Chapter 6
Rational Selection and Utilization of Opioid Analgesics in Critical Care

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Introduction

An important part of patient care is facilitating comfort and reducing anxiety in order to improve interactions between the patients, staff, and caregivers. Pain is frequently present in critically ill patients regardless of whether they are admitted to medical or surgical units [1]. Although pain is often attributed to invasive procedures, monitoring devices, or wounds, a significant number of patients report pain *at rest* while in the intensive care unit (ICU) [1]. Recognition of pain is important, not only to be able to relieve the discomfort and suffering of the patient but also to mitigate downstream physiologic effects including increased stress hormone production, hemodynamic instability, vasoconstriction, increased catabolism, impaired tissue perfusion, immunosuppression, and impaired wound healing. Other long-term effects including chronic pain and post-traumatic stress symptoms (PTSS) are highly prevalent among ICU survivors [2]. The first step in treating discomfort or pain, however, is recognizing it. Critically ill patients are frequently intubated, sedated, or otherwise unable to communicate their symptoms to healthcare providers. Unless regularly screened for and treated with targeted interventions, pain can be mismanaged and lead to worsened psychological and physical outcomes.

Pain management has emerged as a major focus in critical illness as sedation practices have shifted and providers target lighter sedation with the goal of having more interactive patients. These changes are driven by emerging research demonstrating benefits of decreased sedation, increased patient interactions, and more frequent mobilization [3, 4]. Along with improved patient awareness is the increased recognition and need to keep patients comfortable and calm. The management of

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pain with opioids to assist in these practices has become a major goal of ICU practitioners that has led to the practice of analgesia-based sedation, or "analgosedation." Within this practice, analgesia is prioritized over sedation or hypnosis to encourage a more interactive, lucid, and comfortable patient [2]. Unless contraindicated, current guidelines recommend for the use of targeted analgesia-based sedation with limited use of additional sedative or hypnotic medications [3]. Once initiated, targeted pain management with assessment-driven clinical practices can improve the quality of care provided to patients as well as their outcomes following ICU survival. The evidence behind a targeted analgesia-based approach has proven to be associated with a reduction in hypnotic agents use, duration of mechanical ventilation, and ICU length of stay [3].

This chapter aims to describe pain in the critically ill patient, identify tools to aid in diagnosis and quantification of pain, provide guidance when choosing opioids in patients with various pathophysiologic derangements, and define clinical targets for titration of medications.

Origins of Pain in Critical Illness

Pain is the unpleasant sensory or emotional experience associated with actual or potential tissue damage [5]. This definition allows for the broad interpretation of the diagnosis and experience of pain in patients owing to the multiple physiologic and psychologic pathways that interplay to contribute to this condition. The experience of pain is not limited to those patients who are conscious enough to describe it—pain is frequently reported as a significant memory among critical illness survivors despite appearing unaware or unconscious [6]. For both the psychiatric and physiologic benefits of patients, it is particularly important to assess and treat pain in critically ill populations unable to articulate their experiences. Additionally, there is an increasing prevalence of chronic pain within the community, affecting approximately 1 in 10 adults at baseline [7]. Such patients present with baseline pain levels and can have hyperalgesic (pain out of proportion to stimulus) or allodynic (pain cause by non-painful stimulus) [8] responses to stimuli while in the ICU. For these reasons, it is important to have a systematic and consistent approach to the assessment and management of pain across all patients.

Pain in the ICU can be most simply broken down into rest pain and procedural pain. Rest pain is pain or discomfort that exists while the patient is inactive. This includes baseline chronic pain, musculoskeletal pain from immobility or pressure, wound, fracture, or surgical site pain, gastrointestinal discomfort, or pain related to indwelling lines or tubes [2]. Procedural pain involves regular activities including patient turning, bathing, oral care, or invasive procedures (monitor placement, drain insertion, suture laceration, etc.) that elicit discomfort for the patient while the finite activity is ongoing. Distinction between these types of pain is noteworthy as they carry different sets of risk factors. Recognition by bedside providers of these

Table 6.1 Risk factors for rest and procedural pain [3, 9–15]

Rest pain risk factors	Procedural pain risk factors
Younger age	Younger age
Anxiety	Female sex
Depression	Non-white ethnicity
Comorbidities	Patient positioning
Baseline disability	Type of procedure
History of surgery	Pre-procedural pain intensity
Delay in analgesic initiation	Peri-procedural opioid use[a]
Disproportionate to expectations	Underlying surgery or trauma
Increased ICU length of stay	
Expectation of future poor quality of life	

[a]Conflicting evidence [16, 17]

different types of pain allows identification of patients at increased risk of unrelieved pain—allowing earlier implementation of pain management strategies to mitigate discomfort. A summary of risk factors for resting and procedural pain is listed in Table 6.1.

As shown, this list includes both non-modifiable and potentially modifiable risk factors for active pain. Potentially modifiable risk facts should be addressed as soon as possible to mitigate downstream pain and discomfort for patients as well as stress and anxiety of family members.

In the broader realm of acute pain management, pain is classified by origin of insult as either nociceptive or neuropathic since treatment approaches and efficacy of strategies for pain management differ between these types of pain. Nociceptive pain represents ongoing tissue injury and can be further broken down into somatic pain (affecting superficial and/or peripheral tissues, i.e., skin, tissue, muscle, or bone pain) or visceral pain (affecting the abdomen or organ-related injury, i.e., internal organ pain) [18]. Neuropathic pain is often the result of abnormal nervous system function or dysregulation [18]. It is frequently associated with hyperalgesia and/or allodynia—additional consequences of a dysregulated nervous system. Patients are not limited to one classification, however, and frequently experience a combination of these types of pain. It is helpful to distinguish the origin of pain as treatment options will vary in efficacy depending on pain type (Table 6.2).

In addition to identifying the type of pain to better assign effective treatment therapies, it is also important to identify pain that can signal further risk to the patient. Pain is a basic protective mechanism teleologically. History and physical exam is the most important factor in classifying pain. For example, pain from a fractured leg can be an appropriate cause of somatic rest pain in a critically ill patient. But failing to perform a physical exam when the pain is worsening can delay the identification of neuropathic pain caused by acute compartment syndrome, which carries different albeit as acute of a condition if this change in pain is unrecognized or inappropriately classified.

Table 6.2 Classification, origin, and management strategies for acute pain [18–20]

Classification of pain	Origin of pain	Examples	Pain management strategies
Nociceptive	Ongoing tissue damage		Treat underlying cause, non-steroidal anti-inflammatory drugs, acetaminophen, ketamine, dexmedetomidine, anticonvulsants (e.g., gabapentin, carbamazepine), neuraxial analgesia or peripheral nerve blocks, music therapy
	Somatic	Burns, fractures, invasive lines	
	Visceral	Angina, pancreatitis, bowel distension	
Neuropathic	Damaged nerves or dysregulated nervous system	Spinal cord injury pain, phantom limb pain, multiple sclerosis, neuropathy (diabetic, alcoholic, chemotherapy-related)	Antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors, bupropion), anticonvulsants (e.g., gabapentin, pregabalin), ketamine, topical anesthetics (e.g., lidocaine), opioids, peripheral nerve blocks, physical therapy and complementary therapies (transcutaneous electrical nerve stimulation [TENS], relaxation or massage therapy, music therapy)

Diagnosing and Quantifying Pain in the ICU Patient

Acute pain is highly individual and patients have different experiences, expectations, and tolerance for pain. For these reasons, critical care providers should not assume a linear relationship between injury severity and pain experienced. Validated tools to objectively quantify and qualify pain are available and should be routinely employed to optimize recognition of pain and delivery and titration of analgesic medications. Traditionally, pain has been assessed by a self-reported pain scale such as the numerical rating scale (NRS) or the numerical rating scale with a visual format (NRS-V), see Chap. 7 [21, 22]. Such pain scales are frequently administered along with verbal and/or the visual pain scales, such as the Wong-Baker FACES Pain Rating Scale [23] discussed in Chap. 7. Most ICU patients, however, are unable to participate reliably with the NRS-V, verbal, or facial scales due to mental status derangements from illness, sedation, presenting pathology, or a combination thereof and alternative assessment methods must be utilized. In the scenario where the patient is unable to verbalize due to intubation or other causes, the Behavior Pain Scale (BPS) [24] or the Critical-Care Pain Observation Tool (CPOT) [25] may be used to quantify pain. Both of these scales are well validated within the critically ill population and recommended by current guidelines (see Chap. 7) [26, 27].

As shown in Table 6.3, the CPOT is divided into four main behavioral domains: facial expression, body movements, ventilator compliance (when applicable), and muscle tension. This assessment can be performed quickly by a bedside nurse or

Table 6.3 Critical-care pain observation tool scoring table [25]

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluated by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with the ventilator (intubated patients)	Alarms no activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: Blocking ventilation, alarms frequently activated	Fighting ventilator	2
OR			
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Signing, moaning	Signing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			0–8

other clinical care providers. Each domain is scored between 0 and 2, with total possible scores ranging from 0 to 8. A score of 3 or greater indicates pain. Importantly, this tool assesses for the presence of pain and is not a linear scale. It also does not correlate to the same number score on the self-reported scales.

Another common tool used to assess pain in the ICU is the Behavior Pain Scale (BPS) [24]. The BPS is broken down into three main behavioral domains: facial expression, upper limb movements, and compliance with mechanical ventilation. These are scored from 1 to 4, as shown in Table 6.4. A score of ≤ 3 indicates no pain, 4–5 indicates mild pain, 6–11 unacceptable amount of pain, and ≥ 12 indicates maximum pain. This scale is similar to the CPOT in that it

Table 6.4 Behavior pain scale scoring table

Indicator	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4
Total		
	No pain	0–3
	Mild pain	4–5
	Unacceptable amount of pain	6–11
	Maximum pain	12

can also be done quickly and effectively at the bedside with good reliability and validity [28]. One major difference is that the BPS scale additionally quantifies the degree of pain, whereas CPOT is designed primarily for identification of the presence of pain [29].

While both of these scoring methods have been validated and shown effective at identifying pain in conscious and unconscious critically ill patients, neither has been shown to be superior in sensitivity or specificity [30]. As such, the routine use of any of these validated pain tools is the most important aspect of assessment. Hemodynamic changes and intermittent non-validated qualitative assessments by bedside providers are not a reliable method for assessing pain in critical care and result in the failure to recognize pain—particularly in unconscious patients. Although recognition of these changes are important aspects of bedside care and should not be ignored, they also cannot be depended on for routine pain assessments in critically ill patients. Protocol-based analgesia and sedation approaches are not only important from a humane perspective in that they improve patient pain scores [31], but they offer additional proven clinical benefits as well. Institution of protocol-guided analgesia and sedation administration have been shown to reduce total sedation received [32], days of mechanical ventilation, and ICU length of stay [33, 34]. It is therefore imperative that validated screening methods be implemented and routinely performed throughout the ICU stay for all patients.

Pathophysiology and Opioid Selection

There are several factors that should be included when making the decision of which opioid medication to administer. These include medication availability, underlying pathophysiology, patient-specific factors, as well as staff familiarity, and local practice. Per current guidelines, pain should be treated first in a targeted-practice strategy with sedation used to augment patient comfort, per analgesia-based sedation or "analgosedation." Pain management strategies, however, are not limited to opioid medications. Pain management should involve multimodal components including patient positioning, non-pharmacologic strategies, regional analgesia as indicated, and non-opioid medications (i.e., muscle relaxants, intravenous lidocaine/ketamine, gabapentinoids, non-steroidal anti-inflammatory drugs, or NSAIDs) as indicated for optimal results. These adjunct medications, however, are not benign and accumulation of either medication or active metabolites secondary to impaired metabolism can cause significant, even life-threatening, complications. Additionally, although they may help accomplish other clinical goals, adjunct medications may not be reliably associated with reduction in opioid use [35, 36]. It is recommended that doses be adjusted for metabolic clearance or avoided entirely if patients have evident decreased renal or hepatic metabolism. Table 6.5 lists non-opioid analgesics recommended for use by current guidelines for pain, along with their primary route of clearance and relative contraindications [3].

Non-pharmacologic strategies to be considered include music therapy, relaxation techniques, massage, or transcutaneous electrical nerve stimulator (TENS) therapy. Where these opioid sparing and non-pharmacologic strategies fail, opioids should be considered for additional acute pain management. The optimal opioid medication is cost-effective, quick acting, has a short context-sensitive half-life, is rapidly titratable, and does not interact with other medications or hemodynamic parameters. While no opioid medication on the market fully meets all of these criteria, we will discuss their relative indications and contraindications.

Opioids recommended for pain management in the ICU include remifentanil, fentanyl, hydromorphone, and morphine [3]. All will have dose-dependent side effects, with higher doses associated with greater respiratory depression and

Table 6.5 Non-opioid analgesics, primary metabolic clearance, and relative contraindications

Medication	Metabolic clearance	Contraindication
Acetaminophen	Hepatic	Cirrhosis (> 2 g/24 h)
Gabapentinoids	Renal	Renal failure
Ketamine	Hepatic	PTSD/psychiatric disorders
NSAIDs[a]	Renal	Food and Drug Administration warning after coronary artery bypass graft surgery, renal impairment

[a]recommended for discrete use in infrequent procedures as an alternative to opioids

Table 6.6 Pharmacokinetics of commonly utilized opioid medications [37]

Medication	Onset (IV)	Elimination half-life	Context-sensitive half-life	Active metabolites	Metabolic pathway
Remifentanil	1–3 min	3–10 min	3–4 min	No	Hydrolysis by plasma esterases
Fentanyl	1–2 min	2–4 hrs	200 min (6 hr. infusion); 300 min (12 hr. infusion)	No	Demethylation CYP3A4 substrate
Hydromorphone	5–15 min	2–3 hrs	N/A	No	Glucuronidation
Morphine	5–10 min	3–4 hrs	N/A	6- and 3-glucuronide metabolite	Demethylation, Glucuronidation

hypotension. When deciding which agent to use, one should factor in time of onset, planned duration of use, alterations in renal or hepatic metabolism, respiratory status, and external factors such as utilization of extra-corporeal membrane oxygenation (ECMO). Table 6.6 describes pharmacokinetic properties of commonly utilized opioid medications in the ICU that should factor in to opioid choice. In addition to these, individual medication factors must also be considered.

For example, fentanyl is a quick-acting opioid medication owing in large part to its relative lipophilicity. This same property, however, will allow it to absorb within ECMO cannula tubing [38]. While not necessarily a contraindication, higher doses may be required for these patients to achieve target concentration. Alternatively, one could transition to a less lipophilic alternative such as morphine or hydromorphone. Additionally, several opioid medications have been shown to cause clinically significant histamine release impacting patient hemodynamics. Morphine is the most frequently implicated in this adverse event and patients should be monitored closely, especially if presenting with a history of immunologic sensitivity [39]. Finally, remifentanil is often used for short procedures given the cost of prolonged infusions as well as its association with increased hyperalgesia following discontinuation [40]. In patients with impaired renal function, prolonged infusions have been associated with glycine toxicity and should be used with caution in ICU patients with impairments in renal metabolism [41]. In general, because fentanyl causes less histamine release than morphine and does not undergo renal elimination, it is the preferred opioid analgesic in hemodynamically unstable patients or those with renal insufficiency.

Few comparative trials between opioid regimens have been performed in the ICU. Remifentanil appears to provide better outcomes than morphine with regard to time at sedation target, use of supplemental sedation, and duration of mechanical ventilation in one randomized double-blind study [42, 43]. Meanwhile, remifentanil and fentanyl have displayed equal efficacy in achieving time at target sedation with no difference in extubation times [43]. Patients receiving fentanyl required more

frequent administration of additional sedatives but experienced less pain after extubation compared to those receiving remifentanil [43].

Regardless of the opioid medication used, patients should be continually assessed using validated scoring systems following medication administration for titration of medication and early identification of adverse events.

Targeted Opioid Medication Utilization

The Saturday Review in 1895 published an article by George Bernard Shaw in which he used the phrase "a shot in the dark." In present day medicine, we are fortunate to have guidelines and validated scales to shed light on our target. Intensivists are challenged with the task of providing sedation that is analgesia-based and assessment-driven [3]. Several studies have produced results demonstrating improved outcomes when analgesia is managed primarily [37, 39–42]. We will describe this strategy below.

Analgosedation protocols begin using the same tools presented earlier in this chapter. Multimodal pain management strategies are initiated for patients guided by validated CPOT or BPS scales. When indicated, providers should choose opioids with the previously mentioned considerations as a guide. They should then titrate these medications to achieve adequate pain relief as determined using either CPOT, BPS, or other validated scoring systems. An earlier review of appropriate opioid selection should guide the critical care team in devising a protocol appropriate for each unique institution while considering the clinical condition and cost. A step-wise approach in concordance with current recommendations guiding opioid utilization for managing acute pain is presented in Table 6.7.

In the case that the patient remains agitated, sedation should then be initiated (i.e., propofol, dexmedetomidine) and guided by validated sedation scare targets. There are several validated scales that can be utilized to describe patient sedation or agitation—the most common being the Ramsay Scale [44] and the Richmond Agitation-Sedation Scale (RASS) [45], described in Tables 6.8 and 6.9. Following these scales, clinicians should target sedation to achieve a Ramsay score of 1–2 or a RASS score of −1 to +1.

Table 6.7 General approach to treating acute pain in critical illness

Situation	Preferred intervention
Acute pain	Intermittent (IV or enteral) opioid administration
Acute pain that persists/recurs	Opioid infusion +/− IV boluses for breakthrough pain
Acute pain in chronic opioid user	Account for previous opioid use when using IV opioid; may consider ketamine or other multimodal adjunct
Planned transition out of ICU and patient on IV opioid infusion	Initiate scheduled enteral opioid therapy

Table 6.8 Ramsay scale

Ramsay scale	
Scale	Description
1	Anxious, agitates, or restless
2	Cooperative, oriented
3	Response to commands only
4	Brisk response to light touch or loud auditory commands
5	Sluggish response to light touch or loud auditory commands
6	No response to light touch or loud auditory commands

Table 6.9 Richmond agitation-sedation scale (RASS)

Richmond agitation-sedation scale (RASS)		
Score	Term	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 non-purposeful 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 s) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 s) 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

Once the targeted sedation level is achieved, clinicians should continue to re-assess and adjust sedative medications for continued maintenance of light sedation in addition to continued concurrent pain assessments and control. These re-assessments and interventions are critical to maintaining a safe and alert patient with optimized pain control. Importantly, for all patients intubated and maintained on sedation, daily pauses in sedation should be performed along with daily spontaneous breathing trials, unless otherwise contraindicated. When performed together, this practice is associated with a decrease in ventilator days, ICU days, and improved survival up to 1 year following hospital discharge [46].

Further, the use of analgesic-based sedative regimens targeting light sedation have shown clinical benefits across study centers and in diverse populations. Patients maintained on primary analgesia-driven sedation with protocolized assessments and minimal, as-needed, sedation have also been shown to have decreased length of stay in the ICU, more days alive without mechanical ventilation, and improved sedation scores [31, 47, 48]. These analgesia-based protocols serve as a tool for

providers to both target and titrate analgesic and sedative regimens in critically ill patients. Although specific medications and doses can vary among protocols, the primary basis remains administration of short-acting, readily titratable medications driven by frequent patient assessments.

While opioids have been discussed here as the primary tool for analgosedation and acute pain, the clinician must not minimize the current opioid crisis. The previously stated adverse effects should remind providers to employ a multimodal approach to analgesia that incorporates both pharmacologic and non-pharmacologic agents. Utilizing the whole spectrum of the critical care team (clinical psychologists, physical and occupational therapists, nursing staff, physicians) is further recommended to achieve success in this realm.

Summary

Inappropriate sedation and pain management contribute to worse patient outcomes [47, 48]. The shift away from deep sedation in mechanically ventilated patients to more awake and interactive patients has directed the focus toward analgesia-based strategies in critical illness. Recognizing the cause and type of pain present in patients is the first step toward treatment. A foundational knowledge of opioids and non-opioid adjuncts is essential for implementation and targeted pain relief therapy. Clinicians should employ opioid adjuncts to pain management with individual derangements in pathophysiology and institutional constraints and familiarity in mind. Most importantly, ICUs should employ and perform validated assessments of pain and modify analgesia and sedation using targeted goal-directed protocols. Adherence with these goal-directed analgesia and pain management strategies has been shown to improve outcomes for critically ill patients.

References

1. Chanques G, Sebbane M, Barbotte E, Viel E, Eledjam JJ, Jaber S. A prospective study of pain at rest: incidence and characteristics of an unrecognized symptom in surgical and trauma versus medical intensive care unit patients. Anesthesiology. 2007;107(5):858–60.
2. McGovern C, Cowan R, Appleton R, Miles B. Pain, agitation and delirium in the intensive care unit. Anaesthe Intens Care Med. 2018;19(12):634–40.
3. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825–73.
4. Treggiari MM, Romand JA, Yanez ND, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med. 2009;37(9):2527–34.
5. Bonica JJ. The need of a taxonomy. Pain. 1979;6(3):247–8.
6. van de Leur JP, van der Schans CP, Loef BG, Deelman BG, Geertzen JH, Zwaveling JH. Discomfort and factual recollection in intensive care unit patients. Crit Care. 2004;8(6):R467–73.

7. Mansfield KE, Sim J, Jordan JL, Jordan KP. A systematic review and meta-analysis of the prevalence of chronic widespread pain in the general population. Pain. 2016;157(1):55–64.
8. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. Lancet Neurol. 2014;13(9):924–35.
9. Carroll KC, Atkins PJ, Herold GR, et al. Pain assessment and management in critically ill postoperative and trauma patients: a multisite study. Am J Crit Care Off Publ Am Assoc Crit Care Nurs. 1999;8(2):105–17.
10. Al Sutari MM, Abdalrahim MS, Hamdan-Mansour AM, Ayasrah SM. Pain among mechanically ventilated patients in critical care units. J Res Med Sci. 2014;19(8):726–32.
11. Navarro-Garcia MA, Marin-Fernandez B, de Carlos-Alegre V, et al. Preoperative mood disorders in patients undergoing cardiac surgery: risk factors and postoperative morbidity in the intensive care unit. Rev Esp Cardiol. 2011;64(11):1005–10.
12. Desbiens NA, Wu AW, Broste SK, et al. Pain and satisfaction with pain control in seriously ill hospitalized adults: findings from the SUPPORT research investigations. For the SUPPORT investigators. Study to understand prognoses and preferences for outcomes and risks of treatment. Crit Care Med. 1996;24(12):1953–61.
13. Puntillo KA, Morris AB, Thompson CL, Stanik-Hutt J, White CA, Wild LR. Pain behaviors observed during six common procedures: results from thunder project II. Crit Care Med. 2004;32(2):421–7.
14. Arroyo-Novoa CM, Figueroa-Ramos MI, Puntillo KA, et al. Pain related to tracheal suctioning in awake acutely and critically ill adults: a descriptive study. Intensive Crit Care Nurs. 2008;24(1):20–7.
15. Faigeles B, Howie-Esquivel J, Miaskowski C, et al. Predictors and use of nonpharmacologic interventions for procedural pain associated with turning among hospitalized adults. Pain Manag Nurs. 2013;14(2):85–93.
16. Puntillo KA, Max A, Timsit JF, et al. Determinants of procedural pain intensity in the intensive care unit. The Europain(R) study. Am J Respir Crit Care Med. 2014;189(1):39–47.
17. Puntillo K, Weiss SJ. Pain: its mediators and associated morbidity in critically ill cardiovascular surgical patients. Nurs Res. 1994;43(1):31–6.
18. Pandharipande PP, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. J JAMA. 298(22):2644–53.
19. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008;70(18):1630–5.
20. Kerstman E, Ahn S, Battu S, Tariq S, Grabois M. Neuropathic pain. Handb Clin Neurol. 2013;110:175–87.
21. Chanques G, Viel E, Constantin JM, et al. The measurement of pain in intensive care unit: comparison of 5 self-report intensity scales. Pain. 2010;151(3):711–21.
22. Rahu MA, Grap MJ, Ferguson P, Joseph P, Sherman S, Elswick RK Jr. Validity and sensitivity of 6 pain scales in critically ill, intubated adults. Am J Crit Care Off Public Am Assoc Crit Care Nurs. 2015;24(6):514–23.
23. Chambers CT, Hardial J, Craig KD, Court C, Montgomery C. Faces scales for the measurement of postoperative pain intensity in children following minor surgery. Clin J Pain. 2005;21(3):277–85.
24. Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29(12):2258–63.
25. Gelinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care Off Public Am Assoc Crit Care Nurs. 2006;15(4):420–7.
26. Dehghani H, Tavangar H, Ghandehari A. Validity and reliability of behavioral pain scale in patients with low level of consciousness due to head trauma hospitalized in intensive care unit. Arch Trauma Res. 2014;3(1):e18608.

27. Joffe AM, McNulty B, Boitor M, Marsh R, Gelinas C. Validation of the critical-care pain observation tool in brain-injured critically ill adults. J Crit Care. 2016;36:76–80.
28. Rijkenberg S, Stilma W, Bosman RJ, van der Meer NJ, van der Voort PHJ. Pain measurement in mechanically ventilated patients after cardiac surgery: comparison of the Behavioral pain scale (BPS) and the critical-care pain observation tool (CPOT). J Cardiothorac Vasc Anesth. 2017;31(4):1227–34.
29. Ahlers SJ, van der Veen AM, van Dijk M, Tibboel D, Knibbe CA. The use of the Behavioral pain scale to assess pain in conscious sedated patients. Anesth Analg. 2010;110(1):127–33.
30. Severgnini P, Pelosi P, Contino E, Serafinelli E, Novario R, Chiaranda M. Accuracy of critical care pain observation tool and Behavioral pain scale to assess pain in critically ill conscious and unconscious patients: prospective, observational study. J Intensive Care. 2016;4:68.
31. Faust AC, Rajan P, Sheperd LA, Alvarez CA, McCorstin P, Doebele RL. Impact of an analgesia-based sedation protocol on mechanically ventilated patients in a medical intensive care unit. Anesth Analg. 2016;123(4):903–9.
32. Georgiou E, Hadjibalassi M, Lambrinou E, Andreou P, Papathanassoglou ED. The impact of pain assessment on critically ill patients' outcomes: a systematic review. Bio Med Res Int. 2015;2015:503830.
33. Payen JF, Bosson JL, Chanques G, Mantz J, Labarere J. Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit: a post hoc analysis of the DOLOREA study. Anesthesiology. 2009;111(6):1308–16.
34. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA. 2012;308(19):1985–92.
35. Perbet S, Verdonk F, Godet T, et al. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: a randomised double-blind control trial. Anaesth Crit Care Pain Med. 2018;37(6):589–95.
36. Fabritius ML, Geisler A, Petersen PL, et al. Gabapentin for post-operative pain management - a systematic review with meta-analyses and trial sequential analyses. Acta Anaesthesiol Scand. 2016;60(9):1188–208.
37. Barr J, Pandharipande PP. The pain, agitation, and delirium care bundle: synergistic benefits of implementing the 2013 pain, agitation, and delirium guidelines in an integrated and interdisciplinary fashion. Crit Care Med. 2013;41(9 Suppl 1):S99–115.
38. Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA, Tibboel D. Determinants of drug absorption in different ECMO circuits. Intensive Care Med. 2010;36(12):2109–16.
39. Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ. Histamine release by four narcotics: a double-blind study in humans. Anesth Analg. 1987;66(8):723–30.
40. Yu EH, Tran DH, Lam SW, Irwin MG. Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? Anaesthesia. 2016;71(11):1347–62.
41. Bonnet MP, Minville V, Asehnoune K, et al. Glycine and ammonia plasma concentrations during sedation with remifentanil in critically ill patients. Intensive Care Med. 2007;33(7):1179–82.
42. Dahaba AA, Grabner T, Rehak PH, List WF, Metzler H. Remifentanil versus morphine analgesia and sedation for mechanically ventilated critically ill patients: a randomized double blind study. Anesthesiology. 2004;101(3):640–6.
43. Muellejans B, Lopez A, Cross MH, Bonome C, Morrison L, Kirkham AJ. Remifentanil versus fentanyl for analgesia based sedation to provide patient comfort in the intensive care unit: a randomized, double-blind controlled trial [ISRCTN43755713]. Crit Care. 2004;8(1):R1–R11.
44. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J. 1974;2(5920):656–9.
45. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–44.

46. 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 randomised controlled trial. Lancet. 2008;371(9607):126–34.
47. Breen D, Karabinis A, Malbrain M, et al. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomised trial [ISRCTN47583497]. Crit Care. 2005;9(3):R200–10.
48. Rozendaal FW, Spronk PE, Snellen FF, et al. Remifentanil-propofol analgo-sedation shortens duration of ventilation and length of ICU stay compared to a conventional regimen: a Centre randomised, cross-over, open-label study in the Netherlands. Intensive Care Med. 2009;35(2):291–8.