



Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

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To minimize the perception of bias in these Guidelines, individual Task Force members with a significant conflict of interest on a particular topic were recused from grading the literature, writing evidence summaries, and

developing specific statements and recommendations on that topic. Final decisions regarding strength of evidence and strength of recommendations for all questions were voted on anonymously by all Task Force members. Voting distributions for all statements and recommendations can be found on line at <http://journals.lww.com/ccmjjournal>. We refer readers to the Methods Section of these Guidelines for more details.

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The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

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Objective: To revise the “Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult” published in *Critical Care Medicine* in 2002.

Methods: The American College of Critical Care Medicine assembled a 20-person, multidisciplinary, multi-institutional task force with expertise in guideline development, pain, agitation and sedation, delirium management, and associated outcomes in adult critically ill patients. The task force, divided into four subcommittees, collaborated over 6 yr in person, via teleconferences, and via electronic communication. Subcommittees were responsible for developing relevant clinical questions, using the Grading of Recommendations Assessment, Development and Evaluation method (<http://www.gradeworkinggroup.org>) to review, evaluate, and summarize the literature, and to develop clinical statements (descriptive) and recommendations (actionable). With the help of a professional librarian and Refworks® database software, they developed a Web-based electronic database of over 19,000 references extracted from eight clinical search engines, related to pain and analgesia, agitation and sedation, delirium, and related clinical outcomes in adult ICU patients. The group also used psychometric analyses to evaluate and compare pain, agitation/sedation, and delirium assessment tools. All task force members were allowed to review the literature supporting each statement and recommendation and provided feedback to the subcommittees. Group consensus was achieved for all statements and recommendations using the nominal group technique and the modified Delphi method, with anonymous voting by all task force members using E-Survey (<http://www.esurvey.com>). All voting

was completed in December 2010. Relevant studies published after this date and prior to publication of these guidelines were referenced in the text. The quality of evidence for each statement and recommendation was ranked as high (A), moderate (B), or low/very low (C). The strength of recommendations was ranked as strong (1) or weak (2), and either in favor of (+) or against (–) an intervention. A strong recommendation (either for or against) indicated that the intervention’s desirable effects either clearly outweighed its undesirable effects (risks, burdens, and costs) or it did not. For all strong recommendations, the phrase “We recommend ...” is used throughout. A weak recommendation, either for or against an intervention, indicated that the trade-off between desirable and undesirable effects was less clear. For all weak recommendations, the phrase “We suggest ...” is used throughout. In the absence of sufficient evidence, or when group consensus could not be achieved, no recommendation (0) was made. Consensus based on expert opinion was not used as a substitute for a lack of evidence. A consistent method for addressing potential conflict of interest was followed if task force members were coauthors of related research. The development of this guideline was independent of any industry funding.

Conclusion: These guidelines provide a roadmap for developing integrated, evidence-based, and patient-centered protocols for preventing and treating pain, agitation, and delirium in critically ill patients. (*Crit Care Med* 2013; 41:263–306)

Key Words: agitation; analgesia; critical care medicine; delirium; evidence-based medicine; GRADE; guidelines; intensive care; outcomes; pain; protocols; sedation

STATEMENTS AND RECOMMENDATIONS

1. Pain and Analgesia

a. Incidence of pain

- i. Adult medical, surgical, and trauma ICU patients routinely experience pain, both at rest and with routine ICU care (B).
- ii. Pain in adult cardiac surgery patients is common and poorly treated; women experience more pain than men after cardiac surgery (B).
- iii. Procedural pain is common in adult ICU patients (B).

b. Pain assessment

- i. We recommend that pain be routinely monitored in all adult ICU patients (+1B).
- ii. The Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) are the most valid and reliable behavioral pain scales for monitoring pain in medical, postoperative, or trauma (except for brain injury) adult ICU patients who are unable to self-report and in whom motor function is intact and behaviors are observable. Using these scales in other ICU patient populations and translating them into foreign languages other than French or English require further validation testing (B).
- iii. We do not suggest that vital signs (or observational pain scales that include vital signs) be used alone for pain assessment in adult ICU patients (–2C).

- iv. We suggest that vital signs may be used as a cue to begin further assessment of pain in these patients, however (+2C).

c. Treatment of pain

- i. We recommend that preemptive analgesia and/or nonpharmacologic interventions (e.g., relaxation) be administered to alleviate pain in adult ICU patients prior to chest tube removal (+1C).
- ii. We suggest that for other types of invasive and potentially painful procedures in adult ICU patients, preemptive analgesic therapy and/or nonpharmacologic interventions may also be administered to alleviate pain (+2C).
- iii. We recommend that intravenous (IV) opioids be considered as the first-line drug class of choice to treat non-neuropathic pain in critically ill patients (+1C).
- iv. All available IV opioids, when titrated to similar pain intensity endpoints, are equally effective (C).
- v. We suggest that nonopioid analgesics be considered to decrease the amount of opioids administered (or to eliminate the need for IV opioids altogether) and to decrease opioid-related side effects (+2C).
- vi. We recommend that either enterally administered gabapentin or carbamazepine, in addition to IV

- opioids, be considered for treatment of neuropathic pain (+1A).
- vii. We recommend that thoracic epidural anesthesia/analgesia be considered for postoperative analgesia in patients undergoing abdominal aortic aneurysm surgery (+1B).
 - viii. We provide no recommendation for using a lumbar epidural over parenteral opioids for postoperative analgesia in patients undergoing abdominal aortic aneurysm surgery, due to a lack of benefit of epidural over parenteral opioids in this patient population (0,A).
 - ix. We provide no recommendation for the use of thoracic epidural analgesia in patients undergoing either intrathoracic or nonvascular abdominal surgical procedures, due to insufficient and conflicting evidence for this mode of analgesic delivery in these patients (0,B).
 - x. We suggest that thoracic epidural analgesia be considered for patients with traumatic rib fractures (+2B).
 - xi. We provide no recommendation for neuraxial/regional analgesia over systemic analgesia in medical ICU patients, due to lack of evidence in this patient population (0, No Evidence).
2. Agitation and Sedation
- a. Depth of sedation vs. clinical outcomes
 - i. Maintaining light levels of sedation in adult ICU patients is associated with improved clinical outcomes (e.g., shorter duration of mechanical ventilation and a shorter ICU length of stay [LOS]) (B).
 - ii. Maintaining light levels of sedation increases the physiologic stress response, but is not associated with an increased incidence of myocardial ischemia (B).
 - iii. The association between depth of sedation and psychological stress in these patients remains unclear (C).
 - iv. We recommend that sedative medications be titrated to maintain a light rather than a deep level of sedation in adult ICU patients, unless clinically contraindicated (+1B).
 - b. Monitoring depth of sedation and brain function
 - i. The Richmond Agitation-Sedation Scale (RASS) and Sedation-Agitation Scale (SAS) are the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients (B).
 - ii. We do not recommend that objective measures of brain function (e.g., auditory evoked potentials [AEPs], Bispectral Index [BIS], Narcotrend Index [NI], Patient State Index [PSI], or state entropy [SE]) be used as the primary method to monitor depth of sedation in noncomatose, nonparalyzed critically ill adult patients, as these monitors are inadequate substitutes for subjective sedation scoring systems (-1B).
 - iii. We suggest that objective measures of brain function (e.g., AEPs, BIS, NI, PSI, or SE) be used as an adjunct to subjective sedation assessments in adult ICU patients who are receiving neuromuscular blocking agents, as subjective sedation assessments may be unobtainable in these patients (+2B).
 - iv. We recommend that EEG monitoring be used to monitor nonconvulsive seizure activity in adult ICU patients with either known or suspected seizures, or to titrate electrosuppressive medication to achieve burst suppression in adult ICU patients with elevated intracranial pressure (+1A).
- c. Choice of sedative
- i. We suggest that sedation strategies using nonbenzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients (+2B).
3. Delirium
- a. Outcomes associated with delirium
 - i. Delirium is associated with increased mortality in adult ICU patients (A).
 - ii. Delirium is associated with prolonged ICU and hospital LOS in adult ICU patients (A).
 - iii. Delirium is associated with the development of post-ICU cognitive impairment in adult ICU patients (B).
 - b. Detecting and monitoring delirium
 - i. We recommend routine monitoring of delirium in adult ICU patients (+1B).
 - ii. The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable delirium monitoring tools in adult ICU patients (A).
 - iii. Routine monitoring of delirium in adult ICU patients is feasible in clinical practice (B).
 - c. Delirium risk factors
 - i. Four baseline risk factors are positively and significantly associated with the development of delirium in the ICU: preexisting dementia, history of hypertension and/or alcoholism, and a high severity of illness at admission (B).
 - ii. Coma is an independent risk factor for the development of delirium in ICU patients (B).
 - iii. Conflicting data surround the relationship between opioid use and the development of delirium in adult ICU patients (B).
 - iv. Benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients (B).
 - v. There are insufficient data to determine the relationship between propofol use and the development of delirium in adult ICU patients (C).
 - vi. In mechanically ventilated adult ICU patients at risk of developing delirium, dexmedetomidine infusions administered for sedation may be associated with a lower prevalence of delirium compared to benzodiazepine infusions (B).

- d. Delirium prevention
 - i. We recommend performing early mobilization of adult ICU patients whenever feasible to reduce the incidence and duration of delirium (+1B).
 - ii. We provide no recommendation for using a pharmacologic delirium prevention protocol in adult ICU patients, as no compelling data demonstrate that this reduces the incidence or duration of delirium in these patients (0,C).
 - iii. We provide no recommendation for using a combined nonpharmacologic and pharmacologic delirium prevention protocol in adult ICU patients, as this has not been shown to reduce the incidence of delirium in these patients (0,C).
 - iv. We do not suggest that either haloperidol or atypical antipsychotics be administered to prevent delirium in adult ICU patients (-2C).
 - v. We provide no recommendation for the use of dexmedetomidine to prevent delirium in adult ICU patients, as there is no compelling evidence regarding its effectiveness in these patients (0,C).
- e. Delirium treatment
 - i. There is no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients (No Evidence).
 - ii. Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C).
 - iii. We do not recommend administering rivastigmine to reduce the duration of delirium in ICU patients (-1B).
 - iv. We do not suggest using antipsychotics in patients at significant risk for torsades de pointes (i.e., patients with baseline prolongation of QTc interval, patients receiving concomitant medications known to prolong the QTc interval, or patients with a history of this arrhythmia) (-2C).
 - v. We suggest that in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, continuous IV infusions of dexmedetomidine rather than benzodiazepine infusions be administered for sedation to reduce the duration of delirium in these patients (+2B).
4. Strategies for Managing Pain, Agitation, and Delirium to Improve ICU Outcomes
 - a. We recommend either daily sedation interruption or a light target level of sedation be routinely used in mechanically ventilated adult ICU patients (+1B).
 - b. We suggest that analgesia-first sedation be used in mechanically ventilated adult ICU patients (+2B).
 - c. We recommend promoting sleep in adult ICU patients by optimizing patients' environments, using strategies to control light and noise, clustering patient care activities, and decreasing stimuli at night to protect patients' sleep cycles (+1C).
 - d. We provide no recommendation for using specific modes of mechanical ventilation to promote sleep

in mechanically ventilated adult ICU patients, as insufficient evidence exists for the efficacy of these interventions (0, No Evidence).

- e. We recommend using an interdisciplinary ICU team approach that includes provider education, pre-printed and/or computerized protocols and order forms, and quality ICU rounds checklists to facilitate the use of pain, agitation, and delirium management guidelines or protocols in adult ICUs (+1B).

Since these guidelines were last published, we have made significant advances in our understanding of how to provide physical and psychological comfort for patients admitted to the ICU (1). The development of valid and reliable bedside assessment tools to measure pain, sedation, agitation, and delirium in ICU patients has allowed clinicians to manage patients better and to evaluate outcomes associated with both nonpharmacologic and pharmacologic interventions (2, 3). Our expanded knowledge of the clinical pharmacology of medications commonly administered to treat pain, agitation, and delirium (PAD) in ICU patients has increased our appreciation for both the short- and long-term consequences of prolonged exposure to these agents (4–6). We have learned that the methods of administering and titrating these medications can affect patient outcomes as much as drug choice (7–16). For most ICU patients, a safe and effective strategy that ensures patient comfort while maintaining a light level of sedation is associated with improved clinical outcomes (9–13, 16–20).

Ensuring that critically ill patients are free from pain, agitation, anxiety, and delirium at times may conflict with other clinical management goals, such as maintaining cardiopulmonary stability while preserving adequate end-organ perfusion and function (21, 22). Management goals may be further complicated by the growing number of “evidence-based” bundles and clinical algorithms, some of which have been widely adopted by regulatory agencies and payers (23–30). Finally, tremendous worldwide variability in cultural, philosophical, and practice norms, and in the availability of manpower and resources, makes widespread implementation of evidence-based practices challenging (31–36).

The goal of these clinical practice guidelines is to recommend best practices for managing PAD to improve clinical outcomes in adult ICU patients. We performed a rigorous, objective, transparent, and unbiased assessment of the relevant published evidence. We balanced this evidence against the values and preferences of ICU patients, family members, caregivers, and payer and regulatory groups, and important ICU clinical outcomes, to develop relevant statements and recommendations that can be applied at the bedside.

The scope of these guidelines includes short- and long-term management of PAD in both intubated and nonintubated adult medical, surgical, and trauma ICU patients. These guidelines only briefly address the topic of analgesia and sedation for procedures, which is described in more detail in the American Society of Anesthesiologists guidelines on conscious sedation

(37). The American College of Critical Care Medicine (ACCM) is currently developing separate guidelines on analgesia and sedation for pediatric ICU patients.

This version of the guidelines places a greater emphasis on the psychometric aspects of PAD monitoring tools. It includes both pharmacologic and nonpharmacologic approaches to manage PAD in ICU patients. There is also greater emphasis placed on preventing, diagnosing, and treating delirium, reflecting our growing understanding of this disease process in critically ill patients. These guidelines are meant to help clinicians take a more integrated approach to manage PAD in critically ill patients. Clinicians should adapt these guidelines to the context of individual patient care needs and the available resources of their local health care system. They are not meant to be prescriptive or applied in absolute terms.

METHODS

The ACCM's 20-member multidisciplinary task force, with expertise in PAD management, was charged with revising the 2002 "Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult" (1). Subcommittees were assigned one of the four subtopic areas: pain and analgesia, agitation and sedation, delirium, and related ICU outcomes. Each subcommittee developed relevant clinical questions and related outcomes, identified, reviewed, and evaluated the literature, crafted statements and recommendations, and drafted their section of the article.

To facilitate the literature review, subcommittees developed a comprehensive list of related key words. A professional librarian (C.K., University of Cincinnati) expanded and organized this key word list; developed corresponding medical subject heading (MeSH) terms (Supplemental Digital Content 1, <http://links.lww.com/CCM/A590>); searched relevant clinical databases; and created an electronic, Web-based, password-protected database using Refworks software (Bethesda, MD). Eight databases were included in all searches: PubMed, MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of

Controlled Trials, CINAHL, Scopus, ISI Web of Science, and the International Pharmaceutical Abstracts. Search parameters included published (or in press) English-only manuscripts on adult humans (> 18 yr), from December 1999 (the search limit for the 2002 guidelines) through December 2010. Studies with less than 30 patients, editorials, narrative reviews, case reports, animal or in vitro studies, and letters to the editor were excluded. Biweekly automated searches were continued beyond this date, and relevant articles were incorporated into the guidelines through July 2012, but studies published after December 2010 were not included in the evidence review and voting process. The 2002 guideline references were also included in the database, and targeted searches of the literature published before December 1999 were performed as needed. Over 19,000 references were ultimately included in the Refworks database.

The statements and recommendations in this 2012 version of the guidelines were developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, a structured system for rating quality of evidence and grading strength of recommendation in clinical practice (<http://www.gradeworkinggroup.org>) (38–40). Subcommittees worked with members of the GRADE Working Group (R.J., D.C., H.S., G.G.) to phrase all clinical questions in either "descriptive" or "actionable" terms. They structured actionable questions in the Population, Intervention, Comparison, Outcomes format and classified clinical outcomes related to each intervention as critical, important, or unimportant to clinical decision making. Only important and critical outcomes were included in the evidence review, and only critical outcomes were included in developing recommendations.

Subcommittee members searched the database for relevant articles and uploaded corresponding PDFs to facilitate group review. Two subcommittee members independently completed a GRADE evidence profile summarizing the findings of each study and evaluated the quality of evidence. The quality of evidence was judged to be high (level A), moderate (level B), or low/very low (level C), based on both study design and specific study characteristics, which could result in a reviewer

TABLE 1. Factors That Affect the Quality of Evidence^a

Level of Evidence	Quality of Evidence	Type of Evidence	Definition
A	High	High quality RCT	Further research is unlikely to change our confidence in the estimate of effect.
B	Moderate	RCT with significant limitations (downgraded) ^b , or high-quality OS (upgraded) ^c	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C	Low	OS	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

RCT = randomized controlled trial; OS = observational study.

^aAdapted from Guyatt et al (40).

^bRCTs with significant limitations: 1) study design limitations (planning, implementation bias); 2) inconsistency of results; 3) indirectness of evidence; 4) imprecision of results; 5) high likelihood of reporting bias.

^cHigh-quality OS: 1) large magnitude of treatment effect; 2) evidence of a dose-response relationship; 3) plausible biases would decrease the magnitude of an apparent treatment effect.

TABLE 2. Factors That Affect the Strength of Recommendations^a

Considerations	Effect on Strength of Recommendation
Quality of evidence	Lower quality of evidence reduces the likelihood of a strong recommendation, and vice versa
Uncertainty about the balance between desirable and undesirable effects	Higher degree of uncertainty about the balance between risks and benefits reduces the likelihood of a strong recommendation, and vice versa
Uncertainty or variability in values and preferences	Wide variability in values and preferences across groups reduces the likelihood of a strong recommendation, and vice versa
Uncertainty about whether the intervention represents a wise use of resources	A higher the overall cost of treatment reduces the likelihood of a strong recommendation, and vice versa

^aAdapted from Guyatt et al (40).

either downgrading or upgrading the quality of the evidence (Table 1). If multiple studies related to a particular outcome demonstrated disparate results, and no published systematic reviews on the topic existed, a meta-analysis of the relevant literature was performed by a member of the GRADE Working Group (R.J.).

Subcommittees collectively reviewed the evidence profiles for each question, and using a nominal group technique, determined the overall quality of evidence (for both descriptive and actionable questions), the strength of recommendation (for actionable questions only), and drafted evidence summaries for review by other task force members. The strength of recommendations was defined as either *strong* (1) or *weak* (2), and either *for* (+) or *against* (–) an intervention, based on both the quality of evidence and the risks and benefits across all critical outcomes (Table 2) (41, 42). A *no recommendation* (0) could also be made due to either a lack of evidence or a lack of consensus among subcommittee members. Consensus statements based on expert opinion alone were not used when evidence could not support a recommendation. A *strong* recommendation either in *favor* of (+1) or *against* (–1) an intervention implied that the majority of task force members believed that the benefits of the intervention significantly outweighed the risks (or vice versa) and that the majority of patients and providers would pursue this course of action (or not), given the choice. A *weak* recommendation either in *favor* of (+2) or *against* (–2) an intervention implied that the benefits of the intervention likely outweighed the risks (or vice versa), but that task force members were not confident about these trade-offs, either because of a low quality of evidence or because the trade-offs between risks and benefits were closely balanced. On the basis of this information, most people might pursue this course of action (or not), but a significant number of patients and providers would choose an alternative course of action (40, 43, 44). Throughout these guidelines, for all strong recommendations, the phrase “We recommend ...” was used, and for all weak recommendations, “We suggest ...” was used.

Group consensus for all statements and recommendations was achieved using a modified Delphi method with an anonymous voting scheme (41, 45). Task force members reviewed the subcommittees’ GRADE Evidence Summaries, and statements and recommendations, and voted and commented anonymously on each statement and recommendation using an on-line electronic

survey tool (E-Survey, <http://www.esurvey.com>, Scottsdale, AZ). Consensus on the *strength of evidence* for each question required a majority (> 50%) vote. Consensus on the strength of recommendations was defined as follows: a recommendation in *favor* of an intervention (or the comparator) required at least 50% of all task force members voting in *favor*, with less than 20% voting *against*; failure to meet these voting thresholds resulted in *no recommendation* being made. For a recommendation to be graded as *strong* rather than *weak*, at least 70% of those voting had to vote for a *strong* recommendation, otherwise it received a *weak* recommendation. This method for reaching consensus has been proposed by the GRADE Working Group and was adopted by the 2008 Sepsis Guidelines Panel to ensure fairness, transparency, and anonymity in the creation of guideline recommendations (46, 47). Polling results and comments were then summarized and distributed to all PAD guideline task force members for review. When one round of voting failed to produce group consensus, additional discussion and a second and/or third round of voting occurred. Polling for all questions was completed by December 2010. Distribution of the final voting tallies along with comments by task force members for each statement and recommendation is summarized in Supplemental Digital Content 2 (<http://links.lww.com/CCM/A591>).

Task force members completed required, annual, conflict of interest statements. Those with significant potential conflicts of interest (e.g., manuscript coauthorship) recused themselves from reviewing and grading evidence and from developing a subcommittee’s evidence statements and recommendations for related questions. All task force members voted anonymously on the final strength of evidence and strength of recommendations for all questions. No industry funding or support was used to develop any aspect of these guidelines.

Psychometric Analyses

These guidelines include statements and recommendations about using a variety of bedside behavioral assessment tools used to 1) detect and evaluate pain, 2) assess depth of sedation and degree of agitation, and 3) detect delirium in critically ill adult patients who are unable to communicate clearly. To date, a comparative assessment of the psychometric properties (i.e., reliability and validity) and feasibility related to the use of these tools in ICU patients has not been published. *Scale reliability*

refers to the overall accuracy of the use of a scale in replicating pain, sedation, or delirium scores over time (i.e., test–retest reliability) or between raters (i.e., inter-rater reliability) (48). *Validity* refers to the conclusions that can be drawn from the results of a test or scale (e.g., does a delirium assessment tool actually detect delirium?) (49). Content, criterion, and discriminant validation are specific strategies of validity testing. A tool can be shown to be both reliable and valid when used for a specific purpose with specified individuals in a given context (48, 49). *Feasibility* refers to the ease with which clinicians can apply a particular scale in the clinical setting (e.g., in the ICU).

The task force evaluated and compared the psychometric properties of behavioral pain scales (BPSs) used in adult ICU patients and compared their analyses to a previously published process (50). Similar scoring systems were not available to evaluate and compare the psychometric properties of sedation and delirium scales, which have different validation strategies from those used for pain scales. With input from three psychometric testing experts (D.S., C.J., C.W.), the task force developed similar scoring systems to assess and compare sedation and delirium scales (48).

The psychometric properties of pain, sedation, and delirium scales were evaluated based on: 1) item selection and content validation, 2) reliability, 3) validity, 4) feasibility, and 5) relevance or impact of implementation on patient outcomes. Psychometric raw scores ranged from 0 to 25 for pain scales, 0 to 18 for sedation scales, and 0 to 21 for delirium scales. Weighted scores were established for each criterion to address variations in scores and to facilitate the interpretation of results, resulting in a total weighted score 0 to 20 for all three domains. The details of each of the three psychometric scoring systems used are summarized in Supplemental Digital Content 3 (<http://links.lww.com/CCM/A592>). Scales with weighted scores ranging from 15 to 20 had very good psychometric properties, 12 to 14.9 had moderate psychometric properties, 10 to 11.9 had some acceptable psychometric properties which required validation in additional studies, and 0 to 9.9 had very few psychometric properties reported and/or unacceptable results. Scales with moderate to very good psychometric properties (i.e., weighted score ≥ 12) were considered to be sufficiently valid and reliable scales for use in adult ICU patients. The quality of evidence for each individual scale was also evaluated using categories similar to those used in the GRADE system, with modifications adapted for the psychometric analyses. All studies were reviewed, and all scales were scored independently by two reviewers.

Pain and Analgesia

Incidence of Pain in ICU Patients. The International Association for the Study of Pain defines pain as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (51). This definition highlights the subjective nature of pain and suggests that it can be present only when reported by the person experiencing it. Most critically ill patients will likely experience pain sometime during their ICU stay (52) and identify it as a great source of stress (53–56). However, many critically ill patients

may be unable to self-report their pain (either verbally or with other signs) because of an altered level of consciousness, the use of mechanical ventilation, or high doses of sedative agents or neuromuscular blocking agents (57). Yet, the ability to reliably assess patient’s pain is the foundation for effective pain treatment. As the International Association for the Study of Pain also states, “the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment” (58). Therefore, clinicians must be able to reliably detect pain, using assessment methods adapted to a patient’s diminished communication capabilities. In such situations, clinicians should consider patients’ behavioral reactions as surrogate measures of pain, as long as their motor function is intact (59). Detection, quantification, and management of pain in critically ill adults are major priorities and have been the subject of research for over 20 yr (60). Despite this fact, the incidence of significant pain is still 50% or higher in both medical and surgical ICU patients (61, 62).

In addition to experiencing pain at rest (61) and pain related to surgery, trauma, burns, or cancer, patients also experience procedural pain (63–70). This was highlighted in the first practice guideline published on acute pain management 20 yr ago by the Agency for Health Care Policy and Research (71). Pain related to procedures is ubiquitous, and inadequate treatment of procedural pain remains a significant problem for many ICU patients (68).

The negative physiologic and psychological consequences of unrelieved pain in ICU patients are significant and long-lasting. For many years, ICU patients have identified pain as their greatest concern and a leading cause of insufficient sleep (72). More recently, studies on ICU-discharged but still-hospitalized patients showed that 82% ($n = 75$) (56) remembered pain or discomfort associated with the endotracheal tube and 77% ($n = 93$) remembered experiencing moderate to severe pain during their ICU stay (73). One week after discharge from the ICU, 82% ($n = 120$) of cardiac surgery patients reported pain as the most common traumatic memory of their ICU stay; 6 months later, 38% still recalled pain as their most traumatic ICU memory (74). Granja and colleagues (75) noted that 17% ($n = 313$) of patients remembered experiencing severe pain 6 months after an ICU stay and 18% were at high risk of developing posttraumatic stress disorder (PTSD). Schelling and colleagues (25) conducted a long-term follow-up (median, 4 yr) questionnaire study of 80 patients who had been treated in the ICU for acute respiratory distress syndrome. In comparison with normal controls, both medical and surgical patients who recalled pain and other traumatic situations while in the ICU had a higher incidence of chronic pain (38%) and PTSD symptoms (27%), and a lower health-related quality of life (21%).

The stress response evoked by pain can have deleterious consequences for ICU patients. Increased circulating catecholamines can cause arteriolar vasoconstriction, impair tissue perfusion, and reduce tissue-oxygen partial pressure (76). Other responses triggered by pain include catabolic hypermetabolism resulting in hyperglycemia, lipolysis, and breakdown of muscle

TABLE 3. Pharmacology of Opiate Analgesics (1, 128, 440, 472)

Opiates	Equi-Analgesic Dose (mg)		Onset (IV)	Elimination Half-Life	Context-Sensitive Half-Life	Metabolic Pathway
	IV	PO				
Fentanyl	0.1	N/A	1–2 min	2–4 hr	200 min (6 hr infusion); 300 min (12 hr infusion) ^a	N-dealkylation CYP3A4/5 substrate
Hydromorphone	1.5	7.5	5–15 min	2–3 hr	N/A	Glucuronidation
Morphine	10	30	5–10 min	3–4 hr	N/A	Glucuronidation
Methadone	N/A ^c	N/A ^c	1–3 d	15–60 hr	N/A	N-demethylation CYP3A4/5, 2D6, 2B6, 1A2 substrate
Remifentanyl	N/A	N/A	1–3 min	3–10 min	3–4 min	Hydrolysis by plasma esterases

PO = oral; N/A = not applicable; IBW = ideal body weight.

^aAfter 12 hrs, and in cases of end-organ dysfunction, the context-sensitive half-life increases unpredictably.

^bMay increase dose to extend dosing interval; hydromorphone 0.5 mg IV every 3 hrs, or morphine 4–8 mg IV every 3–4 hrs.

^cEquianalgesic dosing tables may underestimate the potency of methadone. The morphine- or hydromorphone-to-methadone conversion ratio increases (i.e., the potency of methadone increases) as the dose of morphine or hydromorphone increases. The relative analgesic potency ratio of oral to parenteral methadone is 2:1, but the confidence intervals are wide.

^dQTc is the Q-T interval (corrected) of the electrocardiographic tracing.

to provide protein substrate (77). Catabolic stimulation and hypoxemia also impair wound healing and increase the risk of wound infection. Pain suppresses natural killer cell activity (78, 79), a critical function in the immune system, with a decrease in the number of cytotoxic T cells and a reduction in neutrophil phagocytic activity (80). Acute pain may be the greatest risk factor for developing debilitating chronic, persistent, often neuropathic pain (81). Unrelieved acute pain in adult ICU patients is ubiquitous and far from benign, with both short- and long-term consequences. Adequately identifying and treating pain in these patients require focused attention.

Pain Assessment in ICU Patients. Treating pain in critically ill patients depends on a clinician's ability to perform a reproducible pain assessment and to monitor patients over time to determine the adequacy of therapeutic interventions to treat pain. A patient's self-report of pain is considered the "gold standard," and clinicians should always attempt to have a patient rate his or her own pain first. Chanques and colleagues (82) demonstrated that a 0–10 visually enlarged horizontal numeric rating scale was the most valid and feasible of five pain intensity rating scales tested in over 100 ICU patients. Yet when critically ill patients are unable to self-report their pain, clinicians must use structured, valid, reliable, and feasible tools to assess patients' pain (83). It is essential that pain in ICU patients be assessed routinely and repetitively in a manner that is efficient and reproducible. No objective pain monitor exists, but valid and reliable bedside pain assessment tools that concentrate primarily on patients' behaviors as indicators of pain do exist.

Although reviews of behavioral pain assessment tools have been published, an updated discussion is needed about their development, validation, and applicability to ICU patients (50, 84). A detailed, systematic review of the processes of item selection and psychometric properties of pain scales (i.e., validity and reliability) may encourage clinicians to adopt pain scales and to standardize their use in ICU patients. Recent studies have demonstrated that implementing behavioral pain scales improves both ICU pain management and clinical outcomes, including better use of analgesic and sedative agents and shorter durations of mechanical ventilation and ICU stay (2, 3, 85).

Treatment of Pain. Opioids, such as fentanyl, hydromorphone, methadone, morphine, and remifentanyl, are the primary medications for managing pain in critically ill patients (Table 3) (62). The optimal choice of opioid and the dosing regimen used for an individual patient depends on many factors, including the drug's pharmacokinetic and pharmacodynamic properties (52). The use of meperidine is generally avoided in ICU patients because of its potential for neurologic toxicity (52).

Several other types of analgesics or pain-modulating medications, such as local and regional anesthetics (e.g., bupivacaine), nonsteroidal anti-inflammatory medications (e.g., ketorolac, ibuprofen), IV acetaminophen, and anticonvulsants, can be used as adjunctive pain medications to reduce opioid requirements (Table 4). However, their safety profile and effectiveness as sole agents for pain management have not been adequately studied in critically ill patients. Pharmacologic treatment principles extrapolated from non-ICU studies may not be applicable

TABLE 3 (Continued).

Active Metabolites	Intermittent Dosing	IV Infusion Rates	Side Effects and Other Information
None	0.35–0.5 µg/kg IV q0.5–1 hr	0.7–10 µg/kg/hr	Less hypotension than with morphine. Accumulation with hepatic impairment.
None	0.2–0.6 mg IV q1–2 hr ^b	0.5–3 mg/hr	Therapeutic option in patients tolerant to morphine/fentanyl. Accumulation with hepatic/renal impairment.
6- and 3-glucuronide metabolite	2–4 mg IV q1–2 hr ^b	2–30 mg/hr	Accumulation with hepatic/renal impairment. Histamine release.
N-demethylated derivative	IV/PO: 10–40 mg q6–12 hr IV: 2.5–10 mg q8–12 hr	Not recommended	May be used to slow the development of tolerance where there is an escalation of opioid dosing requirements. Unpredictable pharmacokinetics; unpredictable pharmacodynamics in opiate naive patients. Monitor QTc. ^d
None	N/A	Loading dose: 1.5 µg/kg IV Maintenance dose: 0.5–15 µg/kg/hr IV	No accumulation in hepatic/renal failure. Use IBW if body weight >130% IBW.

to critically ill patients (52). IV acetaminophen has been recently approved for use in the United States and has been shown to be safe and effective when used in conjunction with opioids for postoperative pain in surgical ICU patients following major or cardiac surgery (80, 86–89). Neuropathic pain, poorly treated with opioids alone, can be treated with enterally administered gabapentin and carbamazepine in ICU patients with sufficient gastrointestinal absorption and motility (90, 91).

Methods of dosing analgesics are another treatment consideration. The choice of intermittent vs. continuous IV strategies may depend on drug pharmacokinetics, frequency and severity of pain, and/or the patient's mental status (92). Enteral administration of opioids and other pain medications should be limited to patients with adequate gastrointestinal absorptive capacity and motility. Regional or neuraxial (spinal or epidural) modalities may also be used for postoperative analgesia following selected surgical procedures (93, 94).

Complementary, nonpharmacologic interventions for pain management, such as music therapy and relaxation techniques, may be opioid-sparing and analgesia-enhancing; they are low cost, easy to provide, and safe. Although a multimodal approach to pain management in ICU patients has been recommended, few studies have been published on the effectiveness of nonpharmacologic interventions in these patients (52, 95).

Pain occurs commonly in adult ICU patients, regardless of their admitting diagnoses. Pain can preclude patients from participating in their ICU care (e.g., early mobilization, weaning from mechanical ventilation). Thus, clinicians should frequently reassess patients for pain and carefully titrate anal-

gesic interventions to prevent potential negative sequelae due to either inadequate or excessive analgesic therapy. Clinicians should perform routine and reproducible pain assessments in all critically ill patients, using either patient self-report or systematically applied behavioral measures. Pain management can be facilitated by identifying and treating pain early rather than waiting until it becomes severe (52).

Pain and Analgesia: Questions, Statements, and Recommendations.

1. Incidence of Pain

- a. **Question:** Do adult ICU patients experience *nonprocedural* pain in the ICU and, if so, what events or situations are related to pain? (descriptive)

Answer: Adult medical, surgical, and trauma ICU patients routinely experience pain, both at rest and with routine ICU care (B). Pain in adult cardiac surgery patients is common and poorly treated; women experience more pain than men after cardiac surgery (B).

Rationale: Medical, surgical, and trauma ICU patients experience significant pain, even at rest (61, 63, 73). Therefore, all adult patients in any ICU should be evaluated for pain. Pain at rest should be considered a major clinical diagnostic syndrome. In cardiac surgery patients, pain related to the surgery, coughing, respiratory care procedures, and mobilization remains prevalent and poorly treated; women experience more pain than men after cardiac surgery (73, 96–98). Therefore, activity pain in cardiac surgery patients must be assessed and treated. Pain management should be individualized according to

TABLE 4. Pharmacology of Nonopiate Analgesics (1, 91, 132, 440)

Nonopiates (Route)	Onset	Elimination Half-Life	Metabolic Pathway	Active Metabolites
Ketamine (IV)	30–40 sec	2–3 hr	N-demethylation	Norketamine
Acetaminophen (PO) Acetaminophen (PR)	30–60 min variable	2–4 hr	Glucuronidation, sulfonation	None
Acetaminophen (IV)	5–10 min	2 hr	Glucuronidation, sulfonation	None
Ketorolac ^a (IM/IV)	10 min	2.4–8.6 hr	Hydroxylation, conjugation/ renal excretion	None
Ibuprofen (IV)	N/A	2.2–2.4 hr	Oxidation	None
Ibuprofen (PO)	25 min	1.8–2.5 hr	Oxidation	None
Gabapentin (PO)	N/A	5–7 hr	Renal excretion	None
Carbamazepine immediate release (PO)	4–5 hr	25–65 hrs initially, then 12–17 hr	Oxidation	None

PO = orally; PR = rectally; max = maximum; IM = intramuscular; N/A = not applicable.

^aFor patients > 65 yr or < 50 kg, 15 mg IV/IM every 6 hrs to a maximum dose of 60 mg/day for 5 days.

the patient's experience of pain, with special attention to its occurrence in women (97).

- b. *Question:* What is the pain experienced by adult ICU patients undergoing procedures? (descriptive)

Answer: Procedural pain is common in adult ICU patients (B).

Rationale: Pain associated with nonsurgical procedures such as chest tube removal or wound care is prevalent in adult ICU patients (68, 99). Generally at a moderate level (68), pain is influenced by preprocedural pain levels and the administration of analgesics (100). Less than 25% of patients receive analgesics before the procedures (68). Procedural pain varies with age (64, 66) and is greater in non-Caucasians than in Caucasians (64, 66, 68). Differences in procedural pain between nonsurgical and surgical patients vary according to procedure (64, 66). Hemodynamic changes are not valid correlates of procedural pain (99). Available information suggests that preemptive analgesia has benefits, but the risks of procedural pain and the lack of preemptive treatment are unclear.

2. Pain Assessment

- a. *Question:* Should pain assessments be routinely performed in adult ICU patients? (actionable)

Answer: We recommend that pain be routinely monitored in all adult ICU patients (+1B).

Rationale: Routine pain assessments in adult ICU patients are associated with improved clinical outcomes. Pain assessment, especially if protocolized, has been significantly associated with a reduction in the use of analgesic medications, ICU length of stay (LOS), and duration of mechanical ventilation (3, 62). Pain assessment is essential for appropriate treatment, especially when part of a comprehensive pain management protocol. Although the quality of evidence is moderate, a strong recommendation for performing routine pain assessments in all ICU patients is appropriate, as the benefits strongly outweigh the risks.

- b. *Question:* What are the most valid and reliable behavioral measures of pain in critically ill adult patients who are unable to self-report? (descriptive)

Answer: The Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOP) are the most valid and reliable behavioral pain scales for monitoring pain in medical, postoperative, or trauma (except for brain injury) adult ICU patients who are unable to self-report, and in whom motor function is intact and behaviors are observable. Using these scales in other ICU patient populations and translating them into foreign languages other than French or English require further validation testing (B).

TABLE 4 (Continued).

Dosing	Side Effects and Other Information
Loading dose 0.1–0.5 mg/kg IV followed by 0.05–0.4 mg/kg/hr 325–1000 mg every 4–6 hr; max dose ≤ 4 g/day	Attenuates the development of acute tolerance to opioids. May cause hallucinations and other psychological disturbances. May be contraindicated in patients with significant hepatic dysfunction.
650 mg IV every 4 hrs – 1000 mg IV every 6 hr; max dose ≤ 4 g/day 30 mg IM/IV, then 15–30 mg IM/IV every 6 hr up to 5 days; max dose = 120 mg/day × 5 days	Avoid nonsteroidal anti-inflammatory drugs in following conditions: renal dysfunction; gastrointestinal bleeding; platelet abnormality; concomitant angiotensin converting enzyme inhibitor therapy, congestive heart failure, cirrhosis, asthma. Contraindicated for the treatment of perioperative pain in coronary artery bypass graft surgery.
400–800 mg IV every 6 hr infused over > 30 mins; max dose = 3.2 g/day 400 mg PO every 4 hrs; max dose = 2.4 g/day	Avoid nonsteroidal anti-inflammatory drugs in following conditions: renal dysfunction; gastrointestinal bleeding; platelet abnormality; concomitant angiotensin converting enzyme inhibitor therapy, congestive heart failure, cirrhosis, asthma. Contraindicated for the treatment of perioperative pain in coronary artery bypass graft surgery.
Starting dose = 100 mg PO three times daily; maintenance dose = 900–3600 mg/day in 3 divided doses	Side effects: (common) sedation, confusion, dizziness, ataxia. Adjust dosing in renal failure pts. Abrupt discontinuation associated with drug withdrawal syndrome, seizures.
Starting dose = 50–100 mg PO bid; maintenance dose = 100–200 mg every 4–6 hr; max dose = 1200 mg/day	Side effects: (common) nystagmus, dizziness, diplopia, lightheadedness, lethargy; (rare) aplastic anemia, and agranulocytosis; Stevens–Johnson syndrome or toxic epidermal necrolysis with HLA-B1502 gene. Multiple drug interactions due to hepatic enzyme induction.

Rationale: A total of six behavioral pain scales were analyzed: BPS; BPS—Non-Intubated (BPS-NI); CPOT; Non-Verbal Pain Scale (NVPS), both initial and revised (NVPS-I, NVPS-R); Pain Behavioral Assessment Tool (PBAT); and the Pain Assessment, Intervention, and Notation (PAIN) Algorithm. **Table 5** summarizes their psychometric scores. Observational studies, although somewhat limited, provide consistent evidence that the BPS (3–12 total score) and CPOT (0–8 total score) scales have good psychometric properties in terms of: inter-rater reliability (101–109), discriminant validity (101, 102, 104, 107, 109, 110), and criterion validity (103–105, 109, 110), in medical, postoperative, and trauma ICU patients. A CPOT score of greater than 2 had a sensitivity of 86% and a specificity of 78% for predicting significant pain in postoperative ICU adults exposed to a nociceptive procedure (111, 112). Investigators suggested a similar cutoff score for the BPS (> 5), on the basis of descriptive statistics in nonverbal ICU adults during nociceptive procedures compared with patients at rest (62). The CPOT and BPS can be successfully implemented in the ICU following short, standardized training sessions (2, 85). Their regular use can lead to better pain management and improved clinical outcomes in ICU patients (2, 3, 85). The BPS-NI is derived from the BPS

and adapted for nonintubated ICU patients (113), but it has been tested in a group of only 30 patients so far, and replication studies are needed to support its psychometric properties. More studies are also necessary to examine the psychometric properties of the NVPS (114), NVPS-R (115), PBAT (116), and PAIN (117).

- c. **Question:** Should vital signs be used to assess pain in adult ICU patients? (actionable)

Answer: We do not suggest that vital signs (or observational pain scales that include vital signs) be used alone for pain assessment in adult ICU patients (–2C). We suggest that vital signs may be used as a cue to begin further assessment of pain in these patients, however (+2C).

Rationale: Observational studies with major limitations provide inconsistent evidence of the validity of vital signs for the purpose of pain assessment in medical, postoperative, and trauma ICU patients. Even if there is a trend for vital signs to increase when critically ill patients are exposed to painful procedures, these increases are not reliable predictors of pain (66, 101, 105, 107, 110). Vital signs have been reported to increase both during nociceptive and nonnociceptive procedures (109) or to remain stable during nociceptive exposure (99). Vital signs do not correlate with either patients' self-report of pain (105, 110)

or behavioral pain scores (101, 107). But because vital signs may change with pain, distress, or other factors, they can be a *cue* to perform further pain assessments in these patients (118).

3. Treatment of Pain

- a. *Question:* Should procedure-related pain be treated preemptively in adult ICU patients? (actionable)

Answer: We recommend that preemptive analgesia and/or nonpharmacologic interventions (e.g., relaxation) be administered to alleviate pain in adult ICU patients prior to chest tube removal (+1C). We suggest that for other types of invasive and potentially painful procedures in adult ICU patients, preemptive analgesic therapy and/or nonpharmacologic interventions may also be administered to alleviate pain (+2C).

Rationale: Our strong recommendation is that patients undergoing chest tube removal should be preemptively treated for pain, both pharmacologically and nonpharmacologically. Significantly lower pain scores were reported by patients if they received IV morphine plus relaxation (119), topical valdecoxib (120), IV sufentanil, or fentanyl (121) prior to chest tube removal. According to these studies, the desirable consequences outweigh undesirable effects. One can reasonably assume that most ICU patients would want their pain preemptively treated with nonpharmacologic and/or pharmacologic interventions prior to other painful procedures as well.

- b. *Question:* What types of medications should be administered for pain relief in adult ICU patients? (actionable)

Answer: We recommend that IV opioids be considered as the first-line drug class of choice to treat non-neuropathic pain in critically ill patients (+1C). All available IV opioids, when titrated to similar pain intensity endpoints, are equally effective (C). We recommend that either enterally administered gabapentin or carbamazepine, in addition to IV opioids, be considered for the treatment of neuropathic pain (+1A). We suggest that nonopioid analgesics be considered to decrease the amount of opioids administered (or to eliminate the need for IV opioids altogether) and to decrease opioid-related side effects (+2C).

Rationale: For non-neuropathic pain, evidence supports using an opiate-based regimen to decrease pain intensity (87, 90, 91, 122–136). Apart from drug cost and resource utilization, all opioids administered IV appear to exhibit similar analgesic efficacy and are associated with similar clinical outcomes (e.g., duration of mechanical ventilation, LOS) when titrated to similar pain intensity endpoints. For non-neuropathic pain, nonopioids such as IV acetaminophen (87), oral, IV, or rectal cyclooxygenase inhibitors (122, 123, 135), or IV ketamine (132, 137) can be used in addition to opioids. Using nonopioids may also decrease the overall quantity of opioids administered and the incidence and severity of opioid-related side effects. In patients with neuropathic pain, IV opioid use plus oral gabapentin or carbamazepine provides superior pain relief in mechanically ventilated patients

compared to IV opioid use alone (90, 91). A lack of direct comparisons between opioids and nonopioids hinders conclusions regarding the effect of nonopioid analgesics, particularly in ICU patients.

- c. *Question:* What mode of analgesic delivery (i.e., either neuraxial or parenteral) is recommended for pain relief in critically ill adults who have undergone either thoracic or abdominal surgery or who have traumatic rib fractures (including both mechanically ventilated and non-mechanically ventilated ICU patients)? (actionable)

Answer: We recommend that thoracic epidural anesthesia/analgesia be considered for postoperative analgesia in patients undergoing abdominal aortic surgery (+1B). We provide no recommendation for using a lumbar epidural over parenteral opioids for postoperative analgesia in patients undergoing abdominal aortic aneurysm surgery, due to a lack of benefit when these routes of administration are compared in this patient population (0,A). We provide no recommendation for the use of thoracic epidural analgesia in patients undergoing either intrathoracic or nonvascular abdominal surgical procedures, because of insufficient and conflicting evidence for this mode of analgesic delivery in these patients (0,B). We suggest that thoracic epidural analgesia be considered for patients with traumatic rib fractures (+2B). We provide no recommendation for neuraxial/regional analgesia over systemic analgesia in medical ICU patients, due to lack of evidence in this patient population (0, No Evidence).

Rationale: High-quality evidence suggests that thoracic epidural anesthesia/analgesia in patients undergoing abdominal aortic surgery when the epidural catheter is placed preoperatively provides superior pain relief to parenteral opioids alone; rare complications of thoracic epidurals in these patients include postoperative heart failure, infections, and respiratory failure (138, 139). High-quality evidence demonstrates no benefit with lumbar epidural compared with parenteral opioids in these patients (139–141). Several shortcomings in research design make it difficult to recommend the use of thoracic epidural analgesia in patients undergoing either intrathoracic or nonvascular abdominal surgical procedures (142–149). Epidural analgesia administered to patients with rib fractures improved pain control, especially during coughing or deep breathing, lowered the incidence of pneumonia, but increased the risk of hypotension (150, 151). No evidence supports using neuraxial/regional analgesia in medical ICU patients.

Agitation and Sedation

Indications for Sedation. Agitation and anxiety occur frequently in critically ill patients and are associated with adverse clinical outcomes (152–156). Sedatives are commonly administered to ICU patients to treat agitation and its negative consequences (157). Prompt identification and treatment of possible underlying causes of agitation, such as pain, delirium, hypoxemia, hypoglycemia, hypotension, or withdrawal from alcohol and other drugs, are important. Efforts to reduce anxiety and

TABLE 5. Psychometric Scores for Pain Scales

Psychometric Criteria Scored	Scales					
	Critical Care Pain Observation Tool	BPS	BPS-Nonintubated	Nonverbal Pain Scale ^a	Pain Behavioral Assessment Tool	Pain Assessment and Intervention Notation
Item selection description	2	2	2	1	2	1
Content validation	2	0	0	1	1	1
Limitations presented	1	0	0	1	1	1
Internal consistency	2	1	2	I = 1/Rev = 2	0	0
Inter-rater reliability	2	2	2	2	0	0
Inter-rater reliability tested with nonresearch team	1	1	1	1	1	1
Intra-rater reliability tested if inter-rater reliability is low or inconsistent	0	0	N/A	I = N/A /Rev = 0	0	0
Total number of participants	2	2	1	2	2	1
Criterion validation: correlation with "gold standard"	1	2	0	0	1	0
Criterion validation: sensitivity	1	0	0	0	0	0
Criterion validation: specificity	2	0	0	0	0	0
Discriminant validation	2	2	2	2	2	0
Feasibility	1	1	0	0	0	0
Directives of use	1	0	1	0	1	1
Relevance of scale in practice	0	1	0	0	0	1
Total score (range: 0–25)	20	14	11	I = 11/Rev = 12	11	7
Weighted score ^b (range: 0–20)	14.70	12.00	10.20	I = 9.2/Rev = 8.7	7.50	5.90
Quality of psychometric evidence (based on weighted score)	M	M	L	VL	L	VL

BPS = Behavioral Pain Scale; I = initial; Rev = revised; N/A = not applicable; M = moderate; L = low; VL = very low.

^aNonverbal pain scale has two versions: I and Rev.

^bWeighted score range (0–20): Very good psychometric properties (Very good): 15–20; Good psychometric properties (M): 12–14.9; Some acceptable psychometric properties, but remain to be replicated in other studies (L): 10–11.9; Very few psychometric properties reported, or unacceptable results (VL): < 10.

agitation, including maintenance of patient comfort, provision of adequate analgesia, frequent reorientation, and optimization of the environment to maintain normal sleep patterns, should be attempted before administering sedatives.

Sedatives can be titrated to maintain either light (i.e., patient is arousable and able to purposefully follow simple commands) or deep sedation (i.e., patient is unresponsive to painful stimuli). Multiple studies have demonstrated the negative consequences of prolonged, deep sedation, and the benefits of maintaining lighter sedation levels in adult ICU patients (10, 14, 15, 20, 158). The use of sedation scales, sedation protocols designed to minimize sedative use, and the use of nonbenzodiazepine medications are associated with improved ICU patient outcomes, including a shortened duration of mechanical ven-

tilation, ICU and hospital LOS, and decreased incidences of delirium and long-term cognitive dysfunction (7–10, 12, 13, 18, 19, 159–162).

Clinical Pharmacology of Sedatives. Historically, benzodiazepines (i.e., midazolam and lorazepam) and propofol have commonly been used to sedate ICU patients. The 2002 guidelines recommended midazolam only for short-term sedation, lorazepam for long-term sedation, and propofol for patients requiring intermittent awakenings (1). Recent surveys assessing sedation practices demonstrate that midazolam and propofol remain the dominant medications used for ICU sedation, with decreasing lorazepam use, and rare use of barbiturates, diazepam, and ketamine in the ICU (62, 163–166). Dexmedetomidine, approved

TABLE 6. Clinical Pharmacology of Sedative Medications (1)

Agent	Onset After IV Loading Dose	Elimination Half-Life	Active Metabolites	Loading Dose (IV)	Maintenance Dosing (IV)	Adverse Effects
Midazolam	2–5 min	3–11 hr	Yes ^a	0.01–0.05 mg/kg over several minutes	0.02–0.1 mg/kg/hr	Respiratory depression, hypotension
Lorazepam	15–20 min	8–15 hr	None	0.02–0.04 mg/kg (≤ 2 mg)	0.02–0.06 mg/kg q2–6 hr prn or 0.01–0.1 mg/kg/hr (≤10 mg/hr)	Respiratory depression, hypotension; propylene glycol-related acidosis, nephrotoxicity
Diazepam	2–5 min	20–120 hr	Yes ^a	5–10 mg	0.03–0.1 mg/kg q0.5–6 hr prn	Respiratory depression, hypotension, phlebitis ^e
Propofol	1–2 min	Short-term use = 3–12 hr Long-term use = 50 ± 18.6 hr	None	5 µg/kg/min over 5 min ^b	5–50 µg/kg/min	Pain on injection ^f , hypotension, respiratory depression, hypertriglyceridemia, pancreatitis, allergic reactions, propofol-related infusion syndrome; deep sedation with propofol is associated with significantly longer emergence times than with light sedation
Dexmedetomidine	5–10 min	1.8–3.1 hr	None	1 µg/kg over 10 min ^c	0.2–0.7 µg/kg/hr ^d	Bradycardia, hypotension; hypertension with loading dose; loss of airway reflexes

^aActive metabolites prolong sedation, especially in patients with renal failure.

^bAdminister IV loading dose of propofol only in those patients in whom hypotension is unlikely to occur.

^cAvoid IV loading doses of dexmedetomidine in hemodynamically unstable patients.

^dDexmedetomidine maintenance infusion rate may be increased to 1.5 µg/kg/h as tolerated.

^ePhlebitis occurs when diazepam is injected into peripheral veins.

^fPain at the injection site occurs commonly when propofol is administered through peripheral veins.

in the United States shortly before completion of the 2002 guidelines, is now more commonly administered for ICU sedation (166–168). The clinical pharmacology of sedatives prescribed for ICU patients is summarized in **Table 6**.

Benzodiazepines. Benzodiazepines activate γ -aminobutyric acid A (GABA_A) neuronal receptors in the brain. They have anxiolytic, amnestic, sedating, hypnotic, and anticonvulsant effects, but no analgesic activity (169, 170). Their amnestic effects extend beyond their sedative effects (171). Lorazepam is more potent than midazolam, which is more potent than diazepam. Midazolam and diazepam are more lipid soluble than lorazepam, resulting in a quicker onset of sedation and a larger volume of distribution than for lorazepam. Elderly patients are significantly more sensitive to the sedative effects of benzodiazepines (171). Benzodiazepines can cause respiratory depression and systemic hypotension, especially when administered in conjunction with other cardiopulmonary depressants, particularly opioids (172). Benzodiazepine-induced cardiopulmonary instability is more likely to occur in critically ill patients with baseline respiratory insufficiency and/or cardio-

vascular instability (172). Tolerance to benzodiazepines develops with long-term administration.

All benzodiazepines are metabolized by the liver. Benzodiazepine clearance is reduced in patients with hepatic dysfunction and other disease states, in elderly patients, and when administered with other medications that inhibit cytochrome P₄₅₀ enzyme systems and/or glucuronide conjugation in the liver (173–175). The elimination half-life and duration of clinical effect of lorazepam are also increased in patients with renal failure (176, 177). The active metabolites of midazolam and diazepam may accumulate with prolonged administration, especially in patients with renal dysfunction (178). Benzodiazepine clearance decreases with age (175, 179, 180).

Delayed emergence from sedation with benzodiazepines can result from prolonged administration of benzodiazepines (due to saturation of peripheral tissues), advanced age, hepatic dysfunction, or renal insufficiency (171, 175, 181). Because of the greater potency and slower clearance of lorazepam, emergence from short-term sedation (1–2 days) with lorazepam may be

longer than with midazolam. However, comparative studies on the prolonged use of these drugs in ICU patients suggest greater variability and longer time to awakening with midazolam than with lorazepam (171, 175, 182–184). Diazepam has a prolonged duration of action due to saturation of peripheral tissues and active metabolites that can accumulate in patients with renal insufficiency (185).

Parenteral formulations of lorazepam contain propylene glycol as a diluent, which can cause toxicity in ICU patients (186–190). Propylene glycol toxicity manifests as metabolic acidosis and acute kidney injury. Because these conditions occur frequently in critically ill patients, their possible association with lorazepam administration may be overlooked. Although initially thought to accumulate only in patients receiving very high lorazepam doses via continuous infusion (i.e., 15–25 mg/hr), current evidence suggests that total daily IV doses as low as 1 mg/kg can cause propylene glycol toxicity (191). The serum osmol gap has been used as a reliable screening and surveillance tool; an osmol gap greater than 10–12 mOsm/L may help identify patients receiving lorazepam who have significant propylene glycol accumulation (187, 191).

Propofol. Propofol is an IV sedative that binds to multiple receptors in the central nervous system to interrupt neural transmission, including GABA_A, glycine, nicotinic, and M₁ muscarinic receptors (192–194). Propofol has sedative, hypnotic, anxiolytic, amnestic, antiemetic, and anticonvulsant properties, but no analgesic effects (195, 196). In ICU patients, propofol's amnestic effects at light sedation levels are less than that of benzodiazepines (197). Propofol is highly lipid soluble and quickly crosses the blood-brain barrier, resulting in the rapid onset of sedation. Because of its high lipid solubility, propofol also rapidly redistributes into peripheral tissues. This rapid redistribution, combined with high hepatic and extrahepatic clearance, results in a rapid offset of effect following short-term propofol administration. Because of its short duration of sedative effect, propofol may be useful in patients requiring frequent awakenings for neurologic assessments and it may facilitate daily sedation interruption protocols (183, 198, 199). However, long-term propofol administration can lead to the saturation of peripheral tissues and prolonged emergence (198).

Propofol causes dose-dependent respiratory depression and hypotension due to systemic vasodilation. These effects may be more pronounced when propofol is administered with other sedative and opioid medications. Cardiopulmonary instability with propofol administration is more likely to occur in patients with baseline respiratory insufficiency and/or cardiovascular instability. Other side effects include hypertriglyceridemia, acute pancreatitis, and myoclonus (200–204). Propofol is dissolved in a 10% lipid emulsion containing egg lecithin and soybean oil, which can precipitate allergic reactions in patients with either egg or soybean allergies. Some generic formulations of propofol contain sulfite preservatives, which may also cause allergic reactions (196).

Propofol administration is rarely associated with developing propofol infusion syndrome (PRIS). The signs and symptoms of PRIS vary but may include worsening metabolic acidosis, hypertriglyceridemia, hypotension with increasing vasopressor

requirements, and arrhythmias. Acute kidney injury, hyperkalemia, rhabdomyolysis, and liver dysfunction have also occasionally been reported with PRIS (205, 206). Possible PRIS mechanisms include mitochondrial dysfunction, impaired fatty acid oxidation, diversion of carbohydrate metabolism to fat substrates, and propofol metabolite accumulation (207). PRIS is usually associated with prolonged administration of high propofol doses (> 70 µg/kg/min), but it may also occur with low-dose infusions (208, 209). The incidence of PRIS with propofol infusions is approximately 1% (210). Mortality from PRIS is high (up to 33%) and may occur even after discontinuing the infusion (202). The variable presentation, lack of diagnostic specificity, and infrequent occurrence of PRIS make detection of this potentially life-threatening condition difficult. Early recognition and discontinuation of propofol in patients with suspected PRIS are critically important. Management of patients with PRIS is otherwise supportive.

Dexmedetomidine. Dexmedetomidine is a selective α_2 -receptor agonist with sedative, analgesic/opioid sparing, and sympatholytic properties, but with no anticonvulsant properties (211, 212). Dexmedetomidine produces a pattern of sedation that differs considerably from other sedative agents. Patients sedated with dexmedetomidine are more easily arousable and interactive, with minimal respiratory depression (213, 214). The onset of sedation occurs within 15 mins and peak sedation occurs within 1 hr of starting an IV infusion of dexmedetomidine (167, 215). Sedation onset may be hastened by administering an initial IV loading dose of dexmedetomidine, but this is more likely to cause hemodynamic instability in critically ill patients (216). Dexmedetomidine is rapidly redistributed into peripheral tissues and is metabolized by the liver (217). In patients with normal liver function, the elimination half-life is approximately 3 hrs (215). Patients with severe hepatic dysfunction have impaired dexmedetomidine clearance, can experience prolonged emergence, and may require lower dexmedetomidine doses (218). Although dexmedetomidine has only been approved in the United States for short-term sedation of ICU patients (< 24 hrs) at a maximal dose of 0.7 µg/kg/hr (up to 1.0 µg/kg/h for procedural sedation), several studies demonstrate the safety and efficacy of dexmedetomidine infusions administered for greater than 24 hrs (up to 28 days) and at higher doses (up to 1.5 µg/kg/hr) (216, 219–222).

The most common side effects of dexmedetomidine are hypotension and bradycardia (223). IV loading doses can cause either hypotension or hypertension (215, 224). Because dexmedetomidine does not significantly affect respiratory drive, it is the only sedative approved in the United States for administration in nonintubated ICU patients, and infusions can be continued as needed following extubation (225–227). However, dexmedetomidine can cause a loss of oropharyngeal muscle tone which can lead to airway obstruction in nonintubated patients, so continuous respiratory monitoring for both hypoventilation and hypoxemia in these patients is indicated (225). Dexmedetomidine's opioid-sparing effect may reduce opioid requirements in critically ill patients (219, 220, 224, 228). The mechanism of action for the analgesic properties

TABLE 7. Psychometric Scores for Sedation Scales

Psychometric Criteria Scored	Sedation Scale			
	Observer's Assessment of Alertness/Sedation Scale	Ramsay Sedation Scale	New Sheffield Sedation Scale	Sedation Intensive Care Score
Item selection description	0	0	2	1
Content validation	0	0	0	0
Limitations presented	0	0	1	0
Interrater reliability	0	1	2	2
Interrater reliability tested with nonresearch team	0	1	1	1
Interrater reliability tested if interrater reliability is low or inconsistent	NA	0	NA	NA
Total number of participants	1	2	0	1
Criterion validation	1	2	0	0
Discriminant validation	0	0	0	2
Feasibility	0	0	0	0
Directives of use	1	0	1	0
Relevance of scale in practice	0	0	0	0
Total score (range: 0–18)	3	6	7	7
Weighted score ^a (range: 0–20)	3.7	7.7	8.5	10.5
Quality of psychometric evidence (based on weighted scores)	VL	VL	VL	L

NA = not applicable; VL = very low; L = low; M = moderate; VG = very good.

^aWeighted score range (0–20): Very good psychometric properties (VG): 15–20; Good psychometric properties (M): 12–14.9; Some acceptable psychometric properties, but remain to be replicated in other studies (L): 10–11.9; Very few psychometric properties reported, or unacceptable results (VL): < 10.

of dexmedetomidine remains controversial (229). Although α -2 receptors are located in the dorsal region of the spinal cord and in supraspinal sites, dexmedetomidine's nonspinal analgesic effects have been documented (230). One recent study suggests that ICU patients receiving dexmedetomidine may have a lower prevalence of delirium than patients sedated with midazolam (220).

Agitation and Sedation: Questions, Statements, and Recommendations.

1. Depth of Sedation and Clinical Outcomes

Question: Should adult ICU patients be maintained at a light level of sedation? (actionable)

Answer: Maintaining light levels of sedation in adult ICU patients is associated with improved clinical outcomes (e.g., shorter duration of mechanical ventilation and a shorter ICU LOS) (B). Maintaining light levels of sedation increases the physiologic stress response, but is not associated with an increased incidence of myocardial ischemia (B). The association between depth of sedation and psychological stress in these patients remains unclear (C). We recommend that sedative medications be titrated to maintain a light rather than deep level of sedation in adult ICU patients, unless clinically contraindicated (+1B).

Rationale: Thirteen studies examined the direct relationship between sedative depth and clinical outcomes in ICU patients,

including duration of mechanical ventilation, ICU LOS, measures of physiologic stress, and assessments of post-ICU psychological stress (10, 14, 15, 20, 158, 231–238). Five studies demonstrated that deeper sedation levels are associated with longer durations of mechanical ventilation and ICU LOS (10, 14, 15, 20, 158). Three studies demonstrated evidence of increased physiologic stress in terms of elevated catecholamine concentrations and/or increased oxygen consumption at lighter sedation levels (232, 235, 236), whereas one study did not (233). The clinical significance of this is unclear, because no clear relationship was observed between elevated markers of physiologic stress and clinical outcomes, such as myocardial ischemia, in these patients (232–234).

Four studies examined the relationship between depth of sedation and post-ICU psychological stress (20, 231, 237, 238). One showed that a protocol of daily sedation interruption did not cause adverse psychological outcomes (231), whereas another found a low incidence of such events in patients who were lightly sedated (20). A third study showed that deeper sedation levels were associated with a lower incidence of recall, but that delusional memories did not correlate with lighter levels of sedation (238). However, in the fourth study, periods of wakefulness were associated with recall of stressful ICU memories

TABLE 7 (Continued).

Sedation Scale					
Motor Activity Assessment Scale	Adaptation to the Intensive Care Environment	Minnesota Sedation Assessment Tool	Vancouver Interaction and Calmness Scale	Sedation-Agitation Scale	Richmond Agitation-Sedation Scale
0	2	2	2	1	2
0	1	1	1	1	0
0	1	1	1	1	0
2	2	2	2	2	2
1	1	1	1	1	1
NA	NA	NA	NA	NA	NA
2	2	2	2	2	2
1	0	0	0	2	2
0	0.5	1	2	2	2
0	0	0	0	0	1
1	1	1	1	1	1
0	0	0	0	0	1
7	10.5	11	12	13	14
11	12.3	13	14.3	16.5	19
L	M	M	M	VG	VG

(237). The overall quality of evidence evaluating the relationship between depth of ICU sedation and post-ICU psychological stress is low, and these study results are conflicting. Thus, the overall benefits of maintaining a light sedation level in ICU patients appear to outweigh the risks.

2. Monitoring Depth of Sedation and Brain Function

a. Sedation scales

Question: Which subjective sedation scales are the most valid and reliable in the assessment of depth and quality of sedation in mechanically ventilated adult ICU patients? (descriptive)

Answer: The Richmond Agitation-Sedation Scale (RASS) and Sedation-Agitation Scale (SAS) are the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients (B).

Rationale: Several subjective sedation scales exist for monitoring depth of sedation and agitation in adult ICU patients, and their psychometric properties are well described. But the cumulative degree of psychometric properties tested and the quality of evidence vary widely among scales. We reviewed the psychometric properties of ten subjective sedation scales, each developed for

evaluating the depth and quality of sedation in adult ICU patients: 1) Observer's Assessment of Alertness/Sedation Scale (OAA/S); 2) Ramsay Sedation Scale (Ramsay); 3) New Sheffield Sedation Scale (Sheffield); 4) Sedation Intensive Care Score (SEDIC); 5) Motor Activity Assessment Scale (MAAS); 6) Adaptation to the Intensive Care Environment (ATICE); 7) Minnesota Sedation Assessment Tool (MSAT); 8) Vancouver Interaction and Calmness Scale (VICS); 9) SAS; and 10) RASS. We reviewed 27 studies including 2,805 patients (2, 239–264): 26 were observational studies and one used a blinded and randomized format to evaluate videos of previously scored patient sedation levels (253). **Table 7** summarizes the psychometric scores for all ten sedation scales.

The RASS and SAS yielded the highest psychometric scores (i.e., inter-rater reliability, convergent or discriminant validation) and had a robust number of study participants. Both scales demonstrated a high degree of inter-rater reliability, which included ICU clinicians (240, 262, 263). Both scales were able to discriminate different sedation levels in various clinical situations (246, 250, 258, 261). Moderate to high correlations were found between the sedation scores of these scales and

either electroencephalogram (EEG) or bispectral index (BIS) values (244, 246, 258). In addition, the RASS consistently provided a consensus target for goal-directed delivery of sedative agents, demonstrating feasibility of its usage (2, 246, 254).

We found that the ATICE, MSAT, and VICS had good quality of psychometric evidence, but some psychometric properties (e.g., convergent or discriminant validation) have not been tested (242, 243, 249, 259, 260). The MAAS, SEDIC, Sheffield, Ramsay, and OAA/S scales had a lower quality of evidence; replication studies and psychometric testing of reliability and validity for determining the depth and quality of sedation in ICU patients are needed (239, 241, 242, 245, 247–249, 251–253, 255, 261, 262, 264).

In summary, our comparative assessment of the psychometric properties of sedation scales revealed RASS and SAS to be the most valid and reliable for use in critically ill patients, whereas ATICE, MSAT, and VICS are moderately valid and reliable. Additional testing of the remaining scales is needed to better assess their reliability and validity in determining depth of sedation in critically ill patients.

b. Neurologic monitoring

i. *Question:* Should objective measures of brain function (e.g., auditory evoked potentials [AEPs], bispectral index [BIS], Narcotrend Index [NI], Patient State Index [PSI], or state entropy [SE]) be used to assess depth of sedation in *noncomatose*, adult ICU patients who are not receiving neuromuscular blocking agents? (actionable)

Answer: We do not recommend that objective measures of brain function (e.g., AEPs, BIS, NI, PSI, or SE) be used as the primary method to monitor depth of sedation in noncomatose, nonparalyzed critically ill adult patients, as these monitors are inadequate substitutes for subjective sedation scoring systems (–1B).

ii. *Question:* Should objective measures of brain function (e.g., AEPs, BIS, NI, PSI, or SE) be used to measure depth of sedation in adult ICU patients who are receiving neuromuscular blocking agents? (actionable)

Answer: We suggest that objective measures of brain function (e.g., AEPs, BIS, NI, PSI, or SE) be used as an adjunct to subjective sedation assessments in adult ICU patients who are receiving neuromuscular blocking agents, as subjective sedation assessments may be unobtainable in these patients (+2B).

iii. *Question:* Should EEG monitoring be used to detect nonconvulsive seizure activity and to titrate electro-suppressive medication to obtain burst suppression in adult ICU patients with either known or suspected seizures? (actionable)

Answer: We recommend that EEG monitoring be used to monitor nonconvulsive seizure activity in adult ICU patients with either known or suspected

seizures, or to titrate electrosuppressive medication to achieve burst suppression in adult ICU patients with elevated intracranial pressure (+1A).

Rationale: We reviewed 18 studies comparing objective monitors of sedation to sedation scoring systems in adult ICU patients (244, 248, 258, 265–279). Objective monitors included both raw and processed EEG and AEP monitors. Processed EEG monitors (i.e., conversion of a raw EEG signal to an index by an algorithm) included the Bispectral Index (BIS) and Bispectral Index XP (BIS-XP SE), NI, and the PSI. The overall evidence is conflicting. Fifteen studies of moderate quality found that objective sedation monitors based on either AEP or processed EEG signals, including BIS, NI, SE, and PSI, may be useful *adjuncts* to subjective sedation assessments in critically ill patients (244, 248, 258, 266, 267, 271–273, 276, 278–283). However, most of these studies reported that electromyographic signals negatively affected the correlation between the objective measure in question and sedation scores. Five additional studies of moderate quality found no benefit in using objective monitors over subjective scoring systems to assess depth of sedation (268–270, 277, 284). In most studies, objective monitors distinguished only between deep and light levels of sedation, but their values correlated poorly with specific sedation scores and were negatively influenced by electromyographic signal artifact. Several studies demonstrated that continuous EEG monitoring is useful for detecting nonconvulsive seizure activity in ICU patients either with known seizure activity or who are at risk for seizures (e.g., traumatic brain injury, intracerebral hemorrhage, cerebral vascular accidents, patients with an unexplained depressed level of consciousness) (275, 281). Continuous EEG monitoring may also be useful in titrating electrosuppressive medications to achieve burst suppression in critically ill patients with increased intracranial pressure (275, 281).

3. Choice of Sedative

Question: Should nonbenzodiazepine-based sedation, instead of sedation with benzodiazepines, be used in mechanically ventilated adult ICU patients? (actionable)

Answer: We suggest that sedation strategies using nonbenzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients (+2B).

Rationale: In general, the choice of sedative agent used in ICU patients should be driven by: 1) specific indications and sedation goals for each patient; 2) the clinical pharmacology of the drug in a particular patient, including its onset and offset of effect and its side effect profile; and 3) the overall costs associated

with using a particular sedative. Outcomes studies of the effects of sedative agents in ICU patients typically compare a benzodiazepine (either midazolam or lorazepam) to a nonbenzodiazepine (either propofol or dexmedetomidine) for sedation. At the time of our literature review, only two low-quality studies had been published comparing clinical outcomes in ICU patients receiving propofol vs. dexmedetomidine for sedation (285, 286). No studies have compared clinical outcomes in ICU patients sedated with either ketamine or other sedative agents. Several studies we reviewed suggested that the sustained use of benzodiazepine-based sedative regimens is associated with adverse clinical outcomes, such as prolonged dependence on mechanical ventilation, increased ICU LOS, and the development of delirium (29, 183, 220, 286–293). These findings had not been consistently reported, however (197, 222, 285, 294–297).

We reviewed 13 studies of 1,551 ICU patients comparing clinical outcomes in patients sedated with either benzodiazepines (midazolam or lorazepam) or nonbenzodiazepines (propofol or dexmedetomidine) and found no consistent differences in ICU LOS (183, 197, 220, 222, 285, 286, 292–298). However, our meta-analysis of six trials ranked as moderate to high quality suggested that sedation with benzodiazepines may increase ICU LOS by approximately 0.5 days compared with nonbenzodiazepine sedation ($p = 0.04$) (Fig. 1) (183, 197, 220, 222, 292, 295–297). Limited data suggested that mechanical ventilation is prolonged with benzodiazepine-based sedation (183, 220, 292, 298). There was no apparent difference in mortality with benzodiazepine vs. nonbenzodiazepine sedation (220, 222, 285, 295). Six trials evaluated the influence of benzodiazepine-based sedation on the cost of ICU care (194, 222, 286, 294, 299, 300); only one study found that benzodiazepine-based sedation (i.e., midazolam infusion) was associated with higher ICU costs than sedation with dexmedetomidine (300).

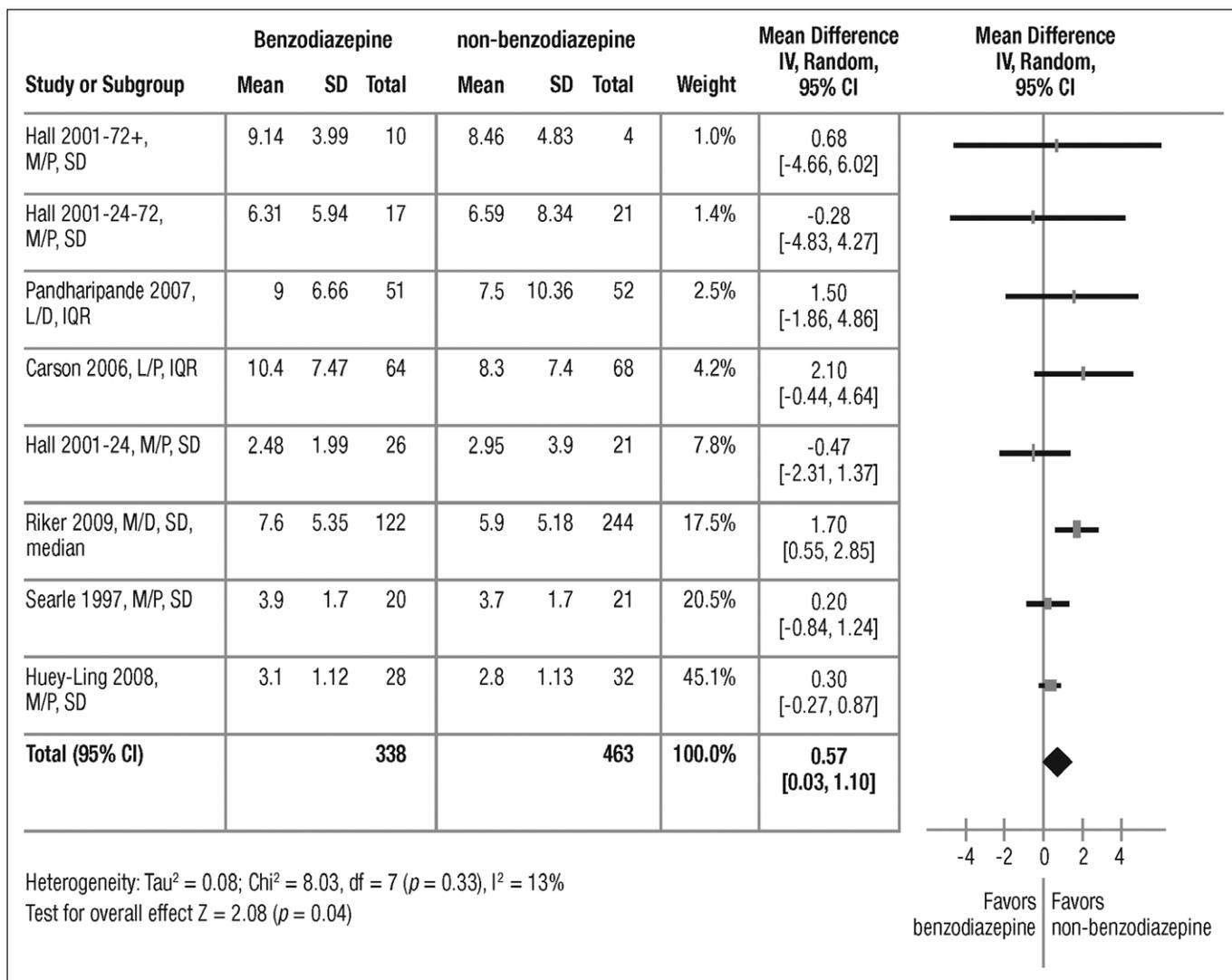


Figure 1. ICU length of stay meta-analysis of high and moderate-quality studies comparing benzodiazepine to nonbenzodiazepine sedation. CI = confidence interval; IQR = interquartile range. L/D = lorazepam vs. dexmedetomidine; L/P = lorazepam vs. propofol; M/P = midazolam vs. propofol; M/D = midazolam vs. dexmedetomidine; SD = standard deviation.

When we compared outcome studies in ICU patients sedated with propofol vs. either midazolam or lorazepam, we found several studies demonstrating that propofol use may be associated with a shorter duration of mechanical ventilation, but this effect varied across patient populations (183, 197, 291, 292, 294–297), and did not necessarily translate into a shorter ICU LOS. There was no apparent difference in the incidence of self-extubation with propofol vs. benzodiazepine sedation (183). A separate systematic review evaluated 16 randomized, controlled trials comparing clinical outcomes in ICU patients receiving either propofol or another sedative agent (291). When this meta-analysis was restricted to a comparison of propofol and midazolam, there was no difference in mortality, a slight reduction in the duration of mechanical ventilation with propofol, but no difference in ICU LOS. The relationship between using either propofol or benzodiazepines for sedation and the development of delirium is unclear. Only two relevant studies have been published comparing the incidence of delirium in ICU patients receiving propofol vs. benzodiazepines for sedation (285, 286). In both studies, patients were randomized to receive propofol, midazolam, or dexmedetomidine for sedation, and the incidence of delirium was similar in patients receiving either propofol or midazolam, but the quality of evidence was low.

We reviewed five studies comparing outcomes in ICU patients receiving either dexmedetomidine or a benzodiazepine (either midazolam or lorazepam) for sedation (220, 222, 285, 286, 293). Three of the four studies evaluating duration of mechanical ventilation showed no difference between these groups (222, 285, 286). However, the largest study did demonstrate a significant reduction in the time to liberation from mechanical ventilation with dexmedetomidine (3.7 days) compared with midazolam (5.6 days) (220). Dexmedetomidine was not associated with a lower incidence of self-extubation compared with benzodiazepines (222). Four of the five studies showed no difference in ICU LOS (220, 222, 285, 286). Five studies, including a subgroup analysis from the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction trial, evaluated the development of delirium in patients receiving either dexmedetomidine or a benzodiazepine for sedation (220, 222, 285, 286, 298). Delirium was reported in terms of frequency of occurrence, prevalence, and delirium-free days. Three studies favored dexmedetomidine (286, 288, 300), although only one was of high quality (220). The subgroup analysis trial favored dexmedetomidine over lorazepam in septic patients only (298). One trial showed no relationship between benzodiazepine use and delirium (222). One very low-quality trial suggested a higher rate of delirium with dexmedetomidine, but suffered from serious methodological flaws including imprecision in the measurement of delirium (285).

The results of two high-quality, randomized, double-blind, comparative trials of dexmedetomidine vs. either midazolam or propofol for ICU sedation were published after the guideline task force had completed its voting and developed its recommendations (301). The relevant outcomes in both studies included duration of mechanical ventilation, and ICU and hospital LOS. Except for a longer duration of mechanical ventilation with midazolam use, no differences between groups

were seen. These results are consistent with both our analysis of previously published data and subsequent recommendation for benzodiazepine-based vs. nonbenzodiazepine-based sedation.

In summary, the current literature supports modest differences in outcomes with benzodiazepine-based vs. nonbenzodiazepine-based sedation. Our meta-analysis of moderate to high-quality trials indicates that benzodiazepine sedation is associated with an increased ICU LOS. Moderate to high-quality data favor using propofol over lorazepam (183) and dexmedetomidine over midazolam (220) to limit the duration of mechanical ventilation. The clinical significance of the comparative deliriogenic effects of benzodiazepines remains uncertain, with one high-quality trial indicating benzodiazepines pose higher risks than dexmedetomidine (220). Additional recommendations to prevent or treat delirium can be found in the Delirium section of these guidelines. Dexmedetomidine may offer an advantage in ICU resource consumption compared to midazolam infusions in health care institutions that are efficient in transferring patients out of the ICU (300). Despite the apparent advantages in using either propofol or dexmedetomidine over benzodiazepines for ICU sedation, benzodiazepines remain important for managing agitation in ICU patients, especially for treating anxiety, seizures, and alcohol or benzodiazepine withdrawal. Benzodiazepines are also important when deep sedation, amnesia, or combination therapy to reduce the use of other sedative agents is required (166, 302).

Delirium

Epidemiology of Delirium in ICU Patients. Delirium is a syndrome characterized by the acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered level of consciousness (303–309). The cardinal features of delirium are: 1) a disturbed level of consciousness (i.e., a reduced clarity of awareness of the environment), with a reduced ability to focus, sustain, or shift attention; and 2) either a change in cognition (i.e., memory deficit, disorientation, language disturbance), or the development of a perceptual disturbance (i.e., hallucinations, delusions) (310). A common misconception is that delirious patients are either hallucinating or delusional, but neither of these symptoms is required to make the diagnosis. Other symptoms commonly associated with delirium include sleep disturbances, abnormal psychomotor activity, and emotional disturbances (i.e., fear, anxiety, anger, depression, apathy, euphoria). Patients with delirium may be agitated (hyperactive delirium), calm or lethargic (hypoactive delirium), or may fluctuate between the two subtypes. Hyperactive delirium is more often associated with hallucinations and delusions, while hypoactive delirium is more often characterized by confusion and sedation, and is often misdiagnosed in ICU patients.

Delirium in critically ill patients is now recognized as a major public health problem, affecting up to 80% of mechanically ventilated adult ICU patients, and costing \$4 to \$16 billion annually in the United States alone (311–314). Over the

past decade, the study of delirium in ICU patients has expanded significantly (315–319). But the underlying pathophysiology of delirium in critically ill patients remains poorly understood (320–322).

Impact of Delirium on ICU Patient Outcomes. Delirium, as a manifestation of acute brain dysfunction, is an important independent predictor of negative clinical outcomes in ICU patients, including increased mortality, hospital LOS, cost of care, and long-term cognitive impairment consistent with a dementia-like state (313, 320–324). ICU team practices affect the incidence of delirium and its consequences (220, 222, 325–329). Critical care professionals strive to understand which aspects of delirium are predictable, preventable, detectable, and treatable.

Preventing, Detecting, and Treating Delirium in ICU Patients. Delirium may be a disease-induced syndrome (e.g., organ dysfunction in severe sepsis), for which timely management of the cause or causes is essential in order to reduce the incidence, severity, and duration of delirium. Iatrogenic (e.g., exposure to sedative and opioid medications) or environmental (e.g., prolonged physical restraints or immobilization) factors may also contribute to delirium in ICU patients. ICU patients should be evaluated for identifiable and avoidable risk factors, and therapeutic interventions should be assessed in terms of their likelihood of either causing or exacerbating delirium in individual patients. Delirium prevention strategies can be categorized as nonpharmacologic (e.g., early mobilization), pharmacologic, and combined pharmacologic/nonpharmacologic approaches. Monitoring critically ill patients for delirium with valid and reliable delirium assessment tools enables clinicians to potentially detect and treat delirium sooner, and possibly improve outcomes.

Patients are frequently given various medications to reduce the severity and duration of delirium once it has occurred. Although no double-blind, randomized, placebo-controlled trials which are adequately powered have established the efficacy or safety of any antipsychotic agent in the management of delirium in ICU patients, administration of antipsychotic medications is endorsed by various international guidelines (330–339), and most critical care specialists use these medications to treat delirious patients (164). In the previous version of these guidelines, the recommended use of haloperidol for the treatment of delirium was a Level C recommendation based only on a case series. These data did not meet the evidence standard for this version of the guidelines. No recent prospective trials have verified the safety and efficacy of haloperidol for the treatment of delirium in adult ICU patients. Data on the use of other antipsychotics in this patient population are similarly sparse. A recent Cochrane Review on using antipsychotics for the treatment of delirium did not address the issue of antipsychotic use in ICU patients (340). Robust data on haloperidol in non-ICU patients that could potentially be applied to the ICU patient population are lacking. Further research is needed to determine the safety and efficacy of using antipsychotics in general, including haloperidol, to treat delirium in ICU patients.

Delirium due to Drug and/or Alcohol Withdrawal. During their ICU stay, critically ill patients may develop a subcategory of delirium related to either drug or alcohol withdrawal, which usually manifests as a hyperactive type of delirium. Withdrawal symptoms may result from abrupt discontinuation of: 1) illicit or prescription drugs that patients were taking chronically; 2) sedatives or opioids administered as part of routine ICU care; or 3) chronic ethanol use. An exhaustive review of the pathophysiology, diagnosis, and treatment of drug and alcohol withdrawal is beyond the scope of these guidelines. Clinicians are referred to other clinical practice guidelines for more detail (341–343).

Patients with long-term exposure to high-dose opiates or sedatives may develop physiologic dependence, and abrupt discontinuation may cause drug withdrawal symptoms (344). Signs and symptoms of acute opiate withdrawal include sweating, piloerection, mydriasis, lacrimation, rhinorrhea, vomiting, diarrhea, abdominal cramping, tachycardia, hypertension, fever, tachypnea, yawning, restlessness, irritability, myalgias, increased sensitivity to pain, and anxiety. The onset of symptoms can occur < 12 hrs following discontinuation of opioids, or be precipitated by either the administration of the opioid antagonist, naloxone, or mixed agonist/antagonists such as nalbuphine (345, 346). Prolonged benzodiazepine use in ICU patients may lead to withdrawal symptoms when the drug is abruptly discontinued, manifesting as anxiety, agitation, tremors, headaches, sweating, insomnia, nausea, vomiting, myoclonus, muscle cramps, hyperactive delirium, and occasionally seizures (344). Reversing the sedative effects of benzodiazepines following long-term exposure with the benzodiazepine receptor antagonist flumazenil may induce symptoms of benzodiazepine withdrawal (347, 348). Adult ICU patients receiving dexmedetomidine infusions for up to 7 days have developed withdrawal symptoms, most commonly nausea, vomiting, and agitation, within 24–48 hrs of discontinuing dexmedetomidine (349). In the largest study to date looking prospectively at the effects of sedation of ICU patients with dexmedetomidine vs. midazolam, the incidence of withdrawal following discontinuation of dexmedetomidine was 4.9% vs. 8.2% in midazolam-treated patients ($p = 0.25$) (220). Signs and symptoms of opioid and sedative withdrawal in critically ill patients may be overlooked or attributed to other causes, such as alcohol or illicit drug withdrawal.

In the past decade, little was published on the pathophysiology and incidence of drug withdrawal from opioids and sedative agents administered to adult ICU patients. Most studies are retrospective and include patients who have received a variety of sedative and analgesic agents, making it difficult to determine specific incidences and risk factors for drug withdrawal in these patients (344, 350). One small prospective study assessed adult ICU patients for signs and symptoms of withdrawal following discontinuation of sufentanil infusions used concurrently with either midazolam or propofol infusions (351). Patients in the sufentanil/midazolam group were sedated for 7.7 days vs. 3.5 days for the sufentanil/propofol group. Withdrawal symptoms occurred more frequently in the midazolam group (35% vs. 28% with propofol). Although specific recommendations

are lacking for the prophylaxis or treatment of opioid or sedative withdrawal in ICU patients, opioids and/or sedatives administered for prolonged periods (i.e., days) should be weaned over several days in order to reduce the risk of drug withdrawal.

Ethanol (ETOH) dependence is present in 15%–20% of all hospitalized patients (352). Between 8% and 31% of hospitalized patients with ETOH dependence, especially surgical and trauma patients, will go on to develop Alcohol Withdrawal Syndrome (AWS) during their hospital stay, with signs and symptoms of neurologic and autonomic dysfunction (353–355). Symptoms of AWS range from mild to life-threatening (356). Up to 15% of hospitalized patients with AWS experience generalized tonic-clonic seizures, and 5% develop delirium tremens (DTs), a life-threatening combination of central nervous system excitation (agitation, delirium, and seizures) and hyperadrenergic symptoms (hypertension, tachycardia, arrhythmias) (357). ICU patients with severe AWS may exhibit prolonged ventilator dependence and extended ICU stays as a result of persistent delirium (353–355).

Prior ethanol dependence is often underestimated in ICU patients, making identification of patients at risk for AWS or DTs difficult. Screening tools for AWS or DTs have not been fully validated in the critical care setting. Differentiating between delirium due to alcohol withdrawal vs. other causes may be difficult. Symptom-oriented treatment of AWS symptoms with drug dosing as needed to specifically target agitation, psychosis, and autonomic hyperactivity decreases the severity and duration of AWS, and medication requirements in ICU patients (358). Benzodiazepines are considered the mainstay of alcohol withdrawal treatment, despite uncertainty about their effectiveness and safety (320). To date, no published studies have compared the safety and efficacy of treating symptoms of severe AWS with dexmedetomidine vs. benzodiazepines. Diagnosis and management of delirium due to AWS in ICU patients remains challenging. It is beyond the scope of these guidelines to describe the validity of alcohol withdrawal measurement tools, of alcohol withdrawal prevention, or of its treatment in the critical care setting.

Delirium: Questions, Statements, and Recommendations.

1. Outcomes Associated With Delirium in ICU Patients

Question: What outcomes are associated with delirium in adult ICU patients? (descriptive)

Answer: Delirium is associated with increased mortality (A), prolonged ICU and hospital LOS (A), and development of post-ICU cognitive impairment in adult ICU patients (B).

Rationale: Numerous prospective cohort studies have demonstrated that patients who develop delirium are at increased risk for adverse outcomes both in the ICU and after discharge. This risk is independent of preexisting comorbidities, severity of illness, age, and other covariates that might be merely associative. Eleven prospective cohort studies examined the relationship between delirium while in the ICU and mortality at various time points:

ICU discharge ($n = 5$), hospital discharge ($n = 4$), 30 days ($n = 1$), 3 months ($n = 1$), 6 months ($n = 3$), and 12 months ($n = 1$) (318, 319, 321, 322, 359–365). All studies classified delirium as present on one or more ICU days; three studies also examined the relationship between delirium duration and mortality (320, 321, 366). Delirium was an independent predictor of mortality in 11 of 15 studies, including the three studies with a high quality of evidence (320, 321, 366). Duration of delirium (after adjusting for coma and in some cases psychoactive medication exposure) was significantly associated with 6- and 12-month mortality rates. In two cohort studies, duration of delirium consistently portended a 10% increased risk of death per day (after adjusting for covariates and appropriately treating delirium as a time-dependent covariate) (320, 321).

Nine prospective cohort studies examined the relationship between one or more days of delirium in the ICU and ICU and/or hospital LOS, as well as duration of mechanical ventilation (318, 319, 322, 323, 360, 361, 363, 364, 367). Delirium was an independent predictor of duration of mechanical ventilation in four studies (360, 363, 364, 367) and of ICU LOS in four studies (318, 319, 364, 367). Both of these outcome variables are particularly at risk for immortal time bias, which is introduced when the exposure to a treatment or independent variable (in this case, delirium) can change daily during the actual outcome measurement (in this case, either duration of mechanical ventilation or ICU LOS) (368). It is therefore important that the predictive relationship between delirium and hospital LOS was also strong in seven of nine studies (318, 319, 322, 323, 361, 364, 367), including three high-quality studies that accounted for immortal time bias (318, 322, 368). Two prospective cohort studies examined the relationship between delirium in the ICU and subsequent cognitive impairment. One study of moderate quality described an association between the presence of delirium on one or more ICU days and a higher incidence of cognitive dysfunction at hospital discharge (322). In a recent prospective cohort study of moderate quality, increasing duration of delirium in ICU patients was associated with significantly greater cognitive impairment in these patients at 3 and 12 months (324).

2. Detecting and Monitoring Delirium

a. *Question:* Should ICU patients be monitored routinely for delirium with an objective bedside delirium instrument? (actionable)

Answer: We recommend routine monitoring for delirium in adult ICU patients (+1B).

Rationale: Delirium is common in both mechanically ventilated (14, 220, 222, 308, 360, 369, 370) and nonmechanically ventilated ICU patients (309, 359, 371–379). ICU personnel often underestimate the presence of delirium in patients because it frequently presents as hypoactive rather than hyperactive delirium (372, 380). Delirium can be detected in both intubated and nonintubated ICU patients using valid

TABLE 8. Psychometric Scores for Delirium Monitoring Tools

Psychometric Criteria Scored	Delirium Monitoring Tools				
	Confusion Assessment Method for the ICU	Intensive Care Delirium Screening Checklist	Cognitive Test for Delirium	Nursing Delirium Screening Scale	Delirium Detection Score
Item selection description	2	1	2	1	1
Content validation	1	0	2	0	0
Limitations presented	1	1	1	0	1
Interrater reliability	2	2	2	2	2
Interrater reliability tested with nonresearch team	1	1	0	0	0
Interrater reliability tested if interrater reliability is low or inconsistent	NA	NA	NA	NA	0
Total number of participants	2	2	2	2	2
Criterion validation: sensitivity	2	2	2	2	0
Criterion validation: specificity	2	1	2	2	2
Predictive validation	2	2	0	1	0
Feasibility	1	0	0	0	0
Directives of use	1	1	1	1	1
Relevance of scale in practice	1	1	0	0	0
Total score (range: 0–19 or 21)	18/19	14/19	14/19	11/19	9/21
Weighted score ^a (range: 0–20)	19.6	16.8	13.0	12.4	8.2
Quality of psychometric evidence (based on weighted scores)	VG	VG	M	M	VL

VG, very good; M = moderate; VL = very low; NA = not applicable.

^aWeighted score range (0–20): Very good psychometric properties (VG): 15–20; Good psychometric properties (M): 12–14.9; Some acceptable psychometric properties, but remain to be replicated in other studies (Low): 10–11.9; Very few psychometric properties reported, or unacceptable results (VL): < 10.

and reliable tools. In most studies, delirium detection was improved when caregivers used a valid and reliable delirium assessment tool (367), also allowing them to reassure frightened and disoriented patients (381). Delirium monitoring rationale includes: 1) most informed patients at moderate to high risk want to be monitored for delirium; 2) high-quality cohort data relating delirium to critical outcomes shows high delirium “miss rates” in the absence of monitoring; 3) clinicians have successfully implemented ICU delirium monitoring programs on a large-scale, using assessment tools recommended in these guidelines; and 4) policy makers can adopt delirium assessment as part of routine, high-quality care in most ICUs (254, 372, 374, 382, 383). Based on moderate evidence, we issue a strong recommendation that ICU patients at moderate to high risk for delirium (e.g., patients: with a baseline history of alcoholism, cognitive impairment, or hypertension; with severe sepsis or shock; on mechanical ventilation; or receiving parenteral sedative and opioid medications) should be routinely

monitored, at least once per nursing shift, for the development of delirium using a valid and reliable delirium assessment tool.

- b. *Question:* Which instruments available for delirium monitoring have the strongest evidence for validity and reliability in ventilated and nonventilated medical and surgical ICU patients? (descriptive)

Answer: The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable delirium monitoring tools in adult ICU patients (A).

Rationale: Five delirium monitoring tools were evaluated for use in ICU patients: Cognitive Test for Delirium (CTD), CAM-ICU, Delirium Detection Score (DDS), ICDSC, and Nursing Delirium Screening Scale (Nu-DESC). **Table 8** compares their psychometric properties. Both the CAM-ICU (308, 359, 371–374, 384–387) and ICDSC (309, 371) demonstrate very good psychometric properties (i.e., validity and reliability), and are explicitly designed for use in ICU

patients both on and off mechanical ventilation. Translated into over 20 languages, these tools are currently in use worldwide (315). The CAM-ICU and ICDSC have shown high inter-rater reliability when tested by ICU nurses and intensivists (308, 309, 373). They both demonstrated high sensitivity and specificity when tested against the American Psychiatric Association's criteria for delirium (319, 359, 379). Predictive validation of the presence of delirium, as detected with the CAM-ICU or ICDSC, was associated with clinical outcomes such as increased ICU and hospital LOS (318, 319, 322, 323, 360, 361, 363, 364, 367) and higher risk of mortality (318, 319, 321, 322, 359–365). Based on our review of the literature, both the CAM-ICU and ICDSC are valid, reliable, and feasible tools to detect delirium in ICU patients (254, 309). While the CTD (388–390) and Nu-DESC (379) reached the minimum weighted psychometric score of 12 in our analysis, some psychometric properties remain to be tested for these tools, including inter-rater reliability in a nonresearch setting and clinical feasibility. Further psychometric testing of the DDS (347) is needed in order to better assess its overall validity, reliability, and feasibility as a delirium monitoring tool in critically ill patients.

Since completing our review and analysis of the literature in 2010 on delirium monitoring tools, several additional studies have been published analyzing the sensitivity, specificity, and reliability of delirium assessment tools in clinical practice (391–394). A meta-analysis of five ICU delirium screening tools found that the CAM-ICU and ICDSC were the most sensitive and specific tools for detecting delirium, consistent with our recommendation (392). A separate meta-analysis of studies comparing the CAM-ICU to the ICDSC also found a high degree of sensitivity and specificity for both tools (393). Additional studies are needed to assess the performance of delirium monitoring tools in routine clinical practice across different types of ICU patients (391, 394).

- c. *Question:* Is implementation of routine delirium monitoring feasible in clinical practice? (descriptive)

Answer: Routine monitoring of delirium in adult ICU patients is feasible in clinical practice (B).

Rationale: Moderate-quality evidence suggests that routine monitoring of delirium is feasible in clinical practice. Numerous implementation studies including over 2,000 patients across multiple institutions showed delirium monitoring compliance rates in excess of 90%. Practicing ICU nurses and physicians demonstrated high inter-rater reliability with trained experts using several of the recommended delirium monitoring tools (254, 372, 374, 382, 383). Although studies show that implementation of delirium monitoring is feasible in the ICU, lack of physician buy-in is a significant barrier (395). Successful strategies for overcoming this hurdle requires a focus on human factors and chang-

ing ICU culture (316). A more recent study of delirium monitoring implementation (published after evidence was graded for this topic), that included over 500 ICU patients (medical, surgical, and cardiac) and over 600 ICU nurses over a 3-yr period, reinforces the conclusion that routine delirium monitoring is feasible in clinical practice (394).

3. Delirium Risk Factors

- a. *Question:* What baseline risk factors are associated with the development of delirium in the ICU? (descriptive)

Answer: Four baseline risk factors are positively and significantly associated with the development of delirium in the ICU: preexisting dementia; history of hypertension and/or alcoholism; and a high severity of illness at admission (B).

Rationale: The following baseline risk factors have been reported as significant in two or more multivariable analyses: preexisting dementia (329, 375, 396); history of baseline hypertension (318, 397); alcoholism, defined as ingestion of two to three or more drinks daily (318, 396); and a high severity of illness at admission (318, 328, 329, 398). Although age has been identified as one of the most significant risk factors for delirium outside the ICU, only two studies reported it to be significant in ICU patients (328, 398), while four studies reported it as insignificant (318, 375, 396, 399). More research is needed to confirm the relationship between age and the development of delirium in ICU patients.

- b. *Question:* Is coma a risk factor for the development of delirium in the ICU? (descriptive)

Answer: Coma is an independent risk factor for the development of delirium in ICU patients. Establishing a definitive relationship between various subtypes of coma (i.e., medication-related, structural, neurological, medical) and delirium in ICU patients will require further study (B).

Rationale: Several reports have shown coma to be an independent risk factor for delirium in ICU patients (318, 399). One study further classified coma into three categories: medical coma (i.e., due to a primary neurological condition), sedative-induced coma, and multifactorial coma (both medical and sedative-induced coma) (318). In this study, sedative-induced coma and multifactorial coma were significantly associated with the development of delirium, but medical coma was not (318).

- c. *Question:* Which ICU treatment-related (acquired) risk factors (i.e., opioids, benzodiazepines, propofol, and dexmedetomidine) are associated with the development of delirium in adult ICU patients? (descriptive)

Answer: Conflicting data surround the relationship between opioid use and the development of delirium in adult ICU patients (B). Benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients (B). There are insufficient data to deter-

mine the relationship between propofol use and the development of delirium in adult ICU patients (C). In mechanically ventilated adult ICU patients at risk for developing delirium, dexmedetomidine infusions administered for sedation may be associated with a lower prevalence of delirium compared to benzodiazepine infusions administered (B).

Rationale: Study designs including opioids varied greatly. Some reported individual medications used (288, 328, 397, 398), while others provided only the medication class (363), and still others combined opioids with sedatives or other analgesics (318, 329, 396). Study results also varied considerably. Most studies reported either an increased risk of delirium with opioids or no association (288, 318, 328, 329, 363, 396–398). One study (400) found that opioids reduced the risk of delirium in burn patients. Only one high-quality study explicitly addressed the association between propofol and delirium risk in ICU patients, and found no significant relationship (328). Benzodiazepines were included in several delirium risk factor studies. As with opioids, study designs varied greatly. Some moderate-quality studies reported a strong relationship between benzodiazepine use and the development of delirium (288, 328), while others found no significant relationship (318, 363, 396–399). Two randomized controlled trials comparing sedation with benzodiazepines vs. dexmedetomidine reported a lower prevalence of delirium (~20%) in patients randomized to receive dexmedetomidine (220, 298). Although these data do not prove that benzodiazepines are causal or that dexmedetomidine is protective, this literature suggests that benzodiazepines may be a risk factor for the development of delirium in the ICU. Whether dexmedetomidine reduces the risk of ICU patients developing delirium is now under study.

4. Prevention of Delirium

- a. *Question:* Should a nonpharmacologic delirium protocol be used in the ICU to reduce the incidence or duration of delirium? (actionable)

Answer: We recommend performing early mobilization of adult ICU patients whenever feasible to reduce the incidence and duration of delirium (+1B).

Rationale: Early mobilization was initially studied in the critical care setting as a nonpharmacologic intervention aiming to improve functional outcomes. In the first multicenter randomized controlled trial of early mobility (326), and in a subsequent implementation study (401), investigators also noted striking reductions in the incidence of delirium, depth of sedation, and hospital and ICU LOS, with an increase in ventilator-free days. These studies suggest that early and aggressive mobilization is unlikely to harm ICU patients, but may reduce the incidence and duration of delirium, shorten ICU and hospital LOS, and lower hospital costs. While more broadly targeted, high-quality non-

pharmacologic protocols have shown favorable results in non-ICU hospitalized patients (402), such multifaceted interventions have not been adequately studied in the ICU setting.

- b. *Question:* Should a pharmacologic delirium prevention protocol be used in the ICU to reduce the incidence or duration of delirium? (actionable)

Answer: We provide no recommendation for using a pharmacologic delirium prevention protocol in adult ICU patients, as no compelling data demonstrate that this reduces the incidence or duration of delirium in these patients (0, C).

Rationale: One prospective, unblinded, randomized controlled trial assessed a nocturnal pharmacologic regimen for maintaining sleep-wake cycles in hospitalized patients following gastrointestinal surgery, with questionable value and applicability to critical care practice (403). A more recent prospective, placebo-controlled, blinded, randomized study did show benefit to administering low doses of haloperidol prophylactic to elderly surgical ICU patients in order to prevent delirium (404). However, these patients were not very ill, and most were not mechanically ventilated. More study is needed to determine the safety and efficacy of using a pharmacologic delirium prevention protocol in ICU patients.

- c. *Question:* Should a combined nonpharmacologic and pharmacologic delirium prevention protocol be used in the ICU to reduce the incidence or duration of delirium? (actionable)

Answer: We provide no recommendation for the use of a combined nonpharmacologic and pharmacologic delirium prevention protocol in adult ICU patients, as this has not been shown to reduce the incidence of delirium in these patients (0, C).

Rationale: One before/after study evaluated the impact of a multidisciplinary protocol for managing PAD in ICU patients. Patients managed with this protocol had a reduced incidence of subsyndromal delirium but not delirium, improved pain control, and a 15% reduction in their total ICU costs (327, 405). Subsyndromal delirium in ICU patients is defined as patients who have less than four points on the ICDSC; patients with subsyndromal delirium have worse clinical outcomes than those without delirium (319). Further research is needed to determine whether a combined nonpharmacologic and pharmacologic protocol reduces the incidence or duration of full-blown delirium in ICU patients.

- d. *Question:* Should haloperidol or atypical antipsychotics be used prophylactically to prevent delirium in ICU patients? (actionable)

Answer: We do not suggest that either haloperidol or atypical antipsychotics be administered to prevent delirium in adult ICU patients (–2C).

Rationale: No high-quality studies with sufficient sample size or effect size demonstrate a benefit of administering prophylactic antipsychotics to the general ICU population. A recent moderate-quality trial demonstrated that low-dose IV haloperidol prophylaxis may reduce the prevalence of delirium in low acuity elderly postoperative patients who are admitted to the ICU (404). Whether these data can be applied to a more diverse population of sicker ICU patients is uncertain. A well-designed, but underpowered, multicenter, randomized controlled trial of delirium prophylaxis with either haloperidol or ziprasidone vs. placebo did not show any benefit with either treatment group as compared to placebo (370). One moderate-quality study suggested that a single dose of sublingual risperidone administered immediately postoperatively to cardiac surgery patients reduced the incidence of delirium (406). Further research is needed to better define the safety and efficacy of typical and atypical antipsychotics for delirium prevention in ICU patients.

- e. *Question:* Should dexmedetomidine be used prophylactically to prevent delirium in ICU patients? (actionable)

Answer: We provide no recommendation for the use of dexmedetomidine to prevent delirium in adult ICU patients, as there is no evidence regarding its effectiveness in these patients (0, C).

Rationale: One cardiovascular ICU study ($n = 306$) addressed the issue of dexmedetomidine and delirium prophylaxis in ICU patients (407). Delirium lasted 2 days in the dexmedetomidine group compared with 5 days in the morphine group ($p = 0.03$), but delirium prevalence was not significantly reduced (9% vs. 15%, respectively, $p = 0.09$). Until more data become available, we provide no recommendation for delirium prophylaxis with dexmedetomidine, given the risks of treatment without clear benefit.

5. Treatment of Delirium

- a. *Question:* Does treatment with haloperidol reduce the duration of delirium in adult ICU patients? (descriptive)

Answer: There is no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients (No Evidence).

- b. *Question:* Does treatment with atypical antipsychotics reduce the duration of delirium in adult ICU patients? (descriptive)

Answer: Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C).

Rationale: In a single small prospective, randomized, double-blind, placebo-controlled study ($n = 36$), ICU patients with delirium who received quetiapine had a reduced duration of delirium (408). Patients with delirium who were being treated with haloperidol were randomized to additionally receive either quetiapine 50 mg or placebo every 12 hrs. The quetiapine dose was increased by 50 mg if more than one dose of haloperidol was given in the previous 24 hrs. All patients

were allowed to receive IV haloperidol 1–10 mg every 2 hrs as needed. The use of haloperidol was not significantly different between the groups. Comparable data are not available for treatment with haloperidol alone. Sufficiently powered, carefully designed, multicenter, placebo-controlled trials are needed to address the hypothesis that antipsychotics are beneficial in the treatment of delirium in critically ill patients.

- c. *Question:* Should treatment with cholinesterase inhibitors (rivastigmine) be used to reduce the duration of delirium in ICU patients? (actionable)

Answer: We do not recommend administering rivastigmine to reduce the duration of delirium in ICU patients (–1B).

Rationale: Rivastigmine, a cholinesterase inhibitor, may be useful in treating delirium in demented elderly patients. However, rivastigmine was compared to placebo in critically ill patients in an investigation stopped for futility and potential harm (409). This multicenter trial was halted after 104 patients were enrolled because the rivastigmine-treated patients had more severe and longer delirium, with a trend toward higher mortality. In another study (published after the evidence analysis for this recommendation), perioperative rivastigmine was administered for delirium prophylaxis in patients undergoing elective cardiac surgery ($n = 120$, patients > 65 yr), and had no effect on the incidence of postoperative delirium in these patients (410).

- d. *Question:* Should haloperidol and atypical antipsychotics be withheld in patients at high risk for torsades de pointes? (actionable)

Answer: We do not suggest using antipsychotics in patients at significant risk for torsades de pointes (i.e., patients with baseline prolongation of QT interval, patients receiving concomitant medications known to prolong the QT interval, or patients with a history of this arrhythmia) (–2C).

Rationale: Torsades de pointes is a dangerous complication associated with antipsychotic administration. Original case reports warned of this arrhythmia in patients receiving IV haloperidol (411, 412) and its association with a prolonged QT interval (413, 414). Although torsades has also been described without QT prolongation (415, 416). Torsades has also occurred in patients receiving atypical antipsychotics, such as ziprasidone (417) and risperidone (418), and recent reports have warned of drug interactions that could heighten this risk (419). Although the quality of evidence is low, the morbidity and mortality associated with this complication is high.

- e. *Question:* For mechanically ventilated, adult ICU patients with delirium who require continuous IV infusions of sedative medications, is dexmedetomidine preferred over benzodiazepines to reduce the duration of delirium? (actionable)

Answer: We suggest that in adult ICU patients with delirium unrelated to alcohol or benzodiazepine with-

drawal, continuous IV infusions of dexmedetomidine rather than benzodiazepine infusions be administered for sedation in order to reduce the duration of delirium in these patients (+2B).

Rationale: Two randomized controlled trials comparing sedation with benzodiazepines vs. dexmedetomidine reported a significant daily reduction (~20%) in delirium prevalence in patients receiving dexmedetomidine (220, 370, 420). These data are inconclusive about whether benzodiazepines raised the risk of delirium, or dexmedetomidine reduced the risk, and further investigations are needed to address this question. But data from these two clinical trials (which included a high percentage of patients at risk for delirium), coupled with delirium risk factor data from observational trials, suggest that benzodiazepines may be a risk factor for the development of delirium in the ICU. These findings led to this recommendation for using dexmedetomidine rather than benzodiazepines for sedation in ICU patients with delirium not due either to benzodiazepine or ethanol withdrawal. There are insufficient data to make recommendations regarding the risks and benefits of using other non-benzodiazepine sedatives, such as propofol, to reduce the duration of delirium in ICU patients.

Management of PAD to Improve ICU Outcomes

Use of Integrated PAD Protocols to Optimize ICU Patient Care. Our ability to effectively manage PAD in critically ill patients enables us to develop potential management strategies that reduce costs, improve ICU outcomes, and allow patients to participate in their own care (9–13, 16–20). Yet the application of these guideline recommendations poses significant challenges to critical care practitioners. A successful strategy is to implement an evidence-based, institutionally-specific, integrated PAD protocol, and to assess, treat and prevent PAD, using an interdisciplinary team approach. Protocols facilitate the transfer of evidence-based “best practices” to the bedside, limit practice variation, and reduce treatment delays (2, 3). A protocolized approach can also significantly improve patient outcomes and serve as a guide for quality assurance efforts (13, 327, 421, 422).

In spite of these recognized advantages, widespread adoption of integrated PAD protocols is lagging. Only 60% of ICUs in the United States have implemented PAD protocols, and even when instituted, protocol adherence is low, which negatively impacts patient outcomes (163, 199). Despite > 20 yr of emphasis on the importance of systematic pain assessment and management, data suggest that: 1) preemptive analgesia for painful procedures is used only 20% of the time in ICU patients; 2) pain and discomfort remain leading sources of patient stress; and 3) at least 40% of ICU patients still report experiencing moderate to severe pain (2, 60, 73, 423). Medication-induced coma has long been thought of as a “humane” therapeutic goal for many ICU patients.

But this strategy leads to increased mortality, prolonged duration of ventilation and ICU LOS, and possibly long-term neuropsychological dysfunction and functional decline of patients (75, 238, 287, 318, 424–426). In spite of the published benefits of ICU sedation strategies that minimize the use of sedatives and depth of sedation in patients, adoption of these sedation practices is not widespread.

ICU protocols that combine routine pain and sedation assessments, with pain management and sedation-minimizing strategies (i.e., daily sedative interruption or protocols that otherwise target light levels of sedation), along with delirium monitoring and prevention, may be the best strategy for avoiding the complications of over sedation. Protocols can also facilitate communication between bedside nurses and other members of the ICU team, helping them to define appropriate pain and sedation management goals, and to assess the effectiveness of treatment strategies for each individual patient (3, 14, 62, 259, 427, 428). Although the impact of routine delirium monitoring on ICU outcomes has never been rigorously evaluated, early recognition of delirium may nevertheless facilitate patient reassurance, help to identify reversible causative factors, and permit implementation of effective delirium treatments. Early detection and treatment of delirium may in turn allow for a patient to be conscious, yet cooperative enough to potentially participate in ventilator weaning trials and early mobilization efforts. However, delirium can only be assessed in patients who are able to sufficiently interact and communicate with bedside clinicians. Optimal pain management and a light level of sedation are essential for this to occur.

Defining Depth of Sedation. Although there are obvious benefits to minimizing sedation in critically ill patients, no clear consensus exists on how to define “light” vs. “deep” sedation. The overarching objectives for the management of pain, agitation, and delirium in ICU patients should be to consistently focus on patient safety and comfort, while avoiding short- and long-term complications associated with either excessive or inadequate treatment. Traditionally, the goals of ICU analgesia and sedation have been to facilitate mechanical ventilation, to prevent patient and caregiver injury, and to avoid the psychological and physiologic consequences of inadequate treatment of pain, anxiety, agitation, and delirium. Avoiding complications of over-sedation, such as muscle atrophy and weakness, pneumonia, ventilator dependency, thromboembolic disease, nerve compression, pressure sores, and delirium, are also important (11, 325, 326, 429). A more precise definition of light vs. deep sedation is offered to guide the creation and implementation of sedation protocols that provide sufficient patient comfort without inducing coma.

Central to these guidelines are the principles that: 1) pain, depth of sedation, and delirium should be frequently monitored using valid and reliable assessment tools; 2) patients should receive adequate and preemptive treatment for pain; 3) patients should receive sedation only if required; and 4) that sedatives should be titrated to allow patient responsiveness and awareness that is demonstrated by their ability to purposefully

respond to commands (i.e., a combination of any three of the following actions upon request: open eyes, maintain eye contact, squeeze hand, stick out tongue, and wiggle toes) (15, 16, 326). This degree of responsiveness and awareness goes beyond patients being merely “sleepy but arousable” and is essential for the evaluation of pain through patient self-report, for assessing patients’ readiness to wean and extubate, for performing delirium assessments, and for implementing early mobility efforts. It remains unclear as to whether it’s better to titrate sedation to a goal that allows patients to be consistently awake, cooperative, and calm, or to provide deeper sedation with a daily awakening trial (16, 430). In the final analysis, both strategies have been shown to reduce the incidence of deep sedation and its associated risks (431).

Outcomes: Questions, Statements, and Recommendations.

1. Sedation Strategies to Improve Clinical Outcomes

- a. *Question:* Should a protocol that includes either daily sedative interruption or a light target level of sedation be used in mechanically ventilated adult ICU patients? (actionable)

Answer: We recommend either daily sedation interruption or a light target level of sedation be routinely used in mechanically ventilated adult ICU patients (+1B).

Rationale: Five unblinded randomized controlled trials involving 699 patients evaluated daily sedation interruption (14–16, 432, 433). All but one (432) were restricted to medical ICU patients; a single pilot trial targeted light sedation as the comparator (16). One low-quality trial suggested harm, but suffered from serious methodological issues (433). Data suggest daily sedation interruption reduces the time that patients spend on the ventilator (or increases ventilator-free days in survivors) and ICU LOS.

An alternative strategy using protocols to maintain light sedation (without daily sedation interruption) was described in 11 unblinded studies involving 3,730 patients. The data suggest this approach reduces the amount of time that patients spend on the ventilator (or increases ventilator-free days for survivors) (7–13, 18, 19, 434). The effect of protocolization on ICU LOS was inconsistent with little data suggesting any detrimental effect (7–13, 17–19, 327, 434). Conflicting data in two studies were likely related to the similarity of control group sedation practices to those offered by the intervention (18, 19). Healthcare systems that employ bedside care models with 1:1 nurse-to-patient ratios or institutions where sedation minimization is a goal may not benefit (435). Data are insufficient to draw firm conclusions on the effect of either daily sedation interruption or protocolization to maintain a level of light sedation on ventilator-associated pneumonia (VAP), delirium prevalence, patient comfort, or cost of ICU care.

In summary, daily sedation interruption is associated with clinical benefit in medical ICU patients, but the benefits remain uncertain in those who are alcohol-dependent or not admitted to a medical ICU service. Studies

investigating the efficacy and safety of this strategy in surgical, trauma, neurologic, and neurosurgical patients are needed. Protocolized management strategies (e.g., hourly titration) to avoid deep sedation are also associated with clinical benefit, but it remains unclear whether combining sedation protocolization with daily sedative interruption would lead to additional benefits (16).

- b. *Question:* Should analgesia-first sedation (i.e., analgo-sedation) or sedative-hypnotic-based sedation be used in mechanically ventilated ICU patients? (actionable)

Answer: We suggest that analgesia-first sedation be used in mechanically ventilated adult ICU patients (+2B).

Rationale: Providing analgesia-first sedation for many ICU patients is supported by the high frequency of pain and discomfort as primary causes of agitation and by reports implicating standard hypnotic-based sedative regimens as having negative clinical and quality-of-life outcomes. Four unblinded studies including 630 medical and surgical ICU patients examined an analgesia-first approach (436–439). Data from one moderate-quality study suggested that analgesia-first sedation is associated with longer ventilator-free time during a 28-day period, and shorter ICU LOS (439). Otherwise, no consistent advantages of analgesia-first sedation over sedative-hypnotic-based sedation were found. Optimal analgesia and sedation were achieved during 97% of the time with either strategy (436, 438). One trial did not demonstrate any harm from the intervention on rates of self-extubation or VAP, but the incidence of agitated delirium was higher in the analgesia-first sedation group (439). Data on delirium, self-extubation, VAP, mortality, or cost of ICU care are insufficient to draw firm conclusions about the influence of this intervention.

High-quality study data are scarce in support of using one opiate over another in ICU patients receiving analgesia-first sedation (127, 134, 407). Clinicians should rely on pharmacology, safety, and cost-effectiveness when making opioid treatment decisions (440). Analgesics that are short-acting and easily titratable may offer an advantage by facilitating frequent neurologic evaluations.

The benefits of analgesia-first approach must be balanced by the potential for opiates to interfere with respiratory drive, reduce gastric motility, and complicate the provision of enteral nutrition (134, 441). Possible pain recurrence and withdrawal upon analgesic discontinuation should be anticipated (130). Furthermore, 18% to 70% of patients treated with analgesia-first strategies will require supplementation with other traditional sedative agents (436–439).

Although data suggest potential additional benefits with analgesia-first sedation, the ultimate role of this strategy remains unclear because one moderate-quality study (439) required a 1:1 nurse-to-patient ratio and the availability of patient “sitters,” and no rigorous pub-

lished studies have specifically compared analgesia-first sedation with conventional GABA-based sedation strategies. Preliminary data suggest that analgesia-first sedation strategies do not have a negative impact on long-term psychological function (442). These data should be confirmed and expanded to explore the influence of analgesia-first sedation on outcomes such as delirium, self-extubation, VAP, mortality, and cost of ICU care, and on long-term cognitive function. Although these studies administered an opioid as the primary analgesic, future studies in critically ill patients should evaluate a multimodal analgesic approach using a combination of opioids and nonopioid analgesics (52).

c. Sleep promotion in ICU patients

- i. *Question:* Should nonpharmacologic interventions be used to promote sleep in adult ICU patients? (actionable)

Answer: We recommend promoting sleep in adult ICU patients by optimizing patients' environments, using strategies to control light and noise, clustering patient care activities, and decreasing stimuli at night to protect patients' sleep cycles (+1C).

Rationale: Sleep deprivation is detrimental in humans, and sleep disruption is common in ICU patients (443, 444). They have few complete sleep cycles, numerous awakenings due to environmental disruptions (noise, light, and physical stimulation), and infrequent rapid-eye-movement sleep (443, 445–448). Sleep deprivation impairs tissue repair and cellular immune function, and may affect the healing response (449). In critically ill patients, sleep deprivation may contribute to the development of delirium (450–454) and increased levels of physiologic stress (455, 456).

Sleep science in the ICU has not advanced in the past decade. Because few studies identify pharmacologic effects of sedatives on sleep in critically ill patients, we focused on nonpharmacologic interventions to promote sleep in the ICU. Two recently published studies ($n > 30$, prospective cohort, before/after study design) demonstrated that implementing quiet time on both day and night shifts and clustering patient care activities reduce disturbances and promote both observed and perceived sleep in adult ICU patients (457, 458). Another descriptive study further confirmed that mechanically ventilated ICU patients do not have uninterrupted periods for sleep to occur (459). From these findings, we hypothesized that nurses should select time periods to promote sleep by avoiding routine ICU care activities (such as the daily bath), turning down the lights, and reducing ambient noise during these periods. In three studies suggesting scheduled rest periods, the periods most likely to be uninterrupted in the ICU were 2–4 AM (458), 12–5 AM (457), and around 3 AM (459).

Another study, using indirect evidence from nursing home patients, suggested that the amount of

daytime light exposure may affect a hospitalized elderly patient's quality and consolidation of sleep at night (460). These findings must be validated in an ICU patient population. Further research is needed to support the positive effects of using eye patches or ear plugs to limit the aversive effects of noise and light (461). High doses of sedative agents and mechanical ventilation disrupt sleep patterns in critically ill patients (459, 462). There is no evidence that light levels of sedation promote sleep in the ICU.

- ii. *Question:* Should specific modes of mechanical ventilation be used to promote sleep in ventilated ICU patients? (actionable)

Answer: We provide no recommendation for using specific modes of mechanical ventilation to promote sleep in adult ICU patients, as insufficient evidence exists for the efficacy of these interventions (0, No evidence).

Rationale: Two small studies ($n < 30$) have demonstrated that modes of mechanical ventilation that reduce the risk of central apnea events may improve the quality of sleep in adult ICU patients (463, 464). Larger, well-designed prospective clinical trials are needed to validate these findings.

2. Strategies to Facilitate Implementation of ICU Analgesia, Sedation, and Delirium Guidelines

Question: Should an interdisciplinary educational and behavioral strategy be used to facilitate the implementation of sedation protocols and guidelines in adult ICUs? (actionable)

Answer: We recommend using an interdisciplinary ICU team approach that includes provider education, preprinted and/or computerized protocols and order forms, and quality ICU rounds checklists to facilitate the use of PAD management guidelines or protocols in adult ICUs (+1B).

Rationale: The bulk of data from 12 unblinded studies involving 2,887 patients suggests that one or more interventions, along with the protocol implementation to provide patient comfort in the ICU, reduces the duration of mechanical ventilation (or increases ventilator-free days for survivors (7–10, 12, 13, 18, 19, 159–162)). Interventions to implement protocols had inconsistent impact on ICU LOS, with little data suggesting harm within the 11 studies involving 2,707 patients (7–10, 12, 13, 18, 19, 159, 160, 162). There was no evidence for harm with this intervention when the incidence of self-extubation was examined. Lastly, data were insufficient to support a recommendation based on the time patients spent within their defined sedation goal or on patient or nurse satisfaction. Data suggest that the primary benefit of using one or more interventions (e.g., education, additional staff, electronic reminders) is to limit time on mechanical ventilation, but the overall benefit is uncertain. Low risk and minimal cost are associated with implementing one or more strategies to improve the use of an integrated sedation protocol in the ICU.

Tools for Facilitating the Application of the These Recommendations to Bedside Care

Closing the gap between the evidence highlighted in these guidelines and ICU practice will be a significant challenge for ICU clinicians (465, 466) and is best accomplished using a multifaceted, interdisciplinary approach (4, 467). The

recommendations supported by clinical practice guidelines should be adapted to local practice patterns and resource availability, and used as a template for institution-specific protocols and order sets. Successful implementation will require augmentation with education, engagement of local thought leaders, point-of-use reminders, and caregiver-spe-

A	
<ul style="list-style-type: none"> • Agitation in critically ill patients may result from inadequately treated pain, anxiety, delirium, and/or ventilator dyssynchrony. • Detection and treatment of pain, agitation, and delirium should be reassessed often in these patients. • Patients should be awake and able to purposely follow commands in order to participate in their care unless a clinical indication for deeper sedation exists. • For a comprehensive list of Guideline Statements, Recommendations and GRADES, see back of card. 	
Assess and Treat	Statements and Recommendations
PAIN	<ul style="list-style-type: none"> • Pain assessment should be routinely performed in all ICU patients (1B). • Self report is preferred over the use of behavioral pain scales to assess pain in ICU patients who are able to communicate (B). • The BPS and CPOT are the most valid and reliable behavioral pain scales for use in ICU patients who cannot communicate (B). • Vital signs should not be used alone to assess pain, but they may be used adjunctively for pain assessments (2C). • Preemptively treat chest tube removal with either analgesics and/or non-pharmacologic therapy (1C). • Suggest preemptively treating other types of procedural pain with analgesic and/or non-pharmacologic therapy (2C). • Use opioids as first line therapy for treatment of non-neuropathic pain (1C). • Suggest using non-opioid analgesics in conjunction with opioids to reduce opioid requirements and opioid-related side effects (2C). • Use gabapentin or carbamazepine, in addition to intravenous opioids, for treatment of neuropathic pain (1A). • Use thoracic epidural for postoperative analgesia in abdominal aortic surgery patients (1B). • Suggest thoracic epidural analgesia be used for patients with traumatic rib fractures (2B).
AGITATION	<ul style="list-style-type: none"> • Depth and quality of sedation should be routinely assessed in all ICU patients (1B). • The RASS and SAS are the most valid and reliable scales for assessing quality and depth of sedation in ICU patients (B). • Suggest using objective measures of brain function to adjunctively monitor sedation in patients receiving neuromuscular blocking agents (2B). • Use EEG monitoring either to monitor non-convulsive seizure activity in ICU patients at risk for seizures, or to titrate electro suppressive medication to achieve burst suppression in ICU patients with elevated intracranial pressure (1A). • Target the lightest possible level of sedation and/or use daily sedative interruption (1B). • Use sedation protocols and checklists to facilitate ICU sedation management (1B). • Suggest using analgesia-first sedation for intubated and mechanically ventilated ICU patients (2B). • Suggest using non-benzodiazepines for sedation (either propofol or dexmedetomidine) rather than benzodiazepines (either midazolam or lorazepam) in mechanically ventilated adult ICU patients (2B).
DELIRIUM	<ul style="list-style-type: none"> • Delirium assessment should be routinely performed in all ICU patients (1B). • The CAM-ICU and ICDSC delirium monitoring tools are the most valid and reliable scales to assess delirium in ICU patients (A). • Mobilize ICU patients early when feasible to reduce the incidence and duration of delirium, and to improve functional outcomes (1B). • Promote sleep in ICU patients by controlling light and noise, clustering patient care activities, and decreasing stimuli at night (1C). • Avoid using rivastigmine to reduce the duration of delirium in ICU patients (1B). • Suggest avoiding the use of antipsychotics in patients who are at risk for torsades de pointes (2B). • Suggest not using benzodiazepines in ICU patients with delirium unrelated to ETOH/benzodiazepine withdrawal (2B).

Figure 2. A, Pocket card operationalizing the PAD guideline recommendations (front side). (Continued.)

B	
Summary of PAD Guidelines	
PAIN AND ANALGESIA	<ol style="list-style-type: none"> 1. ICU patients routinely experience pain at rest and with ICU care (B). Pain in cardiac surgery patients, especially women, is poorly treated (B). Procedural pain is common in ICU patients (B). 2. Perform routine pain assessment in all patients (1B). In motor intact patients unable to self report, we suggest using behavioral pain scales rather than vital signs to assess pain (2C). The BPS and CPOT are the most valid and reliable behavioral pain scales (B). Vital signs should only be used as a cue for further pain assessment (2C). 3. For non-neuropathic pain, use intravenous opioids as first line analgesic therapy (1C); use non-opioid analgesics to reduce opioid side effects (1C); and use either gabapentin or carbamazepine in conjunction with intravenous opioids for neuropathic pain (1A). 4. Suggest preemptively treating procedural pain (2C), especially chest tube removal (1C). 5. Use thoracic epidural analgesia for abdominal aortic surgery (1B), and suggest also using for traumatic rib fractures (2B). No evidence guides the use of lumbar epidural analgesia for abdominal aneurysm surgery (0A), or thoracic epidural analgesia for either intrathoracic or nonvascular abdominal surgical procedures (0B). No evidence guides the use of regional vs. systemic analgesia in medical ICU patients (0).
AGITATION AND SEDATION	<ol style="list-style-type: none"> 1. Maintaining lighter levels of sedation in ICU patients is associated with improved clinical outcomes (B); light levels of sedation should be maintained in these patients (1B). 2. The RASS and SAS scales are most valid and reliable instruments for assessing adequacy and depth of sedation (B). 3. Use Brain Function monitors only as adjuncts to subjective sedation scales in unparalyzed patients (1B), but suggest using brain function monitors to primarily monitor depth of sedation in patients receiving neuromuscular blocking agents (2B). 4. Use EEG monitoring to monitor non-convulsive seizure activity in ICU patients at risk for seizures, and to titrate burst suppression therapy in ICU patients with elevated intracranial pressure (1A). 5. Use either use daily sedative interruption or titrate sedative medications to maintain light levels of sedation (1B). Suggest using Analgesia-first sedation (2B). Suggest using non-benzodiazepines rather than benzodiazepine infusions for sedation (2B). Use sedation protocols and daily checklists to integrate and to facilitate management of pain, sedation, and delirium in ICU patients (1B).
DELIRIUM	<ol style="list-style-type: none"> 1. Delirium is associated with increased mortality (A), prolonged ICU and hospital LOS (A), and post-ICU cognitive impairment (B). 2. Delirium risk factors include: pre-existing dementia, HTN, history of alcoholism, and a high severity of illness at baseline (B); coma (B); and benzodiazepine use (B). Mechanically ventilated ICU patients at risk for delirium have a lower delirium prevalence when treated with dexmedetomidine rather than with benzodiazepines (B). 3. Routinely monitor ICU patients for delirium (1B). The CAM-ICU and ICDSC are the most valid and reliable instruments for this purpose (A). 4. Pursue early mobilization to reduce the incidence and duration of delirium (1B). 5. Suggest not using either haloperidol or atypical antipsychotics prophylactically to prevent delirium (2C). 6. Promote sleep in adult ICU patients by optimizing patients' environments, using strategies to control light and noise, to cluster patient care activities, and to decrease stimuli at night in order to protect patients' sleep cycles (1C). 7. Do not use rivastigmine to reduce the duration of delirium in ICU patients (1C). 8. Suggest withholding antipsychotics in patients with baseline QT prolongation, a history of Torsades de Pointes, or in those receiving concomitant medications known to prolong the QT interval (2C). 9. When sedation is required in delirious ICU patients, suggest using dexmedetomidine rather than benzodiazepine infusions for sedation in these patients, unless delirium is related to either alcohol or benzodiazepine withdrawal (2B).

Figure 2 (Continued). B. Pocket card summarizing specific pain, agitation, and delirium (PAD) guideline statements and recommendations (back side). BPS = Behavioral Pain Scale; CPOT = Critical-Care Pain Observation Tool; RASS = Richmond Agitation and Sedation Scale; SAS = Sedation-Agitation Scale; EEG = electroencephalography; CAM-ICU = Confusion Assessment Method for the ICU; ICDSC = ICU Delirium Screening Checklist; ETOH = ethanol; LOS = length of stay; HTN = hypertension.

sific practice feedback, together with continuous protocol evaluation and modification (7–10, 12, 13, 18, 19, 159–162, 468). Incorporating electronically based guidelines into clinical decision-support tools may facilitate bedside knowledge

transfer and application (465, 466). To support this effort, we have developed a pocket card summarizing these guideline recommendations (Fig. 2) and a template for a PAD care bundle (Fig. 3) (469).

A	PAIN	AGITATION	DELIRIUM
	<p>Assess pain ≥ 4x/shift & prn Preferred pain assessment tools:</p> <ul style="list-style-type: none"> • Patient able to self-report \rightarrow NRS (0-10) • Unable to self-report \rightarrow BPS (3-12) or CPOT (0-8) <p>Patient is in significant pain if NRS ≥ 4, BPS > 5, or CPOT ≥ 3</p>	<p>Assess agitation, sedation ≥ 4x/shift & prn Preferred sedation assessment tools:</p> <ul style="list-style-type: none"> • RASS (-5 to +4) or SAS (1 to 7) • NMB \rightarrow suggest using brain function monitoring <p>Depth of agitation, sedation defined as:</p> <ul style="list-style-type: none"> • <i>agitated</i> if RASS = +1 to +4, or SAS = 5 to 7 • <i>awake and calm</i> if RASS = 0, or SAS = 4 • <i>lightly sedated</i> if RASS = -1 to -2, or SAS = 3 • <i>deeply sedated</i> if RASS = -3 to -5, or SAS = 1 to 2 	<p>Assess delirium Q shift & prn Preferred delirium assessment tools:</p> <ul style="list-style-type: none"> • CAM-ICU (+ or -) • ICDSC (0 to 8) <p>Delirium present if:</p> <ul style="list-style-type: none"> • CAM-ICU is positive • ICDSC ≥ 4
	<p>Treat pain within 30' then reassess:</p> <ul style="list-style-type: none"> • Non-pharmacologic treatment—relaxation therapy • Pharmacologic treatment: <ul style="list-style-type: none"> – Non-neuropathic pain \rightarrow IV opioids +/- non-opioid analgesics – Neuropathic pain \rightarrow gabapentin or carbamazepine, + IV opioids – S/p AAA repair, rib fractures \rightarrow thoracic epidural 	<p>Targeted sedation or DSI (<i>Goal: patient purposely follows commands without agitation</i>): RASS = -2 - 0, SAS = 3 - 4</p> <ul style="list-style-type: none"> • If <i>under sedated</i> (RASS > 0, SAS > 4) assess/treat pain \rightarrow treat w/sedatives prn (non-benzodiazepines preferred, unless ETOH or benzodiazepine withdrawal is suspected) • If <i>over sedated</i> (RASS < -2, SAS < 3) hold sedatives until at target, then restart at 50% of previous dose 	<ul style="list-style-type: none"> • Treat pain as needed • Reorient patients; familiarize surroundings; use patient's eyeglasses, hearing aids if needed • Pharmacologic treatment of delirium: <ul style="list-style-type: none"> – Avoid benzodiazepines unless ETOH or benzodiazepine withdrawal is suspected – Avoid rivastigmine – Avoid antipsychotics if \uparrow risk of Torsades de pointes
	<ul style="list-style-type: none"> • Administer pre-procedural analgesia and/or non-pharmacologic interventions (e.g., relaxation therapy) • Treat pain first, then sedate 	<ul style="list-style-type: none"> • Consider daily SBT, early mobility and exercise when patients are at goal sedation level, unless contraindicated • EEG monitoring if: <ul style="list-style-type: none"> – at risk for seizures – burst suppression therapy is indicated for \uparrow ICP 	<ul style="list-style-type: none"> • Identify delirium risk factors: dementia, HTN, ETOH abuse, high severity of illness, coma, benzodiazepine administration • Avoid benzodiazepine use in those at \uparrow risk for delirium • Mobilize and exercise patients early • Promote sleep (control light, noise; cluster patient care activities; decrease nocturnal stimuli) • Restart baseline psychiatric meds, if indicated

B	PAIN	AGITATION	DELIRIUM
	<ul style="list-style-type: none"> • % of time patients are monitored for pain ≥ 4x/shift • Demonstrate local compliance and implementation integrity over time in the use of ICU pain scoring systems 	<ul style="list-style-type: none"> • % of time sedation assessments are performed ≥ 4x/shift • Demonstrate local compliance and implementation integrity over time in the use of ICU sedation scoring systems 	<ul style="list-style-type: none"> • % of time delirium assessments are performed Q shift • Demonstrate local compliance and implementation integrity over time in the use of ICU delirium assessment tools
	<ul style="list-style-type: none"> • % of time ICU patients are in significant pain (i.e., NRS ≥ 4, BPS ≥ 6, or CPOT ≥ 3) • % of time pain treatment is initiated within 30" of detecting significant pain 	<ul style="list-style-type: none"> • % of time patients are either optimally sedated or successfully achieve target sedation during DSI trials (i.e., RASS = -2 - 0, SAS = 3 - 4) • % of time ICU patients are <i>under sedated</i> (RASS > 0, SAS > 4) • % of time ICU patients are either <i>over sedated</i> (<i>non-therapeutic coma</i>, RASS < -2, SAS < 3) or fail to undergo DSI trials 	<ul style="list-style-type: none"> • % of time delirium is present in ICU patients (CAM-ICU is positive or ICDSC ≥ 4) • % of time benzodiazepines are administered to patients with documented delirium (not due to ETOH or benzodiazepine withdrawal)
	<ul style="list-style-type: none"> • % of time patients receive pre-procedural analgesia therapy and/or non-pharmacologic interventions • % compliance with institutional-specific ICU pain management protocols 	<ul style="list-style-type: none"> • % failed attempts at SBTs due to either over or under sedation • % of patients undergoing EEG monitoring if: <ul style="list-style-type: none"> – at risk for seizures – burst suppression therapy is indicated for \uparrow ICP • % compliance with institutional-specific ICU sedation/agitation management protocols 	<ul style="list-style-type: none"> • % of patients receiving daily physical therapy and early mobility • % compliance with ICU sleep promotion strategies • % compliance with institutional-specific ICU delirium prevention and treatment protocols

Figure 3. A, ICU pain, agitation, and delirium (PAD) care bundle (469). **B**, ICU PAD care bundle metrics; NRS = Numeric Rating Scale; BPS = Behavioral Pain Scale; CPOT = Critical-Care Pain Observation Tool; nonpharmacologic therapy = relaxation therapy, especially for chest tube removal; IV = intravenous; AAA = abdominal aortic aneurysm; NMB = neuromuscular blockade; RASS = Richmond Agitation and Sedation Scale; SAS = sedation-Agitation Scale; brain function monitoring = auditory evoked potentials (AEP), Bispectral Index (BIS), Narcotrend Index (NI), Patient State Index (PSI), or State Entropy (SE); DSI = daily sedation interruption (also referred to as Spontaneous Awakening Trial [SAT]); ETOH = ethanol; nonbenzodiazepines, propofol (use in intubated/mechanically ventilated patients), dexmedetomidine (use in either intubated or nonintubated patients); SBT = spontaneous breathing trial; EEG = electroencephalography; ICP = intracranial pressure; CAM-ICU = Confusion Assessment Method for the ICU; ICDSC = ICU Delirium Screening Checklist.

Care bundles have facilitated translation of practice guidelines to the bedside to manage a number of complex ICU problems, including VAP, catheter-associated bloodstream infections, and sepsis (470, 471). A care bundle includes elements most likely to improve patient outcomes. Elements should be: easy to implement, beneficial, supported by sound scientific and clinical reasoning, and relevant across patient populations and healthcare systems (31). Adherence to each bundle element should be measurable and linked to one or more specific patient outcomes. Quality assurance data should facilitate caregiver feedback and allow rapid-cycle improvement to further customize bundles. This PAD Care Bundle is based on systematically identifying and managing PAD in an integrated fashion, and assessing the effectiveness of these strategies (Fig. 3).

SUMMARY

The goal of these guidelines is to define best practices for optimizing the management of PAD in adult ICU patients. These guidelines were developed by performing a rigorous, objective, transparent, and unbiased assessment of the relevant published evidence based on the GRADE methodology. Statements and recommendations were developed by taking into consideration not only the quality of the evidence but also important clinical outcomes and the values and preferences of ICU stakeholders. We believe that these guidelines provide a practical roadmap for developing evidence-based, best practice protocols for integrating the management of PAD in critically ill patients.

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