Guideline

Guidelines for the Management of Pain, Agitation/Anxiety and Delirium in Mechanically Ventilated Adult ICU Patients

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PURPOSE & RECOMMENDATION SUMMARY

The purpose of this guideline is to provide recommendations to staff for optimal management of pain, agitation and delirium in the adult intensive care units (ICU). The general goals of ICU analgesia and sedation are to facilitate mechanical ventilation, prevent patient and caregiver injury and avoid the psychological and physiologic consequences of inadequate treatment of pain, agitation and delirium.[1] Pain occurs commonly in adult ICU patients, regardless of the admitting diagnosis, through routine and interventional care.[2] Therefore, frequent assessment of pain and administration of analgesic medications are important. Once pain is addressed, anxiolytic/sedative medications can be utilized to treat agitation and anxiety, with the goal to maintain a light level of sedation. Non-benzodiazepine based sedation is recommended as benzodiazepines are associated with many adverse clinical outcomes.[1] Delirium should be treated by addressing the cause (i.e., pain, withdrawal) and utilizing non-pharmacologic measures first before pharmacologic agents. This guideline provides evidence-based recommendations on the use of bedside assessment tools and pharmacologic interventions that are associated with improved clinical outcomes for adult patients on mechanical ventilation.[1]

PRESCRIBING/ORDERING

1. The "Critical Care IV Sedation / Pain Agitation Delirium Adult" PowerPlan should be initiated in patients who have a secure airway and require invasive mechanical ventilation.
2. The provider determines the appropriate medications used for analgesia, anxiety and delirium.
3. Analgesia and sedative agents are titrated to goals determined by the provider.
4. Upon receipt of an order for fentanyl, ketamine, dexmedetomidine, or propofol continuous infusion, the pharmacist will modify the dosing weight in the order from actual body weight to ideal body weight. As an alternative, an adjusted body weight may be used based on patient-specific clinical response.

PAIN

1. Assessment
    a. In the ICU, pain is monitored using the Numeric Rating Scale (NRS) or Critical Care Pain Observation Tool (CPOT).
    b. NRS is the gold standard of pain assessment (Table 1).

i. Criteria for using NRS:
    1. RASS greater than -2, and
    2. Ability to tighten the hand grip upon request
ii. Exclusion criteria:
    1. Severe brain injury
    2. Quadriplegia
    3. Severe dementia or intellectual disability

Table 1. Numeric Rating Scale [1]

Score	Severity
0	None
1	Mild
2	
3	
4	Moderate
5	
6	
7	Severe
8	
9	
10	

c. If the patient is unable to communicate pain level, the nurse can assess non-verbal indicators (e.g., facial grimacing, moaning, tachypnea, hypertension) and conduct further assessment using CPOT (Table 2; Appendix A for details).

Table 2. Critical Care Pain Observation Tool[1,3]

Subscale	Description	Score
Facial Expression	Relaxed, neutral	0
	Tense	1
	Grimacing	2
Body movements	Absence of movements	0
	Protection	1
	Restlessness	2
Muscle tension	Relaxed	0
	Tense, rigid	1
	Very tense or rigid	2
Compliance with ventilation **OR** Vocalization (extubated patients)	Tolerating ventilator or movement	0
	Coughing but tolerating	1
	Fighting ventilator	2
	Talking in normal tone or no sound	0
	Sighing, moaning	1
	Crying out, sobbing	2
Total Score	**≥3 indicates significant pain**	**0-8**

d. Nurse should conduct pain assessment every 4 hours at minimum and additional times as needed whenever new signs of agitation or discomfort are observed. Pain should be reassessed 30 minutes after the administration of an analgesic agent.

2. Management
    a. Bolus doses of analgesic should be used for signs of pain. Treatment of pain is indicated for NRS ≥ 4 and/or CPOT ≥ 3.
    b. Mechanically ventilated patients should receive **analgesia first sedation**, also known as analgosedation. The primary goal of this strategy is to address pain and discomfort first then, if necessary, add an anxiolytic agent.[1,4]
    c. Analgesia first sedation has the following benefits:
        i. Reduction of dose requirement of anxiolytic agents
        ii. Decreased duration of mechanical ventilation
        iii. Decreased incidence of ventilator associated pneumonia
        iv. Improvement in the probability of successful extubation
        v. Shortened ICU length of stay
    d. Treatment of the primary disorder with anxiolytic or antipsychotic agents are sometimes preferred over analgesia first sedation in the following select situations:
        i. Alcohol withdrawal
        ii. Drug induced agitation (i.e., serotonin syndrome, neuroleptic malignant syndrome, delirium)
            1. Note: Opioids should be avoided in serotonin syndrome
    e. Analgesic options for mechanically ventilated patients include:
        i. Fentanyl: Drug of choice for patients requiring continuous infusion. Intermittent bolus doses (at least 3) should be attempted first before starting infusion.
        ii. Hydromorphone: Continuous infusions may be used as an alternative to fentanyl infusions in times of low drug supply of fentanyl or when tachyphylaxis to fentanyl is suspected.
            1. Note: Use with caution in opioid naïve patients (dose equivalence: 1.5 mg IV hydromorphone = 100 mcg fentanyl).
        iii. Ketamine: A continuous infusion may be used as an adjunct agent when patient is on an intravenous opioid and CPOT is not within goal range.
        iv. Morphine: Intermittent doses may be considered for those without renal dysfunction and who are hemodynamically stable (i.e., SBP > 100 mmHg, MAP > 65 mmHg and/or not requiring vasopressor support). Continuous infusions of morphine may be considered for patients who are receiving comfort care.
    f. Oral agents may be used to reduce IV opioid requirements or to transition patients to an oral regimen who have developed opioid dependence as a result of prolonged exposure to IV opioids.
        i. Oral methadone 5-40mg q8h is preferred for patients with normal QTc < 500 msec.
        ii. Oral oxycodone 10-40mg q4h or oral hydromorphone 4-16mg q4h may be used for patients with elevated QTc > 500 msec.

Table 3. Recommended Opioid Continuous Infusion Titration for CPOT < 3 and RASS Goal 0 to -2

RASS Score	Infusion Rate Change	Bolus
≥ 1	Increase the infusion rate* in a stepwise fashion every 30 minutes	Once infusion begins, continue with bolus** IV every 5 minutes as needed until CPOT < 3. If 3 boluses are given within one hour without reaching target CPOT and RASS, increase infusion rate.
0 to -2	No change	No bolus
-3 to -5	1. Reduce sedation medication per Tables 6-10 if applicable and reassess in one hour 2. If still not at goal, reduce opioid infusion by 25% and reassess in one hour 3. Repeat Step 1-2 as needed until at goal	No bolus

*Fentanyl infusion titration by 0.5mcg/kg/min and hydromorphone infusion titration by 0.5mg/hr
**Fentanyl bolus defaults to 50mcg, and hydromorphone bolus defaults to 0.5mg

Table 4. Recommended Opioid Continuous Infusion Titration for RASS Goal -4 to -5

RASS Score	Infusion Rate Change	Bolus
≥ -3	Increase the infusion rate* in a stepwise fashion every 30 minutes	Once infusion begins, continue with bolus** IV every 5 minutes as needed until CPOT < 3. If 3 boluses are given within one hour without reaching target CPOT and RASS, increase infusion rate.
-4 to -5	No change	No bolus

*Fentanyl infusion titration by 0.5mcg/kg/min and hydromorphone infusion titration by 0.5mg/hr
**Fentanyl bolus defaults to 50mcg, and hydromorphone bolus defaults to 0.5mg

AGITATION/SEDATION

1. Assessment
    a. The level of sedation/agitation is monitored using the Richmond Agitation Sedation Scale (RASS) (Table 5).

Table 5. Richmond Agitation Sedation Scale[1]

Score	Classification	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	**Alert and calm**	
-1	**Drowsy**	**Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice**
-2	**Light sedation**	**Briefly (less than 10 seconds) awakens with eye contact to voice**
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

    b. Goal RASS for most ICU patients is 0 to -2 (light level of sedation), unless otherwise specified by the provider.
    c. Nurse should conduct RASS every 4 hours at minimum and additional times as needed.
    d. If RASS is outside of goal range, refer to treatment algorithm for appropriate intervention, unless otherwise specified by the provider.
    e. Patients requiring neuromuscular blockade must have continuous infusions of analgesic and amnestic sedative agents at all time, with a deeper RASS goal (-4 to -5). Refer to the Guidelines for the Use of Continuous Infusion Neuromuscular Blocking Agents in Adults.

2. Management
    a. Address possible underlying causes of agitation and anxiety, such as:
        a. Pain
        b. Delirium
        c. Hypoxemia
        d. Hypotension
        e. Withdrawal from alcohol or drugs

b. Analgesia first sedation should be attempted first to manage pain and provide sedation in appropriate patients. Analgesia alone may be adequate to reach RASS goal of 0 to -2. Anxiolytic/sedative agents should be considered if the patient remains agitated despite adequate analgesia (i.e., CPOT is at goal, but RASS is not at goal).[1]
c. **A non-benzodiazepine anxiolytic agent, such as propofol or dexmedetomidine, is preferred** due to negative outcomes associated with benzodiazepines, such as[1]:
    a. Delirium
    b. Oversedation
    c. Delayed extubation
    d. Longer time to discharge
d. The choice of anxiolytic agents should be based on the desired level of sedation (i.e., light or deep sedation). Medications to maintain light sedation (RASS 0 to -2) include:
    a. Propofol: Drug of choice for most ICU patients requiring an anxiolytic. Propofol has a quick onset (1-2 minutes) and offset action, facilitating frequent neurological assessment and liberation from mechanical ventilator.[5]
    b. Dexmedetomidine: An option for hemodynamically stable patients (i.e., SBP > 100 mmHg, MAP > 65 mmHg, HR > 60 bpm and/or not requiring vasopressor support). It allows for more awake, interactive status of the patient and is associated with less delirium.[6,7] Recommended for patients who are intolerant to propofol and/or benzodiazepine or those with planned extubation who do not tolerate reduction of ventilator support without sedation.
        1. Note: Dexmedetomidine by itself does not provide adequate level of analgesia for ICU patients. Concomitant infusion of an intravenous opioid is recommended.
    c. Ketamine: Continuous infusions have both anxiolytic and analgesic properties and may be used as an adjunct agent for patients whose CPOT and/or RASS is not within goal.
    d. Benzodiazepine: Intermittent doses may be considered for light sedation. Midazolam is the preferred agent due to short onset of action (2-5 minutes). Intermittent doses of lorazepam may also be considered if longer duration of action is desired.
e. Oral agents may be used as adjunct agents to minimize use of IV anxiolytic agents.
    a. Oral phenobarbital 60-200mg q6h may be used to reduce IV anxiolytic use.
    b. Oral clonidine may be used to reduce IV dexmedetomidine use, especially in patients who have received dexmedetomidine for >1 week and may have developed dependency
        1. Consider 0.2 mg every 6 hours for dexmedetomidine doses < 0.7 mcg/kg/hr, BMI < 100 kg, or older patients
        2. Consider 0.3 mg every 6 hours for dexmedetomidine doses of ≥ 0.7 mcg/kg/hr, BMI ≥ 100 kg, or younger patients
f. The concurrent use of propofol and dexmedetomidine is not recommended due to increased risk for adverse events (i.e. bradycardia).
g. For patients who require deep level of sedation (RASS -4 to -5):
    a. Propofol: Continues to be the first line option
    b. Benzodiazepine: Infusion may be considered as a second line option if the patient is hemodynamically unstable. May also be considered as second line if patient is unable to tolerate other anxiolytic agents (i.e., propofol related infusion syndrome). Use midazolam infusion with caution in patients who are obese and/or with renal/hepatic dysfunction due to the risk of metabolite accumulation.
h. The use of benzodiazepines as the first line anxiolytic should be reserved for select situations, such as:
    a. Alcohol/benzodiazepine withdrawal
    b. Seizure
    c. Allergy or intolerance to other anxiolytic agents
i. The use **lorazepam continuous infusion should be avoided** due to the risk for metabolic acidosis and acute kidney injury caused by propylene glycol (diluent) toxicity.[1]

a. For dosing titration instruction for lorazepam, follow the instructions for midazolam titration in Tables 7 and 10 (the two drugs are equivalent in dosing).

j. Anxiolytic infusion titration recommendations:
   a. Fentanyl infusion must be at least 1 mcg/kg/hr prior to administering an anxiolytic agent.
   b. Initiate anxiolytic infusion(s) at the following initial rate unless otherwise specified by the provider. Any change from the recommended starting rate should be reflected in the order:
      1. Propofol IV infusion at 5 mcg/kg/min
      2. Midazolam IV infusion at 1 mg/hr
      3. Dexmedetomidine IV infusion at 0.2 mcg/kg/hr
      4. Ketamine IV infusion at 1 mcg/kg/min
   c. For RASS goal range of 0 to -2, titrate propofol per Table 6, midazolam per Table 7 and dexmedetomidine per Table 8. See Guidelines for the Use of Ketamine Continuous Infusion for Adjunctive Analgesia and Sedation in Critically Ill, Mechanically Ventilated Adults for ketamine titrations.

Table 6. Recommended Propofol Continuous Infusion Titration for RASS Goal 0 to -2

RASS Score	Infusion Rate Change	Bolus
≥ 1	Increase the infusion rate by 5 mcg/kg/min every 30 minutes* (Max: 80 mcg/kg/min)	Bolus with sedative of choice (see Table 11). If RASS still not at goal after maximum dose received, may use alternative bolus sedative. **NO propofol bolus**
0 to -2	No change	No bolus
-3 to -5	Reduce by 5 mcg/kg/min and reassess in one hour	No bolus

*If significant hypotension (MAP < 60 mmHg) occurs, do not titrate any further and notify provider.

Table 7. Recommended Midazolam Continuous Infusion Titration for RASS Goal 0 to -2

RASS Score	Infusion Rate Change	Bolus
≥ 1	Increase the infusion rate by 1 mg/hr every 60 minutes (Maximum: 20 mg/hr, but notify physician if adequate sedation not reached at 10 mg/hr)	Bolus midazolam 2 mg IV Q5MIN until goal RASS achieved (if more than 3 doses are needed in one hour, then start midazolam continuous infusion). Once infusion begins, continue bolus doses Q5MIN as needed. If 3 boluses are given within one hour without reaching target sedation, increase infusion rate.
0 to -2	No change	No bolus
-3 to -5	Reduce by 1 mg/hr and reassess in one hour	No bolus

Table 8. Recommended Dexmedetomidine Continuous Infusion Titration for RASS Goal 0 to -2

RASS Score	Infusion Rate Change	Bolus
≥ 1	Increase the infusion rate by 0.1 mcg/kg/hr every 30 minutes* (Max: 1.5 mcg/kg/hr)	Bolus with sedative of choice (see Table 11). If RASS still not at goal after maximum dose received, may use alternative bolus sedative. **NO dexmedetomidine bolus**
0 to -2	No change	No bolus
-3 to -5	Reduce by 0.1 mcg/kg/hr and reassess in one hour	No bolus

*If significant hypotension (MAP < 60 mmHg) or bradycardia (HR < 60 bpm) occurs, do not titrate any further and notify provider.

d. For RASS goal range of -4 to -5, titrate propofol per Table 9 and midazolam per Table 10.

Table 9. Recommended Propofol Continuous Infusion Titration for RASS Goal -4 to -5

RASS Score	Infusion Rate Change	Bolus
≥ -3	Increase the infusion rate by 5 mcg/kg/min every 30 minutes* (Max: 80 mcg/kg/min)	Bolus with sedative of choice (see Table 11). If RASS still not at goal after maximum dose received, may use alternative bolus sedative. **NO propofol bolus**
-4 to -5	No change	No bolus

*If significant hypotension (MAP < 60 mmHg) occurs, do not titrate any further and notify provider.

Table 10. Recommended Midazolam Continuous Infusion Titration for RASS Goal -4 to -5

RASS Score	Infusion Rate Change	Bolus
≥ -3	Increase the infusion rate by 0.5 mg/hr every 30 minutes (Max: 20 mg/hr, but notify physician if adequate sedation not reached at 10 mg/hr)	Bolus midazolam 2 mg IV Q5MIN until goal RASS achieved (if more than 3 doses are needed in one hour, then start midazolam continuous infusion). Once infusion begins, continue bolus doses Q5MIN as needed. If 3 boluses are given within one hour without reaching target sedation, increase infusion rate.
-4 to -5	No change	No bolus

Table 11. Bolus Sedation Options

Medication	Dose	Onset
Haloperidol	5 mg IV every 10 minutes PRN (max 3 doses per 1 hour)	5 min
Ketamine	2 mg/kg IM every 30 minutes PRN (max 4 doses per 12 hour shift)	5 min
Midazolam	2 mg IV every 5 minutes PRN	2 min

Olanzapine	10 mg IM every every 2 hours PRN (max 30 mg per day)	15 min
Phenobarbital	130 mg IV every 6 hours PRN*	5 min

*Dosing is for sedation, please see Adult Alcohol Withdrawal Prevention and Management Protocol for dosing for alcohol withdrawal

k. Patient's social history should be assessed as soon as possible to identify and treat any possible causes of anxiety.
    a. Patients with social history of tobacco use may experience agitation due to nicotine withdrawal. Nicotine patch is recommended at the following dose:
        1. Patient smokes > 10 cigarettes/day: Nicotine 21 mg/day patch
        2. Patient smokes 10 cigarettes or less/day: Nicotine 14 mg/day patch
    b. Patients with alcohol use history should be given appropriate therapies for alcohol withdrawal. Refer to the Adult Alcohol Withdrawal Prevention and Management Protocol.

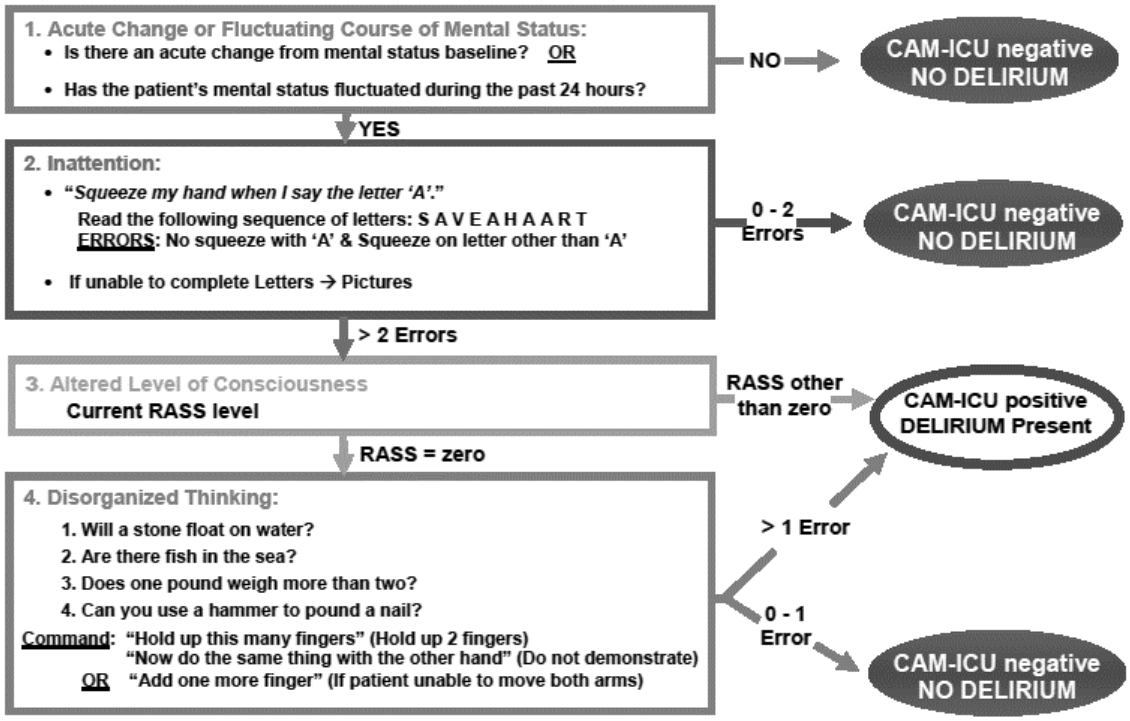
l. Based on the patient's medical history, resume any home medications that can potentially cause withdrawal or severe agitation, unless contraindicated due to critical illness or reason for admission. Examples include but are not limited to:
    a. Anti-psychotic or anti-depressant medication
    b. Pain medication
    c. Certain muscle relaxant (i.e., baclofen)

3. Daily Sedation Awakening Trial/Spontaneous Breathing Trial
    a. All eligible patients should receive daily sedation holiday and/or daily breathing trial.[8] Please refer to the Augusta University Medical Center Daily Sedation Awakening Trial (SAT)/Spontaneous Breathing Trial (SBT) Protocol for Adult Intensive Care Unit Patients.

DELIRIUM

1. Assessment
    a. Delirium is assessed using the Confusion Assessment Method for the ICU (CAM-ICU) (Figure 1).
    b. Nurse should conduct CAM-ICU every 12 hours (once per shift) and at additional times as needed.
    c. Delirium should be assessed in all patients with RASS -3 or higher.

Figure 1. Confusion Assessment Method for the ICU (CAM-ICU)[1]



2. Management
   a. If CAM-ICU is positive, the possible causes of delirium should be addressed:
      i. Disease: Sepsis, COPD, CHF, withdrawal
      ii. Medication: Benzodiazepine, narcotics
      iii. Environment: Immobilization, day/night cycle, need for hearing aids or glasses, noise
   b. Pain management should be optimized first.
   c. No pharmacologic therapies have demonstrated the ability to effectively prevent or reduce the incidence of delirium.[9]
   d. The following non-pharmacologic interventions have been shown to reduce the incidence and duration of delirium:[1,10]
      i. Environmental changes (i.e., noise reduction)
      ii. Sensory aids (i.e., glasses)
      iii. Reorientation and cognitive stimulation
      iv. Sleep preservation and enhancement
      v. Early mobilization (i.e., range of motion exercises, dangling on side of bed, chair position)
   e. In patients with delirium not related to benzodiazepine or alcohol withdrawal, dexmedetomidine should be administered to reduce the duration of delirium.
   f. Antipsychotics may be considered if non-pharmacological interventions have been tried and failed, although the data are insufficient. Monitor QTc while patients are on these agents:
      i. Quetiapine 50 mg PO Q12H initially, then increased by provider up to quetiapine 400 mg daily in divided doses[11]
      ii. Haloperidol 5 mg (maximum of 10 mg) IV/IM over 1 minute, may repeat every 15 minutes until calm; then haloperidol 2.5 mg (maximum of 10 mg) IV/IM/PO no more frequently than every 4 hours with PRN doses
   g. The following sleep aid can be utilized to promote sleep:
      i. Melatonin 3-10 mg enterally every night at bedtime.

SUPPORTIVE CARE

1. All mechanically ventilated patients should be initiated on the following supportive care:
    a. Bowel regimen components:
        i. Docusate 100 mg via feeding tube Q12H
        ii. Senna 187 mg via feeding tube daily
    b. Chlorhexidine 15 mL buccal Q12H to prevent ventilator-associated pneumonia
    c. Stress ulcer prophylaxis (choice of either an H2 receptor antagonist or proton pump inhibitor):
        i. Famotidine 20 mg IV or via feeding tube Q12H preferred
            1. If patient has renal dysfunction (CrCl < 50 mL/min), decrease dose to 20 mg Q24H
        ii. If patient was taking a proton pump inhibitor at home, pantoprazole 40 mg IV or via feeding tube daily may be considered
    d. Venous thrombosis prophylaxis (choice of one of the following):
        i. Enoxaparin 40 mg SQ daily (may require renal adjustment)
        ii. Heparin 5000 units SQ Q8H
2. Chlorhexidine should be discontinued when patient is extubated. Stress ulcer prophylaxis should also be discontinued at the time of extubation, unless the patient has a compelling indication (i.e., coagulopathy or past medical history of gastroesophageal reflux disease).

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APPENDIX A: The Critical-Care Pain Observation Tool Score Sheet

Table 1. Critical Care Pain Observation Tool (CPOT)[3]

Subscale	Description	Score	Description
Facial Expression	Relaxed, neutral	0	No muscle tension observed
	Tense	1	Presence of frowning, brow lowering, orbit tightening and levator contraction or any other change (e.g., opening eyes or tearing during nociceptive procedures)
	Grimacing	2	All previous facial movements plus eyelid tightly closed (the patient may present with mouth open or biting the endotracheal tube)
Body movements	Absence of movements	0	Does not move at all (doesn't necessarily mean absence of pain) or normal position (movements not aimed toward the pain site or not made for the purpose of protection)
	Protection	1	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements
	Restlessness	2	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed
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 or incapacity to complete them
Compliance with ventilation **OR** Vocalization (extubated patients)	Tolerating ventilator or movement	0	Alarms not activated, easy ventilation
	Coughing but tolerating	1	Coughing, alarms may be activated but stop spontaneously
	Fighting ventilator	2	Asynchrony: blocking ventilation, alarms frequently activated
	Talking in normal tone or no sound	0	Talking in normal tone or no sound
	Sighing, moaning	1	Sighing, moaning
	Crying out, sobbing	2	Crying out, sobbing
Total Score		**____ / 8**	