synergistic effect. Hypotension may preclude an increase in comfort medications despite undesired

¹⁶ If the patient is hypotensive, increases in sedative infusions may be held until the patient's blood pressure is stable.

¹⁷ For patients whose SBS remains more positive than prescribed despite morphine and/or midazolam infusions of up to 0.5 mg/kg/hr, or for whom the side effects of increased doses of morphine and/or midazolam are unacceptable, consider the addition of either (1) clonidine (patch plus overlapping enteral for 48 hours); (2) pentobarbital (to reestablish sleep/wake cycles) or (3) ketamine if additional analgesia is required. Note: The use of chloral hydrate as a sedative agent for intubated patients is not recommended.

- clonidine: 5 mcg/kg/day. Since transdermal clonidine may take 36–48 hours for effect, enteral clonidine is provided as 2.5 mcg/kg/dose Q12h x 4 doses at the same time that a clonidine patch delivering approximately 5 mcg/kg/day is applied. Clonidine patches may be cut to as small as ¼ of the packaged size. The smallest clonidine patch that can be used safely is ¼ of a TTS-1 or 100 mcg/24hr patch. Patients <5 kg are only administered enteral clonidine. Clonidine patches are changed every 7 days. Clonidine patches should be covered with a protective covering and dated. In addition, the presence of the clonidine patch should be checked for on each shift. (Rationale: clonidine patches can fall off leading to acute rebound symptoms). Clonidine is weaned 20% per day AFTER the morphine and benzodiazepines are weaned.
- pentobarbital: Usual starting dose: 1 – 2 mg/kg/dose IV Q4-6h PRN agitation; titrate dose and interval to achieve desired SBS
- ketamine: Usual starting dose is 1-2 mg/kg/dose IV Q1h PRN agitation.

	<i>SBS and/or pain score.</i>
Box 16	<p>Titration phase: Desired SBS -1 or 0</p> <p><i>Rationale: The titration phase of illness describes a time in which the patient is considered stable while interventions are not escalating, neuromuscular blockade is off, the underlying problem may still be active but physiologic parameters are within acceptable range for patient's age and condition, and the patient is physiologically tolerant of PICU stress. During this phase the desired SBS is -1 or 0.</i></p>
Box 17	<p>Daily (on Day 2) Arousal Assessment</p> <ul style="list-style-type: none"> • If SBS is -3 turn off all sedatives until SBS is -1 or 0 then reduce sedative doses by 50%.¹⁸ • If SBS -2 then reduce sedative doses by 50%. <p><i>Rationale: During the acute phase, it is not uncommon to overshoot the patient's pharmacologic requirements to produce the desired SBS. More stable patients, by definition, tolerate a more awake state. Daily interruption of continuous infusions limits drug accumulation, facilitates neurological assessments, and is associated with a low incidence of adverse events when accomplished in a controlled manner. If the patient also qualifies for an ERT then sequence the arousal assessment prior to the ERT.¹⁹ Start Daily Arousal Assessment on Day 2 after the start of a continuous sedative infusion.</i></p> <p><i>For SBS -3 complete a Daily Arousal Assessment (stop sedatives until SBS -1 then restart at half (50%) of the pre-test dose then titrate as necessary to maintain SBS -1): If the patient is unresponsive (SBS -3), a daily arousal assessment is performed by temporarily discontinuing both morphine²⁰ and midazolam infusions or by holding a lorazepam dose and allowing the patient to wake up and attend to their environment in a developmentally appropriate manner. Awake is defined as the ability to open eyes and attend to a stimulus; this equates to a SBS of -1. [SBS of -1 is defined as "Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with touch or when name is spoken. Drifts off after stimulation. Follows simple commands."]</i> The daily arousal assessment is only completed in patients who score an SBS of -3. During the daily arousal assessment the nurse stays in close proximity to the patient while providing gentle cares (e.g., bath). As soon as the patient's SBS is -1, the arousal assessment ends and the infusions and/or intermittent lorazepam dose are restarted at half (50%) of the pre-test dose then titrated (by following Box 15 or Box 20) to maintain the SBS -1. Prolonged arousal assessments have been reported in patients with renal and/or liver dysfunction. This is likely due to an impaired ability to metabolize medications.</p>

¹⁸ Kress et al (N Engl J Med 2000;342:1471-1477) RCT comparing daily interruption of all sedatives until patients were awake with traditional practice. Outcomes: Duration of mechanical ventilation (4.9 vs. 7.3 days); Diagnostic testing to evaluate neurological status (9% vs. 27%); Length of ICU stay (6.4 vs. 9.9 days); % days awake (86% vs. 9%); No significant difference in adverse events (e.g., self extubation); Total dose of midazolam and fentanyl was less in patients with daily interruption.

¹⁹ It is unknown whether a protocol that pairs daily spontaneous awakening trials (i.e. interruption of sedatives) with daily spontaneous breathing trials results in better outcomes for ventilated pediatric patients. An adult study that was done is Girard TD, Kress JP, Fuchs BD et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomized controlled trial. Lancet 2008; 371: 126–34.

²⁰ **NOTE:** If the patient's pain score is ≥ 3 at the start of either the full or modified arousal assessment then do not reduce the morphine dose during an arousal assessment.

	<p>For SBS -2 complete a Modified Daily Arousal Assessment (reduce sedatives by 50% until SBS -1 then titrate as necessary to maintain SBS -1): If the patient is responsive to noxious stimuli (SBS -2) then a modified daily arousal assessment is completed. The modified daily arousal assessment is performed by reducing both morphine²⁰ and midazolam infusions or lorazepam dose by 50% and allowing the patient to wake up and attend to their environment in a developmentally appropriate manner. Awake is defined as the ability to open eyes and attend to a stimulus; this equates to a SBS of -1. [SBS of -1 is defined as “Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with touch or when name is spoken. Drifts off after stimulation. Follows simple commands.”] As soon as the patient’s SBS is -1, the arousal assessment ends and the reduced infusions and/or intermittent lorazepam dose are titrated (by following Box 15 or Box 20) to maintain the SBS -1.</p> <p>The daily arousal assessment is immediately aborted if the patient exhibits ventilator dysynchrony or hemodynamic instability.</p> <ul style="list-style-type: none"> • Ventilator Dysynchrony: Patient not breathing in a coordinated manner with the ventilator. (Baseline assumption – the patient is on appropriate ventilator support). • Hemodynamic Instability: Any change in vital signs not tolerated by the patient. <p><u>When the test is aborted infusions are restarted at 100% of the pre-test dose.</u></p>
<p>Box 18</p>	<p>Goal: Minimum yet effective dose</p> <p><i>Rationale: During the titration phase the goal is to maintain the minimum dose that is effective in achieving the prescribed pain and SBS scores. This avoids entraining the status quo.</i></p>
<p>Box 19</p>	<p>Every 8 hours: Adjust sedative doses²¹</p> <p><i>Rationale: Every 8 hours from the last titration, the nurse reviews the patient’s SBS scores and titrates the infusions up or down by following Box 15 or Box 20. This avoids entraining the status quo.</i></p>
<p>Box 15</p>	<p>As previously described (Box 15 on Page 6)</p> <p>IF NO: Patient’s SBS more positive (+) than prescribed, exclude reversible causes of agitation & provide comfort measures. If non-pharmacologic measures are ineffective, administer a morphine and/or midazolam rescue dose. If 3 non-procedural rescue doses are administered in ≤8 hours then increase morphine infusion by 10-20% and/or benzodiazepine by 10-20%.</p> <p><i>Rationale: Allows the infusions to be increased after the daily arousal assessment or increased as the patient needs increased over time.</i></p>
<p>Box 20</p>	<p>IF YES: Patient’s SBS more negative (-) or as prescribed</p> <p>If <3 non-procedural rescue bolus in previous 8 hours then decrease morphine infusion by 10-20% and/or benzodiazepine by 10-20%²² of the current dose.</p> <p><i>Rationale: Allows the infusions to be decreased as the patient’s requirements decrease over time. By turning morphine and midazolam infusions down in tandem, drugs are redistributed from the tissue stores back into the circulation minimizing the accumulation</i></p>

²¹ May alter the Q8h clock for a scheduled surgery/study/procedure.

²² If adjunctive agents (pentobarbital or ketamine) were added then discontinue their use prior to titrating morphine or midazolam. If clonidine was added as an adjunctive agent, wean clonidine last (see box 24)

	<p><i>of sedative medications. Less drug exposure may decrease the incidence or severity of withdrawal.</i></p> <p><i>Percent titration should take into account the patient's trajectory of illness, current and desired SBS, and ability to physiologically tolerate PICU stress. Consider a restrained titration (10% of one agent) if the patient is at or near their desired state or an accelerated titration (20% of both agents) if the patient is too sedated.</i></p> <p>Deintensification: This can be done at any time: <i>Switching from midazolam continuous infusions to intermittent enteral or IV lorazepam. Note this is NOT a wean. Use the same number of mg delivered in 1 hour by the midazolam infusion, but give as lorazepam and administer Q4h or Q6h scheduled. Example: midazolam 4 mg/hr IV infusion would convert to lorazepam 4 mg enteral or IV Q4h or lorazepam 4 mg enteral or IV Q6h.</i>²³</p>
Box 21	<p>Weaning (to Extubation Phase): Desired SBS 0</p> <p>Maintain comfort while transitioning patient to a level of sedation that permits extubation. This phase typically starts when the patient passes their ERT and ends 72 hours after their last opioid dose.</p> <p><i>Rationale: The weaning to extubation phase describes a time in which the goal of therapy is <u>successful endotracheal extubation and to discontinue sedation.</u></i></p> <p><i>If the patient has failed extubation because they do not tolerate an awake and intubated state then consider transition to a short-acting agent 8-12 hours prior to extubation. See Box 8. After starting dexmedetomidine or propofol, reduce morphine and midazolam infusions by 50%. After extubation wean opioids and benzodiazepines per RESTORE (see Box 23).</i>²⁴</p>
Box 22	<p>Goal: Discontinue Sedation</p> <p><i>Rationale: Aside from those in pain, endotracheal extubation removes a major source or PICU stress allowing the discontinuation of opioids and benzodiazepines.</i></p>
Box 23	<p>If the patient received opioids/benzodiazepines for <5 days²⁵ then discontinue all infusions.²⁶</p> <p>If patient on sedation for ≥ 5 days identify target WAT-1 then wean morphine by 10% of dose at morphine wean hour 0 then wean by that same amount Q8h (goal off in 3 days)</p> <p>THEN 8 hours after morphine is discontinued, wean benzodiazepines by 20% of</p>

²³ Consider extending the lorazepam dosing interval from Q4h to Q6h dosing if the patient becomes too sedated post conversion.

²⁴ Example: If morphine and midazolam are at 10 mg/hr each then once dexmedetomidine is started, morphine and midazolam are decreased to 5 mg/hr each. If length of exposure > 5days then after extubation wean morphine by 0.5 mg/hr (i.e. 10% of 5 mg/hr) Q8h until off. When morphine is discontinued then midazolam is weaned by 1 mg/hr (i.e. 20% of 5 mg/hr) daily until off.

²⁵ 5 days equal 5 consecutive 24 hour periods.

²⁶ Two factors impact iatrogenic withdrawal syndrome: total dose and the duration of exposure. The impact of using a minimally effective dose during the titration phase of illness is unknown. Arnold et al. Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. *Anesthesiology* 1990;73:1136-1140. (total fentanyl dose > 1.6 mg/kg for > 5 days). Katz et al. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. *Crit Care Med* 1994;22:763-767. (50%: total fentanyl dose ≥ 1.5 mg/kg for ≥ 5 days; 100%: total fentanyl dose ≥ 2.5 mg/kg for ≥ 9 days). Fonsmark et al. Occurrence of withdrawal in critically ill sedated children. *Crit Care Med* 1999;27(1):196-199. (35% incidence of benzodiazepine withdrawal: total midazolam dose >60 mg/kg; duration not significant.)

	<p>dose at benzodiazepine wean hour 0. Wean by that same amount Q24h (goal off in 5 days)</p> <p><i>Rationale: If the patient received opioids for <5 days (continuous, intermittent, or PRN) they may be discontinued and switched to PRN orders of smaller doses of analgesics or sedatives to manage any pain, agitation or withdrawal symptoms occurring post-extubation.²⁷ Sites may choose to initiate WAT-1 scoring in any patient weaning from sedation as symptoms of iatrogenic withdrawal syndrome have been noted to occur in some patients after 2 days of continuous opioid exposure.</i></p> <p><i>Most patients weaning from opioids will exhibit some signs/symptoms of withdrawal.²⁸ Assess baseline WAT-1 score and reassess WAT-1 a minimum of once per shift. The multidisciplinary team will determine the upper limit of acceptable WAT-1 score by defining symptoms of withdrawal that will and will NOT be tolerated based on the patient's condition. Whereas "Iatrogenic Withdrawal" has been associated with a WAT-1 of 3, the exact score depends on the individual patient; specifically, the combination of symptoms that constitute the WAT-1 score and the individual resiliency of the patient.</i></p> <p><i>The patient's weaning plan is written out (paper or Excel RESTORE Weaning Worksheet) and included with the patient's management plan. If the patient was on infusions for ≥ 5 days, the morphine infusion is decreased Q8h by 10% increments of the original dose at the start of the wean for a total of 10 weans. The morphine can be discontinued in 72 hours if the weans proceed on course without interruption.</i></p> <p><i>The benzodiazepine should not be weaned during the opioid wean. The only benzodiazepine change that may be considered at this time is to transition the benzodiazepine infusion to intermittent dosing. Midazolam infusions are converted to intermittent doses of lorazepam. Note: This is NOT and cannot be considered a wean. These doses may be administered intravenously or enterally. (This change is the same as box 20: Switching from midazolam continuous infusions to intermittent enteral or IV lorazepam. Use the same number of mg delivered in 1 hour, but give as lorazepam and administer Q4h or Q6h scheduled. Example: midazolam 4 mg/hr IV infusion would convert to lorazepam 4 mg enteral or IV Q4h or lorazepam 4 mg enteral or IV Q6h.) This results in a dose of lorazepam that is 1/4 to 1/6 the total daily midazolam dose.</i></p> <p><i><u>The weaning plan maybe modified in patients receiving low-dose infusions.</u>²⁹ In these situations the clinical team may consider (1) a more dilute drug concentration infusion within unit-based standards to deliver an infusible volumetric rate; (2) converting the infusions to intermittent dosing; or (3) discontinuing the infusion.³⁰</i></p>
<p>Box 24</p>	<p><u>During morphine wean, if WAT-1 > target hold one wean step and consider rescue doses of morphine, then slow the morphine wean or consider adding clonidine, then consider adding methadone.</u></p>

²⁷ If the patient has ongoing requirements for pain management, reduce morphine to the minimum effective dose using the guidelines in the titration phase.

²⁸ Withdrawal: Physical signs and symptoms that manifest when the administration of an analgesic or sedative is abruptly discontinued in a patient who is physically tolerant. Symptomatology varies depending on the agent involved, patient age, and cognitive state and associated medical conditions. We monitor withdrawal using the WAT-1 (Withdrawal Assessment Tool- version 1).

Physiologic dependence: Need to continue an analgesic or sedative to prevent withdrawal. Tobias JD. CCM 2000; 28:2122-2132.

²⁹ Given the wide variation in infusion pumps, a safe "low dose" mg/kg/hr rate cannot be recommended.

³⁰ If infusions are discontinued the clinical team completes a mock-weaning schedule. If the patient exceeds their WAT-1 target, then bolus and start the wean schedule at the date/time the WAT-1 was exceeded.

	<p><i>Rationale: If the patient's WAT-1 score is greater than deemed acceptable then hold one step in the scheduled wean and</i></p> <ol style="list-style-type: none"> <i>1. Provide rescue doses of opioids and benzodiazepines; specifically, morphine and/or midazolam 0.05 mg/kg/dose or one hour's worth of continuous infusion IV Q1h PRN.</i> <i>2. If progress is not achieved in 24 hours and WAT-1 >target, then hold one step in the wean and either slow the wean by reducing the morphine dose by 10% Q12h (rather than Q8h) and/or consider adding a clonidine patch with overlapping enteral administration of clonidine (see footnote 15).</i> <i>3. If progress³¹ is not achieved in 72 hours and WAT-1 >target then consider the patient's trajectory of illness. If the patient is fragile, not tolerating enteral feedings and cannot be managed on the ward continue to titrate IV morphine; if the reciprocal is true (tolerating enteral feedings and can be transferred to the ward) then consider converting the patient to enteral methadone (see Appendix A).</i>
<p>Box 25</p>	<p><u>During benzodiazepine wean, if WAT-1 >target hold one wean step and consider rescue doses of benzodiazepine, then slow wean to 10% dose reductions Q24h.</u></p> <p><i>After the morphine is discontinued, wean benzodiazepine by 20% Q24h (off in 5 days).</i></p> <p><i>If WAT-1 >target during benzodiazepine wean, then hold the daily wean and administer rescue doses of benzodiazepine. Then slow the benzodiazepine wean to 10% dose reductions Q24h (off in 10 days).</i></p>

³¹ Progress is defined as at least a 50% total dose reduction from the start time/time zero of the wean.

Appendix A**Guidelines for the initial conversion of morphine infusion to intermittent methadone doses (to be used when Box 24 has failed).**

Note: clinical response to methadone is highly individualized and any regimen must be carefully monitored and adjusted as needed based on the patient's status. The following general principles apply:

1. Methadone has a longer half-life and a steady-state may not be achieved for 3 – 5 days.
2. To prevent gaps in coverage, start methadone then taper morphine; specifically, decrease the morphine infusion to 50% at the time of 2nd methadone dose, then turn morphine off at the time of the 3rd methadone dose.
3. Rescue doses of morphine are prescribed at the start of the transition process for management of acute withdrawal symptoms. Patients who have been converted to methadone or lorazepam may require higher rescue doses of morphine and/or midazolam.
4. Methadone should be held for signs of excess sedation; methadone has a cumulative effect over time.

morphine IV³²	methadone IV or Enteral³³
1 – 10 mg/hr	methadone X mg IV/enteral Q6h Where X = one hour's worth of morphine infusion

The methadone wean is done by lengthening the interval of administration from Q6h to Q8h and then to Q12h prior to decreasing the amount per dose.

For example:

1. methadone X mg IV Q6h x72 hours
2. methadone X mg IV Q8h x72 hours
3. methadone X mg IV Q12h x72 hours (transition to Q12h not always possible)
4. methadone 0.9X mg IV Q8h or Q12h x48 hours
5. methadone 0.8X mg IV Q8h or Q12h x48 hours
6. methadone 0.7X mg IV Q8h or Q12h x48 hours
7. methadone 0.6X mg IV Q8h or Q12h x48 hours
8. methadone 0.5X mg IV Q8h or Q12h x48 hours
9. methadone 0.4X mg IV Q8h or Q12h x48 hours
10. methadone 0.3X mg IV Q8h or Q12h x48 hours
11. methadone 0.2X mg IV Q8h or Q12h x48 hours
12. methadone 0.1X mg IV Q8h or Q12h x48 hours³⁴

³² If on fentanyl because of initial hypotension or reactive airways disease convert hourly dose rate of fentanyl (mcg/hr) x 0.075 = methadone dose Q6h; For example: Pt wt = 25 kg; fentanyl Infusion Rate = 2 mcg/kg/hr = 50 mcg/hr; 50 mcg/hr x 0.075 mg/mcg = 3.75 mg methadone IV/enteral Q6h then follow guidelines.

³³ Depending on concomitant medications, IV and enteral doses of methadone may or may not be equivalent. If the patient is on a medication known to be a strong CYP 3A4 inhibitor, consider using an IV:enteral ratio of less than 1:1 (e.g. 1:0.8). If the patient is on a medication known to be a strong CYP 3A4 inducer, consider using an IV:enteral ratio of more than 1:1 (e.g. 1:1.2). Alternatively, you may use a 1:1 conversion, but must have a heightened level of vigilance around monitoring as drug interactions and resultant effects may be highly unpredictable.

³⁴ Clinical judgement should be used to determine when finite doses are too low to be accurately measured for administration. The weaning plan (lengthening the interval and then decreasing the doses by 10%) should be followed until that point is reached. For example, if doses for weaning are <0.2 mg (i.e. <0.1 mL when using a 2 mg/mL oral solution of methadone), it is likely that the methadone can be discontinued.

**Appendix
B**

Daily Test for Patient Readiness for Extubation

Every morning at 6 AM \pm 2 hours³⁵ the patient is assessed for the following:

- Spontaneous breathing
- Oxygenation Index ≤ 6 ³⁶ (MAP/PF ratio x 100; If an ABG is unavailable then estimate the PaO₂ from the “SpO₂ - Estimated PaO₂ Conversion Table”).

If the patient meets these ERT criteria then the patient is tested for extubation readiness:

Extubation Readiness Test (ERT):³⁷

1. Temporarily stop enteral feedings.
2. If FiO₂ not at 0.5, then titrate³⁸ FiO₂ to 0.5 and assess; if tolerated then
3. If PEEP not at 5 cmH₂O, then titrate³⁹ PEEP to 5 cmH₂O and reassess
4. Evaluate SpO₂ after each ventilator change
 - a) If SpO₂ \geq 95% change mode to straight PS with set PS min level based upon the size of the ETT⁴⁰
 - 10 cm H₂O if ETT 3-3.5 mm
 - 8 cm H₂O if ETT 4-4.5 mm
 - 6 cm H₂O if ETT \geq 5 mm
 - b) Monitor SpO₂, exhaled Vt, and RR

The patient is ready for extubation (from a pulmonary perspective) if all 3 of the following are present for \geq 2 hours:

- SpO₂ \geq 95%
- Exhaled Vt \geq 5 mL/kg (ideal weight)⁴¹
- Respiratory rate within respiratory rate goal of age:
<6 months 20-60; 6 mo-2 yrs 15-45; 2-5 yrs 15-40; >5 years 10-35

If the patient does not pass the ERT they are returned to their pre-test ventilator settings and re-tested the next morning. If the clinical team judges that the *patient failed the ERT because of sedation-related hypoventilation then a modified daily arousal assessment (see Box 17) is completed and an ERT is repeated before 4pm*. If the patient does not meet the criteria at 4pm they are returned to their pre-test ventilator settings and re-tested the following morning.

If the patient passes the ERT the patient is placed on comfortable ventilator settings and the medical team is notified that the patient is ready (from a pulmonary perspective) for

³⁵ If a patient procedure, test, or other extenuating circumstance prevents assessment for these criteria between 6 AM - 10 AM then the daily test can be delayed up to 4 hours.

³⁶ Curley MAQ, Fackler JC. Weaning from Mechanical Ventilation: Patterns in Pediatric Patients Recovering from Acute Hypoxemic Respiratory Failure. American Journal of Critical Care 1998;7(5):335-345.

³⁷ The bedside team (nurse and respiratory therapist) work together to optimize the patient's capacity to pass the ERT; specifically, assure that the patient's ETT is clear of secretions and routine cares, CXR, etc are completed before the ERT. If the patient also qualifies for an arousal assessment (AA) then sequence the arousal assessment prior to the ERT.

³⁸ Slowly adjust as tolerated to achieve a FiO₂ 0.5. This may require an increase or decrease in FiO₂.

³⁹ Slowly adjust as tolerated to achieve a PEEP of 5 cmH₂O. Clinical team may adjust this step if patient considered “PEEP-dependent”.

⁴⁰ Min PS is applied above PEEP; for example, measured PS in a patient with a 3.5 ETT & PEEP of 5 would be 15 cmH₂O

⁴¹ Clinicians should use their clinical judgment when evaluating the ERT in a patient with a large air leak. The patient can be extubated with a protocol deviation noting that the exhaled Vt could not be quantified because of the air leak.

	unassisted breathing. Extubation may be delayed for non-pulmonary reasons.
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