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Analagosedation Management in the Adult Critically Ill

Evidence Based Medicine Guideline

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Approved: 5/12/2024 Previous Revision dates: 04/03/01, 03/29/05, 10/24/09, 6/21/22

SUMMARY

RECOMMENDATIONS

- **Level 1**
  - **Light sedation (RASS 0 to -1) is preferred over heavy sedation unless contraindicated.**
  - **Propofol or dexmedetomidine should be used as first line agents over benzodiazepines in critically ill, mechanically ventilated adults.**
  - **Benzodiazepines are the treatment of choice in patients with alcohol withdrawal or seizures/status epilepticus (see "Alcohol Withdrawal" guideline).**
- **Level 2**
  - **Pain management should be guided by routine pain assessment and addressed before a sedative agent is considered.**
    - **Continuous infusion opioids, such as fentanyl, may be used as part of an analgesia-first sedation strategy prior to adding additional sedative agents.**
    - **Opioids may also be used as an adjunct to a first line sedative agents to achieve the desired level of analgosedation.**
  - **Sedatives should be titrated to the appropriate level of desired sedation based on the Richmond Agitation Sedation Scale (RASS).**
  - **Ketamine, at sedative doses (0.5-5 mg/kg/hr), may be an alternative for patients without contraindications (see below).**
  - **Ketamine, at sub-dissociative doses (<0.5 mg/kg/hour IV), may be considered in patients with moderate to severe pain to decrease opioid requirements.**
  - **Benzodiazepines should be used as a last line sedative agent due to the high correlation with ICU delirium.**
  - **Dexmedetomidine should be used in patients where agitation is the main barrier to extubation.**
  - **Daily spontaneous awakening trials should be performed in patients without contraindications.**
- **Level 3**
  - **Propofol is the sedative of choice when rapid neurologic assessment is needed or intracranial hypertension is present.**
  - **Ketamine should be avoided in patients with coronary artery disease, arrhythmias, inability to tolerate an increase in blood pressure or heart rate, severe pulmonary secretions, glaucoma, or psychiatric history (see "Ketamine for Analgesia" guideline).**

INTRODUCTION

Sedation is an essential component of care for critically ill patients. Each sedative medication possesses specific properties, risks and benefits, which must all be considered in choosing an appropriate therapy. The primary goal should be addressing patient comfort through adequate pain control followed by anxiolysis through an appropriate sedation regimen.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Supported by multiple, prospective randomized clinical trials or strong prospective, non-randomized evidence if randomized testing is inappropriate.
- **Level 2:** Supported by prospective data or a preponderance of strong retrospective evidence.
- **Level 3:** Supported by retrospective data or expert opinion.

Analgosedation is the practice of using analgesic agents to treat pain and discomfort prior to using sedative agents (Table 1). The use of analgosedation is thought to lead to lighter sedation levels, which in turn may lead to a shorter duration of mechanical ventilation, a shorter ICU length of stay, and lower overall sedative doses. The idea of targeting lighter levels of sedation (RASS 0 to -1) was first introduced in the 2013 PAD Guidelines, which stated that a lighter level of sedation may shorten the duration of mechanical ventilation and decrease the ICU length of stay (1). This recommendation was later reinforced by the 2018 PADIS Guidelines that recommended using light sedation versus deep sedation (2). Light sedation should be targeted in patients without contraindications (e.g. neuromuscular blockers for paralysis, treatment for status epilepticus, treatment for alcohol withdrawal syndrome, or deep sedation for acute respiratory distress syndrome) (1).

For patients who are unable to meet target sedation with analgesic agents, sedative agents may be added. The goal for sedation in the ICU is to provide comfort in the form of anxiolysis and facilitate mechanical ventilation or invasive procedures. Anxiety is a psychophysiological response to real or imagined danger, while agitation refers to excitement accompanied by motor restlessness. An ideal regimen should control anxiety and agitation and provide amnesia while minimizing adverse effects. Selection of drug therapy should be based on identification and differentiation of pain, anxiety, agitation, and delirium. Monitoring tools frequently include subjective assessments by caregivers or sedation scales. Inappropriate therapy may result in adverse drug reactions, prolonged mechanical ventilation, extended ICU stays, and increased costs. Sedatives routinely used in the ICU setting include propofol, dexmedetomidine, benzodiazepines, and ketamine. When determining which sedative agent to use, it is important to understand the properties, pharmacokinetics, and adverse effects of each agent. This includes onset and offset of action, ease of administration, mode of metabolism and excretion, side effect profile, drug interactions, and cost-effectiveness (Table 2).

Table 1: Commonly Used Analgesics in the ICU

Drug	MOA	Loading	Rate	Onset	Duration	Pharmacokinetics	Side effects
Fentanyl	Mu-selective opioid agonist	50 mcg/kg	Titrate to CPOT<2 Range: 0-500 mcg/hr Standard Dose: 0-250 mcg/hr High Dose: 0-500 mcg/hr	1-2 min	30-60 mins	• $T_{1/2}$ 1.5 hours • Highly lipid soluble • Accumulation in liver impairment • No active metabolites • Minimal vasodilatory effects	• Respiratory depression • Drowsiness • Euphoria • Narcotic ileus (3,4)
Hydro-morphone (Dilaudid)	Mu-selective opioid agonist	0.5 mg	Titrate to CPOT<2 Range: 0-3.5 mg/hr	5-15 min	2-4 hours	• $T_{1/2}$ 2-3 hours • Moderately lipid soluble, delayed effects • Accumulation in liver impairment Metabolites: • Hydromorphone-3-glucuronide - neuroexcitatory	• Respiratory depression • Drowsiness • Euphoria • Narcotic ileus (5,6)
Morphine	Mu, Kappa, delta opioid agonist	2 mg	Titrate to CPOT<2 Range: 1-15 mg/hr	5-10 min	3-4 hours	• T1/2 1.5-2 hours • Vasodilatory effects • Metabolites: • Morphine 3-glucuronide – neuroexcitatory, no analgesia • Morphine 6-glucuronide - analgesic	• Hypotension • Respiratory depression • Narcotic ileus (4)

Table 2: Commonly used Sedatives in the ICU

Drug	MOA	Loading	Rate	Onset	Duration	Pharmacokinetics	Side effects
Propofol	GABA agonist, alternate binding site	Do NOT bolus	10 mcg/kg/min Range: 0-50 mcg/kg/min	<1 min	5 - 10 min	$T_{1/2}$ 30-60 min after infusion; longer with prolonged infusion due to lipophilic properties; metabolized by hepatic glucoronidation	Hypotension due to vasodilation, PRIS, pancreatitis, hypertriglyceridemia, green urine (5,6)
Dexmedetomidine (Precedex)	Alpha-2-agoinst	Do NOT bolus	0.2 mcg/kg/hr Range: 0-1.5 mcg/kg/hr	5-10 min	60-120 min	$T_{1/2}$ 2hr, accumulates with prolonged infusion, metabolized by hepatic glucoronidation and oxidation, no active metabolites	Transient hypertension followed by hypotension, withdrawal, bradycardia, dry mouth, nausea (6)
Ketamine	NMDA antagonist	0.5 mg/kg	0.5 mg/kg/hr Range: 0-5 mg/kg/hr	<1 min	1-2 hrs	$T_{1/2}$ 2.5 hours Metabolized via the CYP450 enzyme system in the liver with renal excretion	Dose dependent; dissociative state, nausea, vomiting, respiratory depression at high doses (6,7)
Midazolam (Versed)	GABAa agonist	2-6 mg	1 mg/hr Range: 0-15 mg/hr	1-5 min	1-2 hrs	$T_{1/2}$ 3-11hr; metabolized by hepatic cytochrome p450; renal excretion of active metabolites; lipophilic	Delirium, respiratory depression, hypotension (8)
Lorazepam (Ativan)	GABAa agonist	1-4 mg	1 mg/hr Range: 0-8 mg/hr	5-20 min	2-6 hrs	$T_{1/2}$ 8-15hr; metabolized by hepatic glucoronidation, no active metabolites, offset more predictable	Delirium, respiratory depression, hypotension (8)

LITERATURE REVIEW

Pain Assessment

Critically ill patients will often be intubated or sedated and therefore unable to verbalize their pain. For patients who are unable to state their level of pain, the Critical Care Pain Observation Tool (CPOT) is used to determine whether pain is present. This scoring tool assesses facial expressions, body movements, muscle tension, and ventilator compliance in mechanically ventilated patients. CPOT scores range from 0-8, with a score greater than 2 indicating pain is present (9).

Critical Care Pain Observation Tool (CPOT)

Indicator	Score		Description
Facial Expression	Relaxed, neutral	0	No muscle tension observed
	Tense	1	Presence of frowning, brow lowering, orbit tightening
	Grimacing	2	All of the above plus eyelid tightly closed or biting at endotracheal tube
Body Movements	Absence of Movements	0	Does not move at all
	Protection	1	Slow, cautious movements, touching or rubbing pain site
	Restlessness/Agitation	2	Pulling at lines, attempting to sit up, striking at staff, thrashing limbs, trying to climb out of bed
Ventilator Compliance or Vocalization	Tolerating ventilator or movement	0	Alarms not activated, easy ventilation
	Coughing but tolerating	1	Coughing, alarms activated but stop spontaneously
	Fighting ventilator	2	Asynchrony, blocking ventilation, alarms frequently activated
	Talking in normal tone or no sound	0	Talking normal tone or no sound
	Sighing, moaning	1	Sighing, moaning
	Crying, sobbing	2	Crying out, sobbing
Muscle Tension	Relaxed	0	No resistance to passive movements
	Tense, rigid	1	Resistance to passive movements
	Very tense or rigid	2	Strong resistance to passive movements

Selecting Analgesia Agents

Several studies have tried to determine the optimal analgesic agent for analgosedation in the ICU. The ANALGESIC trial compared the effects of continuous infusion fentanyl to morphine in mechanically ventilated ICU patients (10). Continuous infusion fentanyl led to greater ventilator-free days and shorter ICU length of stay at 28 days compared to morphine. A secondary analysis of the ANALGESIC trial found that the fentanyl group experienced higher rates of delirium when compared to morphine, however delirium was defined as having an ICD-10 code for delirium or receiving any antipsychotic medication during their hospital stay (11). Choi and colleagues compared the use of continuous infusion fentanyl to continuous infusion hydromorphone in medical, surgical, and cardiac ICU patients requiring mechanical ventilation (12). There were no differences noted in the duration of mechanical ventilation or ICU length of stay between fentanyl and hydromorphone, however the hydromorphone group had higher rates of CPOT >2 and were more likely to require restraints.

More recent trials have evaluated the use of analgosedation in critically ill patients to assess the effects on sedation level, delirium rates, and length of mechanical ventilation. Strom and colleagues looked at an analgesia-only based regimen compared to a conventional sedation regimen in medical and surgical ICU patients receiving mechanical ventilation (13). The analgesia-only group experienced fewer days on mechanical ventilation and had shorter ICU and hospital length of stay compared to the conventional sedation regimen group. Faust and colleagues looked at the duration of mechanical ventilation in medical ICU patients before and after a fentanyl based analgosedation protocol was implemented (14). The post-implementation group experienced a shorter duration of mechanical ventilation, shorter ICU length of stay, and lower RASS and CPOT scores compared to the pre-implementation group (14). A randomized controlled trial by Breen and colleagues looked at analgesia-first sedation with remifentanil prior to midazolam compared to midazolam with fentanyl or morphine in mechanically ventilated medical and surgical ICU patients (15). The analgesia-first group experienced a significantly shorter duration of mechanical ventilation and a lower total midazolam dose compared with the midazolam + fentanyl/morphine group.

Sedation Assessment

Prior to initiation of sedation, it is important for health care providers to determine the indication for using these agents. Providers must also frequently reassess a patient's condition to determine the duration and appropriate level of sedation. Several sedation assessment scales have been developed to objectify a patient's need for sedation as well as determine their current level of sedation in order to titrate appropriate agents. Though the PADIS guidelines do not recommend one sedation assessment scale over another, the Richmond Agitation-Sedation Scale (RASS) is the most commonly used scoring tool.

RASS is a 10-point scale used to determine a patient's level of anxiety and/or agitation versus depth of sedation. The scale is further divided into four levels of agitation (1 to 4), one level to represent a calm and alert state (0), and five levels of light to deep sedation (-1 to -5). In a trained individual, this assessment can be completed in 30-60 seconds using three components: observation, response to verbal stimulus, and response to physical stimulus. According to Sessler and colleagues, there is a high inter-rater reliability among nurse educators and RASS trained bedside nurses (r=0.964) (16). This robust inter-rater reliability was demonstrated for patients from medical, surgical, cardiac surgery, and neuroscience ICUs in patients with and without mechanical ventilation (17).

Richmond Agitation-Sedation Scale (RASS)

Scale	Score	Description
Combative	4	Combative, violent towards staff
Very agitated	3	Pulls at tubes and/or catheters, aggressive towards others
Agitated	2	Frequent non-purposeful movement
Restless	1	Anxious, restless movements
Alert & calm	0	Awake and alert, calm
Drowsy	-1	Not fully alert, sustained awakening
Light sedation	-2	Awakens for < 10 seconds
Moderate sedation	-3	Movement and eye opening to voice
Deep sedation	-4	No response to voice, but opens eyes to physical stimulation
Cannot be aroused	-5	No response to verbal or noxious stimulus

Sedation Agents (Table 2)
Propofol is an anesthetic agent with sedative-hypnotic and anticonvulsant properties. It has a rapid onset and offset of action. Like benzodiazepines, this agent exerts its effects on the GABA receptor in the central nervous system via an alternate binding site. Propofol infusion syndrome (PRIS) is a rare but potentially fatal adverse effect characterized by arrhythmias, metabolic acidosis, rhabdomyolysis, hyperkalemia and cardiac arrest (2,16,17). This is typically seen with infusion rates >65 mcg/kg/min, which is well above the normal dosing range of 0-50 mcg/kg/min, or for a prolonged duration (>48 hours) with a mortality rate reaching up to 85% (7).

Dexmedetomidine is an anesthetic agent which acts as an alpha-2-agonist and carries both sedative and analgesic properties but lacks anti-convulsant properties (2,16,17). This agent is unique in that it has eight times the affinity to alpha-2 receptors when compared to clonidine, however, it does not appear to cause significant effects on respiratory drive. As a result, it is commonly used in non-ventilated patients and mechanically ventilated patients near extubation. It is not necessary to discontinue this agent prior to extubation (17). The DahLIA study found that dexmedetomidine may be beneficial in patients with delirium, though bradycardia may limit its use in some patients (18). During continuous infusion, dexmedetomidine can cause vasodilation resulting in hypotension. Therefore, a bolus prior to continuous infusion is not recommended.

Benzodiazepines function by binding to gamma-aminobutyric acid type A ($GABA_a$) receptors within the central nervous system. As a result, these agents have sedative, amnestic, anxiolytic, and anticonvulsant properties (5-7, 16,17). The most common benzodiazepines used in the ICU setting are midazolam (Versed), lorazepam (Ativan), and diazepam (Valium). While both agents can be used for sedation, Barr and colleagues found that during maintenance sedation, midazolam and propofol were superior in achieving optimal levels of sedation overall when compared to lorazepam. This study also demonstrated prolonged intubation time in patients who received lorazepam (2). When treating alcohol withdrawal syndrome, benzodiazepines are considered first line agents to reduce the severity of withdrawal, as well as the incidence of seizures. Holbrok and colleagues conducted a meta-analysis including 11 randomized controlled trials looking at benzodiazepines for alcohol withdrawal. They found that benzodiazepine use was associated with higher therapeutic success within 2 days when compared to placebo (19).

Ketamine is a dissociative agent that acts through antagonism of N-methyl-D-aspartate (NMDA) receptors causing functional and electrophysiological dissociation. It is believed to block afferent impulses associated with pain from returning to the central nervous system. Through NMDA receptor antagonism, ketamine attenuates centrally-mediated pain processes to reduce the development of opioid tolerance and opioid-induced hyperalgesia. In addition to action on NMDA receptors, ketamine also acts as a weak opioid receptor agonist, alpha-1 and beta-2 receptor agonist and muscarinic acetylcholine receptor inhibitor (7). The analgesic properties of ketamine are observed at subanesthetic doses (<1 mg/kg IV bolus dose and <0.5 mg/kg/hr IV continuous infusion). Higher dosing of ketamine is required to achieve sedation. When used for sedation, ketamine continuous infusion should be initiated at 0.5 to 1 mg/kg/hr and then titrated to an upper dose range of 4 to 5 mg/kg/hr. Ketamine has sedative, amnesic, and analgesic properties without causing respiratory depression or hypotension (20). Adverse effects include neurologic (psychotomimetic effects), cardiovascular (hypertension and tachyarrhythmias), and respiratory (hypersalivation and laryngospasm). Psychotomimetic effects are dose-dependent; therefore, the risk of development is higher with increased doses. Psychotomimetic effects occur in 7-8% of patients given sub-dissociative doses compared to 3.6-5% in placebo patients (7).

Selecting Sedative Agents
Several trials have compared various sedative agents to determine whether one is superior to the rest. Garcia and colleagues compared the use of propofol versus midazolam in a mixed population of medical and surgical ICU patients (21). This meta-analysis found that the use of propofol was associated with reduced mechanical ventilation time and faster extubation time in both surgical and medical ICU patients when compared to midazolam. In surgical ICU patients, propofol was associated with a reduced ICU length of stay compared to midazolam. In a post-hoc analysis of the DESIRE trial, Miyagawa and colleagues compared the use of propofol versus midazolam during the acute sedation phase in mechanically ventilated patients targeting light sedation (22). The use of propofol led to lower rates of coma and delirium when compared to midazolam, as well as a higher number of well-controlled sedation patients by day 3. There were no differences observed in 28-day mortality or ICU length of stay between the two groups. Jakob and colleagues compared the effects of dexmedetomidine and midazolam and propofol in mechanically ventilated patients requiring long term sedation (23). This study concluded that dexmedetomidine was comparable to midazolam and propofol in maintaining light to moderate sedation and ultimately reduced duration of mechanical ventilation, however rates of hypotension and bradycardia were significantly higher with

dexmedetomidine use. Both the SEDCOM and MENDS trials found a greater incidence of bradycardia in the dexmedetomidine group, but neither study found a significant intervention was required for the bradycardia (24,25). The MENDS trial evaluated short-term sedation (≤120 hour) comparing dexmedetomidine and lorazepam in a mixed medical and surgical ICU population. Patients receiving dexmedetomidine had significantly less delirium and coma time compared to the lorazepam group (25). Delirium itself is an independent risk factor for prolonged length of stay, greater neuropsychological dysfunction, and increased mortality; therefore, all efforts should be made to avoid using agents that worsen delirium (26). The MENDS trial did not evaluate time to extubation or ICU and hospital length of stay (25). Another prospective, double-blind, randomized trial reported that patients spent similar time within target sedation level between dexmedetomidine and midazolam (27). However, the dexmedetomidine group had shorter time to extubation than midazolam treated group (3.7 vs. 5.6 days). The MENDS-2 trial looked at the number of days alive without delirium or coma comparing dexmedetomidine and propofol in a mixed medical and surgical ICU population (28). This study found no difference in outcomes between dexmedetomidine and propofol. The 2022 ICM Rapid Practice Guideline provides a weak recommendation for the use of dexmedetomidine in mechanically ventilated adult ICU patients experiencing delirium if the treatment of delirium outweighs the risk of hypotension and bradycardia (29).

Light vs Heavy Sedation

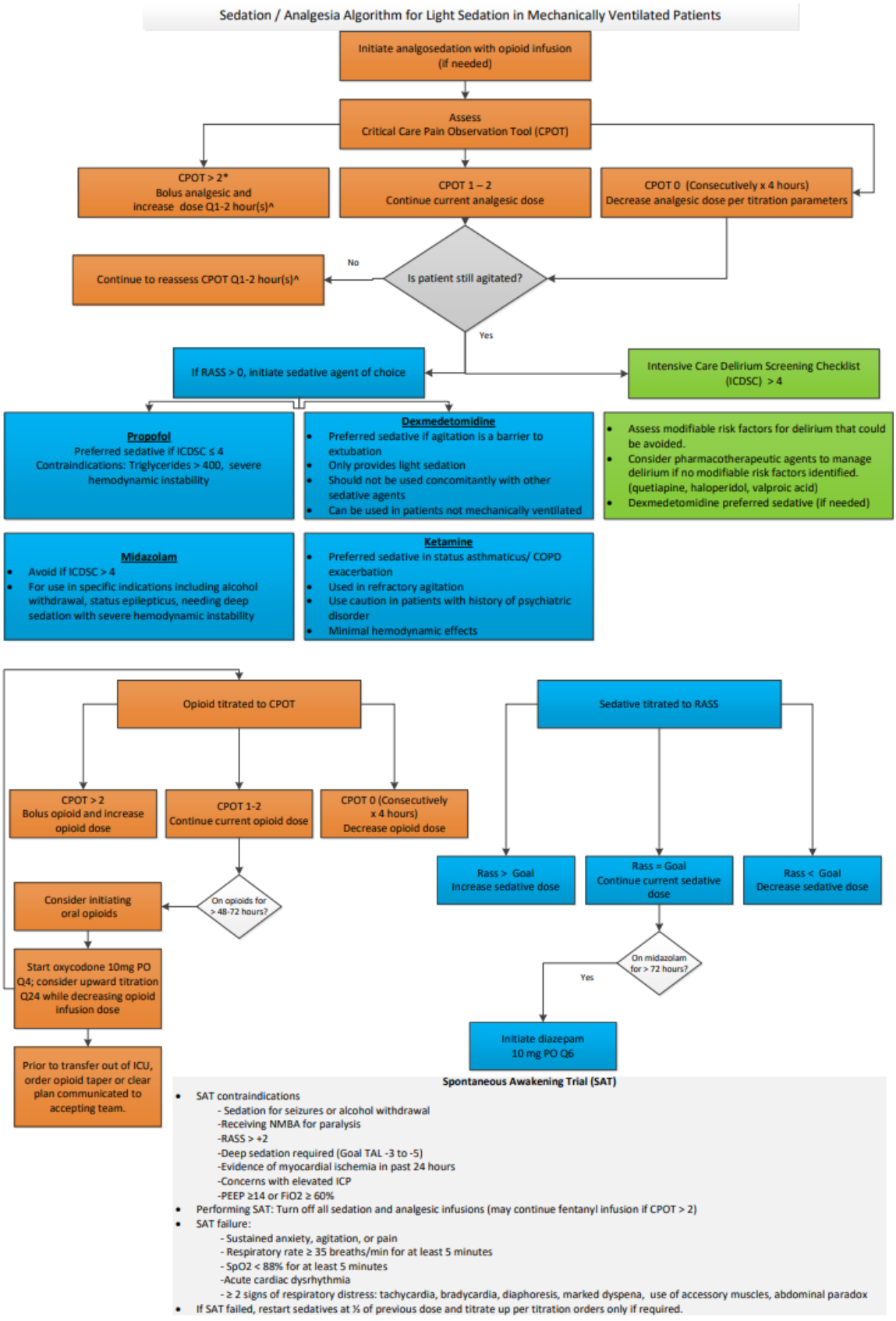
Various studies have compared light sedation to deep sedation in critically ill patients. Bugedo and colleagues looked at an analgesia-based, goal-directed sedation protocol to lighten overall sedation levels (30). A sedation goal of SAS 3-4 (light sedation) was targeted for most patients except for those with severe respiratory failure in which a goal SAS of 1-2 (deep sedation) was permitted for deeper sedation. Those patients who received fentanyl prior to midazolam experienced no difference in outcomes, however the use of lighter sedation was shown to be safe when compared to deeper sedation. Tanaka and colleagues assessed the effects of early deep sedation in critically ill patients who required mechanical ventilation within the first 48 hours of ICU admission (31). This study found that deep sedation was associated with longer duration of mechanical ventilation, increased tracheostomy rates, and increased hospital mortality. In a pilot study by Shehabi and colleagues, the safety of early goal-directed sedation compared to standard sedation was evaluated in patients who required mechanical ventilation for greater than 24 hours (32). Patients were randomized to receive early goal-directed light sedation with dexmedetomidine or standard sedation with propofol and/or midazolam. This study found that there were no differences in vasopressor use or self-extubation rates between the early goal-directed sedation group and the standard sedation group, however the early goal-directed sedation group used less propofol and midazolam overall. Based on this study, early goal-directed sedation appears to be safe for targeting light sedation. Appendix 1 provides a sedation/analgesia algorithm for light sedation in mechanically ventilated adult patients.

Spontaneous awakening trials (SAT) are defined as the routine daily interruption in sedation to reevaluate sedation needs. This commonly excludes patients who require sedation for indications such as alcohol withdrawal syndrome, status epilepticus, increased intracranial pressure, or concomitantly with neuromuscular blockers. For patients who meet criteria for an SAT, all sedation is turned off and oxygen saturation, respiratory rate, and agitation are assessed. If unable to pass an SAT, sedation is resumed at half of the previous dose. The use of SATs is thought to decrease duration of mechanical ventilation and ICU length of stay (33). The 2018 PADIS guidelines recommend daily awakening trials in addition to targeting light sedation (2).

Other related analgesia guidelines on SurgicalCriticalCare.net:

- "Alcohol Withdrawal"
- "Pain Management in Surgery"
- "Gabapentin for Post Operative Pain"
- "Delirium management in the Surgical Patient"
- Ketamine for Analgesia"
- "Muscle Relaxants in Multimodal Pain Management"

Appendix 1



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