Chapter 2
Safety and Monitoring During Pediatric ICU Sedation

Kaitlin M. Best

Ensuring safe care for critically ill children necessitates, in part, effective analgesia and sedation. Yet, the use of analgesic and sedative medications also carries risks. Opioids and benzodiazepines are associated with respiratory depression, the development of tolerance, iatrogenic withdrawal syndrome, and delirium [1–7]. Ketamine can cause hypertension, increased oral secretions, emergence delirium, agitation, and severe hallucinations [6, 8]. Dexmedetomidine has cardiovascular effects, including bradycardia and hypo- or hypertension that may limit its use in select patient subpopulations. It has also been associated with withdrawal after prolonged infusions [8–12]. Several studies have reported that exposure to analgesic and sedative medications early in life has been linked to adverse neurodevelopmental outcomes [13–15]. Although these outcomes have not been reported consistently [16–18], they remain a legitimate cause of longer-term concern. Oversedation can lengthen the duration of mechanical ventilation, increase the risk of extubation failure, and increase healthcare costs, in addition to increased exposure to analgesic and sedative medications, further contributing to the development of tolerance, iatrogenic withdrawal syndrome and delirium [19–21]. Meanwhile, undersedation is associated with agitation; increased risk for adverse events, such as self-extubation or dislodgement of invasive devices; and psychological distress for both patients and their parents [22–25].

Achieving adequate analgesia and sedation in the pediatric intensive care unit (PICU) is an ongoing challenge. Evidence-based guidelines have increasingly advocated for the assessment of analgesia and sedation using standardized observational assessment tools and titrating depth of sedation to a prespecified goal [26–28]. However, surveys and observational studies of critical care practice indicate that the

K. M. Best (✉)
Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Department of Nursing & Clinical Care Services, Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: kbest@upenn.edu

P. P. Kamat, J. W. Berkenbosch (eds.), *Sedation and Analgesia for the Pediatric Intensivist*, https://doi.org/10.1007/978-3-030-52555-2_2

implementation of such practices is far from universal; in one survey, only 36% of respondents reported the use of sedation protocols [29], and in another, only 42% of units routinely set patient-specific sedation goals [30]. There is burgeoning evidence for the safety and role of daily sedation interruption and standardized, goal-directed sedation in reducing cumulative exposure to analgesic and sedative agents [31–40], thereby reducing the incidence of complications, such as withdrawal and delirium [37, 41–44]. Nevertheless, considerable variation exists in the dosing and administration of analgesic and sedative medications across institutions [2, 20, 29, 45–47], in part due to clinician biases and variable implementation of evidence-based practices [48–55]. With the goal of providing safe, developmentally appropriate analgesia and sedation to critically ill children, this chapter will discuss available assessment tools for monitoring sedation and analgesia in the PICU and their roles in the context of analgesia and sedation management, including evidence-based clinical practice guidelines.

Assessment Tools

Pain Assessment

It is increasingly understood that adequate analgesia must be achieved prior to attempting to titrate sedation in a critically ill child. Consequently, increasing sedation in the setting of ongoing pain represents a failure to recognize one key source of patient agitation and contributes to apparent sedation "failures." Painful procedures are common in the PICU environment, with one recent study finding a median of 11 painful and stressful procedures occurring per patient per day [48]. Additionally, there is an increasing recognition that routine care practices in critically ill patients, such as endotracheal tube suctioning, repositioning, and mobilization, are significant sources of pain rather than mere agitation [56–58]. Pain expression also changes across age and developmental spectrums [59]; therefore, different tools have been developed and validated for use in specific age groups and for particular types of pain among critically ill infants and children. Providers must use their clinical acumen to select the appropriate assessment tool for a given patient, based on the child's verbal and cognitive abilities, clinical status, and consideration of the applicable population and purpose of available tools. Any assessment tools that are chosen for use in a given institution should be implemented with extensive education of clinical staff on appropriate application and scoring of the tool, and procedures should be put in place for establishing and maintaining interrater reliability to ensure consistent assessment of pain across raters [60–62].

Self-Report Tools and Surrogate Reporting

Self-report of pain is widely recommended but challenging to achieve in the PICU. In addition to individual patients' developmental capacity, the impact of underlying disease, use of sedation therapies, and endotracheal intubation and

mechanical ventilation may all adversely impact the child's ability to communicate regarding pain, verbally or otherwise. Despite these limitations, research suggests that children age eight and older can provide valid self-reports of pain using a numeric rating scale of 0–10 [63–65] or faces pain scale, such as the widely known Wong–Baker Faces Pain Rating Scale [66]. These scales have been shown to be valid in populations of children as young as 3 years and older who are able to engage in self-report [67]. Unfortunately, development and validation of numeric rating scales or faces pain scales specifically for use in intubated and mechanically ventilated children have received limited research. While recent studies have shown that children can safely be maintained in a more awake state during mechanical ventilation [31], which may facilitate the child's self-report of pain using appropriate augmentative and alternative communication devices [68], further evidence is needed to explore the efficacy and validity of such approaches. Therefore, it is currently recommended that the assessment of pain through self-report be limited to children with verbal abilities who can utilize either a faces pain scale (age 3 and up) or a numeric rating scale (age 8 and up).

Surrogate reporting of pain by a parent or other caregiver familiar with the child's typical pain behaviors can provide valuable information, particularly in nonverbal children or patients who may exhibit more subtle behavioral cues. However, significant discrepancies have been reported between parent, nurse, and patient (when able to self-report) ratings of pain. In a meta-analysis comparing these assessment sources, only moderate correlations between either nurse or parent ratings of pain and the child's self-report were found [69]. A recent cohort study identified only 50–68% agreement between parent and child reports of pain [70], and another reported that parents of children with cerebral palsy tended to report significantly lower pain scores compared with both their children and other observers [71]. Thus, in children unable to self-report pain, it is recommended that a multimodal approach be utilized in which surrogate reporting is combined with other observational methods of pain assessment [72].

Observational Tools

Among neonates and infants, the Crying, Requires increased oxygen, Increased vital signs, Expression, Sleeplessness (CRIES) scale [73] and the Neonatal Pain, Agitation and Sedation Scale (N-PASS) [74, 75] have been developed to evaluate acute procedural and postoperative pain. The N-PASS has additionally been found to have good reliability and validity for assessing prolonged pain, such as that associated with a critical illness [74], and has moderate correlations with nursing assessments of pain and agitation [76]. Both tools can also be used to assess premature neonates. The CRIES has been reported effective in neonates down to 32 weeks gestational age, whereas the N-PASS has been evaluated in neonates as young as 23 weeks gestational age. The CRIES tool has five domains (see above), each scored between 0 and 2, resulting in a summary score ranging from 0 (no pain) to10 (most intense pain severity). Since the N-PASS measures both pain and sedation, its scoring is slightly more complex. It also has five domains (Crying/irritability, Behavior

state, Facial expression, Extremity tone, and Vital signs), which are graded 0–2 for pain/agitation and 0, −1, or −2 for sedation, resulting in scores ranging from −10 (deeply sedated) to 10 (intense pain/agitation). Scores are corrected for gestational age [74]. Older consensus statements on pain assessment in nonverbal neonates and infants have particularly recommended the CRIES [72, 77], but those documents were released prior to the development of the N-PASS. A 2016 policy statement from the American Academy of Pediatrics simply recommends routine assessment of pain in critically ill neonates and infants, without endorsing the use of one particular tool [28]. A recent study comparing five available assessment tools for pain in neonates similarly concluded that the available tools have comparable and acceptable psychometric performance, and the authors recommend that clinical utility and practicality of tool implementation be used as the basis for selection of a specific tool [78].

The Face, Legs, Activity, Cry and Consolability (FLACC) scale was designed to evaluate acute procedural pain in children that are 2 months to 7 years of age in the postanesthesia care unit [79]. Its use was subsequently extended to the assessment of preverbal patients in the PICU [80] and for procedural pain in children that are 5–16 years old [81]. A modified FLACC has been found to be valid for the measurement of acute pain in critically ill and mechanically ventilated children up to 13 years of age [82, 83]. The FLACC tool has five domains scored between 0 and 2, resulting in a summary score ranging 0–10 and higher scores reflecting increasing pain severity. It relies solely upon behavioral indicators of pain, an important consideration since physiologic parameters, such as blood pressure, respiratory rate, and heart rate, have been found to be unreliable measures of pain and poor predictors of analgesic requirements [84, 85]. Consensus recommendations for pain assessment in nonverbal infants and children have encouraged the use of the FLACC [27, 72, 86], and it has been implemented in a variety of clinical settings [29, 45, 87, 88]. For children with cognitive impairment, a revised FLACC with individualized pain behaviors added by parents has demonstrated reliability and validity for postoperative pain assessment [83, 89].

Two additional scales have been published but are more limited in that they have only been validated for use during specific procedures or in specific populations. The Hartwig scale specifically assesses pain during endotracheal tube suctioning and is, thus, limited in generalizability. The scale utilizes five criteria (motor response, facial grimace, eye movement, respiratory pattern, and reaction to endotracheal tube aspiration), each graded from 1 to 5 for a possible score range of 5–25 [90]. In critically ill patients aged newborn to 15 years, the scale has demonstrated good internal consistency and validity [90, 91]. The Cardiac Analgesia Assessment Score (CAAS) was specifically developed to evaluate postoperative pain in mechanically ventilated children following cardiac surgical procedures [92]. It includes one behavioral (motor/respiratory response) and three physiologic (HR, BP, and pupillary size) components, each scored from 0 to 2 for a score range of 0–8. While it has been validated in cardiac surgical patients aged 0–19 years, the specificity of this population makes generalizability to broader PICU populations, surgical or otherwise, unclear.

Agitation and Sedation Assessment

Once adequate analgesia is ensured, the child's level of sedation can be assessed, which typically requires providers to make subjective judgments or conclusions regarding behavioral responses to stimuli. Optimal sedation has been defined in clinical guidelines as a state in which the child is somnolent but responsive to the environment, while tolerating therapeutic procedures without excessive movements [20, 27]. Two instruments have been developed and are used in many ICUs in an attempt to standardize assessment and improve titration of sedative medications [29, 30, 45]: the State Behavioral Scale (SBS) score and the COMFORT score.

Similar to the Richmond Agitation-Sedation Scale (RASS) used in adult critical care, the SBS score describes a patient's level of sedation across a continuum of behavioral responses, from −3 (unresponsive/comatose) to +2 (severely agitated), during normal care [93]. If a child is unresponsive during the initial, pre-stimulus observation period, a progressive stimulus is used to evaluate the patient's level of sedation. The SBS has demonstrated good inter-rater reliability and constructs validity in assessing sedation and agitation among critically ill children across the age spectrum, though it was initially validated in children that are 0–6 years old. It has been incorporated into several published studies and standardized sedation protocols [31, 32, 94, 95].

The COMFORT score was originally developed as a tool with six behavioral dimensions and two physiologic dimensions, to be used for assessment during continuous analgesic and/or sedative infusions in the PICU [96, 97]. However, subsequent psychometric testing and the recognition that physiologic variables may be influenced by both common medications used in the PICU and by critical illness itself, led to the exclusion of physiologic items and development of the COMFORT-Behavioral (COMFORT-B) scale [85]. The COMFORT-B scale demonstrated improved internal consistency, is reliable and valid for the assessment of children that are 0–17 years of age, and discriminates between under- and oversedated children in the PICU, with good sensitivity to change in level of comfort following analgesic and sedative administration [85, 98, 99]. It has six domains scored between 1 and 5, with summary scores ranging 7–30 and higher scores reflecting increasing agitation. However, the tool's length and simultaneous assessment of pain and sedation/agitation has hindered its use in some clinical settings, and the quality of evidence regarding its use is mixed [100]. A recent survey suggested that the SBS score is more commonly used for sedation assessment in the USA, whereas the COMFORT and COMFORT-B scales have been widely implemented internationally [30].

As indicated above, the RASS is commonly utilized in adult critical care while only a single validation study has been performed in critically ill children aged 2 months to 21 years [101]. Scores range from −5 (unarousable) to +4 (combative) with a score of 0 representing an awake, alert, and calm state. Despite this limited evaluation in critically ill children, use of the RASS is likely to continue to grow, as it is the score which both the pediatric Confusion Assessment Method for the ICU (pCAM-ICU) and Cornell Assessment of Pediatric Delirium (CAPD) tools use for determining eligibility to perform delirium screening in children [102–104].

Objective Monitoring Tools

The subjective nature of observational assessment tools has led many clinicians to desire an objective monitoring method that can be used to titrate sedation to more precisely fit an individual patient's needs. From a safety standpoint, cardiorespiratory monitors and pulse oximetry should be considered standards of care in monitoring for sedation-induced effects on hemodynamic status and respiratory effort. For procedural sedation in non-intubated children, the use of end-tidal capnography is additionally recommended to detect hypoventilation that would not be detected by pulse oximetry [105]. Careful examination of the capnographic waveforms can additionally allow early identification of different sources of airway compromise [106]. Heart rate variability (HRV) is an emerging area of interest in analgesia and sedation monitoring. The analgesia nociception index (ANI) is a quantitative value derived from measures of HRV that may allow detection of lesser degrees of nociception during sedation or anesthesia which the above-discussed observational assessment tools are inadequately sensitive to identify [107–109]. Research in critically ill adults suggests that the ANI may be most useful for detection of pain during routine care [110]. However, to date, this tool has not been evaluated specifically in the PICU setting. Its utility may be further limited by the effects of sedative medications common in the critical care setting, such as dexmedetomidine, that affect sympathetic tone and, consequently, HRV [109].

Electroencephalography (EEG) sensitively measures electrical activity within the brain in the clinical setting. However, the complexity of the output typically requires in-depth training and experience to interpret accurately, and the volume of information gleaned generally precludes comprehensive, real-time analysis. Advanced mathematical modeling allows EEG signals to be broken down into frequency, phase, and amplitude components, which can then be interpreted using proprietary algorithms. Such processed EEG measures have been investigated for bedside neurological monitoring and sedation assessment, including the Bispectral Index score (BIS) and amplified EEG (aEEG), which will be reviewed in the sections that follow.

Processed EEG

The BIS was developed and released in the mid 1990s as a brain function monitor to assist with monitoring depth of anesthesia in the operating room, but its use has subsequently been expanded to a number of other clinical areas [111]. The BIS is a processed EEG measure that uses a proprietary and unpublished algorithm to distill cerebral electrical activity into a numeric scale with values ranging from 0 (isoelectric EEG) to 100 (fully awake) [111–113]. Those values can be further stratified into four clinically relevant categories reflecting increasing depth of sedation: from fully awake or lightly sedated with potential for recall, to very deep sedation similar to

general anesthesia. Additional parameters provided along with the BIS value are the suppression ratio, representing the cumulative percentage of burst suppression corresponding to cortical silence over the previous 65 seconds; electromyographic (EMG) activity, reflecting high frequency from muscle movement; and signal quality index (SQI), a global parameter reflecting electrode impedance and artifacts, including EMG activity. Considering the BIS value alongside the suppression ratio, EMG activity and SQI is meant to help the clinician evaluate the quality of the BIS signal and determine whether it is a reliable indicator of the patient's level of sedation.

Though originally developed and tested in adults, several studies have examined the use of BIS monitoring in the pediatric critical care setting in children from neonates to 18 years old [114–124]. BIS values have demonstrated reasonable sensitivity and specificity in differentiating between inadequate and adequate levels of sedation in older children [115, 118, 125, 126], whereas the burst suppression ratio and other EEG parameters have been shown to change with increasing age as a function of cerebral maturation and should be interpreted with caution [118, 126]. In general, it appears that the BIS is more accurate in differentiating inadequate from adequate sedation than it is for differentiating adequate from excessive sedation [114, 119, 120, 125, 126], with low to moderate correlations with sedation scores, such as the COMFORT score [116, 117, 124, 125]. Given the trend towards avoiding deep sedation except when clinically necessary, this drawback is a significant hindrance to extending the use of BIS monitoring. EMG activity can lead to interference that artificially elevates BIS scores [127], which may or may not reflect inadequate analgesia and sedation depending on the source [113, 128]. Elimination of EMG interference by neuromuscular blockade may not improve the accuracy of BIS monitoring [123, 124, 128–130], and in fact reliance on BIS values seems to lead to oversedation [130, 131]. Thus, BIS monitoring may have challenges in both cases of under- and oversedation. BIS monitoring during the use of ketamine and dexmedetomidine may not accurately quantify sedation as those agents appear to affect the EEG differently than other sedatives [111–113, 126, 132], which may be a significant limitation in the context of increasing use of both medications in current sedation practice [2, 6, 133]. Finally, abnormal brain activity as a consequence of delirium, encephalopathy, trauma, or other focal neurologic processes may all be reflected in EEG changes that could be misinterpreted as sedation, depending on electrode placement [113, 116, 128].

Amplitude-integrated EEG (aEEG) filters continuous EEG output to remove both low-frequency (<2 Hz) and high-frequency (>15 Hz) signals, smoothing and reformatting the signal for display in a single time-compressed waveform. In some neonatal ICUs, aEEG has become standard for prognostication after hypoxic–ischemic injury [134], but its use for sedation monitoring is less-well studied. Sedative and antiepileptic medications lower the background EEG amplitude and alter sleep–wake cycling (SWC). However, the results across studies of aEEG use during sedation are mixed: midazolam was shown to delay onset of normal SWC and fentanyl caused continuous low voltage in newborns undergoing cardiac surgery [135], whereas in another study of neonates undergoing noncardiac surgery, neither

morphine nor midazolam altered background aEEG pattern [136]. Giordano et al. (2018) reported that aEEG was able to differentiate between no sedation and either light or deep sedation in ventilated neonates, but, similar to the BIS, it could not sensitively differentiate between light and deep sedation, and it was not superior to assessment using the N-PASS tool [119]. All aEEG parameters were depressed by increasing doses of analgesics and sedatives. Therefore, there is insufficient evidence to recommend the routine use of aEEG alone for sedation monitoring in the PICU, particularly outside the neonatal population given the lack of data in this older pediatric population.

Conventional EEG

Conventional continuous EEG monitoring is currently indicated for use in the PICU for children with refractory status epilepticus, acute encephalopathy, intracranial pressure management, acute brain injury, including traumatic brain injury and hypoxic–ischemic brain injuries, and altered mental status of unknown etiology [137]. There is also evidence that children who have undergone surgery for congenital heart disease are at risk for postoperative seizures [138–140], and continuous EEG monitoring in that population is increasing. For children undergoing sedation with or without neuromuscular blockade, continuous EEG monitoring offers the advantage of identifying nonconvulsive electrographic seizures; the majority of which may not have visible clinical signs but are associated with poor outcomes [137]. Reported practice among neonatologists is to perform continuous EEG monitoring for 1–2 days if no seizures are detected [141], though it has been suggested that duration of monitoring be tailored to the patient's age, clinical status, and cause of acute encephalopathy if seizures may reasonably be expected to arise with changing clinical status (e.g., during rewarming after therapeutic hypothermia) [137]. The most common use of continuous EEG data in altering the plan of care is initiating, titrating, or discontinuing anticonvulsant medications due to seizure identification (or lack thereof).

Evaluation of continuous EEG background features, such as burst suppression, discontinuity, attenuation, reactivity, and periodic or multifocal epileptiform discharges, has been used to aid in prognostication in patients who have sustained cardiac arrest, status epilepticus, or hypoxic–ischemic injuries [142, 143]. However, the need for real-time interpretation of EEG data and limited availability of neurologists during acute changes in patient status has led to increased interest in quantitative EEG algorithms that can be interpreted by bedside clinicians [134]. While such algorithms are commercially available, their use is subject to substantial variability in correct identification of seizure activity dependent upon user experience, and to date their use in practice is infrequent [137]. Given the difficulties with implementing an easily interpreted quantitative EEG in the PICU for seizure detection, it is unlikely that continuous EEG could feasibly be used for titration of sedation in the PICU, particularly given the complexities of sedative medication impact on EEG spectra in various brain regions [132, 144–146] and significant interindividual and age-related variability in calculated EEG parameters [147].

Conclusions

There is insufficient evidence for any of the currently available objective monitoring technologies to be used as stand-alone modalities for monitoring sedation in the PICU and, when used, information from these devices should be weighed in conjunction with observational assessment tools to form a global impression of the patient's level of sedation [112, 128]. In particular, it is important to consider the effect of the chosen analgesic and sedative regimen on EEG activity [112, 113], as well as altered pharmacokinetics and pharmacodynamics of analgesic and sedative medications during critical illness that may not be reflected in EEG or other objective monitoring parameters [6]. The exception to this may be the child in whom continuous neuromuscular blockade is being utilized and in whom BIS monitoring in particular may be helpful in trending depth of sedation. More research is needed to establish the role and utility of EEG-based monitoring devices, and this work is in progress; a working group of clinical and engineering experts is currently designing a "neuroPICU" display that would support rapid review of neurologic and physiologic data in specialized visualizations which would be modifiable based on the specialty of the reviewer [148]. However, such a device will require extensive testing prior to implementation to determine its efficacy specifically for sedation monitoring, as well as its effect on relevant patient outcomes, such as sedative exposure and iatrogenic complications. Furthermore, use of objective monitoring devices should not supersede the implementation of evidence-based practices, including setting sedation targets and utilizing standardized, goal-directed sedation protocols that incorporate validated pain and sedation assessment tools.

References

1. Best KM, Wypij D, Asaro LA, Curley MAQ. Patient, process, and system predictors of iatrogenic withdrawal syndrome in critically ill children. Crit Care Med. 2017;45(1):e7–15.
2. Anand KJS, Clark AE, Willson DF, Berger J, Meert KL, Zimmerman JJ, et al. Opioid analgesia in mechanically ventilated children: results from the multicenter measuring opioid tolerance induced by fentanyl study. Pediatr Crit Care Med. 2013;14(1):27–36.
3. Ista E, van Dijk M, Gamel C, Tibboel D, de Hoog M. Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: a first evaluation. Crit Care Med. 2008;36(8):2427–32.
4. Traube C, Silver G, Gerber LM, Kaur S, Mauer EA, Kerson A, et al. Delirium and mortality in critically ill children: epidemiology and outcomes of pediatric delirium. Crit Care Med. 2017;45(5):891–8.
5. Mody K, Kaur S, Mauer EA, Gerber LM, Greenwald BM, Silver G, et al. Benzodiazepines and development of delirium in critically ill children: estimating the causal effect. Crit Care Med. 2018;46(9):1486–91.
6. Zuppa AF, Curley MAQ. Sedation analgesia and neuromuscular blockade in pediatric critical care: overview and current landscape. Pediatr Clin North Am. 2017;64(5):1103–16.
7. Smith HAB, Gangopadhyay M, Goben CM, Jacobowski NL, Chestnut MH, Thompson JL, et al. Delirium and benzodiazepines associated with prolonged ICU stay in critically ill infants and young children. Crit Care Med. 2017;45(9):1427–35.

8. Johnson PN, Miller JL, Hagemann TM. Sedation and analgesia in critically ill children. AACN Adv Crit Care. 2012;23(4):415–34.
9. Shutes BL, Gee SW, Sargel CL, Fink KA, Tobias JD. Dexmedetomidine as single continuous sedative during noninvasive ventilation. Pediatr Crit Care Med. 2018;19(4):287–97.
10. Whalen LD, Di Gennaro JL, Irby GA, Yanay O, Zimmerman JJ. Long-term dexmedetomidine use and safety profile among critically ill children and neonates. Pediatr Crit Care Med. 2014;15(8):706–14.
11. Riker RR, Fraser GL. Adverse events associated with sedatives, analgesics, and other drugs that provide patient comfort in the intensive care unit. Pharmacotherapy. 2005;25(5 Pt 2):8S–18S.
12. Gong M, Man Y, Fu Q. Incidence of bradycardia in pediatric patients receiving dexmedetomidine anesthesia: a meta-analysis. Int J Clin Pharm. 2017;39(1):139–47.
13. Duerden EG, Guo T, Dodbiba L, Chakravarty MM, Chau V, Poskitt KJ, et al. Midazolam dose correlates with abnormal hippocampal growth and neurodevelopmental outcome in preterm infants. Ann Neurol. 2016;79(4):548–59.
14. Kocek M, Wilcox R, Crank C, Patra K. Evaluation of the relationship between opioid exposure in extremely low birth weight infants in the neonatal intensive care unit and neurodevelopmental outcome at 2years. Early Hum Dev [Internet]. 2016;92:29–32. Available from: https://doi.org/10.1016/j.earlhumdev.2015.11.001.
15. van Zellem L, Utens EM, de Wildt SN, Vet NJ, Tibboel D, Buysse C. Analgesia-sedation in PICU and neurological outcome: a secondary analysis of long-term neuropsychological follow-up in meningococcal septic shock survivors. Pediatr Crit Care Med. 2014;15(3):189–96.
16. Giordano V, Deindl P, Fuiko R, Unterasinger L, Waldhoer T, Cardona F, et al. Effect of increased opiate exposure on three years neurodevelopmental outcome in extremely preterm infants. Early Hum Dev [Internet]. 2018;123(June):1–5. Available from: https://doi.org/10.1016/j.earlhumdev.2018.06.010.
17. Watson RS, Asaro LA, Hertzog JH, Sorce LR, Kachmar AG, Dervan LA, et al. Long-term outcomes after protocolized sedation versus usual care in ventilated pediatric patients. Am J Respir Crit Care Med. 2018;197(11):1457–67.
18. Larroque B, Rozé J-C, André M, Ancel P-Y, Marret S, Kaminski M, et al. Prolonged sedation and/or analgesia and 5-year neurodevelopment outcome in very preterm infants. Arch Pediatr Adolesc Med. 2008;162(8):728.
19. Anand KJS, Willson DF, Berger J, Harrison R, Meert KL, Zimmerman J, et al. Tolerance and withdrawal from prolonged opioid use in critically ill children. Pediatrics. 2010;125(5):e1208–25.
20. Vet NJ, Ista E, de Wildt SN, van Dijk M, Tibboel D, de Hoog M. Optimal sedation in pediatric intensive care patients: a systematic review. Intensive Care Med. 2013;39(9):1524–34.
21. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. Chest. 1998;114(2):541–8.
22. Kachmar AG, Irving SY, Connolly CA, Curley MAQ. A systematic review of risk factors associated with cognitive impairment after pediatric critical illness*. Pediatr Crit Care Med. 2018;19(3):e164–71.
23. Lucas Da Silva PS, De Carvalho WB. Unplanned extubation in pediatric critically ill patients: a systematic review and best practice recommendations. Pediatr Crit Care Med. 2010;11(2):287–94.
24. Colville G. The psychologic impact on children of admission to intensive care. Pediatr Clin N Am. 2008;55(3):605–16.
25. Rennick JE, Rashotte J. Psychological outcomes in children following pediatric intensive care unit hospitalization: a systematic review of the research. J Child Health Care. 2009;13(2):128–49.
26. Playfor S, Jenkins I, Boyles C, Choonara I, Davies G, Haywood T, et al. Consensus guidelines on sedation and analgesia in critically ill children. Intensive Care Med. 2006;32(8):1125–36.
27. Harris J, Ramelet A-S, van Dijk M, Pokorna P, Wielenga J, Tume L, et al. Clinical recommendations for pain, sedation, withdrawal and delirium assessment in critically ill infants

and children: an ESPNIC position statement for healthcare professionals. Intensive Care Med [Internet]. 2016;42(6):972–86. Available from: https://doi.org/10.1007/s00134-016-4344-1.
28. Committee on Fetus and Newborn and Section on Anesthesiology and Pain Medicine. Prevention and management of procedural pain in the neonate: an update. Pediatrics. 2016;137(2):e20154271.
29. Guerra GG, Joffe AR, Cave D, Duff J, Duncan S, Sheppard C, et al. Survey of sedation and analgesia practice among Canadian pediatric critical care physicians. Pediatr Crit Care Med. 2016;17(9):823–30.
30. Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children. Crit Care Med [Internet]. 2014;42(7):1592–600. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00003246-201407000-00002.
31. Curley MAQ, Wypij D, Watson RS, Grant MJC, Asaro LA, Cheifetz IM, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure. JAMA. 2015;313(4):379–89.
32. Keogh SJ, Long DA, Horn DV. Practice guidelines for sedation and analgesia management of critically ill children: a pilot study evaluating guideline impact and feasibility in the PICU. BMJ Open. 2015;5(3):1–9.
33. Verlaat CWM, Heesen GP, Vet NJ, De Hoog M, Van Der Hoeven JG, Kox M, et al. Randomized controlled trial of daily interruption of sedatives in critically ill children. Paediatr Anaesth. 2014;24(2):151–6.
34. Gupta K, Gupta VK, Muralindharan J, Singhi S. Randomized controlled trial of interrupted versus continuous sedative infusions in ventilated children. Pediatr Crit Care Med. 2012;13(2):131–5.
35. Thomas M, Dhanani S. Development, dissemination and implementation of a sedation and analgesic guideline in a pediatric intensive care unit... It takes creativity and collaboration. Dynamics. 2010;21(4):16–25.
36. Deeter KH, King MA, Ridling D, Irby GL, Lynn AM, Zimmerman JJ. Successful implementation of a pediatric sedation protocol for mechanically ventilated patients. Crit Care Med. 2011;39(4):683–8.
37. Ista E, de Hoog M, Tibboel D, van Dijk M. Implementation of standard sedation management in paediatric intensive care: effective and feasible? J Clin Nurs. 2009;18(17):2511–20.
38. Randolph AG, Wypij D, Hanson JH, Gedeit RG, Meert KL, Luckett PM, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. J Am Med Assoc. 2002;288(20):2561–8.
39. Wildschut ED, Hanekamp MN, Vet NJ, Houmes RJ, Ahsman MJ, Mathot RAA, et al. Feasibility of sedation and analgesia interruption following cannulation in neonates on extracorporeal membrane oxygenation. Intensive Care Med. 2010;36(9):1587–91.
40. Larson GE, McKeever S. Nurse titrated analgesia and sedation in intensive care increases the frequency of comfort assessment and reduces midazolam use in paediatric patients following cardiac surgery. Aust Crit Care [Internet]. 2018;31(1):31–6. Available from: https://doi.org/10.1016/j.aucc.2017.02.001.
41. Sanchez-Pinto LN, Nelson LP, Lieu P, Koh JY, Rodgers JW, Larson KA, et al. Implementation of a risk-stratified opioid weaning protocol in a pediatric intensive care unit. J Crit Care [Internet]. 2018;43:214–9. Available from: https://doi.org/10.1016/j.jcrc.2017.08.049.
42. Dreyfus L, Javouhey E, Denis A, Touzet S, Bordet F. Implementation and evaluation of a paediatric nurse-driven sedation protocol in a paediatric intensive care unit. Ann Intensive Care. 2017;7(1):36.
43. Neunhoeffer F, Seitz G, Schmidt A, Renk H, Kumpf M, Fideler F, et al. Analgesia and sedation protocol for mechanically ventilated postsurgical children reduces benzodiazepines and withdrawal symptoms-but not in all patients. Eur J Pediatr Surg. 2017;27(3):255–62.
44. Neunhoeffer F, Kumpf M, Renk H, Hanelt M, Berneck N, Bosk A, et al. Nurse-driven pediatric analgesia and sedation protocol reduces withdrawal symptoms in critically ill medical pediatric patients. Paediatr Anaesth. 2015;25(8):786–94.

45. Zeilmaker-Roest GA, Wildschut ED, van Dijk M, Anderson BJ, Breatnach C, Bogers AJJC, et al. An international survey of management of pain and sedation after paediatric cardiac surgery. BMJ Paediatr Open. 2017;1(1):e000046.
46. Jenkins IA, Playfor SD, Bevan C, Davies G, Wolf AR. Current United Kingdom sedation practice in pediatric intensive care. Paediatr Anaesth. 2007;17(7):675–83.
47. Carbajal R, Eriksson M, Courtois E, Boyle E, Avila-Alvarez A, Andersen RD, et al. Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study. Lancet Respir Med. 2015;3(10):796–812.
48. Baarslag MA, Jhingoer S, Ista E, Allegaert K, Tibboel D, van Dijk M. How often do we perform painful and stressful procedures in the paediatric intensive care unit? A prospective observational study. Aust Crit Care. 2019;32(1):4–10.
49. LaFond CM, Van Hulle Vincent C, Oosterhouse K, Wilkie DJ. Nurses' beliefs regarding pain in critically ill children: a mixed-methods study. J Pediatr Nurs. 2016;31(6):691–700.
50. Aukes DI, Roofthooft DWE, Simons SHP, Tibboel D, van Dijk M. Pain management in neonatal intensive care. Clin J Pain. 2015;31(9):830–5.
51. Burns SM. Adherence to sedation withdrawal protocols and guidelines in ventilated patients. Clin Nurse Spec. 2012;26(1):22–8.
52. Hartman ME, McCrory DC, Schulman SR. Efficacy of sedation regimens to facilitate mechanical ventilation in the pediatric intensive care unit: a systematic review. Pediatr Crit Care Med. 2009;10(2):246–55.
53. Tanios MA, de Wit M, Epstein SK, Devlin JW. Perceived barriers to the use of sedation protocols and daily sedation interruption: a multidisciplinary survey. J Crit Care. 2009;24(1):66–73.
54. Twite MD, Rashid A, Zuk J, Friesen RH. Sedation, analgesia, and neuromuscular blockade in the pediatric intensive care unit: survey of fellowship training programs. Pediatr Crit Care Med. 2004;5(6):521–32.
55. Egerod I. Uncertain terms of sedation in ICU. How nurses and physicians manage and describe sedation for mechanically ventilated patients. J Clin Nurs. 2002;11(6):831–40.
56. Cignacco E, Hamers JP, Van Lingen RA, Zimmerman LJ, Muller R, Gessler P, Nelle M. Pain relief in ventilated preterms during endotracheal suctioning: a randomized controlled trial. Swiss Med Wkly. 2008;138:635–45.
57. Duzkaya DS, Kuguoglu S. Assessment of pain during endotracheal suction in the pediatric intensive care unit. Pain Manag Nurs. 2015;16:11–9.
58. Stevens BJ, Abbott LK, Yamada J, Harrison D, Stinson J, Taddio A, Barwick M, Latimer M, Scott SD, Rashotte J, Campbell F, Finley GA. Epidemiology and management of painful procedures in children in Canadian hospitals. CMAJ. 2011;183:E403–10. https://doi.org/10.1503/cmaj.101341.
59. Thrane SE, Wanless S, Cohen SM, Danford CA. The assessment and non-pharmacologic treatment of procedural pain from infancy to school age through a developmental lens: a synthesis of evidence with recommendations. J Pediatr Nurs. 2016;31(1):e23–32.
60. Margonary H, Hannan MS, Schlenk EA. Quality improvement initiative on pain knowledge, assessment, and documentation skills of Pediatric nurses. Pediatr Nurs [Internet]. 2017;43(2):65–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29394479.
61. Walsh TS, Kydonaki K, Antonelli J, Stephen J, Lee RJ, Everingham K, et al. Staff education, regular sedation and analgesia quality feedback, and a sedation monitoring technology for improving sedation and analgesia quality for critically ill, mechanically ventilated patients: a cluster randomised trial. Lancet Respir Med [Internet]. 2016;4(10):807–17. Available from: https://doi.org/10.1016/S2213-2600(16)30178-3.
62. Habich M, Wilson D, Thielk D, Melles GL, Crumlett HS, Masterton J, et al. Evaluating the effectiveness of pediatric pain management guidelines. J Pediatr Nurs [Internet]. 2012;27(4):336–45. Available from: https://doi.org/10.1016/j.pedn.2011.06.002.
63. Bailey B, Daoust R, Doyon-Trottier E, Dauphin-Pierre S, Gravel J. Validation and properties of the verbal numeric scale in children with acute pain. Pain [Internet]. 2010 [cited 2013 Jun 6];149(2):216–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20188471.

64. Voepel-Lewis T, Burke CN, Jeffreys N, Malviya S, Tait AR. Do 0-10 numeric rating scores translate into clinically meaningful pain measures for children? Anesth Analg [Internet]. 2011 [cited 2013 Jun 6];112(2):415–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21127278.
65. von Baeyer CL, Spagrud LJ, McCormick JC, Choo E, Neville K, Connelly MA. Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity. Pain. 2009;143(3):223–7.
66. Wong D, Baker C. Pain in children: comparison of assessment scales. Pediatr Nurs. 1988;14(1):9–17.
67. Tomlinson D, von Baeyer CL, Stinson JN, Sung L. A systematic review of faces scales for the self-report of pain intensity in children. Pediatrics. 2010;126(5):e1168–98.
68. Costello JM, Patak L, Pritchard J. Communication vulnerable patients in the pediatric ICU: enhancing care through augmentative and alternative communication. J Pediatr Rehabil Med [Internet]. 2010 [cited 2013 Jun 6];3(4):289–301. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21791863.
69. Zhou H, Roberts P, Horgan L. Association between self-report pain ratings of child and parent, child and nurse and parent and nurse dyads: meta-analysis. J Adv Nurs. 2008;63(4):334–42.
70. Kamper SJ, Dissing KB, Hestbaek L. Whose pain is it anyway? Comparability of pain reports from children and their parents. Chiropr Man Ther. 2016;24(1):1–7.
71. Hadden KL, Lefort S, Obrien M, Coyte PC, Guerriere DN. A comparison of observers and self-report pain ratings for children with cerebral palsy. J Dev Behav Pediatr. 2015;36(1):14–23.
72. Herr K, Coyne PJ, Key T, Manworren R, McCaffery M, Merkel S, et al. Pain assessment in the nonverbal patient: position statement with clinical practice recommendations. Pain Manag Nurs [Internet]. 2006 [cited 2013 May 25];7(2):44–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16730317
73. Krechel SW, Bildner J. CRIES: a new neonatal postoperative pain measurements score. Initial testing of validity and reliability. Paediatr Anaesth. 1995;5:53–61.
74. Hummel P, Puchalski M, Creech SD, Weiss MG. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. J Perinatol [Internet]. 2008 [cited 2013 Jun 6];28(1):55–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18165830.
75. Hummel P, Lawlor-Klean P, Weiss MG. Validity and reliability of the N-PASS assessment tool with acute pain. J Perinatol [Internet]. 2010 [cited 2013 Jun 6];30(7):474–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19924132.
76. Hillman BA, Tabrizi MN, Gauda EB, Carson KA, Aucott SW. The Neonatal Pain, Agitation and Sedation Scale and the bedside nurse's assessment of neonates. J Perinatol. 2015;35(2):128–31.
77. Anand KJS, International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. Arch Pediatr Adolesc Med. 2001;155(2):173–80.
78. Kappesser J, Kamper-Fuhrmann E, De Laffolie J, Faas D, Ehrhardt H, Franck LS, et al. Pain-specific reactions or indicators of a general stress response? Clin J Pain. 2019;35(2):101–10.
79. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. Pediatr Nurs. 1997;23(3):293–7.
80. Manworren RCB, Hynan LS. Clinical validation of FLACC: preverbal patient pain scale. Pediatr Nurs. 2003;29(2):140–6.
81. Nilsson S, Finnström B, Kokinsky E. The FLACC behavioral scale for procedural pain assessment in children aged 5-16 years. Paediatr Anaesth [Internet]. 2008 [cited 2013 May 28];18(8):767–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18613934.
82. Johansson M, Kokinsky E. The COMFORT behavioural scale and the modified FLACC scale in paediatric intensive care. Nurs Crit Care [Internet]. 2009;14(3):122–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19366409.

83. Malviya S, Voepel-Lewis T, Burke C, Merkel S, Tait AR. The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. Paediatr Anaesth. 2006;16(3):258–65.
84. Büttner W, Finke W. Analysis of behavioural and physiological parameters for the assessment of postoperative analgesic demand in newborns, infants and young children: a comprehensive report on seven consecutive studies. Paediatr Anaesth. 2000;10(3):303–18.
85. Ista E, van Dijk M, Tibboel D, de Hoog M. Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. Pediatr Crit Care Med. 2005;6(1):58–63.
86. McGrath PJ, Walco GA, Turk DC, Dworkin RH, Brown MT, Davidson K, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. J Pain. 2008;9(9):771–83.
87. Crellin DJ, Harrison D, Santamaria N, Babl FE. Systematic review of the face, legs, activity, cry and consolability scale for assessing pain in infants and children: is it reliable, valid, and feasible for use? Pain. 2015;156(11):2132–51.
88. Voepel-Lewis T, Zanotti J, Dammeyer JA, Merkel S. Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients. Am J Crit Care. 2010;19(1):55–61.
89. Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Lauer A, Munro H, et al. Pain management in children with and without cognitive impairment following spine fusion surgery. Paediatr Anaesth. 2001;11(4):453–8.
90. Hunseler C, Merkt V, Gerloff M, Eifinger F, Kribs A, Roth B. Assessing pain in ventilated newborns and infants: validation of the hartwig score. Eur J Pediatr. 2011;170(7): 837–43.
91. Brunow de Carvalho W, Lucas da Silva PS, Paulo CS, Fonseca MM, Belli LA. Comparison between the comfort and hartwig sedation scales in pediatric patients undergoing mechanical lung ventilation. Sao Paulo Med J. 1999;117(5):192–6.
92. Suominen P, Caffin C, Linton S, McKinley D, Ragg P, Davie G, Eyres R. The cardiac analgesic assessment scale (CAAS): a pain assessment tool for intubated and ventilated children after cardiac surgery. Pediatr Anesth. 2004;14:336–43.
93. Curley MAQ, Harris SK, Fraser KA, Johnson RA, Arnold JH. State Behavioral Scale (SBS): a sedation assessment instrument for infants and young children supported on mechanical ventilation. Pediatr Crit Care Med. 2006;7(2):107–14.
94. Heiberger AL, Ngorsuraches S, Olgun G, Luze L, Leimbach C, Madison H, et al. Safety and utility of continuous ketamine infusion for sedation in mechanically ventilated Pediatric patients. J Pediatr Pharmacol Ther. 2019;23(6):447–54.
95. Jeffries SA, McGloin R, Pitfield AF, Carr RR. Use of methadone for prevention of opioid withdrawal in critically ill children. Can J Hosp Pharm. 2012;65(1):12–8.
96. Ambuel B, Hamlett K. Assessing distress in pediatric intensive care environments: the COMFORT scale. J Pediatr Psychol. 1992;17(1):95–109.
97. van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. Pain. 2000;84(2–3):367–77.
98. Bear LA, Ward-Smith P. Interrater reliability of the COMFORT scale. Pediatr Nurs. 2006;32(5):427–34.
99. Boerlage AA, Ista E, Duivenvoorden HJ, de Wildt SN, Tibboel D, van Dijk M. The COMFORT behaviour scale detects clinically meaningful effects of analgesic and sedative treatment. Eur J Pain. 2015;19(4):473–9.
100. Maaskant J, Raymakers-Janssen P, Veldhoen E, Ista E, Lucas C, Vermeulen H. The clinimetric properties of the COMFORT scale: a systematic review. Eur J Pain (United Kingdom). 2016;20(10):1587–611.
101. Kerson AG, DeMaria R, Mauer E, et al. Validity of the Richmond agitation-sedation scale (RASS) in critically ill children. J Intensive Care. 2016;4:65-016-0189-5. eCollection 2016.

102. Smith HA, Boyd J, Fuchs DC, et al. Diagnosing delirium in critically ill children: validity and reliability of the pediatric confusion assessment method for the intensive care unit. Crit Care Med. 2011;39(1):150–7.
103. Silver G, Traube C, Kearney J, et al. Detecting pediatric delirium: development of a rapid observational assessment tool. Intensive Care Med. 2012;38(6):1025–31.
104. Traube C, Silver G, Kearney J, et al. Cornell assessment of pediatric delirium: a valid, rapid, observational tool for screening delirium in the PICU*. Crit Care Med. 2014;42(3):656–63.
105. Saunders R, Struys MMRF, Pollock RF, Mestek M, Lightdale JR. Patient safety during procedural sedation using capnography monitoring: a systematic review and meta-analysis. BMJ Open. 2017;7(6):1–10.
106. Sammartino M, Volpe B, Sbaraglia F, Garra R, D'Addessi A. Capnography and the bispectral index—their role in pediatric sedation: a brief review. Int J Pediatr. 2010;2010:1–5.
107. Avez-Couturier J, De Jonckheere J, Jeanne M, Valleé L, Cuisset JM, Logier R. Assessment of procedural pain in children using analgesia nociception index: a pilot study. Clin J Pain. 2016;32(12):1100–4.
108. Weber F, Geerts NJE, Roeleveld HG, Warmenhoven AT, Liebrand CA. The predictive value of the heart rate variability-derived analgesia nociception index in children anaesthetized with sevoflurane: an observational pilot study. Eur J Pain (United Kingdom). 2018;22(9):1597–605.
109. Gall O, Champigneulle B, Schweitzer B, Deram T, Maupain O, Montmayeur Verchere J, et al. Postoperative pain assessment in children: a pilot study of the usefulness of the analgesia nociception index † † This study was presented, in part, during the 2012 annual meeting of the French Society of Anaesthesia and Intensive Care. Br J Anaesth [Internet]. 2015;115(6):890–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S000709121731437X
110. Chanques G, Tarri T, Ride A, Prades A, De Jong A, Carr J, et al. Analgesia nociception index for the assessment of pain in critically ill patients: a diagnostic accuracy study. Br J Anaesth [Internet]. 2017;119(4):812–20. Available from: https://doi.org/10.1093/bja/aex210.
111. Johansen JW. Update on bispectral index monitoring. Best Pract Res Clin Anaesthesiol. 2006;20(1):81–99.
112. McKeever S, Johnston L, Davidson A. A review of the utility of EEG depth of anaesthesia monitors in the paediatric intensive care environment. Intensive Crit Care Nurs. 2012;28(5):294–303.
113. Fraser GL, Riker RR. Bispectral index monitoring in the intensive care unit provides more signal than noise. Pharmacotherapy. 2005;25(5 II):19S–27S.
114. Twite MD, Zuk J, Gralla J, Friesen RH. Correlation of the Bispectral Index Monitor with the COMFORT scale in the pediatric intensive care unit. Pediatr Crit Care Med. 2005;6(6):648–53.
115. Berkenbosch JW, Fichter CR, Tobias JD. The correlation of the bispectral index monitor with clinical sedation scores during mechanical ventilation in the pediatric intensive care unit. Anesth Analg. 2002;94:506–11.
116. Courtman SP, Wardurgh A, Petros AJ. Comparison of the bispectral index monitor with the comfort score in assessing level of sedation of critically ill children. Intensive Care Med. 2003;29(12):2239–46.
117. Froom SR, Malan CA, Mecklenburgh JS, Price M, Chawathe MS, Hall JE, et al. Bispectral index asymmetry and COMFORT score in paediatric intensive care patients. Br J Anaesth. 2008;100(5):690–6.
118. Lamas A, López-Herce J, Sancho L, Mencía S, Carrillo Á, Santiago MJ, et al. Assessment of the level of sedation in children after cardiac surgery. Ann Thorac Surg. 2009;88(1):144–50.
119. Giordano V, Deindl P, Goeral K, Czaba C, Weninger M, Berger A, et al. The power of N-PASS, aEEG, and BIS in detecting different levels of sedation in neonates: a preliminary study. Paediatr Anaesth. 2018;28(12):1096–104.
120. Powers KS, Nazarian EB, Tapyrik SA, Kohli SM, Yin H, van der Jagt EW, et al. Bispectral index as a guide for titration of propofol during procedural sedation among children. Pediatrics. 2005;115(6):1666–74.

121. Crain N, Slonim A, Pollack M. Assessing sedation in the pediatric intensive care unit by using BIS and the COMFORT scale. Pediatr Crit Care Med. 2002;3(1):11–4.
122. Prins SA, de Hoog M, Blok JH, Tibboel D, Visser GH. Continuous noninvasive monitoring of barbiturate coma in critically ill children using the Bispectral™ index monitor. Crit Care. 2007;11(5):1–7.
123. Lamas A, López-Herce J, Sancho L, Mencía S, Carrillo Á, Santiago MJ, et al. Responsiveness to stimuli of bispectral index, middle latency auditory evoked potentials and clinical scales in critically ill children. Anaesthesia. 2008;63(12):1296–301.
124. Lamas A, López-Herce J, Sancho L, Mencía S, Carrillo Á, Santiago MJ, et al. Analysis of bispectral index and middle latency auditory-evoked potentials parameters in critically ill children. J Clin Neurophysiol. 2009;26(3):150–4.
125. Triltsch AE, Nestmann G, Orawa H, Moshirzadeh M, Sander M, Grobe J, et al. Bispectral index versus COMFORT score to determine the level of sedation in paediatric intensive care unit patients: a prospective study. Crit Care. 2005;9(1):R9–17.
126. Malviya S, Voepel-Lewis T, Tait AR, Watcha MF, Sadhasivam S, Friesen RH. Effect of age and sedative agent on the accuracy of bispectral index in detecting depth of sedation in children. Pediatrics. 2007;120(3):e461–70.
127. Vivien B, Di Maria S, Ouatttara A, Langeron O, Coriat P, Riou B. Overestimation of bispectral index in sedated intensive care unit patients revealed by administration of muscle relaxant. Anesthesiology. 2003;99:9–17.
128. Shander A, Lobel GP, Mathews DM. Brain monitoring and the depth of anesthesia. Anesth Analg. 2017;126(2):705–9.
129. Aneja R, Heard AMB, Fletcher JE, Heard CMB. Sedation monitoring of children by the bispectral index in the pediatric intensive care unit. Pediatr Crit Care Med [Internet]. 2003 [cited 2013 Jun 19];4(1):60–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12656545.
130. Tobias JD, Grindstaff R. Bispectral index monitoring during the administration of neuromuscular blocking agents in the pediatric intensive care unit patient. J Intensive Care Med. 2005;20(4):233–7.
131. Amigoni A, Mozzo E, Brugnaro L, Gentilomo C, Stritoni V, Michelin E, et al. Assessing sedation in a pediatric intensive care unit using comfort behavioural scale and bispectral index: these tools are different. Minerva Anestesiol. 2012;78(3):322–9.
132. Xi C, Sun S, Pan C, Ji F, Cui X, Li T. Different effects of propofol and dexmedetomidine sedation on electroencephalogram patterns: wakefulness, moderate sedation, deep sedation and recovery. PLoS One. 2018;13(6):1–15.
133. Benedetti GM, Silverstein FS, Rau SM, Lester SG, Benedetti MH, Shellhaas RA. Sedation and analgesia influence electroencephalography monitoring in pediatric neurocritical care. Pediatr Neurol. 2018;87:57–64.
134. Riviello JJ. Digital trend analysis in the pediatric and neonatal intensive care units. J Clin Neurophysiol. 2013;30(2):143–55.
135. Bernet V, Latal B, Natalucci G, Doell C, Ziegler A, Wohlrab G. Effect of sedation and analgesia on postoperative amplitude-integrated EEG in newborn cardiac patients. Pediatr Res [Internet]. 2010;67(6):650–5. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L358842921%0Ahttp://dx.doi.org/10.1203/PDR.0b013e3181da44ba.
136. Olischar M, Davidson AJ, Lee KJ, Hunt RW. Effects of morphine and midazolam on sleep-wake cycling in amplitude-integrated electroencephalography in post-surgical neonates ≥32 weeks of gestational age. Neonatology. 2012;101(4):293–300.
137. Abend NS, Chapman KE, Gallentine WB, Goldstein J, Hyslop AE, Loddenkemper T, et al. Electroencephalographic monitoring in the pediatric intensive care unit. Curr Neurol Neurosci Rep [Internet]. 2013;13(3):330. Available from: http://link.springer.com/10.1007/s11910-012-0330-3.
138. Gaynor JW, Nicolson SC, Jarvik GP, Wernovsky G, Montenegro LM, Burnham NB, et al. Increasing duration of deep hypothermic circulatory arrest is associated with an increased

incidence of postoperative electroencephalographic seizures. J Thorac Cardiovasc Surg. 2005;130(5):1278–86.
139. Naim MY, Gaynor JW, Chen J, Nicolson SC, Fuller S, Spray TL, et al. Subclinical seizures identified by postoperative electroencephalographic monitoring are common after neonatal cardiac surgery. J Thorac Cardiovasc Surg [Internet]. 2015;150(1):169–80. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022522315004961.
140. Gunn JK, Beca J, Penny DJ, Horton SB, D'Udekem YA, Brizard CP, et al. Amplitude-integrated electroencephalography and brain injury in infants undergoing Norwood-type operations. Ann Thorac Surg [Internet]. 2012;93(1):170–6. Available from: https://doi.org/10.1016/j.athoracsur.2011.08.014.
141. Abend NS, Dlugos DJ, Hahn CD, Hirsch LJ, Herman ST. Use of EEG monitoring and management of non-convulsive seizures in critically ill patients: a survey of neurologists. Neurocrit Care. 2010;12(3):382–9.
142. Nishisaki A, Sullivan J, Steger B, Bayer CR, Dlugos D, Lin R, et al. Retrospective analysis of the prognostic value of electroencephalography patterns obtained in pediatric in-hospital cardiac arrest survivors during three years. Pediatr Crit Care Med. 2007;8(1):10–7.
143. Kessler SK, Topjian AA, Gutierrez-Colina AM, Ichord RN, Donnelly M, Nadkarni VM, et al. Short-term outcome prediction by electroencephalographic features in children treated with therapeutic hypothermia after cardiac arrest. Neurocrit Care. 2011;14(1):37–43.
144. Sleigh JW, Vacas S, Flexman AM, Talke PO. Electroencephalographic arousal patterns under dexmedetomidine sedation. Anesth Analg. 2018;127(4):951–9.
145. Montandon G, Cushing SL, Campbell F, Propst EJ, Horner RL, Narang I. Distinct cortical signatures associated with sedation and respiratory rate depression by morphine in a pediatric population. Anesthesiology [Internet]. 2016;125(5):889–903. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L611774798%0Ahttp://dx.doi.org/10.1097/ALN.0000000000001303%0Ahttp://sfx.aub.aau.dk/sfxaub?sid=EMBASE&issn=15281175&id=doi:10.1097%2FALN.0000000000001303&atitle=Distinct+Cortical+Signatu.
146. Forsyth A, McMillan R, Campbell D, Malpas G, Maxwell E, Sleigh J, et al. Comparison of local spectral modulation, and temporal correlation, of simultaneously recorded EEG/fMRI signals during ketamine and midazolam sedation. Psychopharmacology. 2018;235(12):3479–93.
147. Walsh EC, Lee JM, Terzakis K, Zhou DW, Burns S, Buie TM, et al. Age-dependent changes in the propofol-induced electroencephalogram in children with autism spectrum disorder. Front Syst Neurosci. 2018;12(June):1–12.
148. Grinspan Z, Eldar Y, Gopher D, Gottlieb A, Lammfromm R, Mangat H, et al. Guiding principles for a pediatric neurology ICU (neuroPICU) bedside multimodal monitor. Appl Clin Inform. 2016;07(02):380–98.