Pain and Analgesia

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LEARNING OBJECTIVES

1. Apply knowledge of the incidence, etiologies, and assessment of pain to the treatment of critically ill patients.
2. Develop evidence-based pain management strategies that include both nonpharmacologic and pharmacologic interventions and that account for transitions of care.
3. Design a pain control strategy for unique patient populations.
4. Evaluate short- and long-term outcomes associated with pain management, and develop methods to improve quality of care.

ABBREVIATIONS IN THIS CHAPTER

BPS	Behavioral Pain Scale
CPOT	Critical-Care Pain Observation Tool
GABA	γ-Aminobutyric acid
ICP	Intracranial pressure
NMDA	*N*-methyl-D-aspartate
NRS	Numeric Rating Scale
OIH	Opioid-induced hyperalgesia
PAD	Pain, agitation, and delirium
PTSD	Posttraumatic stress disorder

Table of other common abbreviations.

INTRODUCTION

The clinical approach to pain management in the ICU has evolved over the past few decades because of new medications, administration methods, assessment tools, and a paradigm shift using analgosedation as an initial intervention for the management of pain and agitation. Despite these advances, most ICU patients experience moderate to severe pain, which is consistently identified as one of the most troublesome memories of survivors of critical illness. Among the many reasons for this are an underappreciation of the problem, given that many patients cannot verbalize their analgesic needs, and an inability of caregivers to recognize the degree of discomfort imposed by routine ICU care. Unrelieved pain is associated with both short- and long-term physical and psychological consequences and should be the focus of evidence-based assessment, treatment, and prevention.

Pain management is extremely complex because pain presents in different ways (e.g., acute, chronic, acute on chronic), develops from different sources (e.g., somatic, visceral, neuropathic, psychogenic), and is perceived and tolerated in a highly variable manner. Add in features of the critically ill population (e.g., immobility, impaired communication, altered mental status, sleep deprivation, mechanical ventilation, procedures and interventions), and the issue becomes overwhelming without a standardized approach.

This chapter discusses these challenges and others associated with analgosedation in the critically ill population. The focus is on ICU pain as a single entity, but it should be

understood that pain, agitation, and delirium (PAD) are interrelated and can interfere with many important aspects of ICU care, including early mobility, sleep, and overall recovery.

Physiology, Etiology, and Causes

Pain is defined by the International Association for the Study of Pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP 1979). Accordingly, pain is a multidimensional issue with both emotional and physical components that are characterized as pain distress and pain severity, respectively.

Nociception represents the process of detecting, transmitting, and processing noxious stimuli caused by chemical, thermal, or mechanical insults. Noxious stimuli initiate nerve impulses (transduction) mediated by the intracellular release of inflammatory substances (e.g., substance P, bradykinin, histamine, prostaglandins, serotonin). These nerve impulses travel to the dorsal horn of the spinal cord, where they mediate the release of both excitatory (i.e., glutamate or aspartate) and inhibitory (i.e., γ-aminobutyric acid [GABA]) neurotransmitters in the thalamus and midbrain. The interplay between these neurotransmitters helps define an individual's response to noxious stimuli (perception). Modulation of the pain signal occurs with the release of endorphins and enkephalins (Reardon 2015).

There are at least three types of pain. Somatic nociception is associated with peripheral tissue injury and is characterized by sharp, stabbing, or dull pain that can be localized. Visceral nociception is associated with organ injury, is typically difficult to localize, and is characterized in vague terms such as *cramping*. Neuropathic pain originates from disorders of the central and peripheral nervous systems. Peripheral neuropathic pain is caused by neuronal lesions related to trauma, infections (e.g., postherpetic neuralgia), and ischemia (e.g., diabetes, vascular disease). Central neuropathic pain results from diseases of the CNS, spinal cord injury, or demyelinating diseases (e.g., multiple sclerosis) (Reardon 2015).

Most ICU patients experience moderate to severe pain from sources such as acute and chronic illness, surgery, trauma, burn injuries, pancreatitis, cancer, comorbidities (e.g., arthritis, chronic pain syndromes), immobility, invasive medical and monitoring devices, and routine ICU care (e.g., procedures) (Box 1-1). In addition, many conditions (e.g., diabetes mellitus, Guillain-Barré syndrome) can lead to neuropathic pain (Sigakis 2015).

Although procedures are known to be common sources of ICU pain, preemptive analgesia is administered less than 25% of the time. A landmark 2014 study of 3851 ICU patients who underwent 4812 procedures measured associated pain intensity. All evaluated procedures were associated with some degree of pain, and three (i.e., chest tube removal, wound drain removal, and arterial line insertion) led to pain intensity more than double from baseline. Of interest, patients perceived procedures performed by nurses as less painful than those done by other caregivers and physicians. Investigators hypothesize that anxiety and its associated increase in pain perception were limited because nurses provide reassurance, compassion, and pre-procedural education and often include family members (Puntillo 2014).

Pain Assessment

Management of ICU pain starts with a careful assessment of its source, duration, and severity. This is difficult in the ICU

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of medications commonly used for analgesia
- Adverse drug effects of analgesic agents
- Pharmacologic properties of opioids

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Society of Critical Care Medicine. ICU Liberation [homepage on the Internet].
- Joint Commission. Sentinel Event Alert Issue 49: safe use of opioids in hospitals.
- Joint Commission. Pain management [homepage on the Internet].
- National Institute on Health and Care Excellence. Opioid use in renal impairment.
- American Pain Society. Guidelines on the management of postoperative pain. J Pain 2016;17:131-57.
- ICU Liberation. Assess, Prevent, and Manage Pain [homepage on the Internet].

Box 1-1. Routine ICU Procedures Associated with Pain

- Turning and repositioning
- Obtaining peripheral blood or intravenous and arterial line insertions
- Endotracheal and tracheal suctioning
- Chest tube and wound drain placement or removal
- Mobilization and respiratory exercises
- Wound care

Information from Puntillo KA, Max A, Timsit JF, et al. Determinants of procedural pain intensity in the ICU. Am J Respir Crit Care Med 2014;189:39-47.

because patients are often unable to communicate or have cognitive impairment. Recent European data suggest that although 80% of ICUs routinely monitor pain using a validated pain assessment tool when the patient is able to self-report, only 30% use validated behavioral pain assessment tools for patients unable to communicate (Luetz 2014). The PAD guidelines identify pain assessment as an area where gaps in practice exist and suggest that assessments be performed and documented at least four times per nursing shift, before and after analgesia has been administered, and with any change in patient condition (Barr 2013). Of importance, systematic assessments of pain can reduce its frequency by 33% and reduce sedative use, mechanical ventilation dependency, ICU length of stay, and mortality (Joffe 2013; Payen 2009).

Self-report

Individual pain tolerance is widely appreciated, but cultural differences may not be. For example, patients of Hebrew, Chinese, and Japanese origins have very few expressions for pain in their vernacular, which may impair their ability to provide detailed descriptions of pain. In contrast, the English language includes 16 categories of pain described by at least 64 words (Puntillo 2009). Self-reporting, therefore, remains the gold standard for pain assessment in the critically ill population. To self-report, a patient cannot be deeply sedated and must be able to interact in a meaningful way with caregivers.

The Numeric Rating Scale Visual (NRS-V) may be the easiest assessment tool to use; moreover, it offers the best negative predictive value and likely represents the most widely used metric (Gelinas 2014). The cutoff score for significant pain using the NRS-V is greater than 3.

The presence of an endotracheal tube or a tracheostomy should not preclude pain assessments. Different methods of communication beyond vocalization can and should be used (e.g., tight eye squeezing, blinking, finger gestures). A laminated tool with a numeric format that includes body locations where pain is felt, together with words to describe the qualitative nature of pain (e.g., sharp, aching, burning), is often beneficial.

Vital Signs

Vital signs are not consistent indicators of ICU pain; have not been correlated with patient self-reporting or validated pain assessment tools; and can change in response to fear, anxiety, or other stressors. Acute changes in vital signs, however, can be used as cues to perform an evaluation with a validated tool (e.g., self-report or behavioral-based pain assessments) (Barr 2013). Overall, vital signs should not be used as the sole indicator of pain.

Behavioral Pain Scales

In an effort to improve pain evaluations in noncommunicative patients, assessment tools based on behavioral pain indicators (e.g., facial expression, body movement, muscle movements or tension, compliance with the ventilator) have been developed and tested for reliability and validity. These tools represent a significant advancement in the management of ICU pain, but they should only be used when patient self-report is impossible and when motor function is intact. The PAD guidelines recommend the Critical-Care Pain Observation Tool (CPOT) and the Behavioral Pain Scale (BPS) for use in noncommunicative patients. These tools have common features, but they are not useful for measuring pain intensity and cannot discriminate between pain types. Thresholds to identify significant pain in patients are greater than 2 for CPOT and greater than 5 for BPS.

Surrogate Reporting

A patient's family members often serve as advocates, especially when they perceive that their loved one is experiencing pain. Compared with patient self-report, surrogates correctly identify the presence of pain 74% of the time and the severity of pain 53% of the time, with a tendency to overestimate pain intensity (Desbiens 2000). Although consideration of family concerns is important, it remains the responsibility of health care providers to evaluate pain and the need for interventions.

Agreement of pain severity between nurse report and patient report is around 75%. Although this may seem good, nurses underestimate significant pain (NRS greater than 3) almost 60% of the time (Ahlers 2008). These data emphasize the importance of providing light sedation to allow patients to accurately describe their analgesic needs. These data also support the contention that pain assessments should be combined with several sources of information when patient self-report is not possible.

Analgesic Trial

Occasionally, despite the use of evaluative strategies, there is uncertainty about whether a patient is experiencing pain. When this occurs, it is reasonable to offer an analgesic trial followed by observation. If patient behaviors seem to respond to an analgesic trial, consideration of continued administration is indicated. If there is no response to analgesia, other causes of the patient's behaviors should be explored (Herr 2006).

Incidence of Pain

Most patients experience moderate to severe pain during their ICU stay, with the incidence varying according to patient condition and exposure to procedures. Pain even occurs at rest and is moderate to severe in about 50% of patients in both surgical and medical ICUs. Of interest, the source of the pain is different between these two groups, with surgical patients identifying pain at the site of injury and medical patients usually having back and limb pain (Robleda 2016; Chanques 2007).

Relevance: Acute and Long-term Physical and Psychological Consequences

The stress response from painful stimuli activates the autonomic nervous system, causing the release of catecholamines and stress hormones (e.g., glucagon, cortisol),

which can result in vasoconstriction and interfere with tissue perfusion and oxygen delivery. These factors may lead to hypercatabolic states, tachypnea, tachycardia, increased oxygen demand, ischemic injury, impaired wound healing and response to infections, and hyperglycemia (Sigakis 2015).

Unrelieved pain is the most traumatic memory for ICU patients. Pain also interferes with sleep, may hinder effective pulmonary toilet (coughing, deep breathing), impedes mobility and physical therapy efforts, and, if it persists, may lead to long-term issues such as chronic pain, reduced quality of life, and development of post-traumatic stress disorder (PTSD) (Sigakis 2015). However, therapeutic options available for pain management are associated with adverse events that involve the CNS, GI, and pulmonary function. All of these types of pain significantly affect patient outcomes.

MANAGEMENT

Therapeutic Goals, Documentation, and Response

The primary goal of pain management is to acutely provide patient comfort and safety; secondary goals are to prevent the immediate and long-term complications of pain. The complexity of pain management mandates a comprehensive systematic multidisciplinary approach. Pain assessments should be routinely performed and documented (at least four times per nursing shift and within 30 minutes of administering pain-relieving interventions), together with simultaneous efforts to mitigate many of the factors that initiate, sustain, or heighten the awareness of pain. Efforts should include preemptive strategies initiated before painful procedures, identification of outpatient issues such as chronic pain or history of substance abuse and tolerance with a low threshold to restart medications, if appropriate.

Pain management strategies should also be based on patient-focused treatment goals by selecting pharmacologic or nonpharmacologic interventions that consider the desired onset and duration of effect, organ dysfunction, prior response to therapy, and potential for significant drug interactions or adverse events. The exact level of pain relief should be patient-specific because some patients prefer to tolerate a degree of pain in exchange for a clearer sensorium.

Intubation and the provision of sedation offer challenges for patient-to-caregiver communication of analgesic goals, but these is not insurmountable as long as the patient is wakeful and able to use nonverbal communication tools (e.g., note writing, finger-to-word pointing). Comprehensive pain management strategies should include prevention and aggressive management of adverse drug events. Examples include initiating bowel regimens for most patients treated with opioids and providing a tapered dosing schedule for de-escalation of therapy to avoid withdrawal.

Daily interdisciplinary discussions at the bedside should address pain assessment, response to therapy, and complications encountered. Unfortunately, barriers to effective pain management can make this approach difficult to implement. A comprehensive educational approach is recommended to enhance caregiver understanding of the benefits and burdens of pharmacologic pain management, with special emphasis on patient assessment for drug choice, dose titration, and adverse drug reactions.

Barriers to Effective Pain Management

The three primary barriers to effective pain management can be characterized as provider, health care system, and patient based. Caregivers often have an underappreciation of the short- and long-term consequences of unrelieved pain and therefore relegate pain management to a lower priority. In addition, caregivers may not fully understand the extent of pain that ICU patients have and therefore the importance of frequent assessment. A survey of 800 Canadian ICU nurses showed that only 50% were aware of the existence of guidelines for ICU pain management, and even fewer targeted their administration of analgesics using a pain assessment tool (Rose 2012). These data are consistent with a multicenter observational study that found that pain assessment tools were used for only 28% of mechanically ventilated patients, and that analgesia was provided without pain assessment in most patients (Payen 2007). Caregiver personal and cultural biases may influence pain management as well, especially if they have strongly held views about the potential for opioid overuse (e.g., stereotyping or bias based on demographics such as sex, race, history of substance abuse) and drug-seeking behaviors.

The health care system may play a role in suboptimal pain management by not mandating quality improvement processes or not insisting on caregiver responsibility and accountability for pain relief. Even the structure of the provision of care may interfere with pain management such as the absence of a multidisciplinary standardized approach or established protocols. All of these can easily be exacerbated by issues related to inadequate nurse staffing.

Patients may represent significant barriers to pain management; they may accept pain as an inevitable part of illness, or not vocalize the extent of their pain as a means of avoiding adverse drug events. It has even been suggested that patients fear the consequences of reporting pain to a caregiver who may have a stronger sense of bias than empathy (Sigakis 2015; Topolovec-Vranic 2010; Pasero 2009).

Prevention Including Preprocedural Interventions

Data suggest that less than one-half of patients are assessed for pain while undergoing a potentially painful procedure, and less than one-fourth actually receive procedural pain treatment (Payen 2009). The PAD guidelines offer a strong recommendation for the use of preemptive pain control for patients before the removal of chest tubes and a weak recommendation for a similar strategy for other potentially painful procedures.

A recent randomized placebo-controlled trial showed that the use of fentanyl (1–1.5 mcg/kg per dose) before turning in a mixed ICU population of ventilated patients reduced the incidence of pain (as measured by a BPS score greater than 3) by 20%, with a number needed to treat of 5 (Robleda 2016). The authors emphasize the need for caution and careful patient selection, because 10% of patients treated with these aggressive doses of fentanyl experienced respiratory depression.

Nonpharmacologic Approaches to Pain Management

At least 33 nonpharmacologic interventions have been used for pain management in the ICU, but only three (i.e., music, deep breathing, and ice therapy) have been studied; all produced conflicting results (Joffe 2013; Gelinas 2012). Despite these uncertainties, preemptive interventions for known painful procedures should be provided because they are low cost and low risk and have the potential to complement pharmacologic options as part of a multimodal approach to analgesia (Barr 2013; Czarnecki 2011).

Pharmacologic Strategies

The choice of analgesic agent depends on a variety of patient factors, including the type, duration, and severity of pain; hemodynamic status; prior response or tolerance to therapy; presence of organ dysfunction and other comorbidities; potential for harmful drug interactions and adverse drug events; and the required onset and duration of pain relief. The route of administration of analgesia is an important consideration as well. Intravenous administration is generally preferred in the ICU because it provides rapid pain relief and because the GI tract is often not accessible or fully functional. Intermittent intravenous administration is indicated for pain caused by predictable or short-lived noxious stimuli, whereas continuous infusions are appropriate for conditions associated with sustained pain. Patient-controlled analgesia (PCA) allows selected patients control over their pain and its management, but it requires wakefulness and intact motor activity. Of importance, the use of PCA does not absolve the caregiver from assessing pain and the results of treatment. Regional or neuraxial strategies may be useful in the settings of thoracic, abdominal, vascular, and orthopedic surgery.

Multimodal interventions are well established in non-ICU settings because they provide different mechanisms of action and promise to improve analgesia while limiting exposure to opioids. Unfortunately, however, data that are specific to treating nonneuropathic ICU pain are very limited. Nevertheless, the PAD guidelines offer a conditional recommendation for the consideration of non-opioids to be administered in addition to standard opioid therapy.

In addition, an analgesia-first or analgosedation approach has been advocated because surveys show that unrelieved pain remains a significant issue for most ICU patients (Barr 2013). The analgesia-first approach provides sedating medication only after aggressive analgesic approaches have been initiated. This strategy obviates the need for prototypical sedatives in 25%–50% of patients and avoids their often significant associated adverse drug events. Outcomes resulting from an analgesia-first approach include adequate pain relief, as well as less time on the ventilator, and decreases in the ICU and hospital lengths of stay (Strom 2010).

Analgosedation is not indicated in patients with agitation that is related to drug or substance withdrawal (except opioids), drug-induced agitation (serotonin syndrome, neuroleptic malignant syndrome, or encephalopathy), or any agitation associated with a clear and reversible etiology. The general application of an analgosedation approach in the United States should be tempered by an appreciation that almost all data supporting this approach were generated in Europe, where 1:1 nurse-to-patient ratios were common and sitters were available. Furthermore, data on the influence of analgosedation on outcomes such as delirium, pneumonia, mortality, and long-term cognitive impairment are not yet available.

Opioids

Opioids are the mainstay for the treatment and prevention of pain in the ICU because they are familiar to prescribers, offer reliable analgesia, have desirable pharmacodynamic activity, and can be administered using a variety of administration routes (e.g., enteral, rectal, topical, intramuscular, intravenous, epidural). Opiates have been used for thousands of years to treat pain and "ease the harshness of life" (Chu 2008).

Opioids stimulate μ-opioid receptors, a subtype of G protein–coupled receptors that inhibit the release of inflammatory and excitatory mediators and interfere with the propagation of nerve signals, ultimately to dampen the excitability of nociceptors. They also activate N-methyl-d-aspartate (NMDA) receptors, which may lead to stimulation of nociceptors and development of tolerance. When administered in equianalgesic doses, the opioids have similar efficacy and similar non-cardiovascular adverse effects, including tolerance, constipation, suppression of cough reflexes, and respiratory depression.

Fentanyl

Fentanyl is one of the most widely used opioids in the critically ill population because it has a rapid onset of action and is readily titratable. This synthetic opioid is largely metabolized by CYP3A4. Because it is a substrate for this enzyme system, fentanyl may interact with inhibitors such as the azole antifungals, macrolides, protease inhibitors, and nondihydropyridine calcium channel blockers, as well as inducers such as barbiturates, rifampin, and carbamazepine. In addition, fentanyl competes with midazolam for clearance by CYP3A4 and reduces its clearance.

Some tertiary sources suggest that fentanyl doses should be adjusted in the setting of kidney disease. This recommendation is based on data from a handful of patients and has

no biological plausibility because only 10% of fentanyl is excreted unchanged by the kidney, and there are no active metabolites. More recent studies of a mixed critically ill population suggest that the pharmacokinetics of fentanyl are not significantly affected by renal dysfunction, though they are strongly influenced by hepatic disease, heart failure, and body mass (Choi 2016).

Fentanyl, which has 5-hydroxytryptamine 1A agonist properties, has been associated with serotonin syndrome, but the clinical significance of this is uncertain because the data are based largely on animal studies and a few case reports in humans when fentanyl had been used in combination with other agents with known serotonergic activity (Atkinson 2015). A recent retrospective single-center review evaluated the incidence of serotonin syndrome in 4500 patients treated with the combination of fentanyl and serotonergic agents from January 2012 to December 2013. Four patients (0.09%) met the criteria for serotonin syndrome; three received fentanyl patch therapy, and one received intravenous fentanyl. The incidence of serotonin syndrome in the control group (those treated with a serotonergic agent but without concomitant fentanyl) was significantly lower at 0.005% ($p<0.01$) (Koury 2015). These findings suggest that fentanyl contributes to the occurrence of serotonin syndrome, but the incidence of this adverse event is quite small. In addition, a March 2016 FDA drug safety communication warns of the risk of serotonin syndrome in patients receiving opioids, especially fentanyl, oxycodone, and methadone in conjunction with serotonergic medications.

Morphine

Morphine administration is largely limited in the ICU to traditional uses: for the treatment of dyspnea, for the treatment of myocardial infarctions for its preload reducing properties, and in the setting of palliative care because of the potential for accumulation of active metabolites in patients with kidney dysfunction, as well as its ability to cause histamine release, which may result in venodilation and bronchospasm.

Hydromorphone

Hydromorphone is a semisynthetic opioid derived from morphine. Issues with this drug stem from an underappreciation of its potency (about 6.5 times that of morphine) and resultant dosing errors; its relatively long half-life (2–3 hours), limiting easy infusion titration; and the accumulation of a potentially neurotoxic metabolite (hydromorphone-3-glucuronide) with large doses or in renal disease (Gagnon 2015).

Hydromorphone can be used to provide analgesia for patients who do not respond to high doses of other opioids. This strategy is known as opioid rotation, and supporting data are largely derived from the oncology literature. A trial of 1–2 mg of intravenous hydromorphone can be used and continued if the patient responds favorably.

Methadone

Methadone is a unique opioid because it has μ-opioid receptor agonist and NMDA receptor antagonist properties. Methadone has a complex pharmacokinetic profile: its half-life varies from 15 to 60 hours and depends on hepatic metabolism and the presence of interacting substances (Chou 2014). These factors make dose titration difficult. It has been suggested that, when methadone is used to treat chronic pain patients with opioid tolerance or who are switching from an alternative opioid, initial daily dosages should not exceed 30–40 mg, and dose titration should not exceed 10 mg daily at 5- to 7-day intervals (Chou 2014). Reasons for this caution include concerns for drug accumulation and its consequences on mental status, respiratory drive, and QTc prolongation. Recent data suggest that methadone represents the second most common cause of drug-induced ventricular dysrhythmias after dofetilide (Chou 2014). The American Pain Society practice guideline for the use of methadone suggests an ECG for most patients before initiating methadone treatment and avoidance of this agent in patients with a QTc of 500 milliseconds or greater. It is important to maintain serum potassium and magnesium in normal ranges and be mindful of the administration of other QTc-prolonging drugs. Follow-up ECGs are based on clinical context. An ECG should be performed 2–4 weeks after methadone initiation or significant dose increases for patients with risk factors for QTc prolongation, any prior ECG that showed QTc prolongation, and in those with a history of syncope. All patients should have their ECGs checked when the methadone dose reaches 30–40 mg daily and again at 100 mg daily. Finally, ECGs should be performed for all patients with new risk factors for QTc prolongation or for those who have developed arrhythmias.

The PAD guidelines offer no equianalgesic dose for methadone because it depends on the dose of the comparator opioid. In addition, the PAD guidelines offer no firm guidance on the relative potency of enteral versus intravenous administration because enteral bioavailability data are sparse and confidence intervals are wide.

Despite these potential drawbacks, methadone offers potential advantages because it may restore analgesia in patients who have become tolerant to standard opioids or when hyperalgesia is suspected. It has also been used to facilitate the discontinuation of continuous infusion opioids (Al-Qadheeb 2012), which may result in faster liberation from mechanical ventilation (Wanzuita 2012). The impact of methadone on other ICU outcomes such as length of stay and time dependent on mechanical ventilation has not yet been defined.

Remifentanil

Remifentanil is an ultra–short-acting synthetic opioid (half-life 3–10 minutes), which may offer an advantage for patients requiring frequent neurologic evaluations. It is metabolized

by nonspecific plasma esterases to inactive metabolites. It is expensive and can be associated with adverse events involving drug administration. For example, it is vital that the pharmacist and nurse work closely to avoid disruptions in therapy that might result in resurgence of pain or even withdrawal when delays in replenishing intravenous infusions occur. Hyperalgesia, which is thought to be mediated by NMDA receptor activation, has been reported with remifentanil in the perioperative setting, but not in ICU patients. Nonetheless, the potential for hyperalgesia should be anticipated with consideration of adding concurrent acetaminophen, dexmedetomidine, and ketamine to potentially mitigate this issue (Joffe 2013).

Buprenorphine

Buprenorphine is a partial μ-opioid receptor agonist with antagonist properties at the *κ*-opioid receptor with a mean half-life of 36 hours. It is available as a single agent or in combination with naloxone and is increasingly used for patients with opioid dependence and chronic pain. Buprenorphine-treated patients admitted to the ICU represent a challenge for the management of acute pain. Higher doses of standard opioids may be required for buprenorphine-treated patients to overcome the antagonist activity of the drug (Alford 2006).

Tramadol

Tramadol is an oral synthetic opioid that affects pain relief through weak μ-opioid receptor activity, serotonin release, inhibition of norepinephrine reuptake, and NMDA antagonist properties. It is converted in the liver to an active metabolite, *O*-desmethyltramadol, which is a μ-opioid agonist. Tramadol may produce less respiratory depression than typical opioids, but it is infrequently used because it is not very potent; moreover, it reduces the seizure threshold and may be associated with serotonin syndrome.

Non-opioid Analgesics

A summary of the pharmacologic properties and dosing of non-opioid analgesics used in the critically ill population is available on the ICU Liberation website.

Acetaminophen

Acetaminophen is a central cyclo-oxygenase inhibitor that consistently decreases opioid requirements by as much as 20% when used in a multimodal capacity, but the clinical correlation of a reduction in opioid-related adverse events is not clearly defined (Oyler 2015; Joffe 2013). In contrast, ICU data for enteral or intravenous acetaminophen are limited. A small double-blind placebo-controlled study evaluated the effects of intravenous acetaminophen in 40 postoperative ICU patients. Those receiving intravenous acetaminophen required 60% less opioid in the form of meperidine, were extubated quicker, had less pain (as measured by BPS and the visual analog scale), and experienced less nausea and vomiting (Memis 2010). The clinical and economic benefits of intravenous acetaminophen in the ICU setting have not been established, but it seems reasonable to consider this mode of administration for short-term use in patients until they can tolerate enteral medications.

Acetaminophen has a remarkable safety profile, but it should be used with caution and in lower doses in patients who abuse ethanol, have liver disease, or have malnutrition. Of interest, the rate of nausea with the intravenous formulation is 30%. The maximal total daily dose by any route of administration is 4000 mg.

Nonsteroidal Anti-inflammatory Drugs

These agents exert their analgesic properties principally by inhibiting the enzyme cyclo-oxygenase, resulting in a reduction in the synthesis of mediators of the acute inflammatory response, including prostaglandin synthesis in the spinal cord. All NSAIDs are similar in efficacy and adverse events; thus, choice of agent can be based on local preference and costs. These agents offer analgesia that is equivalent to acetaminophen (Joffe 2013), but their adverse effect profile mandates cautious use in patients at risk of bleeding, in those with kidney disease, and in those concomitantly using diuretics. In addition, NSAIDs may not be indicated in the trauma population because their use is associated with impaired bone fracture healing (Oyler 2015).

Ketamine

Ketamine is a noncompetitive NMDA receptor antagonist that blocks the effects of glutamate release. Ketamine offers a clinical advantage in patients with asthma because it provides bronchodilatory effects, relieves pain unresponsive to opioids (because it is a NMDA antagonist), and improves hypotension (through endogenous catecholamine release).

Most published ketamine data are in the setting of non-ICU non-neuropathic pain, where adequate pain control was achieved with a reduction in opioid requirements and their associated adverse effects (Joffe 2013). Although there is enthusiasm for the use of ketamine infusions in the ICU, high-quality data are sparse. A recent systematic review identified one ICU-based placebo-controlled trial published in 2003 that evaluated ketamine as an opioid-sparing agent after major abdominal surgery. Morphine was administered by PCA. No other sedatives or analgesics were used. Cumulative morphine exposure was significantly less in the ketamine group (58 mg) than in placebo (80 mg) ($p<0.05$). All other measured outcomes, including confusion and hallucinations, were similar (Patanwala 2015). However, these data may not be generalizable to more severely ill patients who cannot manage their own analgesic needs.

This systematic review also identified four randomized controlled trials that compared cerebral perfusion and intracranial pressures (ICPs) in ketamine- versus opioid-treated patients with brain injury and found no between-group

differences. These limited data support further study of ketamine in this patient population (Patanwala 2015).

One randomized trial evaluated ketamine versus sufentanil in 25 patients with catecholamine-dependent heart failure receiving midazolam sedation. Hemodynamic monitoring using a pulmonary artery catheter showed that ketamine was associated with a 21% decrease in cardiac index, a 20% increase in pulmonary capillary wedge pressure, and a 38% increase in systemic vascular resistance (Patanwala 2015). Ketamine should be avoided in this population until the risk is further defined by a well-powered trial.

Adverse effects of ketamine include hypertension, diplopia, nystagmus, and nausea and vomiting. The neuropsychiatric adverse effects of ketamine on discontinuation (emergence phenomenon) seem to occur infrequently with the doses that are typically used in the ICU (less than 0.5 mg/kg/hour) and these effects may be blunted by the administration of benzodiazepines. However, data on the sustained use of ketamine in adults are limited, and the potential for neurotoxicity should temper enthusiasm until long-term exposure has shown a reasonable safety profile (Soriano 2012).

The ICU Liberation website lists pharmacokinetic and pharmacodynamic parameters on ketamine, as well as guidance on dosing.

Dexmedetomidine and Clonidine

The mechanism for pain modulation by these agents is unknown, but it may be related to α_2-receptor agonism in the substantia gelatinosa in the dorsal horn of the spinal column inhibiting somatic pain. These agents provide "cooperative" sedation without affecting respiratory drive, and data suggest that they are opioid sparing as well (Oyler 2015). Clonidine and dexmedetomidine are similar, but they can be distinguished by their degree of α_2-receptor specificity (dexmedetomidine has more), administration route (dexmedetomidine is the only intravenous α_2-receptor agent available in the United States), and cost. Cost is a significant limitation for dexmedetomidine, but this may be overcome by rapid transition to enteral clonidine in selected patients (Gagnon 2015). Both agents may cause central sympatholysis by blocking the release of norepinephrine and lead to bradycardia and hypotension.

Lidocaine

Lidocaine is widely used as a local anesthetic, for regional anesthesia, and for nerve blocks, but it is also an effective analgesic when administered intravenously. Lidocaine analgesia is mediated by sodium channel blockade and inhibition of both G protein–coupled receptors and NMDA receptors. Recent systematic reviews have described ICU-relevant data involving perioperative lidocaine infusions (Vigneault 2011; McCarthy 2010). Data in abdominal surgery suggest that lidocaine use is associated with lower pain scores, less opioid exposure, better GI function, and a reduction in hospital length of stay.

The approach to dosing has been remarkably inconsistent, with 1–2 mg/kg loading doses commonly used and sometimes followed by a continuous infusion of less than 3 mg/kg/hour for a variable duration. Serum concentrations, when measured, have consistently been less than 5 mcg/mL, and documented toxicity has been limited to hemodynamically stable arrhythmias and bradycardia (McCarthy 2010). More study is needed to define the benefits and burdens of intravenous lidocaine in ICU patients. Intravenous lidocaine should be avoided in patients with arrhythmias, sinus bradycardia, heart block, heart failure, and coronary artery disease (Adam 2015).

Lidocaine is also available for topical use as a 5% patch. This formulation may be useful as an adjunct to standard opioid therapy in the management of pain related to rib fractures (Oyler 2015). In addition, topical lidocaine administration can limit pain perception before the administration of subcutaneous lidocaine when used to facilitate invasive procedures (Wendlandt 2013).

Anticonvulsants: Gabapentin, Pregabalin, Carbamazepine

Gabapentin and pregabalin are structurally related to GABA and modulate pain response by decreasing intracellular calcium influx, which in turn decreases the release of glutamate and substance P (Oyler 2015). Carbamazepine treats pain by inhibiting sodium channels. Data for the ICU are limited to neuropathic pain associated with Guillain-Barré syndrome, where the use of gabapentin and carbamazepine was associated with greater pain relief in conjunction with fentanyl than with placebo (Barr 2013). The gabapentinoids, which are renally eliminated, require dose adjustment in the setting of kidney disease, whereas carbamazepine is noted for its ability to induce hepatic enzymes, leading to significant drug interactions.

Regional Anesthesia

Regional anesthesia is an established effective means of pain control. This strategy promises to avoid respiratory complications, allow less sedation, promote greater meaningful patient interactions, facilitate early mobility efforts, and improve GI function; however, ICU-specific data are sparse. The use of indwelling catheters has limitations dictated by the expertise of available personnel and by patient-specific relative contraindications (e.g., spinal cord injury, acute neurologic injury, coagulopathy, infections). Local anesthesia can result in high systemic serum concentrations and lead to toxicity involving the heart and CNS. The latter risk is called LAST (local anesthetic systemic toxicity), and recognition of it may be compromised in some ICU patients because of their level of sedation and comorbidities (Stundner 2012). Furthermore, epidural anesthetics are associated with hypotension.

Epidural analgesia is probably the regional anesthetic strategy most often used in the critically ill population, and

thoracic epidural anesthesia is recommended for postoperative pain management after abdominal surgery and in trauma patients with rib fractures. This technique for chest trauma patients improves lung mechanics, which may result in a lower incidence of pneumonias and a shorter duration on mechanical ventilation, but it has been associated with an increased risk of hypotension (Barr 2013). A recent systematic review of regional anesthesia and analgesia in the critically ill population informs the topic and emphasizes the lack of ICU-specific data and the need for further research to define the risks and benefits of these techniques (Stundner 2012).

Adverse Drug Events of ICU Analgesia; Focus on Opioids

Opioid-associated adverse drug events are very common and account for as much as 16% of all inpatient adverse drug reactions. These include respiratory and CNS depression, hypotension, constipation, withdrawal, nausea and vomiting, hyperalgesia, and delirium. The associated clinical and financial implications of adverse events are significant because they carry the risk of prolonged duration of mechanical ventilation and increased ICU and hospital lengths of stay and an associated increase in costs (Devlin 2013).

Respiratory Depression and Oversedation

Opioid-associated respiratory depression is sometimes used clinically to aid in oxygenation by facilitating patient synchrony with mechanical ventilation. However, it can represent a barrier to successful liberation from mechanical ventilation, emphasizing the importance of careful dose titration and establishment of patient-specific goals.

The Joint Commission has identified risk factors for respiratory depression and oversedation, including age older than 60 years, opioid naivety, excessive opioid exposure, morbid obesity, sleep apnea, comorbidities including pulmonary or cardiac dysfunction, concurrent use of other sedating agents, conditions that impede diaphragmatic function (e.g., thoracic surgery), and a history of snoring or smoking. With few exceptions, these risk factors are not modifiable, but strategies to limit the adverse effect include the systematic evaluation of pain; the use of a multimodal approach, when feasible; and consideration of the use of enteral methadone to facilitate the discontinuance of continuous infusions of opioids. The Joint Commission website has a more comprehensive discussion.

Hypotension

Opioid-induced hypotension is typically associated with morphine and its ability to cause histamine release and venodilation. Blood pressure changes can occur with other opioids as well and are generally the result of blunting of the stress response and associated catecholamine release that are a physiologic response to painful stimuli.

Opioid-Induced Constipation

An estimated 40%–90% of patients will experience opioid-induced constipation, which often gives rise to discomfort, agitation, and a delay in meeting nutritional goals. The opioids stimulate GI μ-opioid receptors, which leads to an inhibition of gastric emptying, increased non-propulsive contractions, delays in GI transit in both the small and large intestines, and reduction in water and electrolyte secretion (Chey 2014). Constipation has been associated with adverse clinical outcomes, including inadequate oxygenation, hypotension, longer ICU stays, and even mortality (Gacouin 2010). Although supportive data suggesting benefits in clinical outcomes are sparse, efforts to promote defecation with stool softeners and laxatives should be considered for almost all opioid-treated patients. If opioid-induced constipation is refractory to standard interventions, the peripherally active μ-opioid antagonists methylnaltrexone and naloxegol can be used because they do not cross the blood-brain barrier to interfere with the opioid-mediated analgesic activity. Methylnaltrexone is administered subcutaneously, and the weight-based dose should be adjusted in renal disease. Naloxegol, which is enterally administered, requires dose adjustment when concurrently administered with CYP3A4 inhibitors. Both agents are contraindicated in patients with GI obstruction because of the risk of perforation.

Withdrawal

Few data describe the risk factors, characteristics, and management of opioid withdrawal in adult ICU patients. The most commonly described symptoms are nonspecific (e.g., agitation, diarrhea, vomiting, tachycardia, tachypnea) and mandate heightened caregiver awareness. The incidence of opioid withdrawal is not well defined but may approach 30% in mechanically ventilated patients receiving high-dose opioids for a week or more (Cammarano 1998). The PAD guidelines recommend tapering these drugs over several days, if possible, to avoid withdrawal symptoms (Barr 2013).

Nausea and Vomiting

Opioid-induced nausea and vomiting may be related to direct stimulation of chemoreceptor trigger zone. Treatment options are similar to those for postoperative patients.

Hyperalgesia

Opioid-induced hyperalgesia (OIH), identified more than 100 years ago, leads to increased pain response to minimal noxious stimuli (allodynia) or even the sensation of pain without noxious stimuli after exposure to this class of analgesics. The acute impact of OIH involves unrelieved pain, but the loss of analgesia because of OIH may lead to chronic pain in almost half of ICU survivors 6 months to 1 year after ICU discharge (Reardon 2015). A proposed mechanism for OIH involves sensitization of the pro-nociceptive pathways for pain by activation of NMDA receptors. This causes an influx

of intracellular calcium and heightens pain response. This mechanistic explanation provides a rationale for using NMDA antagonists such as ketamine and methadone for patients in whom OIH may be present (Chu 2008). Data also suggest a role of prostaglandins in the development of OIH by increasing the release of glutamate in the spinal cord dorsal horn that activates NMDA receptors.

A recent systematic review and meta-analysis of 27 randomized controlled trials involving 1494 patients evaluated the clinical impact of high-dose intraoperative opioid use and subsequent perception of pain post-surgery (Fletcher 2014). Remifentanil use increased pain intensity 24 hours after surgery and resulted in an increase in 18 mg of morphine administered during that observation period. Of interest, there was no difference in morphine-associated adverse drug events, despite the increased dose.

Currently, reasonable approaches to OIH include careful opioid dose titration and opioid rotation with methadone, as well as the use of multimodal analgesic strategies with agents such as the NSAIDs, ketamine, and α_2-agonists or the use of regional anesthetic techniques (Belgrade 2010).

Delirium

Cohort trials have inconsistently identified opioid use as a risk factor for developing delirium, but this relationship is confounded by the presence of pain (presumably the reason for using the opioid), which of itself can lead to delirium. One high-quality double-blind randomized trial compared dexmedetomidine with morphine in cardiac surgery patients; no between-group differences were found in the incidence of delirium, but the duration of delirium was longer in patients receiving morphine (Shehabi 2009).

SPECIAL POPULATIONS AND ISSUES

Neurologic and Other Patient Populations

The approach to pain management in the neurocritically ill population includes identifying potential causes of pain/discomfort, providing a close observation of all the variants of patient behaviors related to pain, and administering an analgesic trial when uncertainty about pain is present. A comprehensive online review describes pain assessment for nonverbal patients and updated tools, guidelines, and forms to facilitate bedside application.

A study of 439 assessments in 151 neurologic ICU patients showed that self-report of pain is feasible in almost 70% of patients with brain injury (Yu 2013). These data suggest that a self-report pain assessment strategy should be tried first and in a serial fashion because the ability to self-report waxes and wanes. When self-report is impossible, behavioral pain scales can be considered as long as motor function is intact. It should be appreciated, however, that behavioral responses to pain differ between patients with brain injury and other ICU patients, especially if they have an altered level of consciousness (Gelinas 2013). These patients may respond to noxious stimuli with sudden eye opening, weeping, and limb flexion, whereas typical behaviors such as grimacing and muscle rigidity occur less commonly. Similar to other patient populations, changes in most vital signs have not consistently correlated with painful stimuli, but changes in respiratory rate correlate with pain in traumatic brain injury; however, such changes occur only in patients who are conscious, as measured by a Glasgow Coma Scale score of 13 or more (Arbour 2014).

Brain activity studies of patients with brain injury who are in a vegetative or minimally conscious state support the concept that these patients may have the ability to perceive pain (Gelinas 2013). Pain assessment and management may be particularly important in this group of patients because pain is associated with an increased ICP, a reduction in cerebral venous outflow, and increasing brain metabolism. Furthermore, behavioral signs may be muted because these patients are often deeply sedated to prevent dangerous ICP elevations.

In the critically ill population with brain injury and an altered level of consciousness, pain assessment has yet to be rigorously developed; however, all patients should be evaluated and treated using an analgesic agent with a short half-life that will facilitate frequent neurologic examinations. Adequate analgesia is mandatory for patients with elevated ICP, with special attention during painful procedures. Data suggest that opioid use is related to transient increases in ICP that are likely related to reductions in systemic blood pressures and the resultant autoregulatory cerebral vasodilatation that follows (Roberts 2011). The clinical significance of these findings is uncertain. No firm guidance on the choice of agents exists, but fentanyl and remifentanil may be preferred because they seem to minimally alter cerebral perfusion and minimally interfere with hemodynamic stability.

Dementia

Patients with severe cognitive impairment may be unable to understand and even answer simple questions about their pain, making self-report a less valuable assessment tool. In addition, typical pain-related behaviors are often absent; therefore, caregivers need to be aware of other findings associated with pain in this population such as agitation, confusion, or combativeness. The most common causes of pain in patients with dementia have their origins in musculoskeletal disorders, neuropathies, and acute issues such as falls and infections.

Delirium

Until recently, the ability to evaluate pain in patients with delirium was unknown because this group of patients was excluded from validation studies. Validity of the CPOT was confirmed in a select group of patients with delirium without cognitive impairment and a median Richmond Agitation-Sedation Scale score of zero by comparing measurements before and after painful and nonpainful stimuli. The mean difference between CPOT scores at baseline and after painful procedures was 3

points on an 8-point scale. No such difference was seen with nonpainful procedures (Kanji 2016).

Subarachnoid Hemorrhage–Related Headache

Headaches in patients with subarachnoid hemorrhage occur with a prevalence of 75% during hospitalization; these can be severe and persist for as long as 2–9 years. Data suggest that headache is a leading cause of 30-day hospital readmission for these patients. There are no evidence-based guidelines for managing headaches in this population, though several agents have been used, including NSAIDs, opioids, acetaminophen, gabapentin, dexamethasone, and the combination product containing butalbital, acetaminophen, and caffeine (Glisic 2016).

Pharmacologic Paralysis

Therapeutic paralysis is infrequently used in most ICU patients, except in the setting of acute respiratory distress syndrome and for shivering during targeted temperature management. By definition, these patients cannot self-report and do not have motor activity to guide pain assessment. It is reasonable to assume that significant pain is present and to offer analgosedation as a baseline strategy to ensure comfort (May 2015).

Kidney Disease

Many opioids, including oxycodone, codeine, dihydrocodeine, meperidine, and morphine, degrade to active metabolites and should be used with caution, if at all, in patients with renal disease. Morphine is metabolized to morphine-3-glucuronide (55%) and morphine-6-glucuronide (10%), both of which are renally cleared. Morphine-6-glucuronide has a greater affinity for the μ-opioid receptor than morphine and has prolonged activity because of its slow egress from the CNS and its marked increase in half-life with renal impairment (from 2 to 27 hours in end-stage renal disease). Morphine-3-glucuronide has no analgesic activity, but it is reported in animal studies to be neurotoxic.

Hydromorphone is generally thought to be safe in the setting of renal disease, but recent data suggest that the metabolite, hydromorphone-3-glucuronide, is neurotoxic and may accumulate with impaired glomerular filtration (Gagnon 2015).

As previously mentioned, ICU data do not support the widely held notion that the clearance of fentanyl (an opioid without active metabolites) is significantly affected by kidney function.

Methadone is metabolized to inactive products, and only 20% of the parent drug is eliminated unchanged; it requires no dose adjustment for kidney disease.

Tramadol and its active metabolite, *O*-desmethyltramadol, can accumulate in renal disease. Prolongation of the dosing interval is recommended for patients with a GFR less than 30 mL/minute/1.73 m^2 and avoidance of the extended-release formulation.

Buprenorphine is degraded to metabolites with little analgesic activity. These metabolites accumulate in the setting of renal disease, but associated adverse reactions have not been characterized.

The United Kingdom Medicines Information Pharmacists Group website has a comprehensive document on the safe use of opioids in the setting of renal impairment.

Palliative Care

The incidence of moderate to severe pain in the final 3 days of life in hospitalized patients is about 40% and represents the greatest fear for this population. A recent review offers a stepwise approach to pain in the setting of palliative care, beginning with acetaminophen or an NSAID and advancing to use of an opioid for treating moderate to severe pain. Frequent bolus doses of opioids should be administered until pain is relieved, and these doses can help determine the approximate daily dose of opioid that can be administered as a basal dose using an infusion or scheduled intermittent administration. Provision of intermittent bolus medication for breakthrough pain should also be offered. Patients with neuropathic pain will require a different approach, as mentioned previously, with the use of the combination of an opioid with gabapentin. Other agents that may have utility include glucocorticoids, transdermal lidocaine, antidepressants, and anticonvulsants (Blinderman 2015).

Transitions of Care

A large proportion of ICU patients will receive pain medications during their acute illness; these may be discontinued when pain is no longer an issue, but some patients will require continuation of their analgesia. Consideration for using fentanyl patches, methadone, and oral opioids typically within a multimodal approach with nonopioid analgesics can help facilitate the discontinuance of intravenous infusions of opioids, allow for the transfer of patients to non-ICU settings, and avoid opioid withdrawal symptoms.

The risk specific to the inadvertent continuation of analgesics has yet to be described in the literature, but data analyses of other types of drugs consistently show that 20%–30% of patients continue to receive therapeutic agents begun in the ICU and even after discharge from the hospital, even though they are no longer indicated (Buckley 2015; Kram 2015). Pharmacists can play an important role in limiting this occurrence by medication reconciliation efforts as patients transition from the ICU to another nursing unit, health care setting, or home.

OUTCOMES MEASURES AND QUALITY IMPROVEMENT METRICS

The Joint Commission offers a comprehensive systems approach to improving pain management. It includes guidance on identifying the gaps and opportunities for improving pain management together with specific components of a successful pain management program. The central aspects of any process improvement effort include the prompt recognition and treatment of pain, the involvement of patients

and families in the pain management plan, and the tracking of improved treatment patterns, as well as reassessing and adjusting plans as needed.

Patient Satisfaction

There are financial incentives for improving patient satisfaction from effective pain management. The HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) initiative by the Centers for Medicare & Medicaid Services (CMS) surveys patients after hospital discharge about pain management. In the future, these survey results may dictate payment from CMS and appear in public forums.

Acute Pain

More than 75% of patients remember pain and say that it was the most traumatic memory of their ICU experience. The PAD guidelines suggest that ICUs monitor the percentage of time that pain is assessed, with a goal of at least four times per nursing shift. Furthermore, an intervention to relieve pain should be documented within 30 minutes of identifying pain, together with documentation of its effectiveness. Preprocedural analgesia or nonpharmacologic interventions should also be recorded and tracked (Barr 2013).

Chronic Pain

Pain that exceeds the average duration beyond 2–3 months and has no apparent protective function is defined as chronic pain (Battle 2013). A recent survey suggests that 44% of patients experience pain 6 months to 1 year after ICU discharge, and the most common complaint involves shoulder pain. Risk factors for chronic pain include age, duration and severity of pain, and severe sepsis during critical illness.

Treatment of chronic pain is strongly debated in this era of widespread opioid abuse. There are no high-quality data on the long-term use of opioids for chronic pain, and there is no standardized therapeutic approach. As with any chronic disease, an individualized tactic with careful consideration of the risks and benefits of therapy is needed. The FDA has encouraged comprehensive training of prescribers about this incredibly complex issue (Alford 2016).

Posttraumatic Stress Disorder

Triggers for ICU-related PTSD are thought to be largely related to delusional memories, but several studies have implicated factual memories including trauma, injuries, and pain as important contributors. Recent data suggest that opioid exposure is associated with post-ICU psychiatric symptoms, including depression, anxiety, and PTSD (Huang 2016; Griffiths 2007). The observational cohort design of these studies does not allow for discrimination of opioids as causal factors or surrogates for pain in the development of PTSD. Supporting the latter contention are data from patients injured during combat, in whom the use of morphine reduced the risk of PTSD (Holbrook 2010).

FACILITATING BEDSIDE APPLICATION

The American Society for Pain Management and the American Association of Critical-Care Nurses have suggested a hierarchy of pain assessment techniques that begin with using patient self-report; identifying potential causes of pain such as procedures or pathologic conditions; using behavioral pain assessment tools; acknowledging the lack of specificity of vital signs for pain assessment; using surrogate reporting such as information obtained from family, friends, or caregivers; and finally, if there is reason to suspect pain, offering an analgesic trial, which can be diagnostic as well as therapeutic (Kerr 2006). Supportive information on this strategy for pain management is available online.

Data consistently suggest that a multifaceted approach to changing bedside practice offers the most effective and sustained strategy to improve pain management. Pain management protocols promise to limit practice variation by facilitating best practice to the bedside, providing timely response to pain, and allowing clear communication of treatment goals. Essential components of any pain management protocol include pain assessment tools and their frequency of application, together with desired goals of therapy and therapeutic options that are based on patient context. Order sets based on institution-specific protocols should be created to offer real-time clinical decision support and facilitate practice changes. Daily rounding with a pharmacist or using a quality checklist with the elements of a protocol should be considered as a way to support these efforts by verifying that pain has been addressed in a systematic fashion.

For patients with complex issues and unresolved pain, including referral sources such as an anesthesia-based pain consult service should be considered. These specialists have a wide array of available options for pain relief and can offer local or regional interventions.

CONCLUSION

Most ICU patients experience significant pain and regard it as the most traumatic memory of their illness. Achievement of adequate analgesia is often suboptimal for many reasons, including the inability to easily assess pain for many patients, lack of appreciation for the pain endured at rest and during routine procedures, and lack of a systematic approach for treatment. Data consistently show gaps in clinical performance that include a limited use of behavioral pain assessment tools in ICUs, inappropriate use of vital signs as indicators of pain, and inadequate documentation of pain and titration to identified targets. Some of these issues can be mitigated by providing light sedation that allows for patient self-report and participation in the treatment plan, but most can be rectified by simply offering a systematic protocolized approach with real-time reminders in an electronically based medical record.

There are many frontiers to explore regarding pain management. The most prominent involves the critically ill patient with significant neurologic disease. The pharmacist must be able to better characterize, identify, and manage this pain effectively, as well as overcome the barriers to better pain management that involve caregivers and health care systems. Caregivers must recognize that their understanding about the presence and severity of pain is often incorrect and that using validated pain assessment tools can improve clinical outcomes. Health care systems must foster an environment that focuses on relief from pain and provides adequate resources in personnel and clinical decision support to ensure that pain relief occurs.

Practice Points

Clinical management of ICU pain is evolving as our understanding of its etiology, risk factors, and consequences advances. Unfortunately unrelieved pain remains a common clinical issue and requires continual health care provider vigilance and attention to the following in order to make the ICU a more humane environment:

- **Systematic evaluation of pain at least four times during a nursing shift with valid assessment tools such as NRS and CPOT**
- **Identification of sources of pain (including routine ICU procedures) along with remedial strategies**
- **Appreciation of acute and long-term outcomes associated with unrelieved pain including chronic pain and hyperalgesia**
- **Consideration of potentially useful nonpharmacologic approaches to pain management (music, deep breathing, ice therapy)**
- **Provision of pharmacologic strategies that are based on patient context including the type and severity of pain, hemodynamic stability, prior response or tolerance to therapy, organ dysfunction, drug interactions, and QTc prolongation**
- **Consideration of an analgesia first (analgosedation) approach for ICU agitation because pain and discomfort are the most common precipitants**
- **Implementation of a multimodal approach to pain relief to augment analgesia and to limit adverse events in selected patients**
- **Anticipation and mitigation of adverse drug events such as interference with respiratory drive and gastrointestinal function, hypotension, withdrawal, and hyperalgesia**
- **Implementation of standards of practice through multifaceted approaches to ensure optimal patient-specific pain management is in place**

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Self-Assessment Questions

1. Three months ago, a 26-year-old man (height 71 inches, weight 92 kg) was admitted to the ICU with new-onset tetraparesis in the setting of a recent upper respiratory tract infection. He was given a diagnosis of Guillain-Barré syndrome and completed immunotherapy with intravenous immunoglobulin (0.4 g/kg for 5 days). Now, he is experiencing significant paraesthesias and dysesthesias in his legs during physical therapy while recovering in the ventilator step-down unit. Which one of the following best describes the inhibition or facilitation of pain input from the brain in this patient?

   A. Perception
   B. Modulation
   C. Transduction
   D. Excitation

2. A 45-year-old man (height 71 inches, weight 90 kg) is being treated in the medical ICU for acute respiratory failure caused by a left-sided parapneumonic effusion. On presentation, an indwelling pleural catheter was placed, and pleural fluid was sent for culture, which subsequently grew *Streptococcus pneumoniae*. The patient has been mechanically ventilated and treated with ceftriaxone 2 g intravenously daily and is clinically improving. On ICU day 7, the respiratory therapist completes endotracheal tube suctioning for increased secretions. That same day, the nurse obtains a basic metabolic panel from peripheral blood after inserting a new peripheral intravenous line. Later, on ICU day 7, the team decides to remove the indwelling pleural catheter after a series of reassuring chest radiographs and minimal drainage. Which one of the following ICU day 7 procedures was likely the most painful for this patient?

   A. Endotracheal tube suctioning
   B. Peripheral intravenous line insertion
   C. Peripheral blood obtainment
   D. Chest tube removal

3. A 77-year-old man (height 69 inches, weight 85 kg) is being treated in the ICU for acute respiratory distress syndrome caused by *Pseudomonas aeruginosa* community-acquired pneumonia. He is on hospital day 2 and is being mechanically ventilated. His vital signs include heart rate 102 beats/minute, blood pressure 165/98 mm Hg, temperature 98.8°F (37.1°C), and respiratory rate 17 breaths/minute. His current drugs include piperacillin/tazobactam 3.375 g intravenously every 8 hours, fentanyl 50 mcg/hour, propofol 40 mcg/kg/minute, norepinephrine 0.1 mcg/kg/minute, cisatracurium 37.5 mg/hour, heparin 5000 units subcutaneously every 12 hours, docusate 100 mg twice daily, and sucralfate 1 g every 6 hours. On multidisciplinary rounds, the nurse states she is going to turn off the fentanyl infusion because the patient's most recent CPOT score was zero. Which one of the following is best to recommend for this patient?

   A. The fentanyl infusion can be turned off because the CPOT score is 0, which is below the threshold of 2 for pain identification.
   B. The nurse should be monitoring the patient's vital signs for tachycardia and hypertension, which are proven indicators of pain in the ICU.
   C. CPOT scores cannot be used in this patient because he is being paralyzed with cisatracurium.
   D. A surrogate should be asked to assess the patient's pain before fentanyl is titrated.

4. Which one of the following patient profiles most accurately describes the possible long-term negative impact of unrelieved pain in the ICU?

   A. 62-year-old woman who is experiencing chronic shoulder pain and reduced quality of life, as evidenced by less autonomy and an inability to complete her activities of daily living.
   B. 59-year-old woman with new-onset major depressive disorder and generalized anxiety disorder.
   C. 60-year-old man with cognitive impairment, as evidenced by low scores on the Repeatable Battery for the Assessment of Neuropsychological Status and immobility requiring him to remain in bed most of the time.
   D. 64-year-old man with new-onset dementia and economic hardship because of medical expenses.

5. Staff at your ICU are implementing the recommendations for pain assessment, treatment, and prevention from the 2013 PAD guidelines care bundle. They are specifically interested in increasing pain assessments. As the pharmacist on staff, you highlight the importance of routine pain assessments. Which one of the following is most likely to result from routine pain assessments?

   A. Increase in patient discharge to home after hospitalization.
   B. Decrease duration of mechanical ventilation.
   C. Decrease in the incidence of ICU delirium.
   D. Decrease in the need for tracheostomy.

6. A 72-year-old woman (height 65 inches, weight 70 kg) presents after coiling of a left anterior cerebral artery aneurysm that ruptured. She is post-bleed day 5. The patient has remained intubated because of her inability to protect her airway. Her current drugs include dexmedetomidine 0.7 mcg/kg/hour, fentanyl 50 mcg hourly as

needed for pain, heparin 5000 units subcutaneously every 12 hours, sucralfate 1 g every 6 hours, aspirin 81 mg daily, atorvastatin 40 mg daily, nimodipine 60 mg every 4 hours, and fludrocortisone 100 mcg twice daily. The nurse is preparing to turn the patient and would like a recommendation for procedural pain management. Which one of the following is best to recommend for this patient?

A. 300 mg of gabapentin once before turning
B. 2 mg of enteral hydromorphone once before turning
C. 100 mcg of intravenous fentanyl once before turning
D. 100 mcg of intravenous fentanyl once after turning

Questions 7–9 pertain to the following case.

P.S. is a 62-year-old man (height 72 inches, weight 95 kg) with a history of depression, seizures, and coronary artery disease. He is being treated for methicillin-sensitive *Staphylococcus aureus* bacteremia of unclear etiology. P.S. is currently in septic shock and is intubated and sedated in the medical ICU. His pertinent laboratory results are as follows: Na 140 mEq/L, K 4.8 mEq/L, Cl 100 mEq/L, glucose 143 mg/dL, and SCr 3.2 mg/dL (baseline 0.9 mg/dL). P.S.'s urine output has been 0.2 mL/kg/hour. His current drugs include propofol 30 mcg/kg/minute, fentanyl 75 mcg/hour, norepinephrine 0.3 mcg/kg/minute, hydrocortisone 50 mg intravenously every 6 hours, heparin 5000 units subcutaneously every 12 hours, sucralfate 1 g every 6 hours, simvastatin 40 mg daily, aspirin 81 mg daily, levetiracetam 500 mg every 12 hours, and fluoxetine 80 mg daily. P.S.'s Sedation-Agitation Scale (SAS) score is 3 (sedated, but responds to simple commands), and his CPOT score is 2.

7. The medical intern is seeking pain management advice for P.S. but is concerned about fentanyl accumulation in the setting of acute kidney injury. Which one of the following is best to recommend for P.S.?

   A. Switch to hydromorphone 2-mg intravenous bolus; then initiate an infusion at 1 mg/hour to avoid fentanyl accumulation in renal failure.
   B. Discontinue the fentanyl infusion, and initiate fentanyl 100 mcg every hour as needed for pain to avoid accumulation in the setting of renal failure.
   C. The patient needs no analgesia because his most recent CPOT score was 2.
   D. Continue the current infusion fentanyl infusion rate because the patient's pain is well controlled, and fentanyl does not accumulate to a clinically significant degree in the setting of renal failure.

8. Five days later, the nurse approaches you about P.S.'s pain management. He has been scoring 6 or 7 on the CPOT, and there is concern that he is experiencing pain, despite receiving 200 mcg/hour of fentanyl. P.S.'s laboratory test results at this time are as follows: Na 141 mEq/L, K 4.9 mEq/L, Cl 101 mEq/L, glucose 160 mg/dL, and SCr 3.7 mg/dL (baseline 0.9 mg/dL). His urine output has been about 0.1 mL/kg/hour. Which one of the following is best to recommend to manage P.S.'s pain?

   A. Double the fentanyl dose to 400 mcg/hour.
   B. Discontinue the fentanyl infusion and bolus with 1 mg of hydromorphone, and if the patient responds, initiate a hydromorphone infusion at 1.5 mg/hour.
   C. Discontinue the fentanyl infusion and bolus with 10 mg of morphine, and if the patient responds, initiate a morphine infusion at 7.5 mg/hour.
   D. Continue the current fentanyl infusion rate, and add adjunctive tramadol 100 mg every 6 hours as needed.

9. Ten days into P.S.'s hospitalization, the nurse notifies the team that he has not had a bowel movement. He had been tolerating enteral tube feeds at 40 mL/hour, but now, he has significant gastric residuals of greater than 500 mL. P.S.'s laboratory results at this time are as follows: Na 139 mEq/L, K 5.0 mEq/L, Cl 98 mEq/L, glucose 158 mg/dL, and SCr 3.9 mg/dL (baseline 0.9 mg/dL). His urine output is 0.2 mL/kg/hour. A kidney, ureter, and bladder radiography reveals no obstruction, and the patient has a nasogastric tube in place. The team would like to administer a drug for suspected opioid-induced constipation. P.S. has not responded to docusate 100 mg every 12 hours, bisacodyl 10 mg rectally daily, and polyethylene glycol 17 g daily. Which one of the following is best to recommend for P.S.?

   A. Methylnaltrexone 12 mg subcutaneously every 48 hours as needed
   B. Naloxone 1 mg three times daily by nasogastric tube until a bowel movement occurs
   C. Methylnaltrexone 6 mg subcutaneously every 48 hours as needed
   D. Naloxegol 12.5 mg once daily by nasogastric tube until a bowel movement occurs

10. A 40-year-old man (height 71 inches, weight 101 kg) with a history of intravenous drug abuse (opioids) is admitted to the surgical ICU with septic shock caused by necrotizing fasciitis of his left lower extremity. Three days into his ICU stay, he continues to report substantial pain because of serial debridement (NRS-V score 10/10). His current drugs include hydromorphone 6 mg intravenously every 4 hours, fentanyl 200 mcg intravenously every hour as needed for moderate to severe pain (2000 mcg in the past 24 hours), heparin 5000 units subcutaneously every 8 hours, docusate 100 mg every 12 hours, polyethylene glycol powder 17 g by mouth daily, vancomycin 1500 mg every 12 hours, piperacillin/tazobactam 4.5 g intravenously every 8 hours, and clindamycin 900 mg intravenously every 8 hours. The care team decides to consult the acute pain management service, which recommends initiating a ketamine infusion. Which one of the following properties of this agent is the most likely reason for this recommendation?

A. It is a GABA receptor antagonist, which may restore analgesia.
B. It is a NMDA receptor antagonist, which may restore analgesia.
C. It is a sigma opioid receptor agonist, which may increase the pain threshold.
D. There is no clear indication for ketamine in this patient, and the recommendation should be rejected.

11. A surgical resident is preparing to take a patient to the operating room for an exploratory laparotomy because of concern for an ischemic bowel. The resident is interested in administering perioperative lidocaine to reduce the need for opioids postoperatively and to expedite the return of bowel function. Which one of the following is best to recommend for this patient?

A. Give 1 mcg/kg intravenous loading dose followed by a continuous intravenous infusion at 1.5 mg/kg/hour until 1 hour after the procedure.
B. Give 1 mg/kg intramuscular loading dose followed by a continuous intravenous infusion at 1.5 mg/kg/hour until 1 hour after the procedure.
C. Give 1 mg/kg intravenous loading dose followed by a continuous intravenous infusion at 1.5 mg/kg/hour until 1 hour after the procedure.
D. No data support using lidocaine for this indication.

12. A 52-year-old man is being treated for a right middle cerebral artery ischemic stroke in the neurologic ICU. He has received tissue plasminogen activator and endovascular clot extraction, but he is at a high risk of malignant cerebral edema because he has infarcted more than two-thirds of his right middle cerebral artery territory. The patient is currently intubated and sedated because of an aspiration pneumonia. The neurosurgeon would like to provide analgosedation with remifentanil so that frequent neurologic examinations can reliably be done. The neurologic ICU team is unfamiliar with this agent, and they ask you why the neurosurgeon has ordered it. Which one of the following is the most appropriate response to this question about remifentanil?

A. It is rapidly metabolized by CYP3A4 to inactive metabolites, leading to a short and predictable half-life.
B. It is inexpensive and can be substituted for fentanyl purely on the basis of cost savings.
C. It is rapidly metabolized by nonspecific tissue and plasma esterases to inactive metabolites, leading to a short and predictable half-life.
D. It is rapidly metabolized by glucuronidation to its active metabolite, remifentanil acid, which is renally eliminated.

13. A 32-year-old man (height 72 inches, weight 100 kg) is being treated in the surgical ICU after a fall that resulted in several rib fractures and a pelvic fracture. He has undergone tracheostomy and percutaneous endoscopic gastrostomy and is ready to transition to the ventilator step-down unit. The team has been trying to wean the patient off a hydromorphone infusion for the past week without success. The intensivist would like to transition the patient to enteral methadone. The patient is not receiving QTc-prolonging agents and has normal liver function. If transitioned to methadone, which one of the following is this patient most likely to experience?

A. Shorter ICU length of stay
B. Reduced total duration of mechanical ventilation
C. Shorter hospital length of stay
D. Faster mechanical ventilator weaning

14. A 25-year-old woman (height 64 inches, weight 70 kg) is being treated for a traumatic brain injury in the surgical ICU after a motor vehicle crash. She has several small intraparenchymal hemorrhages and a diffuse subarachnoid hemorrhage. An external ventricular device was placed for early hydrocephalus. The patient's intracranial pressure has been 30–35 mm Hg, despite hyperventilation, permissive hypernatremia, and mannitol boluses. A pentobarbital infusion has been initiated for refractory intracranial pressure. The pulmonary/critical care fellow would like a recommendation on how to manage her analgosedation. Which one of the following is best to recommend for this patient?

A. Morphine 5–10 mg intravenously every 2 hours as needed for pain.
B. Ketorolac 15 mg intravenously every 6 hours for 5 days.
C. Hydromorphone 2-mg bolus; then 1–5 mg/hour as a continuous infusion.
D. Fentanyl 100-mcg bolus; then 25–100 mcg/hour as a continuous infusion.

15. A 63-year-old woman (height 64 inches, weight 68 kg) is being treated in the medical ICU for a UTI caused by an extended-spectrum β-lactamase–producing *Escherichia coli*. Her current drugs include fentanyl 50 mcg intravenously every 1 hour as needed for pain, midodrine 10 mg every 8 hours, meropenem 1 g intravenously every 8 hours, heparin 5000 units subcutaneously twice daily, aspirin 81 mg daily, lovastatin 20 mg daily, and citalopram 20 mg daily. The patient's confusion assessment method for the ICU assessment is positive, and her answers to questions about pain are nonsensical. The medical resident would like to use another pain assessment method.

Which one of the following is best to recommend for this patient?

A. Use the BPS.
B. Use the CPOT.
C. Monitor for tachycardia and hypertension.
D. Use the pain-behavioral assessment tool.

16. A 37-year-old woman (height 66 inches, weight 77 kg) is recovering from a subarachnoid hemorrhage caused by a ruptured posterior communicating artery aneurysm. She underwent coil embolization and is now post-bleed day 22. The patient is experiencing severe headaches, and the neurocritical care team is looking for help with her pain management. Her current drugs include ibuprofen 600 mg every 6 hours, butalbital/acetaminophen/caffeine 50 mg/325 mg/40 mg 2 tablets every 4 hours, dexamethasone 2 mg every 6 hours, oxycodone 5–10 mg every 4 hours as needed for headache (one dose in the past 24 hours because of lack of response), fludrocortisone 200 mcg twice daily, and heparin 5000 units subcutaneously every 12 hours. Which one of the following is best to recommend for this patient?

A. Fentanyl 25 mcg/hr patch every 72 hours
B. Acetaminophen 975 mg orally every 6 hours
C. Gabapentin 300 mg orally every 8 hours
D. Methadone 5 mg orally every 8 hours

17. A 94-year-old woman in your medical ICU is being transitioned to comfort care in the setting of ovarian cancer. Her current laboratory values are as follows: Na 140 mEq/L, K 3.9 mEq/L, Cl 99 mEq/L, glucose 133 mg/dL, and SCr 1.1 mg/dL (baseline 0.9 mg/dL). She has been making more than 0.9 mL/kg/hour of urine over the past 24 hours. Her cognition remains intact, but she cannot swallow medications. The medical resident enters the following drugs for comfort care: ondansetron 4 mg intravenously every 8 hours as needed for nausea, lorazepam 1 mg intravenously every 3 hours as needed for anxiety, morphine 5 mg intravenously every 3 hours as needed for pain, acetaminophen 1000 mg intravenously every 6 hours as needed for pain, hydromorphone 2 mg intravenously every 4 hours as needed for pain, and glycopyrrolate 0.2 mg intravenously every 2 hours as needed for excessive secretions. Her SAS score is 3 (sleepy but able to respond to commands with stimulation), and her NRS-V score is 2, indicating mild pain. Which one of the following is best to recommend for this patient?

A. Hydromorphone 2 mg intravenously
B. Morphine 5 mg intravenously
C. Acetaminophen 1000 mg intravenously
D. No pain medications indicated in this setting

18. As the ICU pharmacist, you are asked to do a quality assurance project on the continuation of opioids and other psychoactive medications on ICU discharge. You unexpectedly find that 25% of patients are being discharged from the ICU on opioids. Which one of the following would best reduce the inappropriate continuation of these medications on ICU discharge?

A. Discontinue all opioids and psychoactive medications on ICU discharge.
B. Incorporate 5-day stop dates on all opioids and psychoactive medication orders for ICU patients.
C. Continuing opioids and psychoactive medications in 25% of patients is acceptable and does not require remediation.
D. Do medication reconciliations on transitions of care to ensure that opioids and psychoactive medications are appropriately continued or discontinued.

Questions 19 and 20 pertain to the following case.

The ICU staff at HealthSure Hospital is seeking to improve their pain management practices. As the staff pharmacist, you review the 2013 PAD guidelines and make several clinical improvements, but you would like to make some systems changes as well (e.g., tracking improvement, workflow optimization).

19. Which one of the following organizations would be the best resource in forming the HealthSure Hospital systems approach to improving pain management?

A. Joint Commission
B. Agency for Healthcare Research and Quality
C. Pharmacy Practice Model Initiative
D. Centers for Medicare & Medicaid Services

20. Which one of the following organizations would be best for the HealthSure Hospital team to consult for a hierarchy of pain assessment techniques?

A. American College of Clinical Pharmacy
B. American Society of Health-System Pharmacists
C. American College of Critical Care Medicine
D. American Association of Critical-Care Nurses