The Pain, Agitation, and Delirium Care Bundle: Synergistic Benefits of Implementing the 2013 Pain, Agitation, and Delirium Guidelines in an Integrated and Interdisciplinary Fashion

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Objective: In 2013, the American College of Critical Care Medicine published a revised version of the pain, agitation, and delirium guidelines. The guidelines included an ICU pain, agitation, and delirium care bundle designed to facilitate implementation of the pain, agitation, and delirium guidelines.

Design: Review article.

Setting: Multispecialty critical care units.

Patients: Adult ICU patients.

Interventions: This article describes: 1) the ICU pain, agitation, and delirium care bundle in more detail, linking pain, sedation/agitation, and delirium management in an integrated and interdisciplinary fashion; 2) pain, agitation, and delirium implementation strategies; and 3) the potential synergistic benefits of linking pain, agitation, and delirium management strategies to other evidence-based ICU practices, including spontaneous breathing trials, ICU early mobility programs, and ICU sleep hygiene programs, in order to improve ICU patient outcomes and to reduce costs of care.

Results: Linking the ICU pain, agitation, and delirium management strategies with spontaneous awakening trials, spontaneous breathing trials, and early mobility and sleep hygiene programs is associated with significant improvements in ICU patient outcomes and reductions in their costs of care.

Conclusions: The 2013 ICU pain, agitation, and delirium guidelines provide critical care providers with an evidence-based, integrated, and interdisciplinary approach to managing pain, agitation/sedation, and delirium. The ICU pain, agitation, and delirium care bundle provides a framework for facilitating implementation of the pain, agitation, and delirium guidelines. Widespread implementation of the ICU pain, agitation, and delirium care bundle is likely to result in large-scale improvements in ICU patient outcomes and significant reductions in costs. (*Crit Care Med* 2013; 41:S99–S115)

Key Words: agitation; critical care; delirium; implementation; intensive care; outcomes; pain; pain, agitation, and delirium care bundle; pain, agitation, and delirium guidelines; sedation

The American College of Critical Care Medicine recently published a revised version of the ICU pain, agitation, and delirium (PAD) guidelines (1). Readers are referred to a more in-depth description of the methodology used to develop the 2013 PAD guidelines published earlier in this supplement (2a). The PAD guidelines are the most extensive set of critical care clinical practice guidelines ever to be published. They focus only on adult ICU patients, with a separate set of PICU PAD guidelines in preparation. The PAD guidelines include both short- and long-term PAD management for both intubated and nonintubated ICU patients. They provide a more diverse set of recommendations for both medical and surgical ICU patients, and they include specific recommendations for using regional analgesia in ICU patients.

A central tenet of these PAD guidelines is the importance of managing pain, agitation/sedation, and delirium in critically ill patients in an integrated and interdisciplinary fashion. Compared with previous versions of these guidelines, the 2013 PAD guidelines are more evidence based and patient centered. There is a much greater emphasis on the need for better recognition and treatment of pain and delirium in critically ill patients and for minimizing the use of sedatives in ICU patients. The PAD guidelines include strong recommendations for the use of valid and reliable assessment tools for detecting

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significant pain, over- or under-sedation, and delirium in critically ill patients. PAD treatment strategies focus more on the process and approach to PAD management rather than making specific recommendations for using certain medications in different clinical situations. They include strong recommendations for assessing and treating pain first before administering sedatives and for maintaining a light level of sedation that allows for ICU patients to interact in a meaningful way with the ICU environment, without agitation. They include specific recommendations to both prevent and treat delirium in ICU patients, using both nonpharmacologic and pharmacologic strategies.

An ICU PAD care bundle was created as part of the PAD guidelines to help facilitate guideline implementation. The PAD care bundle focuses on assessing, treating, and preventing PAD in an integrated and interdisciplinary fashion. It also links PAD management to other evidence-based ICU practices, such as spontaneous awakening trials (SATs), spontaneous breathing trials (SBTs), ICU early mobility (EM) programs, and ICU sleep hygiene programs, in order to achieve synergistic benefits in ICU outcomes and to reduce costs. This article describes the ICU PAD care bundle in greater detail, along with PAD implementation strategies, and outlines the potential benefits of linking PAD management to other ICU best practices.

METHODS

The 2013 PAD guideline recommendations have been incorporated into an ICU PAD care bundle (**Fig. 1, *A*** and ***B***) that provides a systematic approach to help operationalize the PAD guideline recommendations in a stepwise fashion, integrating the *assessment*, *treatment*, and *prevention* of pain, agitation/sedation, and delirium in critically ill patients (1). The bundle also links PAD management strategies with other ICU interventions (i.e., SAT, SBTs, EM protocols, and sleep management strategies to preserve patients' sleep-wake cycles), in order to achieve additional improvements in ICU patient outcomes.

Assessment of Pain, Agitation-Sedation, and Delirium

PAD Assessments—Pain. Pain assessments using *valid* and *reliable* assessment tools should provide the basis for the treatment of pain in critically ill patients. This includes using a numerical rating scale (NRS) (i.e., Likert scale) for patients who can self-report their pain and the use of one of the behavioral pain scales (BPSs) for those ICU patients who cannot. Most critically ill patients are likely to experience significant pain at some point during their ICU stay (2b) and identify it as a great source of stress and discomfort (3–6). Significant pain is not limited to surgical ICU patients; at least 50% of both medical and surgical ICU patients experience significant pain during their ICU stay (7, 8). Procedures are also a significant source of pain for critically ill patients, and inadequate treatment of procedural pain remains a significant problem for many ICU patients (9–16). In spite of the ubiquitous nature of pain in the ICU, many critically ill patients may be unable to self-report their pain, either verbally or with gestures, because of an altered level of consciousness, the use of sedatives or neuromuscular blocking agents, or mechanical ventilation (17).

The PAD guidelines make a strong recommendation for performing routine pain assessments in all ICU patients, regardless of whether patients can self-report their pain or not. Patients' self-reporting is considered the "gold standard" in pain assessment. A recent study by Chanques et al (18) compared five commonly used self-report pain assessment tools in ICU patients and found that the 0–10 visually enlarged laminated NRS had the highest degree of sensitivity and specificity for detecting significant pain in critically ill patients who can self-report. In the absence of an objective method for measuring pain in critically ill patients who cannot self-report, a valid and reliable bedside pain assessment tool that incorporates patients' behaviors as indicators of pain should be used. A rigorous psychometric analysis of six BPSs included in the PAD guidelines found that the BPS and the Critical-Care Pain Observation Tool (CPOT) are the most valid and reliable for use in ICU patients (1). A recently updated psychometric analysis of eight BPSs, including studies published since 2010, came to a similar conclusion (19).

Although NRSs or symbolic equivalents are commonly used as ICU pain assessment tools, BPSs have yet to be widely adopted in ICUs (20). In the absence of a BPS, pain assessments in nonverbal ICU patients are often left to self-interpretation by ICU nurses and physicians, who frequently use patients' vital signs as a metric for untreated pain. But reliance on vital signs to predict pain may be misleading, since they correlate poorly with the presence or absence of pain in these patients (21–24). Because of this fact, the PAD guidelines recommend that changes in patients' vital signs should only be considered as a cue to begin further pain assessments (1). Implementing BPSs (e.g., BPS or CPOT) improves both ICU pain management and clinical outcomes, including better use of analgesic and sedative agents, and shorter durations of mechanical ventilation and ICU length of stay (LOS) (20, 25, 26).

The ICU PAD care bundle mandates that pain assessments be performed and documented in ICU patients at least four times per nursing shift (i.e., q2–3 hr), and more frequently as needed. Patients are considered to be in significant pain if they self-report their pain intensity of 4 or greater (0–10 NRS) or have either a BPS score of 6 or greater (BPS range = 3–12) or CPOT score of 3 or greater (CPOT range = 3–8) if they cannot self-report.

PAD Assessments—Agitation/Sedation. Agitation and anxiety occur frequently in critically ill patients and can lead to adverse clinical outcomes (27–31). Common causes of agitation and anxiety in ICU patients include untreated pain, delirium, hypoxemia, hypoglycemia, hypotension, or withdrawal from alcohol and other drugs. Although prompt identification of the underlying cause of patient agitation is important, sedatives are commonly administered to these patients in order to prevent and treat agitation and its negative consequences (32).

A

	PAIN	AGITATION	DELIRIUM
ASSESS	Assess pain ≥4x/shift & prn Preferred pain assessment tools: • Patient able to self-report → NRS (0-10) • Unable to self-report → BPS (3-12) or CPOT (0-8) Patient is in significant pain if NRS ≥ 4, BPS > 5, or CPOT ≥ 3	Assess agitation, sedation ≥4x/shift & prn Preferred sedation assessment tools: • RASS (-5 to +4) or SAS (1 to 7) • NMB → suggest using brain function monitoring Depth of agitation, sedation defined as: • *agitated* if RASS = +1 to +4, or SAS = 5 to 7 • *awake and calm* if RASS = 0, or SAS = 4 • *lightly sedated* if RASS = -1 to -2, or SAS = 3 • *deeply sedated* if RASS = -3 to -5, or SAS = 1 to 2	Assess delirium Q shift & prn Preferred delirium assessment tools: • CAM-ICU (+ or -) • ICDSC (0 to 8) Delirium present if: • CAM-ICU is positive • ICDSC ≥ 4
TREAT	Treat pain within 30' then reassess: • Non-pharmacologic treatment–relaxation therapy • Pharmacologic treatment: – Non-neuropathic pain → IV opioids +/- non-opioid analgesics – Neuropathic pain → gabapentin or carbamazepine, + IV opioids – S/p AAA repair, rib fractures → thoracic epidural	Targeted sedation or DSI (*Goal: patient purposely follows commands without agitation*): RASS = -2 – 0, SAS = 3 - 4 • If *under sedated* (RASS >0, SAS >4) assess/treat pain → treat w/sedatives prn (non-benzodiazepines preferred, unless ETOH or benzodiazepine withdrawal is suspected) • If *over sedated* (RASS <-2, SAS <3) hold sedatives until at target, then restart at 50% of previous dose	• Treat pain as needed • Reorient patients; familiarize surroundings; use patient's eyeglasses, hearing aids if needed • Pharmacologic treatment of delirium: – *Avoid* benzodiazepines unless ETOH or benzodiazepine withdrawal is suspected – *Avoid* rivastigmine – *Avoid* antipsychotics if ↑ risk of Torsades de pointes
PREVENT	• Administer pre-procedural analgesia and/or non-pharmacologic interventions (e.g., relaxation therapy) • Treat pain first, then sedate	• Consider daily SBT, early mobility and exercise when patients are at goal sedation level, unless contraindicated • EEG monitoring if: – at risk for seizures – burst suppression therapy is indicated for ↑ ICP	• Identify delirium risk factors: dementia, HTN, ETOH abuse, high severity of illness, coma, benzodiazepine administration • Avoid benzodiazepine use in those at ↑ 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
ASSESS	• % 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	• % of time sedation assessments are performed ≥4x/shift • Demonstrate local compliance and implementation integrity over time in the use of ICU sedation scoring systems	• % of time delirium assessments are performed Q shift • Demonstrate local compliance and implementation integrity over time in the use of ICU delirium assessment tools
TREAT	• % 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	• % 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 *under sedated* (RASS >0, SAS >4) • % of time ICU patients are either *over sedated* (non-therapeutic coma; RASS <-2, SAS <3) or fail to undergo DSI trials	• % 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)
PREVENT	• % of time patients receive pre-procedural analgesia therapy and/or non-pharmacologic interventions • % compliance with institutional-specific ICU pain management protocols	• % failed attempts at SBTs due to either over or under sedation • % of patients undergoing EEG monitoring if: – at risk for seizures – burst suppression therapy is indicated for ↑ ICP • % compliance with institutional-specific ICU sedation/agitation management protocols	• % 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 1. A, The ICU pain, agitation, and delirium (PAD) care bundle. **B**, ICU PAD care bundle Metrics (1). NRS = numeric rating scale, BPS = behavioral pain scale, CPOT = Critical-Care Pain Observation Tool, nonpharmacologic therapy = relaxation therapy (especially for chest tube removal), AAA = abdominal aortic aneurysm, NMB = neuromuscular blockade, RASS = Richmond Agitation-Sedation Scale, SAS = Sedation-Agitation Scale, brain function monitoring = auditory evoked potentials (AEPs), Bispectral Index (BIS), Narcotrend Index (NI), Patient State Index (PSI), or State Entropy (SE); DSI = daily sedation interruption (or spontaneous awakening trial [SAT]), HTN = hypertension, ETOH = ethanol, nonbenzodiazepines = propofol (use in intubated/mechanically ventilated patients) and 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.

The PAD guidelines strongly recommend the use of a valid and reliable sedation scoring system to routinely assess depth of sedation and agitation in ICU patients, and the results of these sedation/agitation assessments should provide the basis for the use of sedatives in critically ill patients (1). The administration of sedatives to critically ill patients without titrating these medications to a specific sedation scale endpoint often results in ICU patients becoming oversedated (33). This can result in prolongation of mechanical ventilation, an increased prevalence of ICU delirium and neuropsychological sequelae, increased ICU LOS, and an increased risk of death in these patients (34–39). The use of sedation scales, as part of an ICU sedation protocol, allows for ICU clinicians to administer and titrate sedative agents more appropriately in critically ill patients and results in significant improvements in these clinical outcomes (40–45).

The PAD guidelines included a rigorous psychometric analysis of 10 sedation scales and concluded that 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. A more recent analysis of the psychometric properties of 11 sedation scales, including studies published since 2010, came to a similar conclusion regarding the RASS and SAS scales (see article by Robinson et al [46] in this supplement).

The ICU PAD care bundle mandates that sedation/agitation assessments be performed and documented in all ICU patients, using either the RASS or SAS sedation scale, at least four times per nursing shift (i.e., q2–3 hr), and more frequently as needed. The RASS scale uses 10 discrete levels to define depth of sedation and agitation, ranging from –5 (unarousable) to +4 (combative) (47). By contrast, the SAS scale has seven discrete levels ranging from 1 (unarousable) to 7 (dangerously agitated) (48). Depth of sedation in patients using either of these scales is defined as follows: *agitation* if RASS = +1 to +4 or SAS = 5 to 7; *awake and calm* if RASS = 0 or SAS = 4; *lightly sedated* if RASS = –1 to –2 or SAS = 3; and *deeply sedated* if RASS = –3 to –5 or SAS = 1 to 2.

PAD Assessments—Delirium. Delirium is 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 (49–54). Patients with delirium may either be agitated (i.e., hyperactive delirium), calm or lethargic (i.e., hypoactive delirium), or may fluctuate between the two subtypes. Hyperactive delirium is more often associated with hallucinations and delusions, whereas hypoactive delirium is more often characterized by confusion and sedation and is often undetected.

Delirium occurs commonly in critically ill patients. It is estimated that in up to 80% of critically ill patients delirium develops during their ICU stay (53, 55, 56). The presence of delirium in ICU patients is associated with significant negative outcomes, including prolonged duration of mechanical ventilation (57), prolonged hospital LOS (53, 56, 58), postdischarge institutionalization (59), long-term cognitive dysfunction (60, 61), an increased risk of death (56), and higher costs of care (62). ICU delirium has also recently been associated with a greater likelihood of patients developing long-term cognitive dysfunction (60). Hypoactive delirium occurs much more commonly than hyperactive delirium in ICU patients and is associated with a longer duration of mechanical ventilation and ICU LOS and a higher mortality risk than hyperactive delirium (63–67).

Reliable detection and diagnosis of delirium is essential for delirium treatment and for improving delirium-related ICU outcomes. Currently, only 25–59% of intensivists routinely screen their patients for delirium (68, 69), and 62% of intensivists in North America rely on a general clinical assessment to screen for delirium, which lacks sufficient sensitivity to detect delirium in these patients (70–72). Uninformed delirium assessments by ICU nurses are also notoriously unreliable for detecting delirium. One study comparing delirium observations by ICU nurses with delirium assessments performed by a trained ICU nurse using the Confusion Assessment Method for the ICU (CAM-ICU) delirium assessment tool showed poor agreement between the two, with a sensitivity of only 27% for casual assessments of delirium by untrained ICU nursing staff (73). ICU personnel often underestimate the presence of delirium in patients because it frequently presents as hypoactive rather than hyperactive form of delirium (74, 75).

The PAD guidelines make a strong recommendation for routinely monitoring ICU patients for delirium, using a valid and reliable delirium assessment tool (1). The PAD guidelines included a rigorous psychometric analysis of five delirium monitoring tools and concluded that the CAM-ICU (53) and the Intensive Care Delirium Screening Checklist (ICDSC) (54) are the most valid and reliable delirium monitoring tools for use in adult ICU patients.

The ICU PAD care bundle mandates that delirium assessments be performed and documented in all ICU patients, using either the CAM-ICU or the ICDSC tool, at least once a shift (i.e., q8–12 hr), and more often as needed. A patient is considered delirious if they are either CAM-ICU positive or their ICDSC score is greater than or equal to 4 (ICDSC scale range = 0–8).

PAD Treatment Strategies

The results of these PAD assessments should ultimately be incorporated into the daily discussions on interdisciplinary ICU rounds, with ICU teams addressing each patient's current pain score and analgesia regimen, current and target sedation scores and sedation regimen, and current delirium score and delirium risk factors and treatment regimen. These assessments should then be incorporated into a treatment plan tailored to each patient for managing pain, agitation or oversedation, and delirium, using PAD protocols specific to the culture and formulary of each individual ICU. PAD protocols can help to facilitate the transfer of evidence-based "best practices" to the bedside, limit practice variation, and reduce treatment delays (20, 26). A protocolized approach to managing PAD can also significantly improve ICU patient outcomes and serve as a guide for quality assurance efforts (45, 76–78). The

ICU PAD care bundle does not propose a one-size-fits-all drug treatment strategy for all ICU patients, but the treatment goals for all ICU PAD protocols should nevertheless be the same: 1) focus on patients' pain management first, then sedate patients only if needed; 2) choose sedatives based on their pharmacologic profile and the individual sedation goals for each patient, using nonbenzodiazepines preferentially; 3) maintain a light level of sedation in ICU patients, which allows for patients to meaningfully interact with the ICU environment without agitation whenever possible; and 4) use both nonpharmacologic and pharmacologic treatment strategies to manage delirium in ICU patients.

Pain Management. Optimize pain management in critically ill patients by assessing and treating their pain first, *then* sedating them only if needed. It is important to recognize that ICU patients, even those who are mechanically ventilated, may require little or no sedative medications as long as their pain is well controlled (20, 79). And ICU patients who are managed with an analgesia-first (i.e., analgosedation) strategy have significant reductions in their duration of mechanical ventilation and ICU LOS (79, 80). Treat all significant pain in a timely fashion (i.e., < 30 min of diagnosing significant pain), employing patient-specific pain management strategies (i.e., opioids ± nonopioids for nonneuropathic pain, gabapentin or carbamazepine ± opioids for neuropathic pain, and epidural analgesia for postoperative pain and rib fractures) (1).

Opioids remain the primary analgesic of choice in critically ill patients with nonneuropathic pain, with all IV opioids being equally effective at equipotent doses (81–97). Oral opioids may be variably absorbed with reduced bioavailability in critically ill patients. Nonopioids (i.e., acetaminophen), nonsteroidal medications (i.e., ketorolac, ibuprofen), and ketamine can provide adjunctive pain relief, reduce overall opioid requirements, and help to minimize opioid side effects in critically ill patients (81, 84, 85, 93, 98). Either oral gabapentin or carbamazepine should be administered as first-line treatment of neuropathic pain in critically ill patients, using both nonopioids and opioids for adjunctive pain relief in these patients (82, 83). Neuraxial analgesia, specifically thoracic epidural analgesia, should be reserved for critically ill patients with rib fractures and in patients who have undergone abdominal aortic surgery (99–102). Lumbar epidurals provide no clear benefit over parenteral opioids for postoperative analgesia in patients who have undergone abdominal aortic surgery, and thoracic epidurals provide no clear benefit over parenteral opioids in patients who have undergone intrathoracic or nonvascular abdominal surgical procedures (100, 103–111). Once the appropriate pain medications have been administered, ICU patients should have their pain reassessed within 30 minutes using an appropriate pain assessment tool to determine analgesic efficacy.

Sedation Management. Optimize sedation management by sedating ICU patients only as needed while maintaining a light level of sedation. A light level of sedation is defined in the PAD guidelines as a level of consciousness that allows for ICU patients to be responsive and aware, as demonstrated by their ability to follow three of five specific commands upon request (i.e., open eyes, maintain eye contact, squeeze hand, stick out tongue, and wiggle toes) (112–115). This degree of patient responsiveness and awareness is essential for the evaluation of pain through patients' self-report, for assessing patients' readiness to wean and extubate, for performing delirium assessments in patients, and for implementing EM efforts. Light sedation may be achieved using *either* targeted sedation strategies (TSSs) or daily sedation holidays.

The PAD guidelines did not recommend the use of daily sedation interruption (DSI) strategies that allows ICU patients to emerge from deeper levels of sedation to a light level of sedation on a daily basis over sedation protocol that routinely targets light sedation (i.e., TSS), due to the lack of high-quality studies comparing these two strategies. A more recent multicenter trial by Mehta et al (116) found no clear benefit of combining TSS with DSI to manage sedation in ICU patients. However, there are major shortcomings to this study. It is not clear from their results as to what percentage of time both the treatment and control groups achieved their target level of sedation (i.e., SAS = 3–4 or RASS = –3 to 0). In addition, both groups received moderate doses of sedatives and opioids throughout the study period. Specifically, the treatment group received an average sedative dose of 4.24 mg/hr, and the control group received an average of 3.4 mg/hr in terms of *midazolam* equivalents, and the treatment group received an average opioid dose of 74 μg/hr, whereas the control group received an average of 45 μg/hr in terms of fentanyl equivalents. Pharmacologic modeling of these doses of midazolam and fentanyl suggests that a significant number of patients in both the treatment and control groups were likely to be at a deeper level of sedation than the sedation protocol specified for much of the time, which may account for the lack of difference in outcomes between the two groups (117).

Sedative choice in ICU patients should be based primarily upon using sedatives that minimize side effects and improve patient outcomes. IV benzodiazepines, especially midazolam, are the most commonly used sedative-hypnotics for sedation of adult ICU patients, followed by propofol and dexmedetomidine (8, 68, 118–120). Barbiturates, diazepam, and ketamine are used rarely for sedation of adults in the ICU. Over the past decade, there is a growing body of evidence that the use of IV benzodiazepines for sedation of ICU patients, specifically midazolam and lorazepam, is associated with worse ICU outcomes than sedation with nonbenzodiazepines (specifically propofol and dexmedetomidine) (40–45, 121–126).

As part of the PAD guidelines, a meta-analysis was conducted of 13 studies (n = 1,551) comparing clinical outcomes in ICU patients sedated with either benzodiazepines (midazolam or lorazepam) or nonbenzodiazepines (propofol or dexmedetomidine) (1). Across all 13 studies, there was no significant difference in ICU LOS (127–139). But a more limited meta-analysis of 6 of the 13 studies that were of moderate to high quality demonstrated that benzodiazepines did increase ICU LOS by approximately 0.5 days compared with nonbenzodiazepines (127–139). Four studies suggested that mechanical ventilation is prolonged with benzodiazepine-based sedation

(127–139), and four studies showed no apparent difference in mortality with benzodiazepine versus nonbenzodiazepine sedation (127–139).

An updated version of benzodiazepine versus nonbenzodiazepine meta-analysis published by Fraser et al (140) in this supplement supports the findings of the PAD guideline meta-analysis. This updated meta-analysis included a total of six ICU sedation outcome studies (n = 1,235) comparing midazolam versus dexmedetomidine (127–139, 141), lorazepam versus dexmedetomidine (139), midazolam versus propofol (128), and lorazepam versus propofol (127). This meta-analysis showed that the use of either dexmedetomidine or propofol for ICU sedation was associated with an even shorter ICU LOS (1.6 d) and a significant reduction in mechanical ventilation (1.9 d) than with benzodiazepine sedation. There was no effect on delirium prevalence or short-term mortality in this meta-analysis, though heterogeneity in the way delirium prevalence was measured in the two studies (139) may have resulted in these results given that both studies showed reductions in delirium prevalence over time (139).

There are several important differences between the two versions of these meta-analyses of sedative-related outcomes. The original meta-analysis included in the PAD guidelines was limited to assessing ICU LOS as the only outcome, and three of the six studies included in this meta-analysis were in cardiac surgery patients, a patient population with distinct clinical practices and generally a shorter ICU LOS (136–138). By contrast, the meta-analysis by Fraser et al excluded studies of cardiac surgery patients but included one high-quality multicenter trial (i.e., the Midazolam vs Dexmedetomidine for Sedation During Prolonged Mechanical Ventilation or MIDEX trial), which was published since the PAD guidelines meta-analysis was initially performed (141). The outcomes of interest in the MIDEX trial included duration of mechanical ventilation as well as ICU and hospital LOS, but not delirium prevalence or mortality. In addition to looking at ICU LOS, this newer meta-analysis also looked at duration of mechanical ventilation, delirium prevalence, and short-term mortality—outcomes, which were not included in the original PAD guideline meta-analysis due to an insufficient number of studies. The exact relationship between the use of benzodiazepines and delirium prevalence in ICU patients could not be answered in this meta-analysis, due to an insufficient number of high-quality studies designed to address this issue and the heterogeneity in these studies. The findings of the meta-analysis by Fraser et al nevertheless reinforce the PAD guideline recommendations for preferentially using nonbenzodiazepines for sedating adult ICU patients.

At the time of the initial literature review for the PAD guidelines, only two low-quality studies had been published comparing clinical outcomes in ICU patients receiving propofol versus dexmedetomidine for sedation (131, 132). Since that time, the results of a single large, multicenter study has been published (i.e., the Propofol vs Dexmedetomidine for Sedation During Prolonged Mechanical Ventilation or PRODEX trial), comparing ICU outcomes related to propofol versus dexmedetomidine for ICU sedation (141). In that study (n = 498), there were no differences observed in terms of duration of mechanical ventilation, ICU or hospital LOS, or mortality between the two treatment groups. Delirium prevalence was not an outcome measure in the PRODEX trial. More studies are needed to address this issue of delirium prevalence as it relates to sedative choice in ICU patients. Of note, there are currently no published studies comparing clinical outcomes in ICU patients sedated with ketamine versus other sedative agents.

In spite of the apparent benefits of using nonbenzodiazepines, it is important to note that the PAD guidelines do not specifically recommend that benzodiazepines should never be used for ICU sedation. Given their anxiolytic, amnesic, and anticonvulsant properties, benzodiazepines remain an important class of drugs for sedating critically ill patients. Benzodiazepines are still recommended as the sedative of choice for treating drug withdrawal syndromes in critically ill patients, especially ethanol or benzodiazepine withdrawal (142). Benzodiazepines may also be indicated for sedation of critically ill patients with intractable seizures. Finally, benzodiazepines can provide synergistic sedative effects in ICU patients who cannot otherwise be effectively sedated with propofol and/or dexmedetomidine alone or in whom required doses of each individual sedative cannot be reduced (120, 143).

Decisions regarding the choice of sedative agent to use in critically ill patients should ultimately be driven by: 1) the specific indications for sedation and the sedative goals for each patient; 2) the compatibility between the clinical pharmacology of a sedative, its side effect profile, and the relative contraindications for its use in a critically ill patient; and 3) the overall costs (not limited to pharmacy costs) associated with using a particular sedative.

Delirium Management. The first step in treating delirium is to identify and eliminate potential contributing factors such as treatable disease states that can induce delirium (i.e., sepsis, shock states, glycemic dysregulation, electrolyte disorders, and hypoxia); inadequately treated pain; drug withdrawal; discontinuation of patients' psychiatric medications; exposure to deliriogenic medications (i.e., benzodiazepines) or adverse drug effects; and environmental factors (i.e., sleep deprivation, disorientation, prolonged immobilization, and use of restraints). If delirium persists once identifiable causes have been eliminated, delirium treatment should include both nonpharmacologic and pharmacologic treatment strategies, with an emphasis on using nonpharmacologic interventions first. Proven nonpharmacologic delirium treatment strategies (some in non-ICU and others in ICU patients as well) include: 1) frequent reorientation of ICU patients, giving them access to their eyeglasses and hearing aids, if needed (144); 2) maintaining patients' sleep-wake cycles by minimizing environmental and procedural disturbances at night (145); and 3) advancing patients' mobility during the day as tolerated, with the ultimate goal of getting patients out of bed each day, even when they are intubated and mechanically ventilated (146, 147). Pharmacologic treatment of delirium should include: 1) adequate analgesia; 2) discontinuation of benzodiazepines (except in patients with suspected ethanol or benzodiazepine withdrawal); 3) resumption of patients' psychiatric

medications, if indicated; 4) treatment of drug withdrawal syndromes, if suspected; and 5) antipsychotics, if needed.

The 2013 PAD guidelines have a limited number of recommendations on the use of antipsychotics for the management of delirium in ICU patients, primarily due to a lack of clear evidence for the safety and efficacy of these medications in this patient population. A Cochrane review published in 2007 on the use of antipsychotics for the treatment of delirium did not specifically address their use in ICU patients (148). A more recent review of the literature published in 2012 concluded that the pharmacologic efficacy of antipsychotics for the treatment of ICU delirium is limited by "the small size of many studies, the inconsistency by which nonpharmacologic delirium prevention strategies were incorporated, the lack of a true placebo arm, and a failure to incorporate ICU and non-ICU clinical outcomes" (149). Robust studies of the treatment of delirium with haloperidol and other antipsychotics in non-ICU patients that could potentially be applied to ICU patients are also lacking. Nevertheless, antipsychotics, and haloperidol in particular, are commonly administered for the treatment of delirium in critically ill patients (68). The administration of antipsychotic medications for the treatment of delirium in ICU patients is also endorsed in several other clinical practice guidelines (150–158).

To date, there are only three published studies on the safety and efficacy of using antipsychotics for the treatment of delirium in ICU patients. The largest of these (n = 103), the Modifying the Incidence of Delirium trial, found that the number of delirium- or coma-free days was not different between ICU patients receiving ziprasidone (an atypical antipsychotic), haloperidol, or placebo for delirium (159). Devlin et al (160) compared delirium outcomes in ICU patients receiving haloperidol plus either quetiapine (atypical) or placebo (n = 36) and found that the addition of quetiapine to haloperidol was associated with a shorter duration of first episode of delirium, with no significant differences in ICU LOS or duration of mechanical ventilation. The shortcomings of this study were its small sample size and the fact that it did not reach its enrollment target. Skrobik et al (161) compared the safety and efficacy of olanzapine (atypical) versus haloperidol for the treatment of delirium in ICU patients (n = 73) and found improvements in the severity of delirium symptoms and a reduction in the need for sedatives over time, without significant differences between the two treatment groups. But patients treated with haloperidol in this study experienced more extrapyramidal side effects. Sufficiently powered and carefully designed, multicenter, placebo-controlled trials are needed to determine the safety and efficacy of using antipsychotics for the treatment of delirium in critically ill patients.

The PAD guideline recommendations for the use of antipsychotics in the treatment of delirium are limited to: 1) haloperidol for the treatment of delirium—*no recommendation*, due to a lack of evidence; 2) atypical antipsychotics may reduce the duration of delirium in ICU patients (based only on the study by Devlin et al [160]); 3) a strong recommendation *against* the use of rivastigmine (a cholinesterase inhibitor) for the treatment of delirium in ICU patients (based on a multicenter trial demonstrating that treatment of delirium in ICU patients with rivastigmine increases the severity and duration of delirium and the likelihood of death in these patients) (162); and 4) a weak recommendation against the use of antipsychotics in patients with prolonged Q-T interval or other risk factors for torsades de pointes (163–173).

PAD Prevention Strategies

The ICU PAD care bundle includes several important PAD prevention strategies. These include: 1) preemptively treating procedural pain in all ICU patients; 2) minimizing the need for sedation by linking SBTs with sedation protocols to facilitate patients' weaning from mechanical ventilation; and 3) preventing delirium by promoting EM and preserving sleep-wake cycles in ICU patients.

Pain Prevention. Procedure-related pain occurs commonly in ICU patients, and inadequate treatment of procedural pain remains a significant problem for many of these patients (14, 174). Pain in ICU patients can trigger a significant stress response, leading to hemodynamic instability, impaired wound healing, hyperglycemia, and an increased risk of infections (175–179). Pain also has significant negative short- and long-term psychological consequences in ICU patients, including sleep deprivation during their stay in the ICU (180), persistent recollections of them experiencing significant pain in the ICU (6, 181–183), and a higher likelihood of patients developing chronic pain, Posttraumatic stress disorder symptoms, and a lower health-related quality of life after ICU discharge (184).

The prevalence and severity of procedural pain varies across ICU patient populations. Procedural pain varies with age (10, 12) and is more intense in non-Caucasians than in Caucasians (10, 12, 14). Differences in procedural pain between nonsurgical and surgical patients also vary according to the procedure (10, 12, 14).

In spite of its high prevalence, less than 25% of ICU patients receive analgesics prior to initiating procedures in the ICU (14). Preprocedural administration of analgesics, particularly opioids, significantly reduces the prevalence of significant procedural pain in ICU patients (185). Although opioids remain the systemic analgesics of choice for procedural pain, both nonopioids and relaxation therapy may provide adjunctive pain relief in these instances. The PAD guidelines recommend that procedural pain be preemptively treated in all ICU patients, given the prevalence of significant pain associated with invasive procedures, the short- and long-term negative consequences of untreated pain in these patients, and the minimal risks associated with preemptive analgesic therapy.

Sedation/Agitation Prevention. The best way to reduce the risks associated with ICU sedation is to reduce the need for sedation in these patients. Mechanical ventilation remains the major indication for the administration of sedative medications in the ICU, and ventilator weaning protocols that include daily SBTs can significantly reduce the duration of mechanical ventilation in critically ill patients (186). But it can be difficult to perform SBTs in ICU patients who are in a

drug-induced coma, and deep sedation has been identified as an independent risk factor for both delaying the weaning and extubation of critically ill patients and prolonging their ICU LOS (38, 39, 43, 113, 187).

SATs or DSI, when performed in conjunction with SBTs, can help to facilitate the liberation of ICU patients from mechanical ventilation (187–189). Data from several studies suggest that DSI protocols significantly reduce the duration of mechanical ventilation and ICU LOS (113, 114, 187, 190). However, it may not be necessary to suspend sedative medications altogether before performing an SBT, as long as ICU patients are alert enough to cooperate (i.e., a baseline RASS of –3 to 0 or SAS of 3–4), and have a sufficient respiratory drive to breathe spontaneously when the SBT is performed. Data from studies assessing the impact of TSSs that maintain a light level of sedation without DSI have also been shown to be effective in facilitating weaning from mechanical ventilation in ICU patients (40–45, 121, 122, 191, 192). As previously discussed, it remains unclear as to whether combining a TSS sedation protocol with DSI has any synergistic benefit to facilitating SBTs in ICU patients; the one study designed to address this issue showed no benefit, but suffered from a number of methodological flaws (116). More research is needed to address this issue. Given the equivocal nature of the evidence, the PAD guidelines recommend that *either* DSI or TSS be used to facilitate daily SBTs in mechanically ventilated ICU patients, in order to shorten the duration of mechanical ventilation and reduce the need for continuous sedation in these patients (1). Of note, no study has demonstrated worsening of outcomes when combining DSI with TSS.

Delirium Prevention. The PAD guidelines focus primarily on *nonpharmacologic* strategies preventing delirium, including recommendations for early mobilization and environmental management to promote sleep in ICU patients (1). Two studies have demonstrated that the institution of an ICU EM program is associated with significant reductions in the prevalence of delirium and other improvements in ICU outcomes (146, 147). In both of these studies, the functional status of patients admitted to a medical ICU was assessed on a daily basis by an interdisciplinary ICU team that included ICU physicians, nurses, respiratory therapists, physical therapists (PTs), and occupational therapists (OTs). ICU guidelines were developed for obtaining PT/OT consults on all patients, and PT and OT staff members were specifically assigned to the ICU. Sedation management practices were altered to ensure that patients were not deeply sedated, which might preclude them from participating in daily ICU EM activities. Activity levels ordered for all ICU patients were modified from "bed rest" to "as tolerated." Specific criteria were developed as part of a safety screen to determine eligibility of patients for daily physical therapy and mobility. In the study by Needham et al (147), the prevalence of delirium in ICU patients decreased significantly, along with ICU sedative use. In addition, ICU LOS decreased by an average of 2.1 days, and hospital LOS decreased by an average of 3.1 days, while there was no significant change in hospital mortality. In the study by Schweickert et al (146), ICU patients who received routine physical therapy via an ICU EM protocol were more likely to: 1) achieve an independent functional status at the time of hospital discharge (59% vs 35% in the control group, $p = 0.02$); 2) have a shorter duration of delirium (2 d vs 4 d in the control group, $p = 0.02$); and 3) have more ventilator-free days (23.5 d vs 21.1 d in the control group, $p = 0.05$) than ICU patients who did not receive routine physical therapy. Effective strategies for creating and implementing an ICU EM program have been described in more detail elsewhere, including another article published by Engel et al (193) in this supplement (194). Readers are also referred to the Mobilization-Network (195) and Institute for Healthcare Improvement websites for additional details on how to implement an ICU EM program (196).

ICU patients frequently suffer from poor quality of sleep (197–202). The causes of sleep disturbances in critically ill patients are multifactorial and include round-the-clock environmental visual, auditory, and physical stimuli in the ICU, poorly treated pain (180), the use of sedatives and other medications, mechanical ventilation, and underlying disease processes (203, 204). Although sleep deprivation has been associated with delirium in ICU patients, the exact cause and effect relationship between sleep and delirium in these patients remains unclear (203, 205–208). Nevertheless, improving sleep hygiene in the ICU reduces both the prevalence and duration of delirium in critically ill patients (145).

The PAD guidelines include a strong recommendation for developing and implementing programs to promote sleep in ICU patients by using strategies to control light and noise, clustering ICU patient care activities, and decreasing stimuli at night to protect patients' sleep cycles (1). Implementing quiet time on both day and night shifts and clustering patient care activities in the ICU result in both subjective and objective improvements in sleep in ICU patients (209–211). Sleep hygiene programs in non-ICU hospitalized patients have been associated with a reduced prevalence of delirium (212). A recent study by Kamdar et al (145) ($n = 300$) demonstrated that the implementation of an evidence-based sleep hygiene program in a medical ICU resulted in significant nighttime noise reductions in the ICU and a significant decrease in the prevalence of delirium in these patients as well. Nighttime ICU environmental interventions in this study included minimizing overhead pages, turning off patient televisions, dimming hallway lights, and grouping patient care activities at specific time intervals. Daytime interventions to promote normal circadian rhythms and nighttime sleep by ICU patients included raising the window blinds, preventing excessive napping, encouraging patient mobilization during the day, and minimizing caffeine intake in the evening. The use of earplugs by ICU patients has also been shown to improve sleep quality and to reduce the prevalence of delirium in these patients (213). Van Rompaey et al randomized adult ICU patients to the use of nighttime earplug or no earplugs. Patients sleeping with earplugs reported better sleep during the first night in the ICU, and fewer patients in this group subsequently developed delirium or mild confusion during the five-night study period. More broadly targeted, multifactorial programs that

go beyond promoting sleep in non-ICU hospitalized patients have also been shown to be effective at preventing delirium (212, 214–216), but such multifaceted interventions have not been adequately studied in the ICU patient population. ICU light and noise reduction strategies including the use of earplugs, normalizing day-night illumination, minimizing ICU care-related interventions during normal sleeping hours, and interventions promoting ICU patient comfort and relaxation are low risk and inexpensive and should be implemented to prevent delirium in ICU patients.

At the time that the PAD guidelines were developed, there was no clear evidence that prophylactically administering either antipsychotics or dexmedetomidine for sedation was effective at preventing delirium in ICU patients. Thus, no recommendations were made for the use of one or more pharmacologic agents to prevent delirium in critically ill patients. A recent delirium prophylaxis study by van den Boogaard et al (217) in a mixed ICU patient population (n = 476 medical, surgical, trauma, and neurosurgical ICU patients) showed that the administration of haloperidol prophylactically to ICU patients who were at "high risk" for delirium (0.5–1 mg IV q8 hr, age adjusted) significantly reduced the prevalence of delirium in these patients (i.e., 65% vs 75% in the control group, $p = 0.01$). Haloperidol was stopped in 12 patients, however, because of QTc-time prolongation ($n = 9$), renal failure ($n = 1$), and neurological side effects ($n = 2$). Larger studies are needed to confirm the safety and efficacy of haloperidol and other antipsychotics for the prevention of delirium in critically ill patients.

PAD Care Bundle Implementation Strategies

Successful implementation of the ICU PAD care bundle requires an integrated and interdisciplinary team-based approach, led by an ICU clinician-champion (not necessarily a physician) and representative of all ICU stakeholders (i.e., physicians, nurses, respiratory therapists, pharmacists, PTs and OTs, hospital administrators, and ICU patients and families). Broadly targeted staff, patient, and family education on the PAD guidelines and the PAD care bundle elements will be important in order to gain widespread buy-in and support. It is also important to align the principles of family-centered care into the PAD care bundle implementation process, including shared decision making, early and frequent family communication about goals of care and daily care plans, and encouraging direct family involvement in patient care. Engagement and activation of ICU patients and their family members on the PAD care bundle elements will help to facilitate adoption of these practices and to sustain them (218).

ICUs vary in terms of the degree to which they are already incorporating elements of the PAD care bundle into their current ICU practices, so a baseline gap analysis can help ICUs to focus on those areas of the bundle that they have not yet implemented and integrate them with the bundle elements that they are already doing well. Identifying both process and outcome measures for each new PAD element initiative (i.e., pain and sedation protocols and EM) will help teams to better understand what works and what does not in their ICUs. Engaging frontline ICU staff in performing small tests of change, soliciting their feedback on how to further improve processes, measuring performance, and sharing results with all stakeholder groups will help to accelerate and sustain PAD improvements. Readers are referred to the Institute for Healthcare Improvement's website for more details on effective improvement strategies they can use to facilitate implementation of the PAD care bundle in their ICUs (219).

ICUs should begin with implementing specific PAD assessment tools first and demonstrating that ICU staff are performing and interpreting these assessments in a consistent and reliable fashion before implementing PAD treatment and prevention protocols. This will enable ICU staff to correctly identify the need for pain, sedation, and delirium interventions in individual patients and forms the foundation for applying all other PAD care bundle elements to these patients. *Otherwise, you do not know what you do not measure.* The results of these PAD assessments should then be included in discussions on daily ICU rounds, incorporated into ICU patient goals sheets, checklists, and order sets, and become part of the daily PAD care plan for each patient.

PAD treatment and prevention protocols must be developed around existing ICU cultures and hospital formularies and individualized to the needs of each patient. But regardless of your approach to implementing the PAD care bundle in your ICU, the primary goals of any institutional PAD protocols should be to: 1) optimize pain management first; 2) make light sedation the norm; 3) move away from routinely using benzodiazepines, especially in ICU patients who are at risk for or those who already have delirium (note: benzodiazepines may be preferred medications, however, for treating anxiety, seizures, and alcohol or benzodiazepine withdrawal, or as adjunctive sedative therapy in ICU patients who cannot tolerate propofol and/or dexmedetomidine for sedation); 4) implement effective delirium prevention and treatment strategies, using both nonpharmacologic and pharmacologic approaches; and 5) use antipsychotics judiciously. All treatment interventions, whether they be pharmacologic or nonpharmacologic, should have corresponding safety screens applied to each patient beforehand—not all ICU patients will tolerate dexmedetomidine for sedation or be able to get out of bed to a chair. Readers are referred to a recent article by Pun et al (220) that includes a more in-depth description of these PAD implementation strategies.

RESULTS

The effects of implementing the ICU PAD care bundle in its entirety have yet to be fully measured in terms of its overall impact on ICU patient care. But individual elements have been shown to significantly improve both short- and long-term ICU patient outcomes and reduce costs of care (**Table 1**). When two or more of these elements have been combined with one another, additional synergistic benefits to ICU outcomes and cost reductions have been realized.

TABLE 1. Expected Benefits of Implementing the 2013 ICU Pain, Agitation, and Delirium Guidelines

↓ Duration of mechanical ventilation and associated complications
↓ ICU length of stay
↓ Hospital length of stay
↓ Patient transfers to skilled nursing facilities
↓ ICU, hospital, and postdischarge mortality rates
↓ ICU, hospital, societal costs per patient
↓ Long-term societal burdens of ICU survivors (postintensive care syndrome [232])
↑ ICU patient throughput and bed availability
↓ Prevalence and duration of ICU delirium
↑ Long-term cognitive function and mobility
↑ Number of ICU patients discharged to home

In 2008, Girard et al (187) published the Awakening and Breathing Coordination (ABC) Trial, which compared outcomes in ICU patients (n = 336) managed with SATs, coupled with SBTs, to ICU patients managed with SBTs alone and usual physician-directed sedative administration. The SAT + SBT treatment group had significantly better outcomes than the SBT-only treatment group, in terms of decreased duration of mechanical ventilation (↓ by 3.1 d, p = 0.02), shorter ICU LOS (↓ by 3.8 d, p = 0.01), and shorter hospital LOS (↓ by 4.3 d, p = 0.04). Although more ICU patients in the SAT + SBT group self-extubated than in the control group (16 vs 6 patients, p = 0.03), the number of ICU patients requiring reintubation after self-extubation was similar (five vs three patients, p = 0.47), as were total reintubation rates (13·8% vs 12·5%, p = 0·73) between the two groups. Furthermore, within the first year after study enrollment, patients in the SAT + SBT group were less likely to die than were patients in the SBT only group (HR, 0.68; 95% CI, 0.50–0.92; p = 0·01). So for every seven patients treated with the SAT + SBT protocol, one life was saved (note: number needed to treat was 7.4; 95% CI, 4.2–35.5).

Strong evidence also demonstrates that most ICU patients can be safely maintained at lighter sedation levels and actively mobilized, even while intubated. A study by Morris et al (221) showed that linking the ABC protocol with an ICU EM protocol in mechanically ventilated ICU patients (n = 330) reduced ICU and hospital LOS by an additional 1.4 days (p = 0.025) and 3.3 days (p = 0.006), respectively. In addition, ICU patients treated with ABC + EM had physical therapy initiated more frequently in the ICU (91% vs 13% usual care, p < 0.001) and were out of bed earlier (5 d vs 11 d, p < 0.001) than patients treated with the ABC protocol alone. Overall complication rates were similarly low in both groups, and there were no untoward events during any ICU mobility session in the treatment group. Including the costs of implementing the mobility team, there were no cost differences between the two treatment groups in this study. A 1-year follow-up of these patients showed that a *lack* of early ICU mobility therapy was a strong predictor of hospital readmission or death in these patients (odds ratio, 1.77; 95% CI, 1.04–3.01; p < 0.01) (222). Another study of mechanically ventilated ICU patients (n = 104) by Schweickert et al (146) demonstrated that linking SATs with an ICU EM protocol significantly reduced the duration of delirium (i.e., by 2 d, p = 0.02), increased the number of ventilator-free days (23.5 d vs 21.1 d, p = 0.05), and achieved nearly a three-fold increase in the likelihood that ICU patients would regain an independent functional status by the time of hospital discharge (p = 0.02) (i.e., patients were able to perform six activities of daily living and walk independently). In other words, more of these ICU patients could ultimately go home from the hospital instead of to a skilled nursing facility. A recent meta-analysis of ICU EM studies demonstrated that ICU EM programs improve quality of life, physical function, and peripheral and respiratory muscle strength in critically ill patients (223). ICU EM Programs also significantly reduce both ICU and hospital LOS and reduce the duration of mechanical ventilation.

In 2010, Vasilevskis et al (224) captured the essence of taking an integrated approach to ICU sedation, ventilator, and delirium management by coining the phrase "ABCDE bundle," which stands for awakening and breathing coordination, delirium prevention and monitoring, and early mobility and exercise. Although the ABCDE bundle is arguably less comprehensive than the ICU PAD care bundle (i.e., most notably, it does not include strategies for pain management), it nevertheless captures the spirit of the PAD care bundle by linking sedation and delirium management in ICU patients with SATs, SBTs, and ICU EM programs. A recent study published by Balas et al (225) assessed the impacts of implementing the ABCDE bundle in seven mixed medical and surgical ICUs at a large, tertiary, academic medical center. Following widespread implementation of the ABCDE bundle at this facility, mechanically ventilated ICU patients were more likely to receive an SAT (71% vs 53%, p = 0.04), and an SBT (84% vs 71%, p = 0.03), and spent more days breathing without ventilator assistance (21 d vs 24 d, p = 0.04). The number of patients who self-extubated and who subsequently required reintubation did not differ significantly between the two groups. Implementation of the ABCDE bundle also decreased the duration of delirium in these patients by 50% (1 d vs 2 d, p = 0.004). The prevalence (20% vs 40%, p = 0.02) and duration of delirium were also significantly reduced in a separate analysis of nonmechanically ventilated ICU patients in this study (226). There were no significant differences observed in terms of ICU or hospital LOS, discharge disposition, or mortality between the pre- and postimplementation ABCDE bundle groups.

Implementation of the ICU PAD care bundle is also likely to result in considerable cost savings. Skrobik et al (76) implemented an integrated ICU PAD management protocol in a mixed medical-surgical ICU (n = 1,133). Their PAD

protocol included patient assessments using valid and reliable PAD assessment tools (i.e., NRS [but none of the valid BPSs], RASS, and ICDSC tools), the results of which formed the basis of treatment with what was primarily a pharmacologically based PAD treatment protocol. Music therapy and patient reorientation were also included as part of their protocol, but PAD management was not specifically linked to SATs, SBTs, an ICU EM program, or any ICU sleep hygiene strategies. Nevertheless, implementation of this ICU PAD protocol resulted in significant reductions in patients' pain scores and analgesic use, including a significant increase in the percentage of patients requiring no opioids, without a concomitant increase in nonopioid use. Benzodiazepine use decreased significantly as well, with a significant increase in the proportion of ICU patients sedated within their target RASS score range of –1 to +1. There was a lower prevalence of subsyndromal delirium (ICDSC > 0 but < 3) and iatrogenic coma, but no significant difference in antipsychotic use or the prevalence of delirium (i.e., ICDSC score ≥ 4) between the pre- and post-PAD protocol treatment groups. Finally, more patients in the PAD protocol treatment group remained cognitively intact during their ICU stay, and these patients were more likely to go home than patients with either subsyndromal delirium or delirium during their ICU stay. Implementation of this ICU PAD protocol significantly reduced ICU LOS (5.4 d vs 6.3 d, $p = 0.009$), hospital LOS (27.1 d vs 55 d, $p < 0.0001$), and the duration of mechanical ventilation (5.9 d vs 7.5 d, $p = 0.01$), while the percentage of ICU patients who were eventually discharged to home significantly increased (74.8% vs 68.2%, $p = 0.05$).

A cost analysis of this study published by Awissi et al (227) showed that the mean total cost of ICU hospitalization decreased from $6,212.64 per patient (in 2004 Canadian dollars) in the pre-PAD protocol group to $5,279.90 per patient in the post-PAD protocol group ($p = 0.02$), which represents an average total cost reduction of approximately 15% per patient. These modest cost reductions would likely have been much greater had the authors linked their PAD management protocol with SBTs, EM protocols, and ICU sleep hygiene programs.

A financial model recently developed by Lord et al (228), using published data, projected cost savings associated with implementing an ICU EM program, based on both conservative and best-case scenarios for estimated ICU and hospital LOS and cost reductions. It also included estimated cost reductions from an actual example of an ICU EM program implemented at their facility. Net cost savings generated from this example scenario, with 900 annual ICU admissions and actual LOS reductions of 22% and 19% for the ICU and floor, respectively, were $817,836 (in 2012 U.S. dollars). This was based on $1,176,312 of cost savings attributable to projected reductions in direct-variable costs due to reduced LOS, which was partially offset by an initial investment of $358,475 to implement the ICU early rehabilitation program. Hypothetical cost savings, based on an estimated reduction in both ICU and floor LOS ranging from 10% (conservative) to 25% (best-case scenario), ranged from $88,000 (net cost) to $3,763,000 (net savings), depending on the number of ICU admissions, direct-variable costs per day, and projected LOS reductions incorporated into the model. However, the model predicted a net cost savings in 20 of 24 possible scenarios. Under best-case scenario assumptions for LOS, the savings associated with implementing an ICU EM program were also projected to consistently increase with the number of ICU admissions (range, $260,000–$3,763,000). These model projections of cost savings associated with the implementation of an ICU EM program need to be tested prospectively at other institutions. But these results suggest that the up-front investment costs of implementing an ICU EM program are likely to be offset by significant cost savings resulting from reduced ICU and hospital LOS for patients.

DISCUSSION

Since the last version of these guidelines was published in 2002 (229), we have gained a greater understanding of how to better provide physical and psychological comfort for critically ill patients. The development of valid and reliable bedside assessment tools to measure pain, sedation, agitation, and delirium separately in ICU patients has allowed clinicians to better assess and manage these patients. Our increased understanding of the clinical pharmacology of medications commonly administered to treat PAD in ICU patients has given us greater insight to both the short- and long-term consequences of prolonged exposure to these agents. And how we administer these medications can affect patient outcomes as much as drug choice. Contrary to conventional wisdom in ICU sedation management, maintaining a light level of sedation while also ensuring patient comfort is associated with improved ICU clinical outcomes in most patients. Finally, our understanding of the risk factors and long-term consequences of delirium in ICU patients has also expanded.

But many important questions remain unanswered in the 2013 ICU PAD guidelines due to significant gaps in the evidence. Nevertheless, we believe that these guidelines, including the ICU PAD care bundle, provide a clearer road map for clinicians to better manage PAD in critically ill patients. And given the ubiquitous nature of PAD in ICU patients, we believe that these guidelines will be transformative in terms of their impact on ICU care, perhaps even more so than the sepsis guidelines have been (230).

The full impact of the ICU PAD care bundle on ICU patient outcomes and costs of care has yet to be tested and measured. But strong evidence indicates that linking PAD management strategies with ventilator weaning, EM, and sleep hygiene protocols in ICU patients results in significant synergistic benefits to clinical outcomes and reductions in costs of care. This suggests that widespread adoption of the ICU PAD care bundle will have a profound and positive effect on a variety of clinical and economic metrics related to care of critically ill patients.

An interdisciplinary team-based approach, using proven model improvement strategies, and ICU patient and family activation and engagement will help to ensure broad implementation of the PAD care bundle across diverse ICUs.

Implementing the PAD guidelines gives ICU practitioners the opportunity to bring the humanity of critically ill patients back into practice and to significantly improve lives beyond the ICU stay. The past decade of critical care medicine has focused on implementing the sepsis care bundle (231). Let this be the decade of the ICU PAD care bundle.

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