Optimal strategies for assessing and managing pain, agitation, and delirium in the critically ill surgical patient: What you need to know

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ABSTRACT: Pain, agitation, and delirium (PAD) are primary drivers of outcome in the ICU, and expertise in managing these entities successfully is crucial to the intensivist's toolbox. In addition, there are unique aspects of surgical patients that impact assessment and management of PAD. In this review, we address the continuous spectrum of assessment, and management of critically ill surgical patients, with a focus on limiting PAD, particularly incorporating mobility as an anchor to ICU liberation. Finally, we touch on the impact of PAD in specific populations, including opioid use disorder, traumatic brain injury, pregnancy, obesity, alcohol withdrawal, and geriatric patients. The goal of the review is to provide rapid access to information regarding PAD and tools to assess and manage these important elements of critical care of surgical patients. (*J Trauma Acute Care Surg.* 2024;96: 166–177. Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Pain; agitation; delirium; surgical critical care.

Critical illness leads to the largest mortality and morbidity among hospitalized patients and the unsustainably high cost of healthcare.[1] Pain, agitation, and delirium (PAD) are pervasive challenges in critically ill patients and have a substantial negative impact on outcomes.[2] Surgical patients, with the contributions of wounds, injury, and anesthesia, are uniquely vulnerable to PAD and require informed management approaches.

We intend to collate the most up-to-date evidence on management of PAD in the intensive care unit (ICU). Many of the principles from the Society of Critical Care Medicine's (SCCM) 2018 Pain, Agitation, Delirium, Immobility, and Sleep Disruption (PADIS) guideline update provide the foundation of the review.[3] Where newer literature, or literature focusing specifically on surgical patients, exists, our recommendations are modified accordingly. Our goal is to provide a compendium of the current evidence in the management of PAD in surgical patients. For this review's scope, we will focus on pain, agitation, and delirium, with the understanding that mobility is an essential therapy for each of these and for minimizing sleep disruption. This is neither an in-depth investigation of all physiologic and pharmacologic parameters of each element of PAD, nor a detailed description of each study's approach. Instead, we hope this is a pragmatic guide for efficient, effective, patient-centered bedside decision making.

The review begins with an overview of the approach to addressing PAD, including principles to consider and an algorithm to facilitate application of current knowledge. This is followed by a pharmacologic review and clinical pearls designed to guide clinicians through the continuous spectrum of decision making for assessment, diagnosis, and management of PAD. Finally, we will end with commonly encountered conditions as special topics that may alter the efficacy of therapy or choices in PAD management.

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APPROACH

The optimal approach to PAD management includes the following principles:

a) protocol-directed practice,
b) assessment-guided diagnosis and management,
c) prevention supersedes therapy,
d) begin with nonpharmacologic prevention and management techniques,
e) analgesia first/no sedation approach,
f) engage a multiprofessional team,
g) incorporate patient experience.

Protocol-Directed Practice

The first principle is not unique to management of PAD, but rather a concept that results in improved performance in many areas of medicine. Protocols create consistency of practice, clarify expectations for both caregivers and patients, enhance the ability to predict patient trajectory, and facilitate application of new practices more efficiently. We have recommended an algorithm (Fig. 1), which guides identification and management of PAD in critically ill patients. Understanding this tight relationship between pain, agitation, and delirium assists with effective therapy. When pain and agitation are effectively managed, delirium risk is decreased.[3] This protocol guides the reader to achieve appropriate analgesia and sedation to limit development and duration of delirium. In addition, it focuses on mobility as a therapy, which limits each element of PAD and aids in minimizing sleep disruption.

A consistent and comprehensive approach to the management of PAD is essential to each critical care program.

Assessment-Guided Diagnosis and Management

Effectively managing PAD in the ICU requires *assessing* patients for these conditions. Because of individual patient perception, tolerance, and altered sensorium, PAD is not always apparent. For example, a patient's inability to self-report pain does not mean absence of pain but requires alternative approaches to assessing pain.[4] The phrase, "The eye sees only what the mind is prepared to comprehend," applies to the management of PAD.[5] Identifying the presence and extent of PAD facilitates prevention, choice of therapeutic intervention, and efficacy of treatment. Therefore, *repeated assessments seeking the presence and extent of each PAD element are crucial*. We have included the most reliable and commonly used tools for assessing each element of PAD in the ICU.

Continuous assessment, intervention, and reassessment are the cornerstones of management of PAD.

Each organization should apply assessment tools for each element of PAD. Based on the 2013 SCCM PAD Guidelines,[6] we recommended selecting one of the two most valid and reliable scoring tools for critically ill intubated patients in each category:

- Pain assessment—Critical Care Pain Observation Tool and Behavioral Pain Scale (BPS). (In patients who can self-report, the 0–10 Numeric Rating Scale is an appropriate choice for assessing pain.)
- Agitation assessment—Richmond Agitation Sedation Scale and Riker Sedation Agitation Score
- Delirium assessment—Intensive Care Delirium Screening Checklist and Confusion Assessment Method for the ICU.

Prevention Supersedes Therapy

As with the predominance of diseases in medicine, prevention of PAD is far more effective for outcome than treatment once the disease occurs. Anticipating the development of PAD for patients in the ICU requires recognizing the risk of development of each element. Therefore, it is helpful to understand the risk factors contributing to a patient developing PAD.[3,7–11] Risk factors unique to surgical patients are denoted with an * and modifiable risk factors for delirium are denoted with [a] ^.

Common sources of pain in critically ill surgical patients include:

- Surgical procedures*
- Injury*
- Endotracheal intubation
- Tube and catheter insertion/removal*
- Turning/repositioning
- Tracheal suctioning

Conditions associated with pain perception in the ICU:

- Surgical history*
- After-effects of trauma*
- Younger age
- Female gender
- Non-White race

Common sources of agitation in the ICU:

- Pain/discomfort
- Fear/anxiety
- Development of delirium

Risk factors for development of delirium in the ICU (modifiable ^):

- Advanced age
- Dementia
- Prior coma
- Pre-ICU emergency surgery/trauma*
- Higher APACHE Score
- Benzodiazepine use^
- Blood transfusion^

Prevention of pain includes ongoing analgesia for patients with continuous sources of pain and discomfort, such as mechanical ventilation, as well as intermittent analgesic dosing prior to procedures such as arterial and venous access, thoracostomy tubes, and wound dressing changes. Prevention of agitation and delirium primarily focuses on mitigating the modifiable contributing factors.

Begin With Nonpharmacologic Prevention and Management Techniques

To limit drug cross-reactivity and side effects and improve outcomes, it is important to identify nonpharmacologic approaches to both prevent and manage PAD. Most medications treating PAD also contribute to generalized muscle weakness and prolong the myopathy of critical illness. Therefore, these medications are primary contributors to the development of a constellation of physical and cognitive impairments and mental health issues affecting survivors of critical illness, or post-ICU syndrome.[12] Improving outcome depends on minimizing the impact of medications contributing to long-term myopathy and psychological impact of

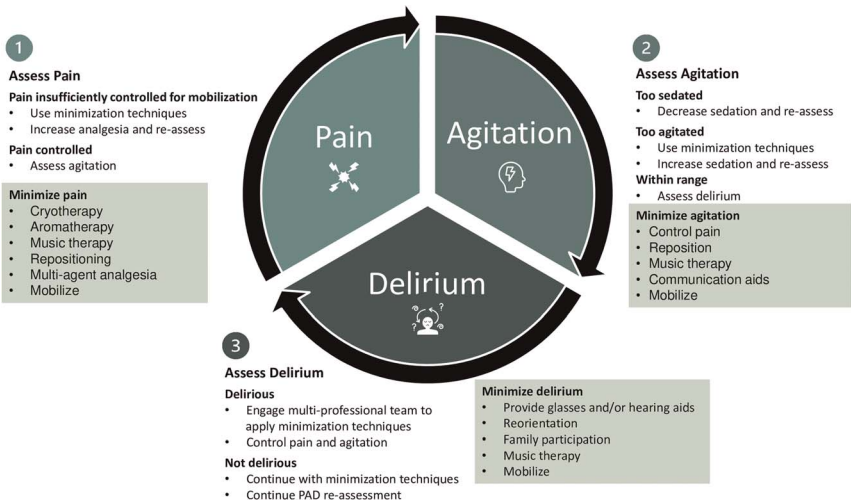

Figure 1. PAD continuous assessment algorithm.

opioids, which alternate approaches to analgesia and sedation can facilitate.

Pharmacologic agents have NOT been demonstrated to prevent or treat delirium. Therefore, management focuses on limiting the physiologic, pharmacologic, and environmental sources, which contribute to the development of delirium.

Nonpharmacologic approaches to analgesia

- Cryotherapy
- Aromatherapy
- Repositioning
- Redirected attention (e.g., music, reading, movies, conversation)
- Mobility

Nonpharmacologic approaches to limit agitation/delirium

- Lights on during the day
- Out of bed during day/progressive increases in mobility
- Maintaining normal sleep/wake cycle
- Eyeglasses
- Music
- Familiar faces and activities.

Mobility is both a mitigating factor and a treatment for pain, agitation, and delirium and should be consistently incorporated into management of critically ill surgical patients.

Analgesia First/No Sedation Approach

Managing analgesia and sedation, particularly for ventilated patients, requires a focus on controlling pain with analgesics prior to using sedatives. Practitioners should attend to the varied interventions or procedures, in addition to injury or surgery, which cause pain during critical illness. Agitation can be a manifestation of pain, and treating the agitation with sedatives without providing analgesia can result in insufficient analgesia, the need for increasing sedation, and delayed recovery.

The value of limiting sedation in surgical patients was reported by Chanques et al.[13] Postoperative patients who had no sedation compared with those with 1.5 days of moderate sedation after surgery for peritonitis and sepsis had reduction in incidence and duration of delirium.[13] Individualized analgesia must be prioritized to achieve clinical patient-care goals quickly without deleterious effects of oversedation. There appears to be clinical equipoise between no continuous sedation and light sedation with regular sedation interruptions.[14] Occasional exceptions occur to the priority of no or light sedation (e.g., neuromuscular blockade), in which deep analgosedation is a priority.

Engage A Multiprofessional Team

Managing surgical patients with critical illnesses requires a team of clinicians with diverse skillsets. Most critically ill patients need direct care for all basic physiologic functions, including ventilation, feeding (often enteral), bathing, and mobilizing. The physical strength required to help patients is extensive, particularly with the high incidence of obesity. Therefore, nurses require the assistance of aides and physical and occupational therapists for many of the mobility activities. This engagement results in deep insight by nursing and therapy staff on the physical capability and strength of patients. Using that insight in the development of care plans is vital to appropriate decision making. Respiratory therapists liberate patients from or prevent the need for the ventilator. Pharmacists provide in-depth understanding of indications, interactions, dosing, and side effects of medications, and the implications for transitions of care. Clinical dieticians provide focused attention on baseline nutritional status and nutrient and caloric needs throughout the evolving critical illness. Each of these specialties requires focused and specific training to deliver the expertise necessary for recovery from critical illness. They also facilitate awareness of society guidelines to promote early adoption of new evidence. While individual physicians, or even teams of physicians, provide the guidance and oversight of patient care, the addition of each of these team members in management and decision making is crucial to optimal patient care/group training.[15]

A focus on team coordination is essential when profession-specific challenges are encountered. If medication-related effects are interfering with mobilization, focused collaboration between the clinical pharmacist and physical therapist to review medication selection and timing can serve as a strategy to optimize the therapy session. Social workers and case managers coordinate long-term needs of patients such as disposition, equipment, and communication. Each of these professional roles contributes to a decrease in anxiety and confusion which alleviates PAD.

Incorporate Patient Experience

Minimization of PAD is the linchpin to positive patient experience. Family member anxiety will decrease when their loved ones' PAD is addressed, and patient-family interaction can play a critical role in successful management of PAD, improving outcome.[2]

PHARMACOLOGIC REVIEW

Regimen Design

Analgesic (Fig. 2) and sedation regimens should be evidence-based, account for adverse effects, reflect optimal administration methods, and include a de-escalation plan. Agent selection and dosing intensity will be influenced by prehospital medications used to manage chronic conditions. For example, clinicians should consider baseline analgesic requirements for patients on prehospital chronic opioids. A scenario is illustrated in Figure 3. Medication administration times should be evaluated to minimize sleep disruption and optimize mobility interventions. Objective goals and endpoints must be established, evaluated, and included in orders for titratable and as-needed medications.

For mechanically ventilated patients, analgosedation targeting light levels is preferred in the absence of a compelling indication for deep sedation.

An ongoing evaluation of drug-drug and drug-route interactions is imperative to navigate access and absorption issues. Before transitioning out of the ICU, an intentional pause or "time-out" can be used as a reminder for clinicians to discontinue medications not appropriate for the post-ICU phase of care.

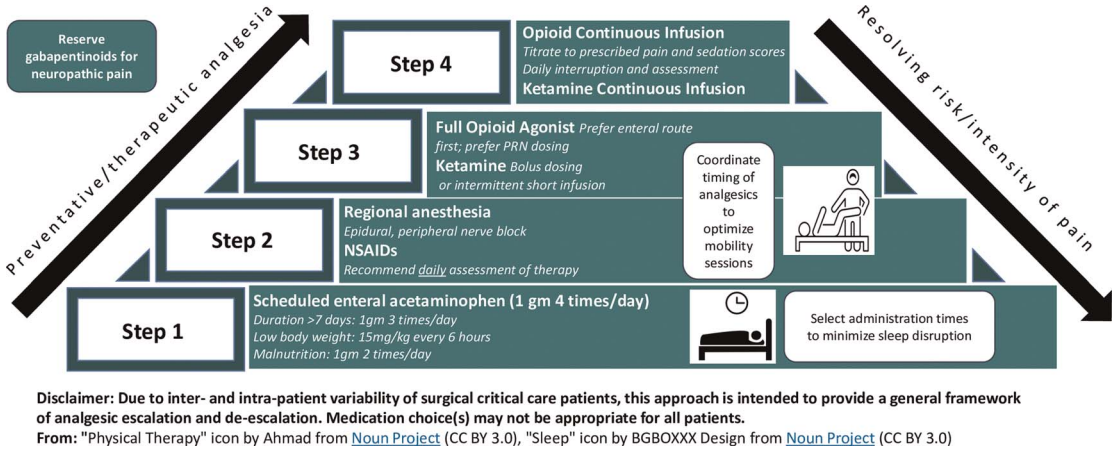

Figure 2. Stepwise approach to designing an analgesic regimen.

Analgesics

Multimodal Analgesic Regimens

While opioids have served as a backbone of pain control in the ICU, the opioid epidemic has led clinicians to seek alternative analgesics, resulting in the emergence of multimodal pain regimens as a strategy to limit opioids to the lowest effective dose.[16–18] Meta-analyses of randomized controlled trials, primarily conducted in surgical ICU patients, demonstrate that nonopioids as adjuvants or replacements reduce opioid consumption compared with opioids alone.[16,17] In trauma patients with rib fractures, addition of a multimodal pain regimen was effective in reducing opioid consumption.[18]

Acetaminophen

Acetaminophen is a centrally acting analgesic that is available in oral, rectal, and intravenous formulations.[19] Clinical practice guidelines provide a conditional recommendation for adjunctive use in critically ill patients to decrease pain intensity and opioid consumption.[3] Recent meta-analyses demonstrate reduced pain and opioid consumption in patients receiving acetaminophen as an opioid adjuvant.[16,17]

Hypotension is an adverse effect specific to intravenous acetaminophen.[20] Fortunately, the oral formulation has a favorable pharmacokinetic profile including excellent bioavailability and peak effects within 30 minutes to 60 minutes.[20] Although most studies have been conducted with the IV formulation, the enteral route remains a less costly option. Furthermore, in an evaluation comparing intravenous and oral formulations, a more rapid initial reduction in pain intensity occurred with the IV formulation, but no difference was observed at subsequent assessment points.[21]

Hepatotoxicity, a well-known adverse effect of acetaminophen, is a concern in the setting of elevated serum acetaminophen concentrations. This occurs due to accumulation of the toxic metabolite N-acetyl-p-benzoquinoneimine.[22] It is, therefore, important to recognize patients at risk for unintentional overdose. While risk factors are not well established, dosing recommendations are provided for several special populations in Figure 2.[20,23]

Given the wide variety of patients encountered in the surgical intensive care unit, as well as heterogeneity among studies, it is challenging to provide a high-certainty recommendation for acetaminophen's place in therapy. However, evidence supports improved pain control and opioid-sparing effects, making acetaminophen a valuable analgesic adjuvant.

Regional Anesthesia

Local anesthetic techniques exist to treat pain, particularly in patients with thoracic trauma or thoracic operations, including

Use equianalgesic dose ratios (EDR) to convert pre-hospital opioid to target opioid to estimate baseline requirement.

Pre-hospital M (PO)	EDR* M (PO) → M (IV) mg	Pre-hospital M (IV) equivalent	EDR* M (IV) → F (IV) mg	Target F (IV) equivalent
60mg/d	2:1	30mg/d	50-100:1	0.3 - 0.6*mg*/d = 12.5 to 25*mcg*/hr
	3:1	20mg/d	50-100:1	0.2 - 0.4*mg*/d = 8 to 16*mcg*/hr

Scenario
Pre-hospital opioid: Morphine ER 30mg PO BID
Target opioid: Fentanyl infusion

Figure 3. *Estimating* equianalgesic opioid requirements. M, morphine; F, fentanyl;. *Due to numerous factors, such as interpatient variability, EDRs are estimates only and based on ranges suggested by Patanwala, et al. for use in the acute care setting. Patanwala AE, Duby J, Waters D, Erstad BL. Opioid conversions in acute care. Ann Pharmacother. 2007;41(2):255–66.

epidural infusions and a variety of paravertebral nerve blocks. Local anesthetics can be injected at a specific site to alleviate pain while limiting systemic effects. Alternatively, both opioids and local anesthetic agents can be administered into the epidural space at the thoracic and lumbar spine levels. Placement of epidural catheters is resource-intensive and requires highly trained clinicians, which may not be readily available.

Agents for epidural anesthesia include lidocaine, bupivacaine, and ropivacaine. They may be combined with opioids, such as hydromorphone, or ketamine. Catheter placement is limited to patients without coagulopathy. The timing of prophylactic anticoagulant administration must be considered pending the placement or removal of an epidural catheter. Adverse effects include loss of genitourinary function, clinically significant hypotension, nausea, and pruritus. Clinical teams must remain cognizant of concomitant antihypertensives, systemic analgesics, and neuroimpairing agents.

Eastern Association for the Surgery of Trauma (EAST) practice guidelines for pain management in thoracic blunt trauma conditionally recommend epidural analgesia over nonregional therapies[24] due to significant improvements in pain scores, ICU length of stay, and need for mechanical ventilation.[24] Other studies have negative findings regarding pain control and other patient-centered outcomes following abdominal and thoracic surgery.[25,26] A large retrospective, multicenter study of nonintubated patients with chest trauma demonstrated that epidural analgesia was not associated with a lower risk of intubation or improved pain scores.[27] These contradictory findings are driving the use of peripheral nerve blocks, such as paravertebral blocks, which may ultimately be more beneficial.

Opioids

Opioids are used for nociceptive pain and analgosedation in critically ill patients.[3] Following initiation, clinicians must remain diligent about opioid exposure. Maximizing opioid-free days in the intensive care unit is a powerful strategy to decrease persistent opioid use following discharge.[28] When opioid dose escalation occurs, ICU team members should accurately identify and address contributing factors, especially when they may represent surgical complications, such as missed injuries, compartment syndrome, and untreated infection. Dose escalation may be observed due to tolerance, which can result with either short- or long-term use.[29] Hyperalgesia, characterized by increased pain with opioid dose increases, decreased pain with dose decreases, and pain resulting from nonpainful stimuli, was emphasized in an April 2023 Food and Drug Administration Drug Safety Communication.[30] Figure 4 provides guidance on these and other opioid-related pharmacologic challenges.

If opioid dose increases paradoxically increase pain, hyperalgesia should be considered.

Iatrogenic opioid withdrawal syndrome (IWS) should be avoided; however, the absence of validated assessment tools for IWS and standardized approaches to prevention makes this a challenge. Recent studies report an IWS prevalence of 12% to 44%,[31–33] with the trauma population being on the upper end of this range. Fentanyl infusions for 72 hours or greater and total daily dose > = 1200 µg have been identified as independent predictors of IWS.[31] Cumulative opioid dose prior to weaning and previous drug use were associated with increased odds of developing withdrawal syndrome in trauma ICU patients.[33]

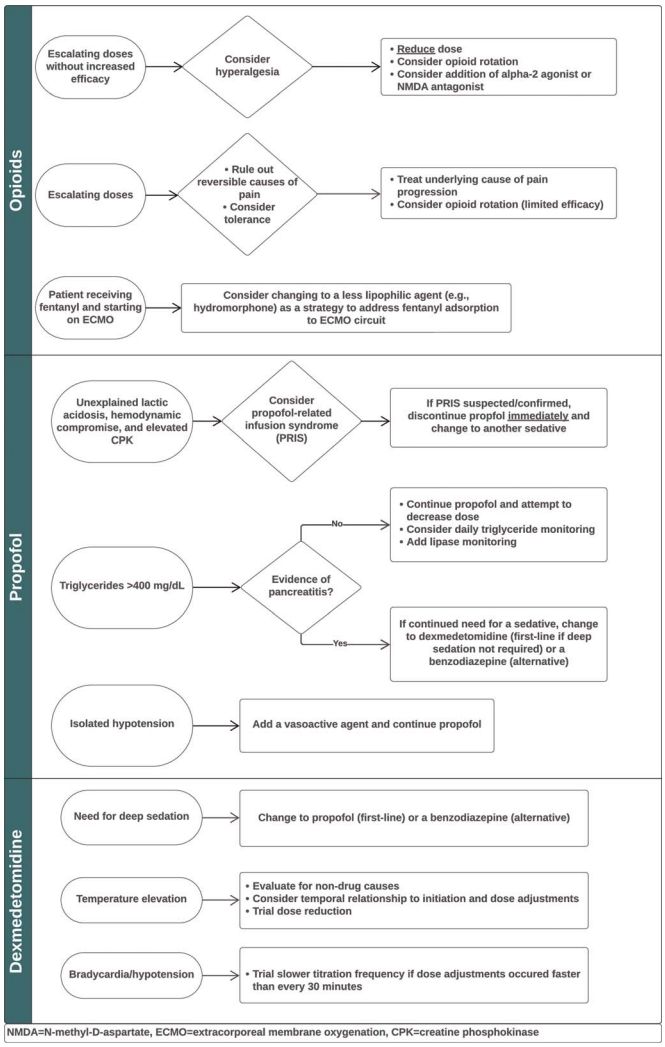

Figure 4. Pharmacologic challenges. NMDA, N-methyl-D-aspartate; ECMO, extracorporeal membrane oxygenation, CPK, creatine phosphokinase.

Weaning patients from intravenous opioids using enteral opioids is routine in ICU care but is not standardized. While guidelines do not recommend methadone for routine analgosedation, there are data describing its use for opioid weaning.[3,34] Enteral methadone use in mechanically ventilated patients who received at least 72 hours of IV opioids resulted in a shorter weaning time than oxycodone, although the authors comment that this is hypothesis generating.[34]

Ketamine

Ketamine exhibits dose-dependent analgesic *and* sedative properties and is attractive as monotherapy or as an adjunct to traditional analgesics.[35,36] A narrow therapeutic index between analgesic and anesthetic effects necessitates precise dosing.[37]

An emergence phenomenon may occur if dosing is incorrect. Weight-based administration via intermittent and/or continuous infusion are used in the ICU. Due to its large volume of distribution, ketamine infusion requirements may decrease due to tissue saturation and accumulation.[38]

Guidelines for the management of acute pain in emergency situations recommend ketamine 0.25 mg/kg to 0.35 mg/kg IV push as a second-line agent or if a procedure is pending.[39,40] Limiting the amount administered is recommended to avoid undesired effects such as the emergence phenomenon and oversedation. Pain, Agitation, Delirium, Immobility, and Sleep Disruption guidelines recommend 0.5 mg/kg IV push followed by 1 to 2 μg/kg/min as an adjunct to opioid therapy for postoperative patients.[3] Systematic reviews demonstrate that ketamine reduces pain and opioid requirements when used as an opioid adjunct..[41,42] Use in adult patients with rib fractures was discussed in an EAST clinical practice guideline.[43] No significant differences in numeric pain scores were observed in two studies; however, a reduction in oral morphine equivalents at 24 hours in patients with an Injury Severity Score >15 was demonstrated in one.[44] The lack of substantial data led the committee to make no recommendation for the use of ketamine in this patient population.[43]

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis.[45] They are effective analgesics; however, a significant knowledge gap exists regarding use in critically ill patients.[3,17,46] Providing an effective, balanced analgesic regimen to patients with rib fractures is particularly challenging, and strategies to incorporate NSAIDs in a limited, safe fashion have been investigated.[47] A retrospective study of critically ill adult trauma patients with one or more rib fractures who received early NSAIDs did not demonstrate renal harm.[47] Until additional data are available to inform best practice, clinicians are encouraged to limit duration of use, minimize exposure to nephrotoxins, and closely monitor for adverse effects. An intentional pause, as previously described, can be used to mitigate inadvertent, prolonged NSAID use.

Gabapentinoids

Gabapentinoids include gabapentin and pregabalin which reduce excitatory neurotransmitter release.[48] Clinical practice guidelines for critically ill patients recommend that gabapentin and pregabalin be used as an adjunct to opioids for neuropathic pain.[3] A conditional recommendation for adjunctive use following cardiothoracic surgery is also provided. Neurologic adverse effects, as well as misuse and withdrawal, are of particular concern.[49] Since publication of the PADIS guidelines, studies have been conducted to better delineate the role of these agents.

Compared with placebo, gabapentin did not decrease numeric pain scores or opioid consumption in adult trauma patients with at least one rib fracture.[50] In a systematic review and meta-analysis of randomized controlled trials conducted in adult surgical patients, gabapentinoids were associated with lower postoperative pain intensity; however, the reduction was not clinically significant, and the authors concluded that routine use is not supported.[51] Another systematic review and meta-analysis concluded that in comparison to opioids alone, the combination of opioids plus gabapentinoids did not decrease opioid consumption.[17]

Gabapentinoid use in trauma, postoperative, or critically ill patients should be reserved for neuropathic pain management.

SEDATION

Sedation is crucial to ensure safe and effective ICU care. Because there are complications associated with its use, familiarity with each sedative is critical. Table 1 and Figure 4 are intended to supplement the information below.

Propofol

Propofol is recommended as a first-line sedative and has a favorable pharmacokinetic profile.[3,52] Characterized by a rapid onset and short half-life, it is easily titrated to prescribed endpoints and allows for assessment of the neurologic examination. Propofol is beneficial for managing acute agitation and supervised sedation for procedures like chest tube placement and orthopedic reductions. It acts via $GABA_A$ receptors, making it effective if needed for concomitant management of status epilepticus and alcohol withdrawal syndrome.

Propofol is a respiratory depressant and should only be used for ICU sedation in mechanically ventilated patients. It is also a direct cardiac depressant and can result in decreased blood pressure and heart rate. Due to negative inotropic effects, propofol should be used with caution in patients with cardiac dysfunction. However, these well-documented hemodynamic effects are also known to occur with other sedatives such as midazolam and dexmedetomidine.[53,54] Sequestration

TABLE 1. Sedative Characteristics and Pearls

Sedative	Onset	Titration Frequency	Usual Dose Range	Deep Sedation
Propofol (first line)	1–2 min	Every 5 min	5–50 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Yes
Dexmedetomidine (first line)	5–10 min	Every 30 min	0.2–1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$	No Do not use for patients requiring chemical paralysis
Benzodiazepines (reserved for select indications only)	Clinical Pearls			
Midazolam	▪ Lipophilicity results in a rapid onset of action and is effective for managing acute agitation. ▪ Short-acting agent; however, erratic pharmacokinetics and accumulation are expected with longer-term use.			
Lorazepam	▪ Hydrophilicity results in a longer onset of action in comparison to midazolam; therefore, clinicians must be cognizant of dose-stacking and accumulation with repeated dosing. ▪ Intermediate-acting, a characteristic that makes titration difficult and is a predisposing factor for accumulation since steady-state concentrations from a given titration can take days.			

TABLE 2. Agents Used for Medication Assisted Therapy

Drugs	Opioid Receptor Effects	Pharmacokinetic Considerations	Clinical Pearls
Methadone	▪ Mu-opioid receptor agonist	▪ Half-life: 15–40 h ▪ Hepatic metabolism	▪ If discontinued, low plasma concentrations are maintained. ▪ CYP450 inducers increase methadone clearance and can precipitate withdrawal. ▪ QTc prolonging agent; concomitant use with other QTc prolonging agents results in an additive effect.
Buprenorphine	▪ Partial mu-opioid receptor agonist (antagonist at higher doses) ▪ Kappa-receptor antagonist	▪ Highly lipophilic ▪ High affinity for mu opioid receptors	▪ Dose reduction to 16 mg/daily or less and dividing the interval to every 6 or 8 h increase mu receptor availability. ▪ Respiratory effects are not readily reversed by naloxone. ▪ When discontinued, withdrawal is delayed for 2–14 d.
Naltrexone	▪ Pure opioid antagonist	▪ Intramuscular duration = 4 wk ▪ Oral duration =24–72 h (dose-dependent)	▪ Clinicians should document the last date of naltrexone administration as opioid effects will be enhanced near the end of the dosing interval.

References[61,63].
CYP450, cytochrome P450.

in fatty tissue may lead to decreased dose requirements in obese patients as tissues become saturated. Propofol-related infusion syndrome is a life-threatening complication and must not be overlooked.

Dexmedetomidine

Dexmedetomidine, a central acting α2-agonist, is an option for light sedation. In comparison to propofol, duration of mechanical ventilation, length of ICU stay, and days alive without coma are similar while rates of delirium are likely decreased.[54] It is recommended as a first-line ICU sedative.[3]

An advantage of dexmedetomidine is that it can be used during and following extubation. Bradycardia and hypotension are common, particularly at high doses or with rapid titration; however, these are comparable to propofol or benzodiazepines. Dexmedetomidine may result in withdrawal following prolonged administration.[55]

Benzodiazepines

Although benzodiazepines are no longer considered first-line sedatives, clinicians must be familiar with their characteristics.[3] Benzodiazepines possess anxiolytic, anterograde amnestic, and anticonvulsant properties. Therapeutic uses include management of alcohol withdrawal syndrome, refractory status epilepticus, and an alternative to propofol when deep sedation is needed.

Prehospital benzodiazepine use is common and may require in-hospital administration to prevent withdrawal syndromes. Alprazolam use represents a unique challenge because substitution with benzodiazepines commonly used in the ICU may not prevent withdrawal.[56] Resuming alprazolam or initiating clonazepam can achieve this endpoint.[57]

For patients with prehospital alprazolam use, resuming alprazolam or initiating clonazepam may be necessary to prevent/treat alprazolam withdrawal.

One of the most concerning effects of the benzodiazepines is their association with delirium. Unfortunately, the critical care community witnessed a resurgence in benzodiazepine use during the COVID-19 pandemic. A point-prevalence study demonstrated 64% of patients received benzodiazepines for an average of 7 days and reinforced that they are a modifiable risk factor for delirium.[58]

Due to their risk of contributing to delirium, benzodiazepines should only be administered when other sedative agents are no longer tolerable.

Quetiapine

Although quetiapine is frequently prescribed in the ICU, data supporting its use for treatment and prevention of delirium remain limited. A study by Devlin et al. found positive benefits when using quetiapine to treat ICU delirium.[59] Despite this, nonpharmacologic principles remain the foundation of prevention and treatment of delirium. Clinical teams should ensure no patient is continued on this therapy following discharge from the ICU.

SPECIAL TOPICS

Opioid Use Disorder

Strategies to manage critically ill patients receiving medications for opioid use disorder (OUD), including methadone, buprenorphine, buprenorphine/naloxone, and naltrexone, are not well described. Survey data demonstrate that only 7% of institutional analgosedation guidelines include considerations specific to patients with OUD.[60] Furthermore, 67% of respondents did not have access to a pain or addiction specialist.[60]

Clinicians must consider medications used for OUD, known as medication-assisted therapy (MAT), when designing an analgosedation plan. In addition to managing acute pain, consideration must be given to preventing opioid withdrawal and minimizing interruptions to OUD treatment.[61] All practitioners are permitted to prescribe buprenorphine for OUD if they have a current Drug Enforcement Administration registration that includes Schedule III authority and if permitted by state law.[62] Table 2 includes valuable information about agents used for MAT.

Steps to consider for management of critically ill surgical patients with OUD include:

- Continue preexisting MAT when possible.
- Provide additional analgesics (i.e., short-acting opioids, multimodal agents) to address acute pain.

- Consult addiction specialist.
- Incorporate OUD pathways within institutional analgesic guidelines.

Although methadone is an effective analgesic, its long duration of action makes titration for acute pain unpredictable. Repeated dosing results in accumulation, and peak respiratory depressant effects occur later than peak analgesia.[63] When continued for MAT, clinicians must be vigilant for drug interactions.

Buprenorphine slowly dissociates from mu opioid receptors, blocking other opioids from their site of action. In the perioperative period, a stepwise approach for patients on buprenorphine is recommended[64] including initiation of analgesic adjuncts, addition of a full mu-opioid agonist (i.e., fentanyl, hydromorphone), and buprenorphine dose reduction if pain persists.[64] If the buprenorphine dose is reduced in the setting of a full agonist, transfer to a monitored setting should be considered.[64] For patients on buprenorphine/naloxone, use of buprenorphine alone eliminates the naloxone component, a pure opioid receptor antagonist. Naltrexone is a long-acting agent that prevents opioids from acting at their site of action. Patients maintained on naltrexone presenting with acute pain may require opioids with a high binding affinity (i.e., fentanyl, hydromorphone).[61]

Continuation of MAT is recommended in the ICU. If this is not feasible, clinicians can use a combination of multimodal agents, opioids, and close monitoring for the development of withdrawal. Buprenorphine products and naltrexone can precipitate withdrawal, so caution is advised when reinitiating these agents if patients have been receiving mu-opioid agonists.

Traumatic Brain Injury

Although there are no level I data for analgesic choices in traumatic brain injury (TBI), a global consensus statement on analgosedation in neurocritical care indicates that 76.3% of international experts strongly recommend fentanyl and acetaminophen as preferred analgesics.[65] In TBI, sedation is used to achieve comfort, allow mechanical ventilation, suppress or stop seizures, and lower intracranial pressure. There is little evidence supporting any sedative as superior.[66] Among sedatives in TBI, propofol is most often used because it has the advantages of rapid onset, short half-life, elevation of the seizure threshold, and some mechanisms of neuroprotection. A disadvantage is the potential for hypotension. Readers are referred to the dedicated propofol discussion above. Although published experience is more limited, dexmedetomidine appears to be safe and reduces agitation in patients with TBI.[67] Ketamine, once thought contraindicated in TBI due to the risk of elevating intracranial pressure, may in fact have significant benefits in TBI. Ketamine is relatively safe, is cost-effective, is opioid-sparing, has no effect on GI motility, is useful in conscious sedation, and is appropriate in both withdrawal and convulsive situations.[68]

Pregnancy

Experience with analgesia and sedation in pregnant patients is limited to small series and case reports. Neonatologists and obstetricians will benefit from an awareness of what analgesic and sedative medications have been administered to the pregnant ICU patient by the ICU team. Analgosedation is perhaps most important in the third trimester because medication effects are more likely to affect a postpartum newborn in addition to the critically ill mother.[69] Fentanyl, morphine, hydromorphone, and remifentanil may be used with confidence in pregnant patients.[69] Some concerns exist around benzodiazepine use in pregnancy but an association between exposure to benzodiazepines and congenital anomalies is controversial.[69] Benzodiazepines do not appear to be superior to other induction and sedation agents, and neither dexmedetomidine nor propofol has been associated with congenital anomalies.[69] Ketamine is safe and might be ideal in cases of hemodynamic instability.[70] Dexmedetomidine may be particularly advantageous in patients with severe hypertension from preeclampsia, especially postpartum.

Obesity

In obese patients, principles of analgosedation are similar to nonobese patients.[71] Of the opiates, remifentanil has the advantage of not accumulating with repeated doses. Long-acting opioids increase the risk of respiratory depression and are best avoided. *Avoidance of benzodiazepines* is the greatest priority. Propofol is safe but prolonged use should be avoided to prevent accumulation and propofol infusion syndrome. Alpha-2 agonists provide potential advantages but pharmacokinetics can be uncertain in obese patients so caution should be used. Dexmedetomidine has significant advantages by not causing respiratory depression while still providing sympatholysis. Dosing based upon weight (ideal, actual, adjusted) may vary and confirmation with clinical pharmacist can achieve optimal efficacy and minimize adverse events.

Alcohol Withdrawal

Alcohol withdrawal syndrome (AWS) presents on a spectrum ranging from mild to severe, with severe manifestations including hallucinations, delirium, seizures, and death. Critical care professionals must be familiar with the diagnosis and treatment of AWS and the involvement of other professionals including social work and addiction medicine may be needed. The nature of surgical critical illness, injury, and acute pain can produce similar symptoms to the sympathetic stimulation seen in AWS, which can make diagnosis difficult. A clinical consensus document produced by the American Association for the Surgery of Trauma (AAST) recommends use of the Alcohol Use Disorders Identification Test (AUDIT) or Prediction of Alcohol Withdrawal Severity Scale (PAWSS) as screening tools.[72] Clinicians must be mindful that the commonly used alcohol screening tool, CIWA-AR, is unproven in trauma patients and seriously limited in nonverbal patients. Modified Minnesota Detoxification Scale (mMINDS) does not require participation and is recommended by the Critical Care Committee of the AAST.[72]

Empiric therapy may be appropriate in patients at high risk for AWS. These include patients with a history of complicated alcohol withdrawal, a long history of alcohol use, significant comorbidity or acute surgical illness that may be severely compromised by concomitant AWS (e.g., ischemic heart disease, TBI), autonomic hyperactivity at the time of presentation, dependence upon benzodiazepines or barbiturates, and high ethanol levels on presentation. Many medications used for ICU sedation also serve to treat, or prophylaxis against, AWS. Although benzodiazepines have been the cornerstone for AWS, phenobarbital is emerging as an agent that is effective and safe in critically ill surgical patients. Although it is a long-acting agent with the potential for oversedation and respiratory compromise, these adverse

effects have not been consistently demonstrated in patients with AWS.[73–75] Importantly, reduced dose options for patients at risk for oversedation and respiratory compromise were included in the protocol.[74,75] Clonidine, dexmedetomidine, propofol and gabapentin are also considered adjunctive in the treatment and prophylaxis of AWS but should always be used in combination with a GABA-active agent.[72]

Geriatrics

Geriatric patients are uniquely susceptible to under-treatment of PAD and the effects of analgesic and sedative medications. Geriatric patients are more vulnerable to delirium and are more likely to have dementia, particularly dementia that has not yet been diagnosed. Therefore, an analgesia-first approach with targeted, objectively measured analgesia and sedation at the lowest effective dose permits wakefulness and participation in decision making.[76] Comprehensive medication review is essential as polypharmacy is common in older patients, increasing the risk of drug interactions or untoward side effects. Deescalation or stopping of drugs added in the ICU is particularly important upon ICU discharge. Finally, optimizing nonpharmacologic measures, such as glasses and hearing aids, is of particular importance in this patient population.

CONCLUSION

Effective management of pain, agitation, and delirium in critically ill surgical patients requires attention to the principles of rigorous and continuous assessment, an analgesic first approach, and an emphasis on nonpharmacologic interventions as primary therapy. Further attention to the unique pharmacologic needs of specific populations can limit iatrogenic exacerbation of each element of PAD. Adhering to these principles can minimize the impact of delirium and improve overall in-hospital and long-term outcome of critically ill surgical patients.

AUTHORSHIP

S.E., W.O., A.B., and G.G. planned the design of the review and participated in literature review, writing, and editing.

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DISCLOSURE

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