2022 Society of Critical Care Medicine Clinical Practice Guidelines on Prevention and Management of Pain, Agitation, Neuromuscular Blockade, and Delirium in Critically Ill Pediatric Patients With Consideration of the ICU Environment and Early Mobility

RATIONALE: A guideline that both evaluates current practice and provides recommendations to address sedation, pain, and delirium management with regard for neuromuscular blockade and withdrawal is not currently available.

OBJECTIVE: To develop comprehensive clinical practice guidelines for critically ill infants and children, with specific attention to seven domains of care including pain, sedation/agitation, iatrogenic withdrawal, neuromuscular blockade, delirium, PICU environment, and early mobility.

DESIGN: The Society of Critical Care Medicine Pediatric Pain, Agitation, Neuromuscular Blockade, and Delirium in critically ill pediatric patients with consideration of the PICU Environment and Early Mobility Guideline Taskforce was comprised of 29 national experts who collaborated from 2009 to 2021 via teleconference and/or e-mail at least monthly for planning, literature review, and guideline development, revision, and approval. The full taskforce gathered annually in-person during the Society of Critical Care Medicine Congress for progress reports and further strategizing with the final face-to-face meeting occurring in February 2020. Throughout this process, the Society of Critical Care Medicine standard operating procedures Manual for Guidelines development was adhered to.

METHODS: Taskforce content experts separated into subgroups addressing pain/analgesia, sedation, tolerance/iatrogenic withdrawal, neuromuscular blockade, delirium, PICU environment (family presence and sleep hygiene), and early mobility. Subgroups created descriptive and actionable Population, Intervention, Comparison, and Outcome questions. An experienced medical information specialist developed search strategies to identify relevant literature between January 1990 and January 2020. Subgroups reviewed literature, determined quality of evidence, and formulated recommendations classified as "strong" with "we recommend" or "conditional" with "we suggest." Good practice statements were used when indirect evidence supported benefit with no or minimal risk. Evidence gaps were noted. Initial recommendations were reviewed by each subgroup and revised as deemed necessary prior to being disseminated for voting by the full taskforce. Individuals who had an overt or potential conflict of interest abstained from relevant votes. Expert opinion alone was not used in substitution for a lack of evidence.

RESULTS: The Pediatric Pain, Agitation, Neuromuscular Blockade, and Delirium in critically ill pediatric patients with consideration of the PICU Environment and Early Mobility taskforce issued 44 recommendations (14 strong and 30 conditional) and five good practice statements.

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CONCLUSIONS: The current guidelines represent a comprehensive list of practical clinical recommendations for the assessment, prevention, and management of key aspects for the comprehensive critical care of infants and children. Main areas of focus included 1) need for the routine monitoring of pain, agitation, withdrawal, and delirium using validated tools, 2) enhanced use of protocolized sedation and analgesia, and 3) recognition of the importance of nonpharmacologic interventions for enhancing patient comfort and comprehensive care provision.

KEY WORDS: analgesia; delirium; guidelines; neuromuscular blockade; pediatric critical care; sedation

ICU care bundles, including the ICU Liberation ABCDEF bundle, provide a new paradigm for liberating critically ill patients from mechanical ventilation (MV) and ICU environment, while optimizing post-ICU outcomes (1, 2). Despite growing appreciation of this bundled patient care approach, PICU sedation and analgesia practices remain highly variable (3–5). Although valuable, previous pain/agitation/delirium guidelines (6, 7) have provided only limited guidance in the areas of prevention and management strategies for these conditions.

The American College of Critical Care Medicine (ACCM) supports the development of new and revised guidelines and clinical practice variables for the critical care practitioner. This document is the culmination of efforts solicited by the ACCM to review and develop guidelines for the identification, assessment, monitoring, and/or management of pain, sedation, neuromuscular blockade, withdrawal, and delirium in critically ill infants and children. The recommendations and good practice statements approved by the taskforce are presented in **Table 1** and are summarized in a "flowchart" format in **Figure 1** for ease of use. The Pain, Agitation, Neuromuscular Blockade, and Delirium in critically ill pediatric patients with consideration of the PICU Environment and Early Mobility (PANDEM) guideline is intended to apply to all infants and children admitted to the medical/surgical/cardiac PICU and not routinely to those infants admitted to a neonatal ICU (NICU). The reader is additionally referred to the **Supplemental Digital Content** (SDC, http://links.lww.com/PCC/B920) which provides further detail informing recommendations, ancillary pharmacology detail, and discussions of questions for which available data were inadequate to make formal recommendations.

METHODS

The pediatric guideline taskforce was formed in 2009 consisting of multidisciplinary experts in the comprehensive clinical care of critically ill pediatric patients, with specific attention to seven domains of critical care including pain, sedation/agitation, iatrogenic withdrawal, neuromuscular blockade, delirium, PICU environment (family and sleep hygiene), and early mobility (EM). The pediatric taskforce leadership team was composed of the cochairs, subgroup leaders, methodologist(s), librarian(s), and SCCM staff.

Search Strategy

Subgroups created actionable Population, Intervention, Comparison, and Outcome (PICO) (8) questions and nonactionable or descriptive questions that are clinically relevant for care of critically ill pediatric patients. MeSH terms (medical subheadings) were chosen, and a hospital-based medical librarian performed an initial literature search restricted to a period from 1990 to 2018, querying electronic databases including PubMed and the Cochrane Library. An updated search was completed by a SCCM-appointed medical information specialist, focusing on the period from January 2012 to January 2020 for systematic reviews and from January 2015 to January 2020 for primary studies. Searches were restricted to studies published in English. Search strategies were conducted in consultation with the taskforce in order to review literature based on the actionable and descriptive questions. A core search pertaining to critically ill children was created with separate searches layered on each topic (e.g., delirium, neuromuscular blockade, sedation). Controlled vocabulary was incorporated (e.g., "ICUs, Pediatric," "Critical Illness," "Ventilators," "Mechanical") along with keywords (e.g., "PICU," "critically ill," "intubation") in addition to a sensitive pediatric filter to identify records specific to this population. All study types (primary reports and systematic reviews) were included within the searches. A detailed search strategy including terms is available in **Appendix 1** (SDC Section I, http://links.lww.com/PCC/B920). Relevant studies were also identified from reference sections of identified studies, review articles, and systematic reviews as well as taskforce members' individual recollections if they were not identified in the literature searches. Studies published after the concluding date of the literature search were considered for inclusion

TABLE 1.
Summary of Recommendations

Recommendations	Strength of Recommendation	Quality of Evidence
Analgesia		
1) *We suggest* that, in critically ill pediatric patients 6 yr old and older who are capable of communicating, pain assessment via self-report be routinely performed using the Visual Analog Scale, Numeric Rating Scale, Oucher Scale, or Wong-Baker Faces pain scale.	Conditional	Low
2) *We recommend* the use of either the Faces, Legs, Activity, Cry, and Consolability or COMFORT-B scales for assessing pain in non-communicative critically ill pediatric patients.	Strong	Moderate
3) *We recommend* the use of observational pain assessment tools rather than vital signs alone for assessment of postoperative pain in critically ill pediatric patients.	Strong	Moderate
4) *We suggest* the use of observational pain assessment tools rather than vital signs alone for assessment of procedure-related pain in critically ill pediatric patients.	Conditional	Low
5) *We recommend* that IV opioids be used as the primary analgesic for treating moderate to severe pain in critically ill pediatric patients.	Strong	Moderate
6) *We recommend* the addition of an adjunct NSAID (IV or oral) to *improve early postoperative analgesia* in critically ill pediatric patients.	Strong	Moderate
7) *We suggest* the addition of an adjunct NSAID agent (IV or oral) to *decrease opioid requirements* in the immediate postoperative period in critically ill pediatric patients.	Conditional	Low
8) *We suggest* the addition of adjunct acetaminophen (IV or oral) to *improve early postoperative analgesia* in critically ill pediatric patients.	Conditional	Low
9) *We suggest* the addition of adjunct acetaminophen (IV or oral) to decrease opioid requirements in the immediate postoperative period in critically ill pediatric patients.	Conditional	Low
10) *We recommend* that music therapy be offered to augment analgesia in critically ill postoperative pediatric patients.	Strong	Moderate
11) We *recommend* that nonnutritive sucking with oral sucrose be offered to neonates and young infants prior to performing invasive procedures.	Strong	High
Sedation		
1) *We recommend* the use of the COMFORT-B Scale or the State Behavioral Scale, to assess level of sedation in mechanically ventilated pediatric patients.	Strong	Moderate
2) *We suggest* the use of the Richmond Agitation-Sedation Scale to assess level of sedation in mechanically ventilated pediatric patients.	Conditional	Low
3) *We suggest* that all pediatric patients requiring MV are assigned a target depth of sedation using a validated sedation assessment tool at least once daily.	Conditional	Low
4) *We suggest* the use of protocolized sedation in all critically ill pediatric patients requiring sedation and/or analgesia during MV.	Conditional	Low
5) The addition of daily sedation interruption to sedation protocolization *is not suggested* due to lack of improvement in outcomes.	Conditional	Low
6) During the periextubation period when sedation is typically lightened, *we suggest* the following bundle strategies to decrease risk of inadvertent device removal: a) Assign a target depth of sedation at increasing frequency to adapt to changes inpatient clinical status and communicate strategies to reach titration goal. b) Consider a sedation weaning protocol. c) Consider unit standards for securement of endotracheal tubes and safety plan. d) Restrict nursing workload to facilitate frequent patient monitoring, decrease sedation requirements, and risk of self-harm.	Conditional	Low
7) *We suggest* the use of alpha$_2$-agonists as the primary sedative class in critically ill pediatric patients requiring MV.	Conditional	Low

(*Continued*)

TABLE 1. (*Continued*).
Summary of Recommendations

Recommendations	Strength of Recommendation	Quality of Evidence
8) *We recommend* that dexmedetomidine be considered as a primary agent for sedation in critically ill pediatric post-operative cardiac surgical patients with expected early extubation.	Strong	Moderate
9) *We suggest* the use of dexmedetomidine for sedation in critically ill pediatric postoperative cardiac surgical patients to decrease the risk of tachyarrhythmias.	Conditional	Low
10) *We suggest* that continuous propofol sedation at doses less than 4 mg/kg/hr (67 µg/kg/min) and administered for less than 48 hr may be a safe sedation alternative to minimize the risk of propofol-related infusion syndrome development.	Conditional	Low
11) Short term (< 48 hr) continuous propofol sedation may be a useful adjunct during the periextubation period to facilitate weaning of other analgosedative agents prior to extubation.	Good practice	
12) *We suggest* consideration of adjunct sedation with ketamine in patients who are not otherwise at an optimal sedation depth.	Conditional	Low
13) During the periextubation period when sedation is typically lightened, *we suggest* the following bundle strategies to decrease risk of inadvertent device removal: 12) Assign a target depth of sedation at increasing frequency to adapt to changes in-patient clinical status and communicate strategies to reach titration goal. c) Consider a sedation weaning protocol. e) Consider unit standards for securement of endotracheal tubes and safety plan. d) Restrict nursing workload to facilitate frequent patient monitoring, decrease sedation requirements, and risk of self-harm.	Conditional	Low
Neuromuscular blockade		
1) *We suggest* that train-of-four monitoring be used in concert with clinical assessment to determine depth of neuromuscular blockade.	Conditional	Low
2) *We suggest* using the lowest dose of NMBAs required to achieve desired clinical effects and manage undesired breakthrough movement.	Conditional	Low
3) Electroencephalogram-based monitoring may be a useful adjunct for assessment of sedation depth in critically ill pediatric patients receiving NMBAs.	Good practice	
4) *We suggest* that sedation and analgesia should be adequate to prevent awareness prior to and throughout NMBA use.	Conditional	Low
5) *We recommend* routine use of passive eyelid closure and eye lubrication for the prevention of corneal abrasions in critically ill pediatric patients receiving NMBAs.	Strong	Moderate
ICU delirium		
1) We *recommend* use of the preschool and pediatric Confusion Assessment Methods for the ICU or the Cornell Assessment for Pediatric Delirium as the most valid and reliable delirium monitoring tools in critically ill pediatric patients.	Strong	High
2) *We recommend* routine screening for ICU delirium using a validated tool in critically ill pediatric patients upon admission through ICU discharge or transfer.	Strong	High
3) Given low patient risk, and possible patient benefit to reduce the incidence and/or decrease duration or severity of delirium *we suggest* the following *non-pharmacologic strategies*: optimization of sleep hygiene, use of interdisciplinary rounds, family engagement on rounds, and family involvement with direct-patient care.	Conditional	Low
4) *We suggest* performing EM, when feasible, to reduce the development of delirium.	Conditional	Low
5) *We recommend* minimizing benzodiazepine-based sedation when feasible in critically ill pediatric patients to decrease incidence and/or duration or severity of delirium.	Strong	Moderate

(*Continued*)

TABLE 1. (*Continued*).
Summary of Recommendations

Recommendations	Strength of Recommendation	Quality of Evidence
6) *We suggest* strategies to minimize overall sedation exposure whenever feasible to reduce coma and the incidence and/or severity of delirium in critically ill children.	Conditional	Low
7) *We do not suggest* routine use of haloperidol or atypical antipsychotics for the prevention of or decrease in duration of delirium in critically ill pediatric patients.	Conditional	Low
8) *We suggest* that in critically ill pediatric patients with *refractory* delirium, haloperidol or atypical antipsychotics be considered for the management of *severe* delirium manifestations, with consideration of possible adverse drug effects.	Conditional	Moderate
9) *We recommend* a baseline electrocardiogram followed by routine electrolyte and QTc interval monitoring for patients receiving haloperidol or atypical antipsychotics.	Strong	Moderate
IWS		
1) *We recommend* use of either the Withdrawal Assessment Tool-1or Sophia Observation Scale for the assessment of IWS due to opioid or benzodiazepine withdrawal in critically ill pediatric patients.	Strong	Moderate
2) *We suggest* routine IWS screening after a shorter duration (3–5 d) when higher opioid or benzodiazepine doses are used.	Conditional	Moderate
3) Until a validated screening tool is developed, monitoring for IWS from alpha$_2$-agonists should be performed using a combination of associated symptoms (unexplained hypertension or tachycardia) with adjunct use of a validated benzodiazepine or opioid screening tool.	Good practice	
4) *We suggest* that opioid related IWS be treated with opioid replacement therapy to attenuate symptoms, irrespective of preceding dose and /or duration or opioid exposure.	Conditional	Low
5) Benzodiazepine-related IWS should be treated with benzodiazepine replacement therapy to attenuate symptoms, irrespective of preceding dose and/or duration of benzodiazepine exposure.	Good practice	
6) Alpha$_2$-agonist–related IWS should be treated with IV and/or or enteral alpha$_2$-agonist replacement therapy to attenuate symptoms, irrespective of preceding dose and/or duration of alpha$_2$-agonist exposure.	Good practice	
7) *We suggest* use of a standardized protocol for sedation/analgesia weaning to decrease duration of sedation taper and attenuate emergence of IWS.	Conditional	Low
Optimizing environment		
1) *We suggest* facilitation of parental or caregiver presence in the PICU during routine care and interventional procedures to a) provide comfort to the child, b) decrease parental levels of stress and anxiety and c) increase level of satisfaction of care.	Conditional	Low
2) *We suggest* offering patients the use of noise reducing devices such as ear plugs or headphones to reduce the impact of non-modifiable ambient noise (*conditional, low-level evidence*).	Conditional	Low
3) *We suggest* that PICU teams make environmental and/or behavioral changes to reduce excessive noise and therefore improve sleep hygiene and comfort, in critically ill pediatric patients.	Conditional	Low
4) *We suggest* performing EM to minimize the effects of immobility in critically ill pediatric patients.	Conditional	Low
5) *We suggest* the use of a standardized EM protocol that outlines readiness criteria, contraindications, developmentally appropriate mobility activities and goals, and safety thresholds guided by the multidisciplinary team and family decision-making.	Conditional	Low

COMFORT-B = COMFORT Behavior, EM = early mobility, IWS = iatrogenic withdrawal syndrome, MV = mechanical ventilation, NMBA = neuromuscular blocking agent, NSAID = nonsteroidal anti-inflammatory drug.

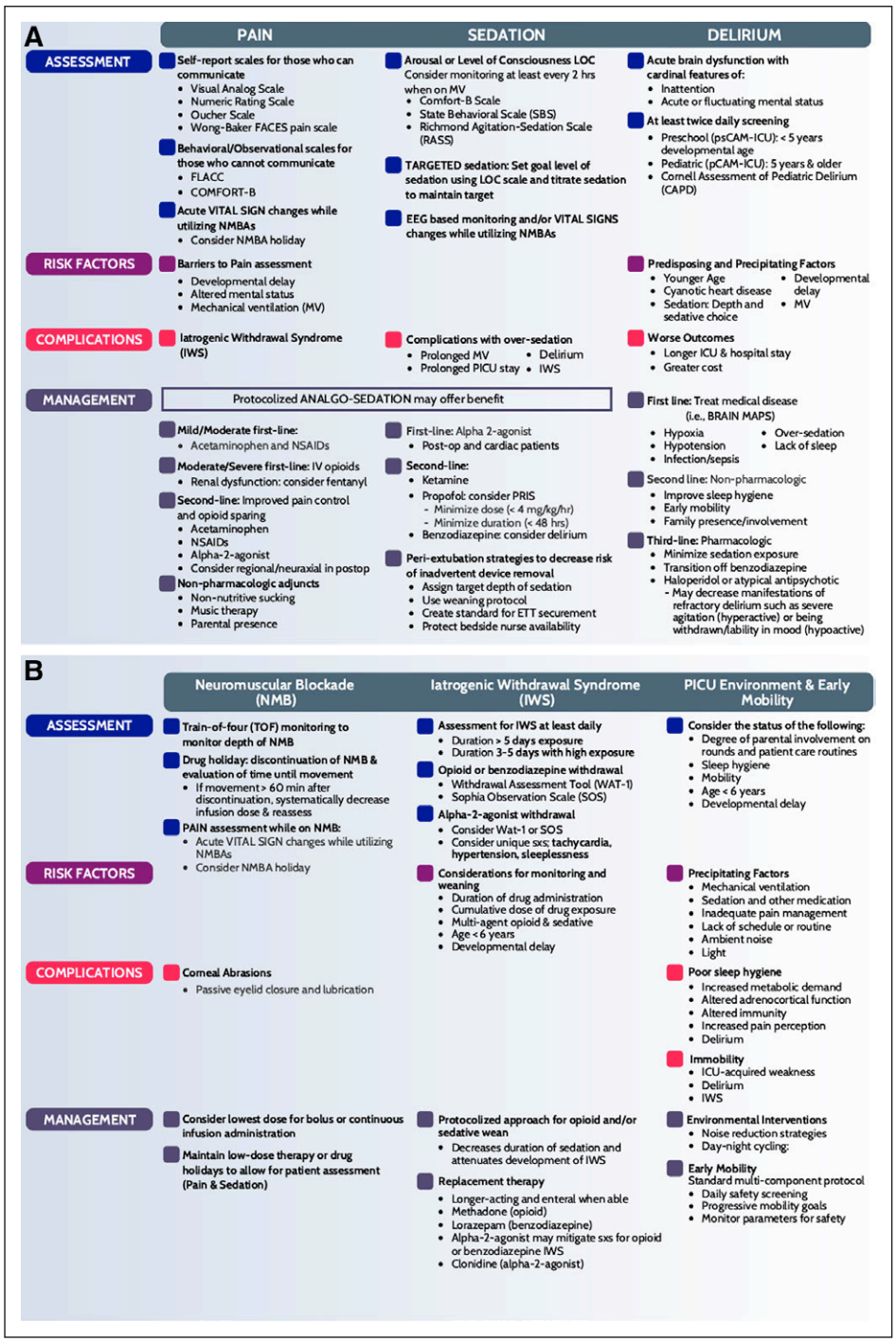

Figure 1. Schematic summary of the key Pain, Agitation, Neuromuscular Blockade, and Delirium in critically ill pediatric patients with consideration of the PICU Environment and Early Mobility (PANDEM) recommendations and representation of the interplay between sedative and analgesic choice on unintended but related outcomes. BRAIN MAPS = Bring oxygen, Remove/Reduce deliriogenic drugs, patient Atmosphere, Immobilization, New organ dysfunction, Metabolic disturbances, Awake, Pain, Sedation, CAPD = Cornell Assessment of Pediatric Delirium, COMFORT-B = COMFORT-Behavior, EEG = electroencephalogram, ETT = endotracheal tube, FLACC = Faces, Legs, Activity, Cry, and Consolability, IWS = iatrogenic withdrawal syndrome, MV = mechanical ventilation, NMBA = neuromuscular blocking agent, NSAID = nonsteroidal anti-inflammatory drug, pCAM-ICU = pediatric Confusion Assessment Method for the ICU, PRIS = propofol-related infusion syndrome, psCAM-ICU = preschool Confusion Assessment Method for the ICU, RASS = Richmond Agitation-Sedation Scale, SBS = State Behavioral Scale, SOS = Sophia Observation Scale, TOF = train-of-four, WAT-I = Withdrawal Assessment Tool-1.

if they were deemed to be of sufficient significance to either alter the strength of evidence or provide a recommendation for an otherwise unanswered question due to insufficient or contradictory evidence.

Literature Review

The taskforce literature review incorporated the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (9–12). The GRADE approach included determination of the following domains: risk of bias, precision, consistency, directness of the evidence, risk of publication bias, presence of a dose-effect relationship, magnitude of effect, and assessment of the effect of plausible residual confounding or bias. Primary and secondary reviewers were assigned literature for each PICO question. The primary reviewer performed the initial literature review which began with title/abstract screening to identify full-text manuscripts to be reviewed. From the list of full-text manuscripts, the primary reviewer then created data spreadsheets consisting of extracted study data, assignment of GRADE ratings, and additional discussion points. These spreadsheets were reviewed and confirmed by a secondary reviewer after which both reviewers together developed recommendations to present to their specific subgroup for discussion and consideration. If conflicts or differences of opinion occurred, further discussion ensued at the taskforce level. If resolution was unable to be achieved, final arbitration

was performed by the cochairs and methodologist when appropriate. Subgroups reviewed recommendations and rationales with quality of evidence descriptions including "high-level evidence" (i.e., randomized controlled trial [RCT] or large prospective cohort study/further research "unlikely" to change confidence estimate of effect), "moderate-level evidence" (i.e., prospective cohort studies/further research "likely" to have some impact on confidence estimate), "low-level evidence" (i.e., retrospective cohort studies/future research "very likely" to have important impact on confidence estimate), and "very low-level evidence" (i.e., case reports/estimate of effect is uncertain). Clinical care proposals were denoted as "strong" using "we recommend" or "conditional" with "we suggest." When evidence quality was "very-low" or "absent" yet consensus by the taskforce was that a clinical practice was beneficial and had no or very low risk, statements were presented as "good practice." No recommendations were made based exclusively on adult or NICU literature, although relevant themes identified from these resources were referenced when appropriate. Topics/questions for which available data were inadequate to make recommendations were identified and explicitly noted as areas for future research.

Recommendations/Voting Procedures

The full taskforce reviewed all subgroup PICO questions, recommendations, and rationales. Suggested amendments and dissenting opinions were sent back to the pertinent subgroup for consideration. Following revision, if required, voting on the final recommendations by the full taskforce proceeded using Survey Monkey (http://www.surveymonkey.com). Individuals who had an overt or potential conflict of interest abstained from relevant votes. Per SCCM standard operating procedure (SOP) voting policies and procedures, recommendation acceptance required both of 1) greater than 70% participation by the taskforce and 2) approval by greater than 80% of voters. All dissenting votes were required to be accompanied by a rationale for the dissent. No recommendations were excluded from the guideline due to dissent or disagreement by a majority of the taskforce.

RESULTS

This guideline includes 44 recommendations (14 strong and 30 conditional) and five good practice statements (Table 1). Figure 1 summarizes the findings of this guideline and provides a graphic representation of the interplay between the seven main domains of care addressed. Information addressing descriptive questions is presented in the preambles for each major domain below. Additional detail may also be found in the SDC (http://links.lww.com/PCC/B920), referenced by clicking on the relevant inserted hyperlinks.

Analgesia

The majority of critically ill pediatric patients experience pain during their PICU course (13–15). Risk factors for experiencing pain in children are varied. Patient-specific factors include developmental and cognitive stage, communication capabilities, mental status, and underlying comorbidities/organ dysfunction, whereas PICU-specific factors include the presence of MV, need for invasive procedures and devices, medication exposures, sleep disruption, and mobility status (16–20). Analgesia is provided to relieve pain, control agitation, prevent accidental removal of devices (i.e., endotracheal tubes [ETTs], thoracostomy tubes, and intravascular devices), improve patient-ventilator synchrony, optimize hemodynamics, decrease oxygen consumption, and modulate the stress response. Providing adequate analgesia is important as persistent pain has adverse physiologic and psychologic consequences including immunosuppression, delayed wound healing, impaired sleep, hyperalgesia (21–26) as well as feelings of helplessness, parental separation, and posttraumatic stress disorder (18, 27, 28).

Accurate assessment of pediatric pain is critical, but significant barriers to this exist including patient-related factors such as developmental variation, premorbid neurocognitive delay, or illness-related neurobehavioral sequelae (29). Caregivers may lack training or time to perform assessments, possess intrinsic bias, have inadequate analgesic availability, or lack understanding of the adverse effects (AEs) of both pain and analgesic agents (22, 29–32). Management of pain in critically ill children involves primarily the use of opioids, either alone or in combination with nonopioid agents (33, 34) (**SDC Tables 1** and **2**, http://links.lww.com/PCC/B920). Nonpharmacologic therapies complement pharmacologic interventions by decreasing environmental stressors, facilitating relaxation and distraction, and facilitating sleep (35, 36). The

reader is referred to **SDC Section B** (http://links.lww.com/PCC/B920) for more detailed discussion of pain assessment tools, analgesic choices and pharmacology, and nonpharmacologic adjuncts.

Assessment of Pain.

Question: What pain assessment tools should be used in critically ill pediatric patients? (**SDC Section B1**, http://links.lww.com/PCC/B920).

Answer:

1) Self-report scales:
   a) "We suggest" that, in critically ill pediatric patients 6 years old and older who are capable of communicating, pain assessment via self-report be routinely performed using the Visual Analog Scale (VAS), Numeric Rating Scale, Oucher Scale, or Wong-Baker Faces pain scale (*conditional, low-level evidence*).
2) Behavioral/Observational scales:
   a) "We recommend" the use of either the Faces, Legs, Activity, Cry, and Consolability (FLACC) or COMFORT-Behavior (COMFORT-B) scales for assessing pain in noncommunicative critically ill pediatric patients (*strong, moderate-level evidence*).
   b) "We recommend" the use of observational pain assessment tools rather than vital signs alone for assessment of postoperative pain in critically ill pediatric patients (*strong, moderate-level evidence*).
   c) "We suggest" the use of observational pain assessment tools rather than vital signs alone for assessment of procedure-related pain in critically ill pediatric patients (*conditional, low-level evidence*) in critically ill pediatric patients.

Rationale: Pain assessment tools can be divided into self-report and observational rating scales. In children able to express themselves, self-report represents the "gold standard" for pain assessment (20, 22, 34–39). The most commonly used pediatric self-report tools are the VAS (40), Numerical Rating Scale (41), Oucher scale (42), and the Wong Baker Faces pain scale (43) (SDC Table 1, http://links.lww.com/PCC/B920). Although all of these tools have been broadly validated in pediatric populations as young as 3 years old, self-report tools are felt to be most reliable in patients who are at least 6 years old (17, 19, 22, 37–39, 44).

Observational pain scoring systems incorporate behavioral ± physiologic variables to assess pain in patients unable to self-report pain (45–48). The FLACC, COMFORT, and COMFORT-B scales have been the most widely applied observational tools in critically ill children (SDC Table 2, http://links.lww.com/PCC/B920) (30, 37, 38, 49, 50). The FLACC score evaluates five behavioral components and is highly valid and reliable in assessing postoperative pain in critically ill children (51, 52). The revised FLACC was developed and validated for use in nonverbal and cognitively impaired children (53). The COMFORT score was initially developed and validated to assess general distress in critically ill pediatric patients but has additionally been shown valid for differentiating pain from other sources of distress (54, 55). The modified COMFORT-B scale removed the vital sign elements of the COMFORT scale due to concerns regarding their reliability for the assessment of pain and distress during critical illness (55, 56).

Although consensus regarding the optimum method of assessing pain in nonverbal children remains elusive, investigators increasingly advocate for scoring systems incorporating a combination of behavioral and physiologic variables (27, 28, 48, 57, 58). No pain or sedation tools have been validated for use in critically ill pediatric patients receiving neuromuscular blocking agents (NMBAs). Consequently, despite reliability limitations, changes in vital signs in these patients may indicate acute pain and should be addressed (59, 60).

Pharmacologic Management of Pain.

Question: What class of analgesic is superior for treating pain in critically ill pediatric patients? (**SDC Section B2**, http://links.lww.com/PCC/B920)

Answer: "We recommend" that IV opioids be used as the primary analgesic for treating moderate to severe pain in critically ill pediatric patients (*strong, moderate-level evidence*).

Rationale: Opioids remain the mainstay of therapy for management of acute surgical and medical pain in the critically ill pediatric patient, including pain associated with MV (33, 34) (**SDC Table 3**, http://links.lww.com/PCC/B920). There are no studies comparing analgesic classes across the spectrum of pediatric critical illness. However, multiple practice survey and intra-analgesic class comparative studies do describe IV opioids as the primary analgesic class used across the spectrum of critically ill pediatric patients (3, 5, 33, 61, 62). A variety of IV opioids have been used in this setting including fentanyl, morphine, hydromorphone, and remifentanil (63–69). Due to lack of active metabolites, fentanyl may be preferred in the setting of renal dysfunction. Morphine and hydromorphone should be used cautiously in patients with

renal dysfunction as active metabolites may accumulate and prolong duration of effects (70, 71).

Question: Should nonopioid analgesic medications be added to opioid-based regimens to improve postoperative pain control?

Answer:

1) "We recommend" the addition of an adjunct nonsteroidal anti-inflammatory drug (NSAID) (IV or oral) to "improve early postoperative analgesia" in critically ill pediatric patients (*strong, moderate-level evidence*).
2) "We suggest" the addition of an adjunct NSAID agent to "decrease opioid requirements" in the immediate postoperative period in critically ill pediatric patients (IV or oral) (*conditional, low-level evidence*).
3) "We suggest" the addition of adjunct acetaminophen (IV or oral) to "improve early postoperative analgesia" in critically ill pediatric patients (*conditional, low-level evidence*).
4) "We suggest" the addition of adjunct acetaminophen (IV or oral) to "decrease opioid requirements" in the immediate postoperative period in critically ill pediatric patients (*conditional, low-level evidence*).

Rationale: Nonopioid adjuncts such as NSAIDs and acetaminophen are commonly used to provide analgesia in critically ill children (**SDC Table 4**, http://links.lww.com/PCC/B920). Multiple studies including systematic reviews have observed that the use of adjunct NSAIDs (primarily ibuprofen and ketorolac) in postoperative cardiac (72) and noncardiac surgical PICU patients (73, 74) is associated with improved pain scores and decrease in opioid requirements (**SDC Table 5**, http://links.lww.com/PCC/B920). However, their use has not been associated with reductions in opioid-related AEs (72–76). Short-term NSAID use was not associated with increased postoperative bleeding, significant changes in renal function, or development of gastritis (77, 78). No trials were found evaluating the use of NSAIDs for adjunct analgesia in nonsurgical PICU patients.

In critically ill pediatric patients following major noncardiac abdominal or thoracic surgery (79) and idiopathic scoliosis repair (80), addition of IV acetaminophen was associated with reduced morphine use (SDC Table 5, http://links.lww.com/PCC/B920). Two systematic reviews evaluated the impact of adjunct oral or IV acetaminophen on opioid requirements in nonICU patients, and 16 of 26 studies found an opioid sparing effect of acetaminophen, regardless of administration route (77, 78). Adjunct acetaminophen at least preserves and in some studies improves pain scores (77, 78). Reductions in opioid-related AEs have not been observed with the addition of acetaminophen (79).

Nonpharmacologic Management of Pain.

Question: Does the use of music therapy decrease postoperative pain in critically ill pediatric patients? (**SDC Section B3**, http://links.lww.com/PCC/B920).

Answer: "We recommend" that music therapy be offered to augment analgesia for critically ill postoperative pediatric patients (*strong, moderate-level evidence*).

Rationale: Benefits of music therapy include reductions in pain, anxiety, medication requirements, and inflammatory markers in addition to improvements in sleep quality and ability to mobilize (16, 81–86). Following general surgical procedures, music therapy is associated with decreased postoperative pain, anxiety and distress, and decreased opioid requirements (35, 87). In critically ill neonates, music therapy is also associated with decreased pain during heel prick procedures (88, 89). Prerecorded music played to pediatric cardiac surgical patients perioperatively was associated with reduced surgical stress response, decreased agitation in the immediate postextubation period, and improved pain scores with lower analgesic requirements compared with controls not exposed to music (90). A systematic review of music therapy via prerecorded music in postoperative patients, including critically ill children, reported significant reductions in pain scores, anxiety scores, and opioid use in the immediate postoperative period (35, 87).

Question: Does the addition of nonnutritive sucking augment analgesia during procedures in critically ill pediatric patients?

Answer: "We recommend" that nonnutritive sucking with oral sucrose be offered to neonates and infants (< 12 mo old) prior to performing invasive procedures (*strong, high-level evidence*).

Rationale: Nonnutritive sucking with oral sucrose and expressed breast milk have been well studied in the NICU population (83, 86, 91–98). The use of oral sucrose has had the biggest effect in some studies, but combinations of all nonnutritive suck techniques with swaddling have shown additive effects on pain reduction during heel stick procedures with no AEs reported among infants (99–101). The use of oral sucrose solution alone is beneficial during painful procedures without evidence of blunting of the analgesic

response with repeated use (102, 103). Compared with no pretreatment, the use of sublingual sucrose was prospectively associated with blunting of the discomfort associated with orogastric tube insertion (104). Since a systematic review of sweet tasting solutions in older children (1–16 yr) reported conflicting evidence in the preschool aged population and no benefit in the school aged population on pain scores, this recommendation is limited to the infant (< 12 mo old) population (105).

Sedation

The majority of patients requiring MV will receive analgesia and/or sedation to reduce anxiety, maintain ventilator-patient synchrony, and facilitate necessary care procedures (106–108). Finding a balance between over- and undersedation is paramount. Undersedation may lead to inadvertent device removal (109, 110), or increased anxiety which may lead to residual psychologic and behavioral sequelae post PICU discharge (106, 111). Oversedation is associated with prolonged MV, increased risk of inadvertent tracheal extubation failure (6, 112), delirium (113), prolonged PICU length of stay (LOS) (106), and the development of tolerance and iatrogenic withdrawal (114–116). The ideal depth of sedation has significant intra- and interpatient variability based on the disease process being treated, stage of disease evolution, invasiveness of therapy required, and developmental abilities to cooperate with treatments and therapies. Multiple sedative options including benzodiazepines, alpha$_2$-agonists, propofol, and ketamine are available to the pediatric critical provider. Although specific recommendations regarding these agents are found below, the reader is also referred to the **SDC, Section C** (http://links.lww.com/PCC/B920) for additional discussion, especially about agents for which evidence was inadequate to make recommendations.

Assessment of Sedation.

Question: What sedation assessment scales are valid for assessing depth of sedation in critically ill pediatric patients? (**SDC Section C1**, http://links.lww.com/PCC/B920).

Answer:

1) "We recommend" the use the Comfort-B Scale or the State Behavioral Scale (SBS) to assess level of sedation in mechanically ventilated pediatric patients (*strong, moderate-level evidence*).
2) "We suggest" the use of the Richmond Agitation-Sedation Scale (RASS) to assess level of sedation in mechanically ventilated pediatric patients (*conditional, low-level evidence*).

Rationale: The Comfort-B Scale (56, 117, 118) and the SBS (119, 120) have both been validated in several PICU settings to assess the level of sedation in mechanically ventilated pediatric patients. Both scales reliably differentiate adequate from over- or undersedation in patients not receiving NMBAs. Their psychometric validity has been supported in a meta-analysis of 13 sedation scales (121). Although the RASS has only been validated in a single trial, it is extensively used in pediatric critical care as it forms the basis for determining the appropriateness of delirium screening with the pediatric Confusion Assessment Method for the ICU (pCAM-ICU) and Cornell Assessment of Pediatric Delirium (CAPD) delirium screening tools (122). Characteristics of each sedation assessment scale are described in detail in **SDC Table 6** (http://links.lww.com/PCC/B920).

Protocolized Sedation.

Question: Should critically ill pediatric patients requiring MV routinely be assigned a target depth of sedation? (**SDC Section C2**, http://links.lww.com/PCC/B920).

Answer: "We suggest" that all pediatric patients requiring MV be assigned a target depth of sedation using a validated sedation assessment tool at least once daily (*conditional, low-level evidence*).

Rationale: Two studies assessing the impact of goal-directed sedation concluded that targeting a sedation score may minimize time the patient is agitated (123, 124). Although a larger multicenter RCT found no difference in rates of inadequate sedation or analgesia, the intervention group in this study was exposed to interventions beyond just targeting sedation depth (69).

Question: Is protocolized sedation superior to non-protocolized sedation in critically ill pediatric patients?

Answer: "We suggest" the use of protocolized sedation in all critically ill pediatric patients requiring sedation and/or analgesia during MV (*conditional, low-level evidence).*

Rationale: Ten studies (1 RCT and 9 before-and-after retrospective reviews) evaluated the impact of protocolized sedation/analgesia on various outcomes including length of MV, PICU LOS, exposure to benzodiazepines and opioids, development of iatrogenic withdrawal syndrome (IWS), and other adverse events

(**SDC Table 7**, http://links.lww.com/PCC/B920) (69, 123–131). In the only RCT, outcomes were compared between PICUs randomized to provide protocolized care (targeted sedation score, arousal assessment, extubation readiness testing, sedation adjustment every 8 hr, sedation weaning, and prescribed sedative/analgesic agent choice and titration) versus units providing nonprotocolized care (69). Although there were no between-group differences in inadequate analgesia or sedation, duration of MV, PICU LOS, opioid or benzodiazepine exposure, or IWS, post hoc analysis revealed a higher percentage of study days in which patients were awake and calm while intubated in the intervention group. Several before-and-after studies also reported associated improvements in one or more of these outcomes, particularly benzodiazepine exposure, with no studies reporting worse outcomes with protocolization.

Daily Sedation Interruptions or Drug Holidays.

Question: Should routine daily sedation interruption (DSI) be implemented in critically ill pediatric patients requiring MV and receiving continuous sedative infusions? (**SDC Section C3**, http://links.lww.com/PCC/B920)

Answer: The addition of DSI to sedation protocolization is "not suggested" due to lack of improvement in outcomes (*conditional, low-level evidence*).

Rationale: A small single-center RCT reported reductions in sedative infusion rates, duration of MV, and PICU LOS with DSI but is limited in that there were multiple exclusions to DSI, and many eligible patients were excluded due to safety concerns (132). A larger multicenter RCT found that protocolized sedation with DSI compared with protocolized sedation alone was not associated with improvements in outcomes, whereas mortality was actually increased in the DSI arm (133). Additionally, one third of patients failed a safety screen preceding the conduct of a DSI which may have biased safety results. A large multicenter RCT comparing outcomes in mechanically ventilated patients receiving either protocolized or nonprotocolized sedation included DSI in the protocolized arm when sedation was deeper than the predefined sedation score (69). Since only 4% of patients required DSI for over sedation, DSI may not be necessary when goal-directed sedation is already being used. There is insufficient literature to enable comment on the role of DSI in patients who are not receiving protocolized sedation (**SDC Table 8**, http://links.lww.com/PCC/B920).

Periextubation Strategies.

Question: Are there interventions that are associated with or decrease the risk of unintended device removal in mechanically ventilated pediatric patients? (**SDC Section C4**, http://links.lww.com/PCC/B920)

Answer: During the periextubation period when sedation is typically lightened, "we suggest" the following bundle strategies to decrease risk of inadvertent device removal (*conditional, low-level evidence*):

1) Assign a target depth of sedation at increasing frequency to adapt to changes in patient clinical status and communicate strategies to reach titration goal.
2) Consider a sedation weaning protocol.
3) Consider unit standard for the securement of ETTs and safety plan.
4) Restrict nursing workload to facilitate frequent patient monitoring, decrease sedation requirements, and risk of self-harm.

Rationale: Studies addressing level of sedation and impact on risks of unplanned events or unintended device removal in mechanically ventilated pediatric patients are heterogeneous in design (**SDC Table 9**, http://links.lww.com/PCC/B920). Institution of DSI or targeted sedation protocols in two separate RCTs demonstrated similar device-related adverse event rates in each group (69, 133, 134). In six quality improvement studies, rates of unintended device removal consistently decreased after implementation of bundle components (standardized ETT securement, standardized ETT suctioning, identification of high risk patients, targeted sedation assessments, sedation standardization and/or protocolization, and sedation weaning protocol during ventilator weaning) (135–140).

Pharmacologic provision of sedation.

Multiple sedative options including benzodiazepines, alpha$_2$-agonists, propofol, and ketamine are available to the pediatric critical provider (**SDC Section C5**, http://links.lww.com/PCC/B920). Although specific recommendations regarding these agents are found below, the reader is also referred to the SDC, Section III (http://links.lww.com/PCC/B920) for additional discussion, especially about agents for which evidence was inadequate to make recommendations. A summary of the relevant pharmacology of these agents is found in **SDC Section C5**, **Table 10** (http://links.lww.com/PCC/B920).

Question: What is the preferred sedative class for sedation of critically ill mechanically ventilated pediatric patients?

Answer: "We suggest" the use of alpha$_2$-agonists as the primary sedative class in critically ill pediatric patients requiring MV (*conditional, low-level evidence*).

Rationale: Five RCTs found that sedation efficacy with an alpha$_2$-agonist was similar to sedation with a benzodiazepine (141–146). Several small RCTs have demonstrated that sedation with alpha$_2$-agonists versus midazolam in mechanically ventilated PICU patients was associated with a reduction in opioid requirements following congenital cardiac surgery, scoliosis surgery, burn injury, and in general PICU patients (141, 144, 145, 147). One study of clonidine use in neonates also demonstrated a reduction in opioid administration (144). One prospective cohort (148) and two RCTs (146, 149) further reported significant reductions in opioid and benzodiazepine exposure with the addition of scheduled enteral clonidine. Although mean heart rates were lower in alpha$_2$-agonist–treated patients (141, 145), bradycardia or hypotension requiring intervention was not increased compared with benzodiazepine sedation. Caution is advised when using alpha$_2$-agonists administered as continuous infusions in patients with underlying bradycardia or in patients concurrently receiving heart rate lowering medications (**SDC Table 11**, http://links.lww.com/PCC/B920). Benzodiazepine use has been independently associated with an increased incidence of delirium development (150–152) (please see *Delirium* section for further discussion).

Question: Should an alpha$_2$-agonist when compared with a benzodiazepine be used for sedation in mechanically ventilated pediatric patients after cardiac surgery?

Answer:

1) "We recommend" that dexmedetomidine be considered as a primary agent for sedation in critically ill pediatric postoperative cardiac surgical patients with expected early extubation (*strong, moderate-level evidence*).
2) "We suggest" the use of dexmedetomidine for sedation in critically ill pediatric postoperative cardiac surgical patients to decrease the risk of tachyarrhythmias (*conditional, low-level evidence*).

Rationale: Several studies including two systematic reviews (153, 154), and two RCTs (143, 155), compared postcardiac surgical outcomes in pediatric patients receiving sedation with dexmedetomidine versus other regimens, primarily benzodiazepines with or without opioids. Two studies reported reduced duration of MV with dexmedetomidine sedation (153, 155), and one showed no difference (143). Both systematic reviews reported aggregate reductions in ICU LOS and tachyarrhythmias, including junctional ectopic tachycardia. No increases in clinically relevant adverse hemodynamic effects were reported. Three retrospective studies reported reduced midazolam use with dexmedetomidine sedation (147, 156, 157) and three similar studies reported reduced opioid use (147, 156, 158). One retrospective study reported that dexmedetomidine use was associated with reduced odds of developing acute kidney injury following cardiac surgery (159) (**SDC Table 12**, http://links.lww.com/PCC/B920).

Propofol.

Question: Is propofol sedation safe in mechanically ventilated children and what is its role?

Answer:

1) "We suggest" that continuous propofol sedation at doses less than 4 mg/kg/hr (67 µg/kg/min) and administered for less than 48 hours may be a safe sedation alternative to minimize the risk of propofol-related infusion syndrome (PRIS) development (*conditional, low-level evidence*).
2) Short term (< 48 hr) continuous propofol sedation may be a useful adjunct during the periextubation period to facilitate weaning of other analgosedative agents prior to extubation (*good practice*).

Rationale: Initially described in 1992, PRIS continues to concern pediatric critical care practitioners (160). Although PRIS developed in 84% of a small cohort receiving propofol at doses exceeding both 4 mg/kg/hr (67 µg/kg/min) and a 48 hour duration (161), in five larger prospective observational series, no cases were reported when high doses (4 mg/kg/hr) and long durations (48 hr) were avoided (160, 162–165). Suggested monitoring/screening for PRIS during continuous propofol sedation includes continuous electrocardiogram (ECG) and intermittent measurement of lactic acid, triglycerides, creatine kinase, serum creatinine, and liver function studies (166). Several small studies have reported successful early extubation using propofol sedation in children following cardiac surgical procedures (163), patients at high risk for extubation failure (167), or burn injury patients (168) (**SDC Table 13**, http://links.lww.com/PCC/B920).

Ketamine.

Question: What is the role of ketamine in the sedation of critically ill pediatric patients?"

Answer: "We suggest" consideration of adjunct sedation with ketamine in patients who are not otherwise at their predefined target sedation depth (*conditional, low-level evidence*).

Rationale: Ketamine appears to be a safe and effective alternative in patients who are not adequately sedated with other agents (alpha$_2$-agonists, benzodiazepines, opioids, barbiturates, or propofol for example) or as part of a drug rotation strategy (169, 170). Although ketamine use has been largely avoided in patients with traumatic brain injury (TBI) due to reports of increases in cerebrospinal fluid pressure (171–173), a more recent prospective trial in 30 mechanically ventilated children with TBI reported that intracranial pressure (ICP) decreased when adjunct ketamine was used for premedication prior to ETT suctioning as well as when administered for refractory intracranial hypertension, during which a small increase in cerebral perfusion pressure also resulted (174). Premedication with ketamine may be considered in 1) critically ill children with raised ICP prior to performing noxious or potentially distressing procedures and 2) in critically ill children with raised ICP refractory to other medical management including deep sedation and analgesia.

Neuromuscular Blockade

Historically, NMBAs have been used for the optimization of patient-ventilator synchrony, reduction of oxygen consumption, and prevention of unintended extubation or device removal (163). More recently, the reliance on NMBAs has declined due to concern regarding associated complications such as residual neuropathy or weakness, and the increasingly recognized benefits of lighter sedation strategies, when appropriate, for neurocognitive recovery (164). However, disease states/conditions that necessitate neuromuscular blockade remain. Relevant pharmacology and dosing of different NMBAs is found in **SDC Section D1, Table 14** (http://links.lww.com/PCC/B920), including considerations and/or cautions in the setting of renal and/or hepatic dysfunction/failure. Potentiation or antagonism of neuromuscular blockade can also occur in the setting of concomitant drug therapy or certain medical disease states or conditions (**SDC Table 15**, http://links.lww.com/PCC/B920) (175–177). The reader is additionally referred to **SDC Sections D2-D4**, (http://links.lww.com/PCC/B920) for discussion of important NMBA-related questions for which specific recommendations were unable to be made.

NMB Monitoring.

Question: How should depth of neuromuscular blockade be monitored in critically ill pediatric patients receiving continuous NMBA infusions?

Answer:

1) "We suggest" that train-of-four (TOF) monitoring be used in concert with clinical assessment to determine depth of neuromuscular blockade (*conditional, low-level evidence*).
2) "We suggest" using the lowest dose of NMBA required to achieve desired clinical effects and manage undesired breakthrough movement (*conditional, low-level of evidence*).

Rationale: The most commonly described method to assess the level of neuromuscular blockade in critically ill patients receiving NMBAs is by peripheral nerve stimulation or TOF monitoring. One to three twitches typically indicates adequate neuromuscular blockade (178). Surveys have reported that TOF monitoring along with clinical assessment is used in 63–84% of critically ill patients receiving NMBAs (179, 180), whereas a small percentage of patients are assessed using only TOF (181). Although studies in adults have reported lower cumulative NMBA exposure, titration is guided by TOF use rather than clinical variables alone (182), corroborating data do not exist in PICU patients. However, since studies do a positive correlation between duration of exposure or cumulative NMBA dose and prolonged recovery time (178), it appears prudent to use the lowest continuous infusion dose and closely monitor blockade depth. TOF reliability may be adversely affected by a number of patient factors including diaphoresis, extremes of skin temperature, peripheral edema, and young age (i.e., use of large electrodes may directly initiate muscle twitch rather than nerve stimulation) (178, 183). Benefits of intermittent NMBA discontinuation to assess the level of sedation/analgesia, facilitate neurologic examination, and reduce the total NMBA drug exposure have been reported and may be valuable, especially when TOF use is unavailable (178, 184, 185).

Question: Should measures of brain activity (raw or processed electroencephalogram) be used rather

than validated clinical scoring tools to assess depth of sedation in critically ill pediatric patients receiving NMBAs?

Answer: Electroencephalogram-based monitoring may be a useful adjunct for assessment of sedation depth in critically ill pediatric patients receiving NMBAs (*good practice*).

Rationale: Assessment of sedation depth during NMBAs use is especially challenging. Formal measurement of brain activity has been proposed as an adjunct modality to complement clinical assessment or be used when clinical assessments are not available. Three electroencephalogram-based monitors have been evaluated in critically ill children including the bispectral index (BIS) (186), the SNAP II monitor (187, 188), and the amplified electroencephalogram (aEEG), although aEEG has been almost exclusively used to predict outcomes following neonatal hypoxemic ischemic injury (189–191). BIS monitoring has been the most widely evaluated tool in critically ill children (186). The only reported correlations between BIS and clinical sedation scores have been with the COMFORT scale, in which BIS was found to better discriminate under—from adequate versus over—from adequate sedation (192–194). Due to significant interpatient variability at similar sedation depths, BIS monitoring is better suited for trending sedation depth rather than targeting a specific score (195, 196). Limitations of BIS monitoring include sensitivity to some psychoactive agents (ketamine) (197–199) and physiologic alterations (hypothermia, hypoglycemia, or cerebral ischemia) leading to erroneous measurements (200–202). The SNAP II monitor has been inadequately studied to date in the PICU environment.

Sedation and Analgesia During NMBA Management.

Question: What is the necessary sedation and analgesia management of pediatric patients requiring NMBAs?

Answer: "We suggest" that sedation and analgesia should be adequate to prevent awareness prior to and throughout NMBA use (*conditional, low-level evidence*).

Rationale: Adequacy of analgesia and sedation cannot be assessed clinically during NMBA use. Historically, variables such as changes in vital signs, diaphoresis, and lacrimation were relied upon to suggest agitation or pain, although these lack specificity compared with objective patient assessment (56, 203). The "fifth National Audit Project of the Royal College of Anesthetists and the Association of Anesthetists of Great Britain and Ireland" reported that the occurrence rate of accidental awareness during general anesthesia in children is one in 135 by direct questioning and one in 51,500 when determined by spontaneous reporting, with the majority of spontaneously reported cases involving unrelieved pain (204). The "Pediatric Acute Lung Injury Consensus Conference" stated that patients with pediatric acute respiratory distress syndrome should receive minimal yet effective targeted sedation and that NMBAs should be used only when sedation alone is inadequate to achieve effective MV (205). To date, no pediatric studies have specifically addressed optimal sedation and analgesia in the setting of NMBA use. Despite this, the standard of practice for sedation and analgesia provision during NMBAs administration should be to avoid the potential of awareness. The use of NMBAs in a "bolus only" manner or scheduled discontinuation of continuous infusions, if clinically appropriate, permits both assessment of the adequacy of analgesia and sedation and the need for ongoing paralysis.

NMBA AEs and Complications.

Question: Should passive eyelid closure and lubrication versus other eye protection measures be used to prevent corneal abrasions in critically ill children receiving NMBAs? (**SDC Section D5**, http://links.lww.com/PCC/B920).

Answer: "We recommend" routine use of passive eyelid closure and eye lubrication for the prevention of corneal abrasions in critically ill pediatric patients receiving NMBAs (*strong, moderate-level evidence*).

Rationale: NMBAs inhibit skeletal muscle contraction including muscles associated with eye closure and the blink reflex. As a result, significant eye drying, corneal ulceration, infection, and/or loss of visual acuity may occur (206). The reported occurrence rate of corneal abrasions in critically ill patients is 8–60%, although pediatric data are less robust (206–210). Standard protective interventions include passive eyelid closure, eye taping, and ophthalmic lubricating ointment. Only one study has specifically evaluated the use of an intervention beyond this to prevent corneal abrasions in children. In a multicenter, RCT of 237 children receiving NMBAs for greater than 36 hours, addition of a moisture chamber to standard care

with routine eye lid closure and lubricating ointment did not decrease the occurrence rate of corneal abrasions (206). The investigators concluded that the use of routine eye closure and ophthalmic lubricating ointment was as effective as a moisture chamber with eye lubrication. As corneal abrasions in children receiving NMBAs may develop quickly (within 48 hr), vigilant use of eye lubrication and passive eyelid closure should be a priority.

ICU Delirium

Delirium is a syndrome of acute brain dysfunction that is characterized by the core features of inattention and unawareness, with possible secondary changes in cognition. Delirium often manifests with a fluctuating course of severity and occurs as a direct physiologic consequence of a medical or surgical condition. The associated acute neurocognitive disturbances will be an alteration from an established or evolving baseline neurocognitive disorder (211). Pathophysiologically, aberrant neurotransmission from an imbalance of stimulatory versus inhibitory neurotransmitter and receptor actions leads to the observed presenting symptoms and behaviors (212–214). Delirium is categorized based on psychomotor symptoms including hypoactivity, hyperactivity, or a mixture of the two.

Delirium is categorized based on psychomotor symptoms. Patients with hypoactive delirium may appear apathetic, withdrawn from the environment, or with depressed levels of arousal (215, 216), and rarely provoke concern despite being more likely to have poorer outcomes (215, 217, 218). Patients with hyperactive delirium suffer from agitation, emotional lability, or disruptive behavior, although this is the least common form of ICU delirium (219, 220). Patients who demonstrate hyperactive and hypoactive behaviors are categorized as having a mixed subtype of delirium.

Delirium is highly prevalent (reported rates up to 80%) across the spectrum of disease states in the PICU and its development should be considered a possibility in all critically ill pediatric patients (113, 152, 221–236). Multiple studies have determined key risk factors for ICU delirium in pediatric patients. "Predisposing risk factors" for delirium include younger age, neurodevelopmental delay, poor nutritional status, and cyanotic heart disease. "Precipitating risk factors" include benzodiazepine exposure, coma and deep sedation, requirement for invasive MV, and prolonged cardiopulmonary bypass time (113, 151, 152, 221, 222, 226, 234, 237–239) (**SDC Section E1, Table 16**, http://links.lww.com/PCC/B920). Delirium in critically ill pediatric patients is associated with increases in hospital and PICU LOS, duration of MV, hospital costs, and in-hospital mortality (113, 151, 221, 222, 224, 234, 237–240).

Delirium Monitoring.

Question: Which delirium screening tools have the best validity and reliability in critically ill pediatric patients? (**SDC Section E2**, http://links.lww.com/PCC/B920).

Answer: "We recommend" use of the preschool and pCAM-ICU (ps/pCAM-ICU) or the CAPD as the most valid and reliable delirium monitoring tools in critically ill pediatric patients (*strong, high-level evidence*).

Rationale: Of five pediatric-specific delirium screening tools available, three are relevant to PICU patients (**SDC Section E2b**, http://links.lww.com/PCC/B920). The ps/pCAM-ICU are considered "point-in-time" assessments, using both observation and interactive components (241), and maintaining the basic foundation of its highly valid and reliable precursor, the adult Confusion Assessment Method for the ICU. The pCAM-ICU was originally validated in a prospective cohort of general medical/surgical PICU patients over 5 years old and performed with a high sensitivity (83%) and specificity (99%) compared with psychiatry assessment, and high interrater reliability (kappa of 0.96) (225). The preschool CAM-ICU psCAM-ICU is an adaptation of the pCAM-ICU for purposes of meeting the language and cognitive deficits in children developmentally less than 5 years old. The psCAM-ICU was initially validated in a large prospective cohort of medical/surgical PICU patients less than 5 years old and demonstrated good sensitivity (75%) and high specificity (91%) compared with psychiatry assessment and good interrater reliability (kappa of 0.79) (226). The psCAM-ICU was subsequently validated in infants less than 6 months old and again performed with a high sensitivity (95%) and specificity (81%) (242). (**SDC Table 17**, http://links.lww.com/PCC/B920). The Cornell Assessment for Pediatric Delirium (CAPD) is an observational delirium instrument, adapted from the Pediatric Anesthesia Emergence Delirium scale, designed to improve the ability to detect all delirium subtypes (223, 227) (**SDC Table 18**,

http://links.lww.com/PCC/B920). In a mixed medical-surgical PICU population, the CAPD performed well, sensitivity (94%) and specificity (79%), compared with psychiatry assessment. Reliability or consistency of scoring between nurse assessors was high with a kappa of 0.94 (214), although this was lower in a recent follow-up nurse assessor reliability study (kappa of 0.6) particularly in patients less than 2 years old (243).

Question: Should critically ill pediatric patients undergo routine delirium screening?

Answer: "We recommend" routine screening for ICU delirium using a validated tool in critically ill pediatric patients upon admission through ICU discharge or transfer (*strong, high-level evidence*).

Rationale: The care of critically ill pediatric patients is complicated and requires the collaboration and effectiveness of an interdisciplinary team. Routine monitoring in the ICU incorporates multiple organ/system surveillance supporting the acute management of ongoing organ dysfunction. Therefore, the recommendation for the implementation of routine monitoring for acute brain dysfunction considers the availability of valid and efficient bedside tools and the ability to identify and modify risk factors by which an opportunity is created to reduce prevalence, morbidity, and mortality associated with delirium. With the availability of validated screening tools (see above), delirium monitoring in the PICU is feasible (152, 224–227, 229, 242). We now recognize that ICU delirium is highly prevalent among critically ill children, with predominance of the hypoactive subtype which is most easily missed without routine screening. The goal of delirium monitoring is ultimately to implement patient care strategies to diminish its occurrence rate and effect on clinical outcomes such as mortality and further understand the role of acute brain dysfunction on the quality of life for pediatric survivors of critical illness.

Delirium Prevention and Management in the PICU.

Nonpharmacologic management of delirium

Question: Among critically ill pediatric patients, what "nonpharmacologic" strategies reduce the incidence and/or decrease duration or severity of delirium? (**SDC Section E3**, http://links.lww.com/PCC/B920).

Answer:

1) Given low patient risk, and possible patient benefit to reduce the occurrence rate and/or decrease duration or severity of delirium, "we suggest" the following "nonpharmacologic strategies": optimization of sleep hygiene, use of interdisciplinary rounds, family engagement on rounds, and family involvement with direct patient care (*conditional, low-level evidence*).
2) "We suggest" performing EM, when feasible, to reduce the development of delirium (*conditional, low-level evidence*) although data are insufficient to make a recommendation regarding the impact of this intervention on the duration or severity of delirium.

Rationale: Environmental impact on the prevention of delirium has yet to be studied in a robust manner in children. Despite the limited data, implementation of environmental modifications such as maintaining day/night cycles with the use of artificial light and sunlight during the day and healthy sleep conditions at night (minimizing noise, light, and stimulation) may impact the occurrence rate and severity of delirium in children (244–246). Interactive approaches such as cognitive stimulation and physical activity during the day may increase orientation during the day and quality sleep at night. Family presence and involvement, familiar care team members, and comforting objects from home can also help reassure and reorient patients. Studies in critically ill adults have shown decreased occurrence rate and duration of delirium with implementation of EM. A single-center prospective study indirectly supports potential effectiveness of this approach in children. Over a 22-month period, phased implementation of protocolized sedation followed by EM was associated with a near 40% reduction in delirium rates (224). Mitigation of delirium is often achieved by resolution of the underlying critical illness or other contributing medical conditions. Therefore, the initial steps in delirium management should focus on identification and treatment of these underlying etiologies (231, 239, 240, 247–249). Differential diagnoses should be considered using a model such as Bring oxygen, Remove/Reduce deliriogenic drugs, patient Atmosphere, Immobilization, New organ dysfunction, Metabolic disturbances, Awake, Pain, Sedation (**SDC Table 19**, http://links.lww.com/PCC/B920) (247).

Pharmacologic management of delirium

Question: What "pharmacologic" sedation strategies reduce the incidence and/or decrease the duration or severity of delirium in critically ill pediatric patients?

Answer:

1) "We recommend" minimizing benzodiazepine-based sedation when feasible in critically ill pediatric patients to

decrease occurrence rate and/or duration or severity of delirium (*strong, moderate-level evidence*).
2) "We suggest" strategies to minimize overall sedation exposure whenever feasible to reduce coma and the occurrence rate and/or severity of delirium in critically ill pediatric patients (*conditional, low-level evidence*).

Rationale: Severe and multiple organ dysfunction or requirement of prolonged sedation for MV complicates the management and successful resolution of delirium. Due to relative nonspecificity of delirium symptoms (e.g., anxiety, agitation, or combativeness), differentiation of delirium from other causes may be challenging, and inappropriately treating delirium symptoms with sedation, for example, further exacerbates symptoms. Benzodiazepine exposure is an independent risk factor for delirium (150–152). Therefore, the avoidance and/or decreased use of benzodiazepine sedation is important for delirium prevention and management. In a small single-center RCT, delirium rates were significantly lower in dexmedetomidine compared with midazolam-sedated patients following scoliosis surgery (125, 141). Other cohort studies have demonstrated improvement of delirium severity or resolution with decreasing or discontinuation of benzodiazepines (150–152). Deep sedation states have also been associated with delirium (113). RCTs in healthy pediatric patients have reported decreased emergence delirium after general anesthesia with the use of dexmedetomidine (250) and melatonin (251), but no such studies have been completed in the PICU setting. Reducing benzodiazepine exposure by addition of or transition to dexmedetomidine sedation has decreased occurrence rate of delirium in several adult RCTs (252–256).

Question: Does the use of haloperidol or atypical antipsychotics reduce the occurrence rate and/or decrease the duration or severity of delirium in critically ill pediatric patients?

Answer:

1) "We do not suggest" routine use of haloperidol or atypical antipsychotics for the prevention of or decrease in duration of delirium in critically ill pediatric patients (*conditional, low-level evidence*).
2) "We suggest" that in critically ill pediatric patients with refractory delirium, haloperidol or atypical antipsychotics be considered for the management of severe delirium manifestations with consideration of possible adverse drug effects (*conditional, moderate-level evidence*).
3) "We recommend" a baseline ECG followed by routine electrolyte and QTc interval monitoring for patients receiving haloperidol or atypical antipsychotics (*strong, moderate-level evidence*).

Rationale: Antipsychotics have been used to manage delirium manifestations in the adult and pediatric populations. However, a recent multicenter RCT in adults found no reduction in delirium duration with use of haloperidol or an atypical antipsychotic (ziprasidone) (257). Although pediatric efficacy data are lacking, in refractory or severe delirium, use of atypical antipsychotics may improve delirium symptoms and facilitate weaning of sedation and MV (258, 259). The global or long-term effects of this strategy are not known. Consequently, routine use of antipsychotics to prevent delirium in critically ill pediatric patients is not suggested although their use may be carefully considered for symptom control in patients with refractory and/or severe delirium. The management of delirium with any antipsychotic is not approved for use in pediatric patients in the United States by the Food and Drug Administration. As antipsychotics do not "treat" the cause(s) of delirium, vigilance to identify and modify exacerbating factors remains key. Due to the cardiac side effects, patients treated with haloperidol or atypical antipsychotics should have electrolyte and ECG monitoring at regular intervals. Management of severe delirium exacerbations should be limited to the smallest effective dose to decrease risk of side effects and occur in concert with low risk nonpharmacologic treatments preferably prior to initiating pharmacologic therapy (**SDC Table 20**, http://links.lww.com/PCC/B920) (244, 245, 260–262). Collaboration with child and adolescent psychiatry may be beneficial when available to provide guidance on pharmacologic management and ongoing care once transferred out of the PICU.

Iatrogenic Withdrawal Syndrome

IWS is a clinical syndrome that manifests after a drug is either stopped, rapidly weaned, or chemically reversed after prolonged exposure (116, 263, 264) and is generally correlated with the development of drug tolerance (**SDC Sections F** and **G**, http://links.lww.com/PCC/B920). IWS symptoms can often be nonspecific, frequently representing autonomic activation and/or dysfunction (tachypnea, tachycardia, hyperpyrexia, and diaphoresis) (116, 265), gastrointestinal dysfunction (vomiting and diarrhea), and/or

CNS alterations (agitation, jitteriness, seizures, hallucinations, delirium) (266–269). The onset of IWS symptoms may be delayed following weaning or discontinuation of drugs with active drug metabolites (e.g., morphine, diazepam, midazolam), or in the setting of renal and/or hepatic dysfunction (265). IWS prevalence following administration of opioid and/or benzodiazepines in PICU patients has been reported to be as high as 87% (61, 263, 264, 267, 269–272). Delineation of the epidemiology of IWS from specific drug classes remains challenging due to the frequent concomitant use of drug classes and variability in weaning strategies. Risk factors for the development of IWS from opioids and/or benzodiazepines include duration and cumulative dose, use of multiple opioids and sedatives, age less than 6 years (particularly < 6 mo), pre-existing cognitive impairment, and critical illness involving the CNS (263, 264, 266, 269, 270, 272). Although substantial variability in cumulative opioid and benzodiazepine dose exposure has been reported to correlate with IWS development, more recent reports of lower doses suggest that liberal thresholds for IWS screening would be prudent (268, 270). Choice of opioid has not been found to significantly impact the risk of IWS, whereas three or more classes of analgesics and/or sedatives have been independently associated with an increased risk of IWS (268) (**SDC Table 21**, http://links.lww.com/PCC/B920). Although a formal description of IWS to alpha$_2$-agonists has yet to be published, a common constellation of symptoms including rebound tachycardia or hypertension, agitation/irritability, sleeplessness, tremors, hypertonicity, emesis, and diarrhea has been described frequently and suggests that IWS to alpha$_2$ agonists occurs and is also quite prevalent (27–83%) (273–278).

Monitoring for IWS.

Question: How should critically ill pediatric patients be monitored for IWS from opioids and/or benzodiazepines?

Answer:

1) "We recommend" use of either the Withdrawal Assessment Tool-1 (WAT-1) or Sophia Observation Scale (SOS) for the assessment of IWS due to opioid or benzodiazepine withdrawal in critically ill pediatric patients (*strong, moderate-level evidence*).
2) "We suggest" routine IWS screening after a shorter duration (3–5 d) when higher opioid or benzodiazepine doses are used (*conditional, moderate-level evidence*).

Rationale: Although clinical symptoms alone may produce suspicion of IWS development, the use of validated screening tools allows for consistency and standardization of diagnosis. Until relatively recently, the only validated tools available to PICU practitioners were those based on neonatal opioid withdrawal such as Finnegan's Neonatal Abstinence Score (114, 115, 264, 269, 279–281). The WAT-1 (282) and the SOS (283) have been validated for the diagnosis of opioid and benzodiazepine-based IWS in PICU populations (284). The WAT-1 uses a 12-point numerical scale and is recommended to be scored at intervals of 12 hours or less. Scores greater than or equal to 3 are consistent with the presence of IWS but cannot differentiate between opioid and benzodiazepine withdrawal (263, 271). The WAT-1 is highly sensitive and specific for IWS from both benzodiazepines and opioids with good interrater reliability. It cannot, however, differentiate between opioid and benzodiazepine withdrawal (271). The SOS has been validated in a single-center study (283). Similar to the WAT-1, sensitivity and specificity are good, as is concurrent validity (267). It is comprised of a 15-item scale incorporating changes in heart rate and respiratory rate in addition to signs of autonomic dysfunction, CNS irritability, and gastrointestinal dysfunction (272, 283). Scores of greater than or equal to 4 are consistent with IWS. Similar to the WAT-1, sensitivity and specificity are good, as is concurrent validity. Due to the additional incorporation of movement disturbances and the presence of hallucinations, the SOS may be more sensitive in screening for benzodiazepine withdrawal although the significance of these differences has not been adequately evaluated.

Question: How should critically ill pediatric patients be monitored for IWS from alpha$_2$-agonists?

Answer: Until a validated screening tool is developed, monitoring for IWS from alpha$_2$-agonists should be performed using a combination of associated symptoms (unexplained hypertension or tachycardia) with adjunct use of a validated benzodiazepine or opioid screening tool (*good practice*).

Rationale: Alpha$_2$-agonist–based sedation regimens are being increasingly used in the PICU setting for care of critically ill pediatric patients. Currently available IWS screening tools including the WAT-1, SOS, and Opioid Benzodiazepine Withdrawal Score are inadequate for assessing alpha$_2$-agonist withdrawal as they do not include several symptoms that appear

to be unique to alpha$_2$-agonist withdrawal, especially otherwise unexplained hypertension and tachycardia (264, 266, 274–276, 278) (**SDC Table 22**, http://links.lww.com/PCC/B920). As opioids and benzodiazepines may also be administered concurrently with alpha$_2$-agonists, overlap of IWS symptoms across all three agent classes may make identification of the agent(s) responsible for IWS development challenging, prevent correct diagnosis, and, thus, prompt initiation of appropriate mitigation strategies. Common to IWS from all agents, the relative nonspecificity of symptoms may also prevent identification of pain, nonwithdrawal based agitation, and delirium, which may further delay appropriately directed interventions (6, 115).

IWS Prevention and Management.

Question: What are the optimal strategies for management of opioid and benzodiazepine IWS in critically ill pediatric patients?

Answer:

1) "We suggest" that opioid related IWS be treated with opioid replacement therapy to attenuate symptoms, irrespective of preceding dose and/or duration or opioid exposure (*conditional, low-level evidence*).
2) Benzodiazepine-related IWS should be treated with benzodiazepine replacement therapy to attenuate symptoms, irrespective of preceding dose and/or duration of benzodiazepine exposure (*good practice*).

Rationale: As IWS is a receptor-based phenomenon, management should include reinstitution of an agent (opioid or benzodiazepine) that has the same receptor activity. The preponderance of studies evaluating opioid replacement therapy for IWS have been performed using methadone, likely due to its high enteral bioavailability and long half-life which allows for less frequent dosing (285, 286). In two RCTs, high dose methadone and a longer taper period tended to be more effective in decreasing the development of IWS (287, 288). Two systematic reviews support methadone safety and efficacy for IWS prevention during opioid weaning and management if symptoms develop (285, 289). As IWS symptoms develop or recur in up to one third of patients using a methadone taper, IWS screening during methadone weaning remains important (290, 291). Data describing use of other enteral opioids (morphine, oxycodone) are limited, and no comparisons of different enteral agents have been performed, precluding the recommendation of a specific agent. In patients not tolerating enteral intake, IV agents may be used.

Fewer data exist regarding treatment of benzodiazepine related IWS. Two retrospective studies reported symptom mitigation with use of gradual taper and/or conversion from IV to longer-acting enteral benzodiazepines (114, 292). Although most studies discussing enteral benzodiazepines for IWS prevention/management use lorazepam due to its longer duration of action, efficacy studies comparing enteral benzodiazepines have not been performed. Limited data from two small prospective series suggest that addition of alpha$_2$-agonist agents may also mitigate the development of opioid and/or benzodiazepine IWS (143, 293) (**SDC Section G3**, http://links.lww.com/PCC/B920).

Question: What are the optimal strategies for management of alpha$_2$-agonist IWS in critically ill pediatric patients?

Answer: Alpha$_2$-agonist–related IWS should be treated with IV and/or or enteral alpha$_2$-agonist replacement therapy to attenuate symptoms, irrespective of preceding dose and/or duration of alpha$_2$-agonist exposure (*good practice*).

Rationale: As with IWS associated with other agents, alpha$_2$-agonist–associated IWS is ideally managed with replacement of an IV or enteral alpha$_2$-agonist. However, data regarding the optimal weaning and/or replacement strategies remain limited. Limited data suggest reduced IWS symptoms, specifically otherwise unexplained tachycardia and hypertension, with adjunct use of enteral clonidine prior to dexmedetomidine infusion weaning and/or discontinuation (156, 294, 295). Based on an international survey of practices related to dexmedetomidine use and withdrawal management, the above practice appears to be common as 81% of respondents reported clonidine initiation in conjunction with a regimented dexmedetomidine wean to prevent withdrawal. However, reported dosing of clonidine in these protocols was variable, and the rate of dexmedetomidine wean was not provided. The survey was also not designed to evaluate the impact of this practice on breakthrough IWS symptoms, leaving this an area requiring further study (273).

Question: Should protocolized analgesic/sedative versus nonprotocolized analgesic/sedative weaning be used to reduce the duration of agent tapering and prevent or reduce IWS development in critically ill pediatric patients?

Answer: "We suggest" use of a standardized protocol for sedation/analgesia weaning to decrease duration of

sedation taper and attenuate emergence of IWS (*conditional, low-level evidence*).

Rationale: Whereas protocolized sedation typically encompasses titration of agents to meet sedation targets during MV, IWS most often occurs during ventilator weaning or following extubation, when sedatives are being weaned. Six studies were found more specifically addressing protocolization of opioid and benzodiazepine weaning (IV and/or enteral agents) and their impact on weaning process duration, cumulative drug exposure, and development of IWS symptoms (**SDC Table 23**, http://links.lww.com/PCC/B920). All five studies evaluating duration of sedative wean reported more rapid weaning with protocolization (124, 296–299) as well as a decrease (124, 297) or no difference (298, 299) in the occurrence rate of IWS development. Two studies reported similar (300) or reduced IWS rates (299) with protocolized versus nonprotocolized weaning with more protocolized patients being totally weaned off sedatives prior to hospital discharge.

Optimizing Environment

The PICU environment may negatively influence patients during management and recovery from critical illness. There may be significant benefit in practicing patient and family-centered care, improving sleep hygiene, and fostering a culture of EM and exercise in the PICU. Although data are limited on the effects of environmental optimization, the risks of implementing such changes are often low with potentially beneficial effects for patients and families. Supporting an environment of parental and caregiver engagement with patient care likely benefits patients directly and can decrease parental stress and anxiety levels. Indeed, the American Academy of Pediatrics and the ACCM recommend a focus on patient and family-centered care, taking into account patient or family needs, values, and preferences when making clinical decisions, keeping families well-informed, and actively involving them in patient care (301).

Environment also directly impacts patient sleep quality and quantity. Sleep deprivation is a significant stressor reported by survivors of critical illness (302, 303) and has been linked to increased metabolic requirements (304), altered adrenocortical axis function (305), altered immune competence (306, 307), increased pain perception (308, 309), and development of delirium in adults (310) and possibly children (311). ICU factors disrupting sleep include patient-related factors such as presence of invasive devices, need for MV, immobility, medication effects, and inadequately controlled pain, as well as environmental factors such as ambient noise and light levels as well as the performance of frequent caregiver assessments (21, 23, 312, 313). Few pediatric studies have assessed environmental interventions effects on sleep and patient outcomes, but simple interventions may positively impact patients (**SDC Section H**, http://links.lww.com/PCC/B920).

Last, the PICU environment routinely leads to a culture of immobility. Prolonged immobility has been shown to increase the risk of comorbidities such as ICU-acquired weakness, delirium, and iatrogenic sedative and analgesic drug withdrawal (314). Adult ICU evidence suggests that EM activities can reduce the complications of immobility and comorbidities, and preliminary data suggest positive benefits in critically ill children (315–317). Recent observational studies have found the implementation of an EM program to be feasible and safe in critically ill children with the use of standardized guidelines and collaboration of an interdisciplinary team to train PICU personnel and provide essential resources (316–321). Despite this, a recent survey of 161 international PICUs reported infrequent presence of mobility protocols (26% of participating PICUs), whereas a point prevalence study of 31 European PICUs found that only 39% of patients received any mobilization procedures on the days of observation (322, 323).

Family Presence.

Question: Does parent or caregiver presence during procedure performance improve outcomes in critically ill pediatric patients?

Answer: "We suggest" facilitation of parental or caregiver presence in the PICU during routine care and interventional procedures to 1) provide comfort to the child, 2) decrease parental levels of stress and anxiety, and 3) increase level of satisfaction of care (*conditional, low-level evidence*).

Rationale: PICU specific studies show parents/caregivers have a decreased level of anxiety and stress when involved in family-centered care, they are more satisfied with the care their child is receiving, and when allowed to be present for procedures or resuscitations, it has helped with the parental or caregiver's coping while maintaining both quality care and patient safety

(324–331). In a PICU study assessing the utility of a daily parental comforting protocol, most parents (70%) and all nurses in the intervention group reported that they felt the intervention had positive patient impact (332). Although concerns have been raised about the impact of parent or caregiver presence during procedures, a study on family presence during tracheal intubation reported no adverse impact on first attempt success, adverse events, or team stress level (333) (**SDC Section H1**, http://links.lww.com/PCC/B920).

Sleep Hygiene.

Question: Do environmental interventions to decrease excessive noise positively impact sleep hygiene and comfort in critically ill pediatric patients?

Answer:

1) "We suggest" that PICU teams make environmental and/or behavioral changes to reduce excessive noise and therefore improve sleep hygiene and comfort, in critically ill pediatric patients (*conditional, low-level evidence*).
2) "We suggest" offering patients the use of noise reducing devices such as ear plugs or headphones to reduce the impact of nonmodifiable ambient noise (*conditional, low-level evidence*).

Rationale: Excessive noise is a ubiquitous problem in the ICU setting. Five studies were found evaluating the impact of a noise reduction strategy in the ICU (311, 334–337). Two studies evaluating the use of a light trigger during both daytime and nighttime hours to remind PICU (338) or NICU (339) staff when ambient noise levels became excessive demonstrated minor (1–3 dB) reductions in average noise levels but no increase in time spent below recommended noise thresholds. NICU studies aimed to reduce anytime ambient noise via staff education similarly have resulted in minimal or no impact (340, 341). A single study in a PICU setting demonstrated significant noise reductions, particularly during evening/nighttime hours, following implementation of a comprehensive delirium bundle, although the bundle components deemed most impactful on noise reduction were not described (303, 311). In neonates, earmuff use for noise reduction was associated with increased quiet sleep time and/or less variability in motor responses (337, 342–344) (**SDC Section H2**, http://links.lww.com/PCC/B920).

Early Mobility.

Question: Does the use of an EM protocol impact clinical outcomes in critically ill pediatric patients?

Answer: "We suggest" performing EM to minimize the effects of immobility in critically ill pediatric patients (*conditional, low-level evidence*).

Rationale: In a three-step quality improvement project, implementation of PICU bundle including delirium screening, protocolized sedation, and an EM protocol was associated with a significant reduction in delirium (224). In a pre- and postcohort study in 75 pediatric liver transplant patients, implementation of an EM protocol was associated with earlier mobility to walk greater than 50 yards and reduced hospital LOS (316). An earlier analysis of 57 post-protocol liver transplantation patients also reported more rapid development of functional mobility but no improvement in length of intubation, PICU stay, and hospital LOS (317). A small RCT, mostly focusing on feasibility and safety, found no statistical differences in hospital or ICU lengths of stay, outpatient physical, occupational, or speech therapy prescription, placement of new technological devices at hospital discharge, or in quality of life and functional scores at 6 months post discharge with a PICU EM protocol (345). Although not statistically significant, less children in the EM protocol group were admitted to an inpatient rehabilitation facility following their hospital stay.

Question: What factors promote success of EM among critically ill pediatric patients?

Answer: "We suggest" the use of a standardized EM protocol that outlines readiness criteria, contraindications, developmentally appropriate mobility activities and goals, and safety thresholds guided by the multidisciplinary team and family decision-making (*conditional, low-level evidence*).

Rationale: Strategies to promote the success of a PICU EM program are primarily based on observational studies (224, 321, 346–348). The implementation of an EM program in these single-center PICUs demonstrated a significant increase in early rehabilitation consults and frequency of EM in critically ill children without increased adverse events. These studies all describe the use of a standardized multicomponent EM protocol that included multidisciplinary daily screening for appropriateness, progressive levels of mobility activities, and variables to monitor for safety and tolerance of the activity (**SDC Section H3**, http://links.lww.com/PCC/B920).

SUMMARY

The current guidelines represent a comprehensive list of practical clinical recommendations for the assessment, prevention, and management of comfort in critically ill pediatric patients. In the development of these guidelines, the multidisciplinary taskforce of pediatric critical care providers sought to ask and provide guidance regarding questions that they felt were relevant to pediatric critical care providers globally and irrespective of preconceptions regarding the quantity or quality of data they felt might be present for questions of interest. Although the above recommendations represent guidance for only questions which the taskforce found adequate evidence to address, many unanswered questions remain, and further discussion of them is found in the provided SDC (http://links.lww.com/PCC/B920). As stated in the *Methods* section, the guidelines above encompass seven distinct but intertwined domains relevant to comfort of the critically ill pediatric patient. However, the authors would also like to note that several key themes may also be identified within these domains. In multiple domains, including pain, agitation, IWS, and delirium, patient assessment must precede intervention. We intend that these guidelines stress the use of validated tools for making these assessments within each domain, and advocate for their development if validated tools are not yet available. Related to comfort management, these guidelines encourage an enhanced use of protocolized sedation and analgesia provision, both during the acute phase of critical illness and during the resolution phases when de-escalations are occurring. We have also attempted to highlight the value of adjunctive/synergistic therapies as well as the importance of nonpharmacologic interventions for enhancing patient comfort and comprehensive care provision, especially given the minimal risks associated with nonpharmacologic interventions and the associated potential benefits of decreasing the need for medications.

These guidelines do have several important limitations which should be mentioned. A significant limitation is the lack of available literature discussing many of the questions taskforce wished to address. Consequently, there are many important questions for which recommendation(s) were unable to be provided and represent opportunities for additional research (see *Future Directions* section below). Although the majority of recommendations made are meant to apply to all critically ill pediatric patients, the taskforce understands that not all critically ill pediatric populations are the same, and although we endeavored to qualify where recommendations may not be relevant for certain populations, we may not foresee all possible nuances for where certain recommendations may not be relevant, either due to patient needs or local resource availability. In retrospect, as some of the questions these guidelines sought to address apply directly to patients and their families, we did not solicit advice from patients and/or the families of critically ill children. We would suggest that this be a consideration made when the time comes for these guidelines to be updated. In similar fashion, we did not solicit input from other ancillary members of the critical care team for questions which might be directly relevant to them, including physical and occupational therapists for EM-related issues and bedside registered nurses (RNs) (although all advanced practice RN members on the taskforce had bedside experience and brought this to the discussion as well).

FUTURE DIRECTIONS

One of the limitations of these guidelines discussed above is the lack of available literature to enable the taskforce to create recommendations for other important clinical questions facing all pediatric critical care practitioners. Consequently, we felt it was appropriate to outline these issues intentionally in the hopes that this listing will both stimulate new research and serve as a guide to subsequent updates of these guidelines. **Table 2** outlines questions that the taskforce found insufficient evidence with which to create either specific recommendations or good practice statements. **Table 3** outlines topics for which recommendations may have been created but within which were still areas the taskforce felt additional study would be of value.

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The American College of Critical Care Medicine, 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 supports development of new and revised guidelines and clinical practice parameters for the critical care practitioner.

TABLE 2.
Unanswered Questions Requiring Further Evaluation

Unanswered Questions
Analgesia
1) What opioid provides a therapeutic advantage for critically ill pediatric patients?
2) Do low-dose opioid antagonists alleviate opioid-induced adverse effects or have opioid-sparing effects?
3) Does the adjunct use of neuraxial or regional analgesia in critically ill pediatric patients shorten the duration of MV or ICU LOS?
4) Does the addition of acupuncture impact outcomes including a decrease in postoperative or procedural pain, decrease in duration of MV, or reduction in PICU LOS?
5) Does the direct application of heat or cold aid in pain management for critically ill pediatric patients?
Neuromuscular blockade
1) How does body mass index impact dosing of NMBA, and what is the role of dosing based on actual body weight vs ideal body weight in the morbidly obese pediatric patient?
2) Does the use of neuromuscular blockade improve clinical outcomes in critically ill pediatric patients suffering from decreased oxygen delivery?
3) Does the use of NMBAs improve outcomes in critically ill pediatric patients with pediatric acute respiratory distress syndrome or severe status asthmaticus?
4) Does the use of neuromuscular blockade improve survival or clinical outcomes for critically ill pediatric patients with acute brain injury or increased intracranial pressure?
5) Does rotation of NMBAs and/or class reduce the development of tolerance?
6) Does the use of routine "drug holidays" reduce prolonged neuromuscular blockade or other NMBA-associated complications in critically ill pediatric patients?
7) In critically ill children receiving NMBA, how are caloric goals altered and what modalities are best to meet these goals?
8) Does use of NMBAs increase the risk of ventilator-associated events?
9) Does concurrent use of corticosteroids affect the risk of myopathy/neuropathy/weakness in pediatric patients receiving NMBAs?
10) In critically ill pediatric patients with myasthenia gravis, how should NMBAs be dosed and clinical effect monitored?
Tolerance/iatrogenic withdrawal syndrome
1) What is the prevalence of, and risk factors for, the development of tolerance to opioids, benzodiazepines, or alpha$_2$-agonists in critically ill pediatric patients?
2) Does goal-directed (targeted) sedation reduce sedation tolerance among critically ill pediatric patients receiving MV?
3) Does the addition of adjunct enteral alpha$_2$-agonists reduce requirements for other sedative or opioid agents in critically ill pediatric patients?
4) What is the prevalence of IWS following exposure to opioids and/or benzodiazepines in critically ill pediatric patients?
5) What is the prevalence of IWS following exposure to alpha$_2$-agonists in critically ill pediatric patients?
6) What are the risk factors for development of IWS to opioids and/or benzodiazepines in critically ill pediatric patients?
7) What are the risk factors for development of IWS to alpha$_2$-agonists?
8) Should protocolized analgesic/sedative vs nonprotocolized analgesic/sedative weaning be used to reduce the duration of agent tapering and prevent or reduce IWS development in critically ill pediatric patients?
9) Does use of an "analgesia with sedative" compared with "single-class" sedation strategy decrease IWS development and associated outcomes in critically ill pediatric patients?
10) Are alpha$_2$-agonists effective in preventing or treating symptoms in critically ill pediatric patients with opioid and/or benzodiazepine-related IWS?
11) In patients with IWS from prolonged alpha$_2$-agonist sedation, what is the optimal replacement strategy for reducing development of or treating alpha$_2$-agonist related IWS?
Optimizing PICU environment
1) Should a parent or caregiver be present during interventional procedures in critically ill infants and children?
2) Do environmental interventions to improve day-night cycling positively impact sleep hygiene in critically ill pediatric patients?
3) Is early mobility safe and feasible in critically ill pediatric patients?
4) What factors promote success of EM among critically ill pediatric patients?

IWS = iatrogenic withdrawal syndrome, LOS = length of stay, MV = mechanical ventilation, NMBA = neuromuscular blocking agent.

TABLE 3.
Topics Requiring Further Investigation

Future Directions
Analgesia
1) Specific study of current or new pain scoring tools in critically ill pediatric patients and specific populations such as neonates, developmentally delayed, nonverbal patients.
2) The impact of other non-opioid adjuncts including gabapentanoids, subanesthetic doses of ketamine on analgesic quality, opioid requirements, and opioid-related adverse effects.
Sedation
1) Identification of the components of protocolized sedation that may impact outcomes in mechanically ventilated pediatric patients.
2) Evaluation of educational strategies which may optimize outcomes (tolerance and withdrawal, drug exposure, delirium development, etc) associated with implementation of protocolized sedation programs.
3) Dosing strategies for the safe and expanded use of propofol as a sedation choice in the PICU with considerations for the avoidance of propofol-related infusion syndrome.
4) Strategies for propofol use during the periextubation period.
5) The effects of propofol vs other agents, including barbiturates, in the setting of traumatic brain injury and intracranial hypertension.
6) The safety, efficacy, and outcomes including resource utilization of enteral vs IV sedative infusions during the acute phase of illness.
7) Scenarios under which daily sedation interruption trials may be safe and appropriate.
Neuromuscular blockade
1) The role and/or utility of brain activity-based monitors to assess sedation depth.
2) Methods with which to better assess indicators of unintended awareness during neuromuscular blocking agent use.
Delirium
1) The valid and reliable assessment of delirium in infants less than 6 mo old, including those with a history of prematurity.
2) Ongoing assessment of risk factors for ICU-delirium with a focus on infants less than 6 mo old and patients with primary or secondary neurologic injury.
3) The impact of sedation strategy on delirium occurrence rate and duration including protocolization and sedation choice (dexmedetomidine, ketamine, barbiturates).
4) The impact of opioid choice on delirium occurrence rate or severity.
5) Further studies evaluating dexmedetomidine-based sedation and delirium in critically ill children are warranted.
6) The impact of the ICU environment (sleep, early mobility, dedicated family care) on delirium development, severity, and duration.
7) The relationship between delirium and long-term outcomes such as cognitive or executive dysfunction, psychologic recovery, and posttraumatic symptoms.
8) The role of antipsychotic use for either prevention or management of ICU delirium.
9) The role of pharmacologic agents to promote sleep quality and how this impacts delirium.
10) Determine possible biomarkers for the diagnosis or prognostication of ICU delirium.
11) Determine whether use of brain activity monitors correlate with delirium presence or severity.
12) Determine whether bundled care practices such as the ABCDEF bundle impact ICU delirium and long-term outcomes.
Tolerance/iatrogenic withdrawal syndrome
1) Development of an operational definition of tolerance.
2) The impact of sedative choice (agent and route) on tolerance development including opioids, benzodiazepines, barbiturates, propofol, and ketamine.
3) Validate a bedside tool for the screening of alpha$_2$-agonist associated withdrawal.
4) The impact of targeted sedation protocols on the development of IWS and related outcomes.
5) The impact of analgosedation strategies (combination sedatives, analgesics vs sedatives alone, analgesics alone, continuous vs intermittent) on the development of IWS and related outcomes.

(*Continued*)

TABLE 3. (*Continued*).
Topics Requiring Further Investigation

Future Directions
6) Best practice for conversion from IV to enteral sedation/analgesia.
7) The impact of early transition to long-acting enteral analgesics and/or sedatives for the prevention of IWS.
Optimizing PICU environment
1) The impact of active parent provision of routine patient care on perceived pain and anxiety, key short-term outcomes (duration of MV and LOS), and long-term cognitive and psychologic outcomes.
2) Describe risks associated with parental involvement and best practice for communication and empowerment.
3) The impact of child life/expressive therapies on environmental comfort in critically ill children.
4) The impact of improved sleep hygiene on outcomes (delirium, length of MV, sedation/opioid exposure, LOS, neurocognitive recovery).
5) Determine objective and efficient monitors of sleep in the PICU.
6) Describe best practices for a successful EM program in the PICU.
7) Determine the impact of EM on outcomes (delirium, duration of MV, sedation/opioid exposure, LOS, neurocognitive recovery, functional recovery).

EM = early mobility, LOS = length of stay, MV = mechanical ventilation.

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