Chapter 1
Introduction to Sedation and Analgesia

Mary Sandquist and John W. Berkenbosch

Brief History of Pediatric Sedation and Analgesia

The first use of operative anesthetic in a pediatric patient occurred in 1842 when Dr. Crawford Long administered sulphuric ether via inhalation to a child for removal of one of two fingers; the author noted that "he suffered from one operation and was insensible during the other" [1]. In 1857, Dr. John Snow reported that the effect of inhaled chloroform occurred "more quickly" in pediatric patients when compared with adults, the first testimonial of a difference between pediatric and adult anesthetic absorption and metabolism. Between the 1800s and the pre–World War II era, minimal distinctions were made between pediatric and adult patients in the field of anesthesia despite the successful anesthesia of countless children. However, in the 1940s–1950s, the expansion of the pediatric surgery field mandated further exploration and refinement of pediatric anesthesia techniques.

Concurrent with advances in anesthesia post–World War II, the advent of the intensive care unit (ICU) corresponded significantly with the development and dissemination of positive-pressure mechanical ventilation capabilities [2]. The first ICU was created in Denmark in 1953 and brought anesthesiology out of the operating room to care for patients requiring longer-term mechanical ventilation during the polio epidemic in the early 1950s [3]. Over the next decade, ICUs became common in larger hospitals in developed countries [4], as did specialized neonatal and

M. Sandquist · J. W. Berkenbosch (✉)
Department of Pediatrics, Division of Pediatric Critical Care, University of Louisville and Norton Children's Hospital, Louisville, KY, USA
e-mail: john.berkenbosch@louisville.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_1

pediatric ICUs [5], which provided the first long-term positive-pressure ventilation to children suffering from diseases such as tetanus. This was typically achieved via tracheostomy, neuromuscular relaxation with curare or mephenesin, and occasionally sedation, typically phenobarbitone [6].

The introduction of anesthesia and analgesia to children outside of the operating room and the development of technologically sophisticated support have led to an evolution in the way pediatric ICU practitioners view pain, discomfort, and the needs surrounding their management. Importantly, this evolution has been characterized by an increasing recognition of the prevalence and sources of pain, discomfort, and anxiety in critically ill children, as well as the adverse consequences of untreated or inadequately treated pain.

Goal of Sedation and Analgesia in the Critically Ill Child

At first glance, the goals of sedation and analgesia provision to the critically ill child appear simple and almost solely altruistic, specifically to ease pain and anxiety at a time the child is highly likely to be experiencing one or both of these stressors. However, additional benefits also exist which may, in the long run, be more significant. Multiple adverse effects of inadequately treated pain have been reported, including increased myocardial oxygen consumption [7, 8], ineffective cough with associated altered pulmonary secretion clearance leading to atelectasis and/or infection [8, 9], immunosuppression [10], delayed wound healing [11], impaired sleep [12, 13], and development of hyperalgesia [14]. From a sedation perspective, adequate sedation is required in many critically ill children to prevent inadvertent removal of life-sustaining devices; facilitate cooperation with therapies, such as mechanical ventilation [15–17]; decrease anxiety; and, in many cases, confer a degree of amnesia. Importantly, sedation must be seen as a balance since inadequate sedation may also be associated with excessive anxiety, post-traumatic stress development post-hospitalization, and aversion to future medical interventions and care [15, 18]. Conversely, oversedation may contribute to increased risks of extubation failure [19, 20], increased duration of pediatric ICU stay [15], development of iatrogenic tolerance and withdrawal syndromes [21, 22], and delirium [23–25].

Despite these recognitions, the literature continues to report that inadequate management of both pain [26, 27] and sedation [28, 29] are common. It is likely that an underappreciation of the adverse effects listed above are partially responsible, but it is also likely that myths regarding the ability of children to sense and process pain continue to exist across all disciplines of healthcare providers. A list of some of these myths and the evidence disputing them can be found in Table 1.1.

Table 1.1 Myths about pain in children [30]

Myth	Evidence disputing
Infants cannot feel pain due to nervous system immaturity	Pain receptors develop from 7 to 20 weeks gestation [31], and pain conduction pathways are present at 13 weeks gestation with full myelination by 30 weeks [32]. Cortical interconnections responsible for pain perception are present by 24 weeks gestation [33].
Children do not feel pain as acutely as adults	While behaviors to pain differ between children and adults, there is no evidence that pain in children is less severe than in adults [34]. As the neuroinhibitory pathways of pain develop later than propogatory mechanisms, it is conceivable that neonates may have an increased sensitivity to pain than adults [33, 35].
Children who are active are not experiencing pain	Children may remain active while in pain to (1) decrease the likelihood that they will be taken to be further examined and managed [36] or (2) use movement and activity as a distraction and/or coping mechanism for dealing with pain [30].
Children who are sleeping must not be experiencing pain	Compared with healthy controls, children with various sources of pain have disordered sleep [37]. However, children with both acute and chronic pain demonstrate sleep architecture by polysomnogram, suggesting that sleep occurs during the presence of pain [38, 39].
Children will always truthfully report their pain presence and severity	While self-report has become the gold standard for pain assessment in children aged 6 years or higher [40, 41], children may also deny pain for fear of reprisals, including parental/caregiver disapproval, cultural norms or attitudes regarding pain, and fear of needing an injection for pain management [42, 43].
Children are not capable of describing and/or localizing their pain	The validity of self-report scales for assessing pain suggests that children are capable of expressing their pain [40, 41]. While children cannot describe the characteristics of their pain in manners as sophisticated as adults, by using body outlines and pointing strategies, children can effectively localize pain sites [36, 44].
When children cry, it is usually due to reasons other than pain (i.e., restraint, anxiety, parental absence, etc.)	While children may cry for reasons other than pain (hunger, anxiety, being restrained, etc.), crying is a frequent behavior associated with pain as well. For this reason, crying is a common component of several validated pain scales, especially those used in younger children/infants or those with developmental delays in whom self-report is not feasible [45, 46].
Parents know all the answers about children's pain	Parents are generally thought to be the most reliable interpreters of their child's behavior. However, in the setting of acute pain, regardless of the cause, the reliability of parental report may be reduced due to their own stress [47]. Especially in children unable to self-report pain, parental report has been shown to vary from bedside caregivers, making true assessment difficult [48].
Opioids are unsafe for treating children's pain	Despite some age-related differences in both pharmacokinetic and pharmacodynamic responses to opioids in children compared with adults [49], an increasing body of evidence suggests that opioids can be safely used in all ages of children [50–52], including the premature neonate [53]. Opioids remain the most commonly used analgesic in critically ill children [20, 54] and should be considered part of the standard of care for managing moderate and severe pain [40, 55].

Physiology of Pain

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" by the International Association for the Study of Pain. Nociception, on the other hand, is the unconscious activity induced by a harmful stimulus applied to sense receptors [56]. Therefore, pain should be interpreted as the emotional response to a nociceptive stimulus with the acknowledgement that the same stimulus may produce variable pain perception in different individuals.

During critical illness, children are exposed to numerous potential sources of pain. These can be broadly divided into four categories, including (a) postsurgical pain, (b) disease-related pain, (c) device-related pain, and (d) treatment-related pain. The first two sources are intuitive and should be readily apparent to caregivers, although consideration of pain related to medical disease appears to be underappreciated compared with surgical pain [57]. Due to developmental capacities and diminished patient awareness while critically ill, it may also be difficult for bedside providers to identify the presence of pain and/or understand its source which may compound inadequate treatment. While data are limited, numerous device and/or treatment sources of pain have been identified in critically ill children. Similar to data in adults [58], endotracheal tube suctioning has been found to be a significant source of procedural pain during critical illness [59, 60]. Other sources of invasive pain not routinely pretreated included venipuncture and/or capillary blood sampling [61]. Care-related sources of pain include dressing changes, skin care, and mobilization [61, 62].

The physiology and neurobiology of the pain response system is complex but can be viewed as having two basic components: the neural pathways and interactions responsible for transmitting and processing the response to a stimulus and the biochemical mediators responsible for activating and mediating those neural pathways.

Pain arises first and foremost from tissue damage. Depending on the location of the insult, the stimulus is detected by either cutaneous nociceptors which are free nerve endings in peripheral tissue or deep-tissue nociceptors (e.g., joints, bones, and viscera). Whereas cutaneous nociceptors transmit a highly localizable response, the receptive field of deep tissue receptors is significantly wider, especially for visceral insults, making the stimulus more difficult to localize. Following nociceptor stimulation, the signal is transmitted via a number of potential neurons to the central locations for processing. Somatic tissue injuries (mechanical and thermal) are transmitted via thinly myelinated A∂ fibers which respond to mechanical and thermal impulses and are considered "fast" velocity. Visceral tissues do not contain A∂ fibers and transmit via C fibers which are much slower in velocity and produce a duller pain sensation [63].

Whereas A∂ fibers utilize glutamate to communicate the immediate localizing response to pain, C fiber transmissions are mediated via both glutamate and substance P. Additionally, chemical mediators of the pain response include release of bradykinin and prostaglandins that sensitize or activate nociceptors, which release substance P and calcitonin gene-related peptide. Substance P causes the degranulation of mast cells, releasing histamine which further activates the nociceptors, and in combination with calcitonin gene-related peptide, release further bradykinin [64].

Complexities of Sedation and Analgesia in the Critically Ill Child

The "critically ill child" can encompass a complex array of heterogeneous conditions involving multiple organ systems, especially in the growing population of chronic complex systems patients being admitted to pediatric ICUs today. These acute and chronic conditions may affect the patient's metabolism and tolerance of the multitude of agents which might be utilized to achieve these previously established goals. While the body of literature is growing, there is inadequate data regarding the pharmacokinetic and pharmacodynamic effects of sedation and analgesic drugs in the critically ill pediatric population. Drug choice and dosing are further complicated by the presence of (1) multi-organ injury, specifically hepatic and renal dysfunction, due to their impacts on drug metabolism and excretion, (2) fluid shifts due to capillary leak syndrome which may alter a drug's volume of distribution and subsequent clearance, and (3) obesity which also significantly impacts drug distribution and clearance. For this population, specifically, the practitioner is encouraged to dose drugs based on ideal rather than actual body weight. It should also be considered that drug accumulation in the adipose tissue can be substantial, especially during the use of continuous infusions, which markedly prolong elimination and dissipation of clinical effects. Periodic "holidays" during which infusions are either stopped or temporarily replaced by alternative agents may be especially important in the obese population to avoid these undesired effects. All of these factors, and likely others, challenge the provider to make calculated choices in drug selection and dosing to both achieve the desired effects for the required duration while minimizing potential adverse effects.

The subsequent chapters are intended to be a guide to all providers caring for critically ill children in making informed choices regarding the provision of appropriate sedation and analgesia in the pediatric ICU, as well as the procedural sedation setting. The principles laid out in this introduction will be expanded upon and encompass choices related to agent choice(s), safety and monitoring, special populations presenting specific risks, and specific situations commonly encountered in either the pediatric ICU or procedural sedation environments.

References

1. Long CW. An account of the first use of sulphuric ether by inhalation as an anaesthetic in surgical operations. South Med Surg J. 1849;5:705–13.
2. Marshall JC, Bosco L, Adhikari NK, Connolly B, Diaz JV, Dorman T, Fowler RA, Meyfroidt G, Nakagawa S, Pelosi P, Vincent JL, Vollman K, Zimmerman J. What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical care Medicine. J Crit Care. 2017;37:270–6.
3. Reisner-Senelar L. The birth of intensive care medicine: Bjorn Ibsen's records. Intensive Care Med. 2011;37:1084–6.

4. Weil MH, Tang W. From intensive care to critical care medicine: a historical perspective. Am J Respir Crit Care Med. 2011;183:1451–3.
5. Levin DL, Downes JJ, Todres ID. History of pediatric critical care medicine. In: Fuhrman BP, Zimmerman JJ, editors. Fuhrman and Zimmermans pediatric critical care. 5th ed. Philadelphia: Elsevier Publishing; 2017. p. 3–18.
6. Smythe PM, Bull A. Treatment of tetanus neonatorum with intermittent positive-pressure respiration. Br Med J. 1959;2:107–13.
7. Ismail A. The challenges of providing effective pain management for children in the pediatric intensive care unit. Pain Manag Nurs. 2016;17:372–83.
8. Nimmo WS, Duthie DJR. Pain relief after surgery. Anaesth Crit Care. 1987;15:68–71.
9. Oakes L. Compact clinical guide to infant and child pain management. New York: Springer; 2011.
10. Eckterowocz N, Quinlan-Colwell A, Vanderveer B, et al. Acute pain management. In: St Marie B, editor. Core curriculum for pain management nursing. 2nd ed. Philadelphia: Saunders; 2010. p. 329–79.
11. American Academy of Pediatrics, American Pain Society. The assessment and management of acute pain in infants, children, and adolescents. Pediatrics. 2001;108:793–7.
12. Aitken LM, Elliott R, Mitchell M, Davis C, Macfarlane B, Ullman A, Wetzig K, Datt A, McKinley S. Sleep assessment by patients and nurses in the intensive care: an exploratory and descriptive study. Aust Crit Care. 2017;30:59–66.
13. Armour AD, Khoury JC, Kagan RJ, Gottschlich MM. Clinical assessment of sleep among pediatric burn patients does not correlate with polysomnography. J Burn Care Res. 2011;32:529–34.
14. Hermann C, Hohmeister J, Demirakc S, et al. Long-term alteration of pain sensitivity in school-aged children with early pain experiences. Pain. 2006;125:278–85.
15. 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;39:1524–34.
16. 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;10:246–55.
17. Nasr VG, DiNardo JA. Sedation and analgesia in pediatric cardiac critical care. Pediatr Crit Care Med. 2016;17:S225–31.
18. Colville G, Kerry S, Pierce C. Children's factual and delusional memories of intensive care. Am J Respir Crit Care Med. 2008;177:976–82.
19. Randolph AG, Wypij D, Venkataraman ST, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. JAMA. 2002;288:2561–8.
20. 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;5:521–32.
21. Fonsmark L, Rasmussen YH, Carl P. Occurrence of withdrawal in critically ill sedated children. Crit Care Med. 1999;27:196–9.
22. 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;36:2427–32.
23. Silver G, Traube C, Gerber LM, et al. Pediatric delirium and associated risk factors: a single-center prospective observational study. Pediatr Crit Care Med. 2015;16:303–9.
24. Traube C, Silver G, Gerber LM, et al. Delirium and mortality in critically ill children: epidemiology and outcomes of pediatric delirium. Crit Care Med. 2017;45:891–8.
25. Patel AK, Biagas KV, Clarke EC, et al. Delirium in children after cardiac bypass surgery. Pediatr Crit Care Med. 2017;18:165–71.
26. Groenewald CB, Rabbits JA, Schroeder DR, Harrison TE. Prevalence of moderate to severe pain in hospitalized children. Pediatr Anesth. 2012;22:661–8.
27. Shoemaker K, Dutton S, Mark M. Pain prevalence and treatment patterns in a US children's hospital. Hosp Pediatr. 2015;5:363–70.

28. Marx CM, Rosenberg DI, Ambuel B, Hamlett KW, Blumer JL. Pediatric intensive care sedation: survey of fellowship programs. Pediatrics. 1993;91:369–78.
29. Curley MAQ, Wypij D, Watson RS, Grant MJC, Asaro LA, Cheifetz IM, Dodson B, Franck LS, Gedeit RG, Angus DC, Matthay MA, and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network for the RESTORE Study Investigators. Protocolized sedation versus usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. JAMA. 2015;313:379–89.
30. Twycross A. Dispelling modern day myths about children's pain. J Child Health Care. 1998;2:31–5.
31. Humphrey T. Some correlations between the appearance of human fetal reflexes and the development of the nervous system. Prog Brain Res. 1964;4:93–135.
32. Biljani V, Rizvi TA, Wadhwa S. Development of spinal substrate for nociception in man. NIDA Res Monogr. 1988;87:167–79.
33. Scanlon JW. Appreciating neonatal pain. Adv Pediatr Infect Dis. 1991;38:317–33.
34. The Royal College of Surgeons of England and the College of Anaesthetists. Report of the working party on pain after surgery. London: The College; 1990. p. 1–36.
35. Taddio A, Katz J, Ilersich AL, Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. Lancet. 1997;349:599–603.
36. Eland J. The child who is hurting. Semin Oncol Nurs. 1985;1:116–22.
37. Valrie CR, Bronberg MH, Palermo T, Schanberg LE. A systematic review of sleep in pediatric pain populations. J Dev Behav Pediatr. 2013;34:120–8.
38. Roizenblatt S, Tufik S, Goldenberg J, et al. Juvenile fibromyalgia: clinical and polysomnographic aspects. J Rheumatol. 1997;24:579–85.
39. Tayag-Kier CE, Keenan GF, Scalzi LV, et al. Sleep and periodic limb movement in sleep in juvenile fibromyalgia. Pediatrics. 2000;106:E70.
40. American Academy of Pediatrics. The assessment and management of acute pain in infants, children, and adolescents. Pediatrics. 2001;108:793–7.
41. Beltramini A, Melojevic K, Pateron D. Pain assessment in newborns, infants, and children. Pediatr Ann. 2017;46:e387–95.
42. McCaffery M, Wong DL. Nursing interventions for pain control in children. In: Schechter NL, Berde CB, Yaster M, editors. Pain in infants, children and adolescents. Baltimore: Williams and Williams; 1993. p. 295–316.
43. McGrath PJ, Unrah AM, Finlay GA. Pain measurement in children. Pain Clin Update. 1995;3:1–4.
44. McGrath PA. Evaluating a child's pain. J Pain Symptom Manage. 1989;4:198–214.
45. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in younger children. Pediatr Nurs. 1997;23:293–7.
46. Voepel-Lewis T, Merkel SI, Tait AR, Trzcinka A, Malviya S. The reliability and validity of the faces, legs, activity, cry, consolability observational tool as a measure of pain in children with cognitive impairment. Anesth Analg. 2002;95:1224–9.
47. Bearden DJ, Feinstein A, Cohen LL. The influence of parent preprocedural anxiety on child procedural pain: mediation by child procedural anxiety. J Pediatr Psychol. 2012;37:680–6.
48. Khin Hla T, Hegarty M, Russell P, Drake-Brockman TF, Ramgolam A, Von Ungern-Sternberg BS. Perception of pediatric pain: a comparison of postoperative pain assessments between child, parent, nurse, and independent observer. Pediatr Anesth. 2014;24:1127–31.
49. Thigpen JC, Odle BL, Harirforoosh S. Opioids: a review of pharmacokinetics and pharmacodynamics in neonates, infants, and children. Eur J Drug Metab. 2019;44:591–609.
50. Brasher C, Gafsous B, Dugue S, Thiollier A, Kinderf J, Nivoche Y, Grace R, Dahmani S. Postoperative pain management in children and infants: an update. Paediatr Drugs. 2014;16:129–40.
51. Palmer GM. Pain management in the acute care setting: updates and debates. J Paediatr Child Health. 2016;52:213–20.
52. Krauss BS, calligaris L, Green SM, Barbi E. Current concepts in management of pain in children in the emergency department. Lancet. 2016;387:83–92.

53. Carter BS, Brunkhorst J. Neonatal pain management. Semin Perinatol. 2017;41:111–6.
54. Jenkins IA, Playfor SD, Bevan C, Davies G, Wolf AR. Current UK sedation practice in pediatric intensive care. Pediatr Anesth. 2007;17:675–83.
55. World Health Organization. Cancer pain relief: with a guide to opioid availability. 2nd ed. Geneva: WHO; 1996. p. 15.
56. Pain terms: a list with definitions on notes and usage, recommended by the IASP Subcommittee on Taxonomy. Pain. 1979;6:249.
57. Taylor EM, Boyer K, Campbell FA. Pain in hospitalized children: a prospective cross-sectional survey of pain prevalence, intensity, assessment, and management in a Canadian pediatric teaching hospital. Pain Res Manage. 2008;13:25–32.
58. Rotondi AJ, Chelluri L, Sirio C, Mendelsohn A, Schulz R, Belle S, Im K, Donahoe M, Pinsky MR. Patients' recollections of stressful experiences while receiving prolonged mechanical ventilation in an intensive care unit. Crit Care Med. 2002;30:746–52.
59. Duzkaya DS, Kuguoglu S. Assessment of pain during endotracheal suction in the pediatric intensive care unit. Pain Manag Nurs. 2015;16:11–9.
60. Fisk AC. The effects of endotracheal suctioning in the pediatric population: an integrative review. Dimens Crit Care Nurs. 2018;37:44–56.
61. 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.
62. Cummings EA, Reid GJ, Finley A, McGrath PJ, Ritchie JA. Prevalence and source of pain in pediatric inpatients. Pain. 1996;68:25–31.
63. Juneja R, Jaggar SI. The physiology of pain. Semant Schol. 2008:1–16. https://www.researchgate.net/publication/237480512_1_The_Physiology_of_Pain.
64. Kim EB, William FG. Ganong's review of medical physiology. New York: McGraw-Hill Medical; 2010.