Analgesia and Sedation in Hospitalized Children

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LEARNING OBJECTIVES

1. Evaluate analgesics and sedative agents on the basis of drug mechanism of action, pharmacokinetic principles, adverse drug reactions, and administration considerations.
2. Design an evidence-based analgesic and/or sedative treatment and monitoring plan for the hospitalized child who is postoperative, acutely ill, or in need of prolonged sedation.
3. Design an analgesic and sedation treatment and monitoring plan to minimize hyperalgesia and delirium and optimize neurodevelopmental outcomes in children.

ABBREVIATIONS IN THIS CHAPTER

GABA	γ-Aminobutyric acid
ICP	Intracranial pressure
PAD	Pain, agitation, and delirium
PCA	Patient-controlled analgesia
PICU	Pediatric ICU
PRIS	Propofol-related infusion syndrome

Table of other common abbreviations.

INTRODUCTION

Pain, anxiety, fear, distress, and agitation are often experienced by children undergoing medical treatment. Contributory factors may include separation from parents, unfamiliar surroundings, sleep disturbance, and invasive procedures. Children receive analgesia and sedatives to promote comfort, create a safe environment for patient and caregiver, and increase patient tolerance to medical interventions such as intravenous access placement or synchrony with mechanical ventilation. However, using these agents is not without risk. Many of the agents used for analgesia and sedation are considered high alert by the Institute for Safe Medication Practices because of their potential to cause significant patient harm, given their adverse effects and the development of tolerance, dependence, and withdrawal symptoms. Added layers of complexity include the ontogeny of the pediatric patient, ongoing disease processes, and presence of organ failure, which may alter the pharmacokinetics and pharmacodynamics of these medications. Therefore, the pharmacist's role is vital in forming the best and safest comfort plan and environment for the patient and provider.

REVIEW OF MEDICATIONS

The primary pillars for safe and effective analgesia and sedation in children are using the lowest effective dose (Table 1-1) with the widest therapeutic index and minimizing adverse effects (Table 1-2). In addition, the pharmacokinetic changes that children undergo across the developmental spectrum must be considered, as must how these will affect each child's drug exposure.

Opioid Analgesics

Fentanyl, morphine, and hydromorphone are the most commonly used parenteral opioid agents in the hospital. Other synthetic

Table 1-1. Initial Doses of Opioids and Sedatives in Children

	Intermittent Dose	Continuous Intravenous Infusion[a]
Chloral hydrate	PO: 0.5–5 mcg/kg	N/A
Clonidine	PO: 0.5–5 mcg/kg	N/A
Dexmedetomidine	IN: 1–4 mcg/kg IV: 0.5–1 mcg/kg	0.2–0.7 mcg/kg/hr
Etomidate	IV: 0.1–0.3 mg/kg	N/A
Fentanyl	IN: 1–2 mcg/kg IV: 0.5–3 mcg/kg	0.5–2 mcg/kg/hr
Hydromorphone	IV: 0.01–0.02 mg/kg	0.003–0.005 mg/kg/hr
Ketamine	IM: 5–10 mg/kg IN: 3–5 mg/kg IV: 0.5–3 mg/kg PO: 5–8 mg/kg	0.3–0.6 mg/kg/hr (5–10 mcg/kg/min)
Lorazepam	IV: 0.05–0.1 mg/kg PO: 0.05 mg/kg	0.05 mg/kg/hr
Midazolam	IM: 0.05–0.15 mg/kg IN: 0.2–0.3 mg/kg IV: 0.05–0.1 mg/kg PO: 0.25–0.5 mg/kg	0.03–0.12 mg/kg/hr
Morphine	IV: 0.03–0.2 mg/kg	0.01–0.04 mg/kg/hr
Pentobarbital[b]	IM: 2–6 mg/kg IV: 1–2 mg/kg PO/PR: 1.5–6 mg/kg	0.5–1 mg/kg/hr
Propofol	IV: 0.5–2 mg/kg	1.2–4.8 mg/kg/hr (20–80 mcg/kg/min)

[a]Actual infusion rates may exceed listed values as infusions are titrated to effect.

[b]Higher loading doses (5–10 mg/kg) may be used to induce pentobarbital coma.

IM = intramuscularly; IN = intranasally; IV = intravenously; N/A = not applicable; PO = orally; PR = rectally.

parenteral opioids such as sufentanil and remifentanil are also used, but typically not outside the operating room. Meperidine is another synthetic opioid with a long history of use in analgesia. However, data do not support the superiority of meperidine to any other opioid for analgesia, and meperidine may place the patient at risk of exposure to the neurotoxin normeperidine (Buck 2011). The American Academy of Pediatrics (AAP), American Pain Society, and Institute for Safe Medication Practices have recommended against the routine use of meperidine for analgesia (ISMP 2007; AAP 2001). Oral opioid analgesics are also used for analgesia in the hospital setting. These agents are often used in the less critically ill patient (e.g., hemodynamically stable) when it is clinically appropriate to transition to the enteral route and a longer-acting analgesic option is desired.

Fentanyl, morphine, and hydromorphone are μ-opioid receptor agonists that produce analgesia through the central and peripheral nervous system. However, these opioids, even when used at high doses, do not induce the deep level of unconsciousness or amnesia necessary for general anesthesia, but they may cause transient euphoria and sedation (Butterworth 2013b). Analgesia-based sedation is gaining momentum as a sedation strategy in adult ICUs because it is recommended by the American College of Critical Care Medicine publication titled "Clinical Practice Guidelines for on the Management of Pain, Agitation, and Delirium [PAD] in Adult Patients in the Intensive Care Unit" (Barr 2013).

Opioid adverse effects include respiratory depression, constipation, nausea, vomiting, and pruritus. Pruritus is more likely with morphine because histamine release is not commonplace with synthetic and semisynthetic opioids like fentanyl and hydromorphone. In addition, histamine release from morphine may induce hypotension and potentially exacerbate reactive airway disease in susceptible patients. Rigid

Table 1-2. Opioid and Sedative Effects

	Analgesia	Sedation	Amnesia	Anxiolysis	Respiratory Effects	Hemodynamic Effects
Chloral hydrate		X			X	
Clonidine	X	X				X
Dexmedetomidine	X	X		X		X
Etomidate		X				
Fentanyl	X	X[a]			X	
Hydromorphone	X	X[a]			X	
Ketamine	X	X	X		X[b]	X
Lorazepam		X	X	X	X	X
Midazolam		X	X	X	X	X
Morphine	X	X[a]			X	X
Pentobarbital		X	X		X	X
Propofol		X	X		X	X

[a]Opioids have transient sedating properties.

[b]Ketamine may induce hypoventilation with high intravenous doses.

chest syndrome is a rare phenomenon that has been associated with the rapid infusion of high-dose fentanyl (e.g., greater than 5 mcg/kg) in adults, but rigid chest syndrome has also been reported at lower fentanyl doses in neonates and infants (Dewhirst 2012). Rigid chest syndrome is characterized by spasms of the respiratory muscles leading to insufficient respirations and inability to ventilate the patient through artificial means. To reverse this syndrome, neuromuscular blockade must be introduced to paralyze the chest wall muscles and allow for effective respirations (Weaver 2016). Case reports have also described success with naloxone in reversing this syndrome (Coruh 2013). Naloxone is a competitive opioid antagonist that reverses the effects of opioids. Naloxone's effects are dose-dependent, in which low doses (less than 0.05 mg/kg) are used for opioid-induced pruritus and partial reversal and larger doses (0.1 mg/kg) are used for full opioid reversal for intoxication.

BASELINE KNOWLEDGE STATEMENTS

Readers of the chapter are presumed to be familiar with the following:

- Pharmacokinetic and pharmacodynamic changes in children

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Academy of Pediatrics (AAP). Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures: Update 2016.
- ICU Delirium and Cognitive Impairment Study Group. ABCDEFs of Prevention and Safety [homepage on the Internet].
- Society of Critical Care Medicine. ICU Liberation Collaborative [homepage on the Internet].

Sedatives

Benzodiazepines

Benzodiazepines potentiate the binding of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), which promotes $GABA_A$ postsynaptic receptor opening to chloride ions, thus hyperpolarizing the cell membrane and preventing the generation of an action potential. Sedation, hypnosis, muscle relaxation, anxiolysis, and anticonvulsant effects are mediated through this mechanism.

Midazolam is a short-acting benzodiazepine that is commonly used as both procedural and long-term sedation. With continuous exposure to midazolam, the half-life and duration of action become prolonged (Patel 2011). The anxiolytic effect is ideal for treating the anxious and uncooperative child and allows for anterograde amnesia, thus inhibiting the formation of memory after administration. This property may

be desired in children undergoing procedures and interventions deemed traumatic; however, it may also contribute to adverse psychological events later because of the patient's inability to recall logical and sequential memories (Trevor 2015). Lorazepam is an intermediate-acting benzodiazepine similar to midazolam in sedative, anxiolytic, amnestic, and hypnotic properties. Unlike midazolam, however, lorazepam is formulated in propylene glycol. Propylene glycol may accumulate when lorazepam is used as a continuous infusion at high doses and in the presence of renal failure (Horinek 2009; Chicella 2002). Toxicity manifests as hyperosmolar metabolic acidosis, lactic acidosis, hypotension, seizures, and cardiac arrhythmias (Horinek 2009).

The benzodiazepines' dose-dependent adverse drug events involve the respiratory and cardiovascular systems. Respiratory depression is increased with benzodiazepine use in children. Particularly, hypnotic doses of benzodiazepines may decrease the muscle tone of the upper airway, which may exacerbate a preexisting breathing pattern such as obstructive sleep apnea. Combining a benzodiazepine with other respiratory-depressing agents such as opioids further increases the risk of adverse respiratory events. The decrease in peripheral vascular resistance from benzodiazepine administration may lead to hypotension in children (Mihic 2011). The hypnotic effect of benzodiazepines does not allow for restorative sleep, which also may contribute to future adverse psychological events if used repeatedly or continuously (Trevor 2015). Flumazenil competitively inhibits benzodiazepines at the GABA/benzodiazepine receptor complex to reverse sedative and respiratory adverse effects. Flumazenil has dose-dependent effects much like naloxone and should be given in small aliquots (0.01 mg/kg or smaller) until the desired resolution of adverse effects.

Barbiturates

Barbiturates as a drug class have sedative, hypnotic, and anticonvulsant properties through a mechanism similar to benzodiazepines, but barbiturates prolong the opening of the chloride channel. Barbiturates have a narrow therapeutic index, making it difficult to achieve an anticonvulsive effect without some degree of CNS depression and thus expanding the use of these agents into the sedation arena. Pentobarbital, methohexital, and thiopental are the three barbiturate agents used most commonly for sedation. Pentobarbital is considered a short-acting barbiturate and has been used for many years for pediatric sedation. Methohexital and thiopental are considered ultra-short-acting barbiturates that are used to induce anesthesia. However, thiopental is no longer available because the sole manufacturer has discontinued the product in the United States and Canada.

Barbiturates have many adverse effects involving the CNS, respiratory system, and cardiovascular system. The hypnotic effects of barbiturates may last a few hours, but prolonged impairment of fine motor skills and alterations in cognition may occur. Barbiturates used at anesthetic doses may induce laryngospasm and coughing, as well as depress the respiratory drive, thus requiring close observation both during and after administration (Mihic 2011). Cardiac adverse events may occur because of the cardiac depressant and vasodilating properties of barbiturates. With pentobarbital, hypotension may be further exacerbated by the 40% propylene glycol diluent (Butterworth 2013a).

Propofol

Propofol is a rapid-acting hypnotic and sedative agent with no analgesic properties that increases the binding affinity of GABA (Mihic 2011). Propofol is labeled for inducing anesthesia in patients older than 3 years and maintaining anesthesia in patients older than 2 months. Propofol is primarily used for short-term sedation in pediatric patients. Propofol has also been used to facilitate extubation in children previously receiving other respiratory-depressing agents (Teng 2011; Sheridan 2003; Cray 2001).

Propofol's adverse effects on the respiratory and cardiovascular system are significant. Propofol may induce apnea, but likely not respiratory depression, and is less likely to incite bronchospasm than barbiturates (Patel 2011). These respiratory effects favor propofol use in the peri-extubation setting. Cardiovascular effects of propofol include hypotension and decreased cardiac output from a decrease in systemic vascular resistance and cardiac contractility (Butterworth 2013a). The cardiac effects are often related to the dose and rate of administration. An isotonic fluid bolus, decrease in infusion rate, or smaller propofol bolus dose may help alleviate the hemodynamic adverse effects. Propofol is a 10% oil-in-water emulsion containing a lipid component composed of egg lecithin and soybean oil that should be avoided in patients with egg and soy allergies.

Propofol-related infusion syndrome (PRIS) has been described in children and adults who have been exposed to high doses (greater than 83 mcg/kg/minute or 5 mg/kg/hour) and prolonged infusions (greater than 48 hours). The pathophysiology of PRIS has been postulated to be mitochondrial toxicity because of direct inhibition of aerobic phosphorylation, respiratory chain uncoupling, and inhibition of fatty acid oxidation. Features of PRIS include unexplained metabolic acidosis, hyperkalemia, rhabdomyolysis, hepatomegaly, triglyceridemia, arrhythmia, and cardiovascular collapse. Metabolic acidosis (77%) and arrhythmias (66%) are common in PRIS. Dose-related adverse effects manifest as cardiac failure, metabolic acidosis, fever, and hypotension. In a recent meta-analysis, infusions greater than 48 hours were associated with arrhythmias, and over 96 hours of exposure was associated with rhabdomyolysis and hypertriglyceridemia, irrespective of dose. Emerging case report data suggest that even short durations of moderate doses (less than 67 mcg/kg/minute or 4 mg/kg/hour) result in PRIS, which is a threshold lower than the FDA warning label (Krajčová 2015).

Ketamine

Ketamine is a unique rapid-acting sedative agent with analgesic properties. Ketamine is chemically similar to phencyclidine, which explains the untoward psychotogenic effects described with ketamine use (Patel 2011). The anesthetic effects are mediated from the noncompetitive antagonism of the *N*-methyl-D-aspartate receptor, which ultimately inhibits the activity of the excitatory neurotransmitter glutamate. Delta- and mu-opioid receptor agonism contributes to ketamine's analgesic property, whereas liberation of dopamine and norepinephrine contributes to its adverse effects (Sleigh 2014). Ketamine's dissociative and analgesic effects can begin at subanesthetic doses, whereas its psychotogenic reactions increase in severity with higher serum concentrations achieved by anesthetic doses (Mion 2013).

Emergence delirium is the psychotogenic phenomenon described as combativeness and disorientation. Delirium is estimated to affect 2% of ketamine-treated patients. However, the incidence of unpleasant sensation and dreams is estimated to be as high as 10% (Sahyoun 2012). According to several studies, post-recovery agitation appears not to be attenuated by premedication with benzodiazepines, as previously thought; instead, airway events and oxygen desaturations increased (Sahyoun 2012; Deasy 2010; Krauss 2006). Agitation and emotional liability are also adverse effects of ketamine; ketamine should be avoided in patients with a significant psychiatric history (Sahyoun 2012).

Unlike other sedative agents discussed, ketamine may cause elevations in blood pressure and heart rate because of stimulation of catecholamine release and inhibition of catecholamine reuptake. Ketamine is a negative inotrope with vasodilating properties, but the indirect sympathomimetic activity preserves cardiac output (Patel 2011). Because of this, ketamine is accepted as an ideal choice in patients with hemodynamic instability, but perhaps a poor choice for patients with traumatic brain injury and elevated intracranial pressure (ICP). However, the "catecholamine surge" theory was debunked after a recent meta-analysis showed no difference in ICP or mean arterial pressure with ketamine compared with opioids. Literature supports ketamine's cardiovascular neutrality and suggests its safety in patients with elevated ICP (Wang 2014). However, ketamine's cardiopulmonary interactions should be considered in children with heart failure or pulmonary hypertension. Negative inotropic effects and increased myocardial oxygen demand from ketamine administration is not advantageous in the failing heart. In a patient with compromised left ventricular dysfunction, ketamine-induced systemic vascular resistance may increase afterload, thus impairing cardiac output. One adult study reported that patients with catecholamine-dependent heart failure had a 21% drop in cardiac index with ketamine infusions (Christ 1997). Reports are conflicting on the increase in pulmonary arterial pressure and pulmonary vascular resistance with ketamine administration. Increases in these parameters would be unfavorable in patients with pulmonary hypertension, though a recent pediatric study showed little change in pulmonary hemodynamics when a ketamine bolus dose was used in a multimodal anesthesia approach in children with pulmonary hypertension (Friesen 2016).

Ketamine preserves the laryngeal reflexes and allows spontaneous respirations, making it favorable for procedural sedation. However, with the rapidly administered, large intravenous doses used in anesthesia induction, ketamine may induce transient hypoventilation and even apnea. In addition, ketamine is a potent bronchodilator. Bronchodilation is thought to be the result of catecholamine release, inhibition of vagal tone, and direct smooth muscle relaxation (Patel 2011). This property makes ketamine a logical choice for sedating a patient with bronchospasm. Ketamine causes excessive salivation, though recent reports have recommended against using an anticholinergic agent to antagonize the sialagogue (Sahyoun 2012; Deasy 2010). A large prospective study of over 900 children who underwent ketamine sedation without adjunctive atropine found excessive salivation as an uncommon adverse effect of ketamine. Only 3.2% of patients were reported to have transient airway complications (e.g., desaturation), and 4.2% required intervention with suctioning (Brown 2008).

α-Adrenergic Agonists

Clonidine and dexmedetomidine are both selective agonists of the α_2-adrenergic receptor in the locus ceruleus from which the sedative-hypnotic properties originate as well as in the spinal cord, which contributes to the analgesic properties. Dexmedetomidine differs from clonidine in its receptor affinity and selectivity. Clonidine has a selectivity ratio of 200:1 for the α_2- versus the α_1-receptor, whereas dexmedetomidine is 8 times more selective than clonidine and has a selectivity ratio of 1620:1 for the α_2-receptor (Capino 2016; Phan 2008). Both clonidine and dexmedetomidine have been used for short- and long-term sedation, and clonidine has been used as an adjuvant to analgesia and for opioid and dexmedetomidine withdrawal symptoms (Capino 2016).

Dexmedetomidine offers arousable sedation, which differs from the level of consciousness induced by the previously discussed agents. Sedation from dexmedetomidine is similar to that from natural sleep, and dexmedetomidine's sedative properties do not reliably induce amnesia. In addition, dexmedetomidine allows for spontaneous respiration, which is advantageous in patients without an artificial airway or mechanical ventilation support.

The adverse effects of the α-agonists are rather limited to the effects mediated by the adrenergic receptor. A dose-limiting adverse effect is bradycardia and hypotension facilitated by the inhibition of norepinephrine release from α_{2A}-adrenergic stimulation in the central and peripheral nervous system (Capino 2016; Phan 2008). Hypertension can present with bolus dosing or higher infusion doses

of dexmedetomidine, which cause stimulation of the α_{2B}-adrenergic receptors in the periphery (Kamibayashi 2000).

Chloral Hydrate

Chloral hydrate is a sedative-hypnotic drug that was first discovered in the 1830s. Its usefulness for sedation was documented as early as 1869 (Gauillard 2002). Chloral hydrate has primarily been used in non-painful diagnostic procedures such as electroencephalography, MRI, and pulmonary function tests (Sahyoun 2012). Chloral hydrate's sedative effects are thought to be GABA mediated. Chloral hydrate is metabolized by alcohol dehydrogenase to the active metabolites trichloroethanol and trichloroacetic acid. The active metabolites have prolonged half-lives compared with the parent drug (8 hours and 67 hours vs. 1 hour, respectively) (Gauillard 2002).

Chloral hydrate, which preceded the Federal Food, Drug, & Cosmetic Act (FD&C) of 1938, has never undergone the rigorous safety and efficacy trials expected of drugs on the U.S. pharmaceutical market. Therefore, chloral hydrate is considered an FDA-unapproved drug, and commercially available chloral hydrate products are no longer manufactured. Compounding chloral hydrate from the pharmaceutical grade powder is still occurring and permitted under the FD&C section 503A (ISMP 2016).

Safety of chloral hydrate use in children is of concern. Extemporaneously prepared products introduce another avenue for medication errors with non-standardized concentrations and preparations. A 2000 review of pediatric adverse events from sedatives showed that chloral hydrate contributed to 21% of the severe adverse effects (e.g., severe neurological injury, death) reported in children (Coté 2000). Dose-dependent hypotension and ventricular arrhythmias have been reported with overdoses. Chloral hydrate–associated respiratory depression or airway obstruction leading to respiratory arrests has been reported in the literature. The long half-lives of the active metabolites create the potential for prolonged sedation and respiratory adverse events, creating an unsafe environment for the patient without an artificial airway or mechanical ventilation (ISMP 2016).

Etomidate

Etomidate is an ultra-short-acting, non-barbiturate hypnotic drug with GABA-like effects. Etomidate has a rapid onset, short duration of action, and few cardiac and respiratory adverse effects, making it ideal for inducing anesthesia and rapid sequence intubation. Etomidate is more cardiac neutral than barbiturates or propofol. Small changes in heart rate, blood pressure, and cardiac output are noted but are hemodynamically insignificant, making etomidate a good choice for patients with hemodynamic instability. Little respiratory depression and apnea is associated with etomidate compared with other agents (Patel 2011).

Etomidate-associated adrenal suppression has evoked much controversy in the critical care area. With little evidence to substantiate the claim in children and the unknown magnitude of adrenal suppression, the consensus panel for pediatric shock recommends avoiding etomidate in the hemodynamically unstable child (Brierley 2009).

Other notable adverse effects of etomidate include myoclonic movements, nausea, vomiting, and hiccups. The myoclonic movements may be attenuated with premedication with opioids or benzodiazepines. Etomidate is formulated in 35% propylene glycol, which contributes to pain with injection (Patel 2011).

Ontogeny Considerations

Children undergo many pharmacokinetic alterations as they grow and mature. Drug distribution changes, hepatic enzymatic capacity matures, and renal function develops. The expression of P-glycoprotein, cell membrane efflux transport protein, plays an important role in opioid movement across the blood-brain barrier. A recent publication described the ontogeny of P-glycoprotein in the human brain. P-glycoprotein has been detected as early as 8–12 weeks' gestation, with the quantity increasing with advancing age. Adult values of P-glycoprotein in the brain were achieved by 3–6 months of age. This finding is significant for opioid exposure in the neonatal period, which is when these drugs may concentrate in the brain from the lower expression of this protein (Lam 2015). In a study of children younger than 3 years receiving intravenous morphine after surgery, changes in volume of distribution and elimination of morphine metabolites were observed. The volume of distribution of morphine almost doubled from birth to 6 months of age, when adult values were achieved (1.2 L/kg vs. 1.9 L/kg). Formation of metabolites by glucuronidation is also affected by age, with morphine-3-glucuronide and morphine-6-glucuronide achieving 80% of adult values by 6 months of age. Metabolite clearance of both entities had a maturation half-life of 129 days and reached 80% of adult values by 6 months and 96% of adult values by 1 year, which mimics the glomerular filtration maturation trajectory (Bouwmeester 2004). The biotransformation capacities of all the phase I and II hepatic enzymes mature at different rates. For example, CYP3A4 is responsible for primarily metabolizing midazolam. The fetal liver has very little CYP3A4 but does have CYP3A7, which has a lower magnitude of catalytic activity. A lower clearance of midazolam would be expected in an infant because of immature CYP3A4 enzyme activity. However, examination of data showed no significant change in hepatic clearance with age (Björkman 2006).

Pharmacogenomic contributions to the ontogenic alterations in drug disposition, drug response, and clinical application are incomplete and not yet fully elucidated (Leeder 2010). Describing the clinical impact of genetic polymorphisms on the phase I and phase II enzymes is a prime example of applying this information. The study of CYP2D6 has shown many polymorphisms that influence ultrametabolism and poor metabolism of certain medications.

A current pediatric example is codeine, which is metabolized to morphine by CYP2D6. Patients who are considered ultra-metabolizers of codeine create a toxic environment of supratherapeutic morphine concentrations. Conversely, poor metabolizers of codeine are at risk of therapeutic failure (Gammal 2016).

Obesity Considerations

Childhood obesity rates are reaching endemic proportions in the United States, with one in six children or adolescents affected (CDC 2016). Developmental changes that influence drug pharmacokinetics in children are well described, but drug pharmacokinetics in obesity is not well understood. Obesity presents a challenge to the delivery of safe and effective medication in children, especially with drugs that have narrow therapeutic windows such as some sedatives and analgesics.

The pharmacokinetic profile in obesity includes a greater total lean mass and higher volume of distribution of lipophilic agents like fentanyl and propofol. Patients with obesity have increased circulating blood volume and higher cardiac output, which may explain their increased hepatic and renal blood flow. Increased organ size and perfusion culminate in higher hepatic drug extraction and glomerular hyperperfusion. With many of the equations available for creatinine clearance based on body measurements in children, the true glomerular filtration rate of children with obesity is likely underestimated, which may lead to suboptimal dosing (Vaughns 2015).

Aside from the pharmacokinetic considerations in children with obesity, choosing the appropriate and optimal dosing weight is perplexing. Given the options of total body weight, lean body weight, ideal body weight, and adjusted body weight for weight-based dosing, a practitioner is faced with a challenge and little evidence to guide decision-making. A decision support tool was published to assist with weight-based dosing in critically ill patients with obesity. The algorithm considers the information available in primary literature as well as volume of distribution, therapeutic window of the specific drug, and the risk of over- or undertreating to create a recommended dosing scheme on the basis of ideal, adjusted, or total body weight. According to the tool, dexmedetomidine, ketamine, lorazepam, midazolam, and morphine should be dosed on the basis of ideal body weight and then titrated to effect. Fentanyl should be dosed on an adjusted body weight, whereas total body weight dosing has been proposed for propofol and pentobarbital (Ross 2015).

POSTOPERATIVE ANALGESIA

Pain is often viewed as the fifth vital sign because it is applicable to all patients and should be assessed often. The Joint Commission has recommended that pain assessment and treatment be outlined in institution-specific policies that center on individual patient and patient population needs (Baker 2016). A 2010 survey on pediatric pain management queried members of the American Society for Pediatric Anesthesia, of whom over half reported a formal pediatric pain service staffed by either a physician or a nurse. Freestanding children's hospitals and hospitals with more than 150 pediatric beds had formalized pain services, which helps address the Joint Commission recommendation (Nelson 2010).

Combination Therapies

The recently published clinical practice guideline for managing postoperative pain strongly recommends the use of multimodal pain treatment. Multimodal therapy uses more than one medication with synergistic or additive analgesic properties. This therapy includes medications given by different administration routes by local, regional, and neuraxial anesthetic techniques as well as integration of nonpharmacologic treatments (Chou 2016).

Acetaminophen and NSAIDs decrease opioid needs and postoperative pain when used in combination. This combination strategy for postoperative analgesia is strongly recommended by several national pain societies and anesthesia groups, though no preference has been given to intravenous versus enteral (Chou 2016).

Recently making its way to the U.S. market, intravenous acetaminophen offers favorable pharmacodynamics with analgesic onset in less than 10 minutes and CNS concentrations peaking at 1 hour after administration. One study described the use of intravenous acetaminophen in children younger than 2 years undergoing bladder surgery. Patients received an admixture of intravenous acetaminophen and fentanyl administered by a patient-controlled analgesia (PCA) infusion device. Compared with the fentanyl-only group, the acetaminophen/fentanyl PCA group had decreased fentanyl use on postoperative days 1 and 2. In addition, the rates of vomiting and sedation were higher in the fentanyl-only group (Hong 2010a). Of interest, a recent randomized, double-blind, placebo-controlled trial of children and adolescents undergoing surgery for scoliosis repair found no difference in opioid requirement in the first 24 hours postoperatively, regardless of whether the children received intravenous acetaminophen at 90 mg/kg/day or placebo. However, the acetaminophen group had improved analgesia, as reported in lower visual analog scale (VAS) pain scores, compared with the placebo group. The rate of nausea and vomiting did not differ between the two groups. The authors cited the study limitations as the small sample size (n=36), the conservative power calculation, and the use of oxycodone PCA in the acetaminophen group for general discomfort instead of for severe pain (Hiller 2012).

Many of the modern analgesic combination studies use intravenous acetaminophen as the non-opioid agent as subjects are recruited from the preoperative, intraoperative, and immediate postoperative setting. A recent systematic review that compared the efficacy of intravenous and oral

acetaminophen in adults found no strong evidence to support intravenous acetaminophen over oral acetaminophen (Jibril 2015). A randomized controlled study compared intravenous with rectal acetaminophen in children undergoing adenotonsillectomy. Both groups had similar fentanyl use postoperatively; however, the rectal acetaminophen group had longer duration of analgesia before the first rescue dose request (median time to rescue dose, rectal: 10 hours; intravenous: 7 hours; p=0.01) (Capici 2008). A retrospective study of infants undergoing a laparoscopic pyloromyotomy assessed the efficacy of rectal versus intravenous acetaminophen. Both groups had similar postoperative pain scores, postanesthesia care unit time, and hospital length of stay. However, the number of additional acetaminophen doses given differed (intravenous group 4.4 ± 5.6 doses vs. rectal group 3.5 ± 3.7 doses) (Yung 2016).

The combination of acetaminophen and NSAIDs appears to be favorable in postoperative analgesia. Using a combination of intravenous acetaminophen and intravenous ketorolac was investigated for possible fentanyl-sparing effects during pediatric inguinal hernia repair. Children 5 years and younger were assigned to receive either intravenous acetaminophen/ketorolac or placebo intraoperatively. The combination group used significantly fewer fentanyl doses and a less-cumulative fentanyl dose than the placebo group. Not surprisingly, sedation and vomiting were more prolific in the placebo group (sedation 55.6% vs. 25.0%; vomiting 33.3% vs. 10.7%; $p<0.05$) (Hong 2010b). A 2010 meta-analysis explored combination acetaminophen/NSAIDs versus acetaminophen alone. Of the 20 studies and 1852 patients reviewed, 606 (33%) were children. Combination therapy was preferred to acetaminophen alone, with a 35% reduction in pain scores and a 38% reduction in supplemental analgesic requirements. In another meta-analysis, results were similar when comparing acetaminophen/NSAIDs with NSAIDs alone. Of the 14 studies and 1129 patients reviewed, 268 patients (24%) were children. Pain scores and supplemental analgesic requirements were reduced in the combination group by 37% and 31%, respectively (Ong 2010). This assimilation of data suggests that combination acetaminophen and NSAID therapy more dramatically affects the ability to achieve postoperative analgesia than monotherapy.

Pain Medication Delivery Devices

Many delivery devices are available for parenteral pain medications. These devices, developed for the adult patient, have expanded use in pediatric patients. Intravenous delivery of opioids by PCA infusion device has increased patient satisfaction in postoperative pain management compared with intramuscular therapies (ASA 2004). Postoperative pain management guidelines recommend PCA when parenteral opioids are needed in adults and children. This delivery device increases patient satisfaction with the quick access to demand injections for pain relief. The bolus dose on a PCA is typically offered in smaller doses and at a greater frequency than intravenous push opioid doses, which leads to overall lower opioid drug use with PCA. Continuous infusions can be maintained through setting a basal rate on the PCA, but this mode is not recommended in the opioid-naive patient (Chou 2016). Some children may not understand the push-button concept for analgesia. Use of PCA-by-proxy (e.g., nurse or parent) has been proposed to expand PCA use. In a 2010 survey of U.S. hospitals with members of the Society for Pediatric Anesthesia, 96% of institutions surveyed had PCA availability, and 59% had no age restrictions for independent use. Of the 38% (95 of 252) of institutions that authorized PCA-by-proxy, 50 allowed nurse-only proxy, 39 allowed a parent or nurse proxy, and 5 allowed parent-only proxy (Nelson 2010). Some safety concerns of PCA use in children stem from the infusion device and drug delivery. It is recommended to use smart pump technology with drug libraries that offer dose error reduction software, as well as limit the available concentrations, and create labeling on the drug product that matches the medication administration record (ISMP 2008).

Assessment and Monitoring

Monitoring of analgesics should include observing for toxicities as well as treatment efficacy. Continuous or intermittent monitoring of vital signs to identify respiratory depression and hemodynamic compromise is common with the use of parenteral opioids. From the Society for Pediatric Anesthesia survey, about 78% (196 or 252) of respondents provided routine monitoring to all patients receiving intravenous opioids, regardless of age. The most common monitoring tool used was pulse oximetry, followed by ECG (Nelson 2010). The 2016 American Pain Society guidelines do not recommend which mechanical monitoring device to use because supporting data are lacking. Pulse oximetry in a patient with oxygen supplementation is not very sensitive for hypoventilation; however, capnography may offer greater sensitivity for detecting opioid-induced hypoventilation and resulting hypercarbia. However, neither of these mechanical monitoring devices should take the place of periodic assessments of alertness, hypoventilation, and hypoxia by a medical professional (Chou 2016). Sedation scales can evaluate the patient's level of sedation after receiving an opioid. The Pasero Opioid-Induced Sedation Scale has been validated for assessing sedation during opioid administration in adult patients, but not in children (Pasero 2009). Other sedation scales may be used (e.g., Ramsay scale, COMFORT); however, these scales evaluate other elements that are not specific to opioid-induced sedation.

The gold standard for monitoring the effectiveness of pain medication is patient self-assessment. The premise of these scales is assigning a numeric value to the perception of pain, such as designating 0 as "no pain" and 10 as "worst pain

imaginable," as presented with the 10-point numeric rating scale. Self-assessment is a good tool to detect the presence of pain as well as the perceived intensity of pain. However, pain self-assessment can be challenging in some pediatric patients because of their limited ability to communicate or comprehend as a result of age or disability. Several nonverbal self-assessment pain scales, such as the VAS, Bieri Faces Pain Scale Revised, and Wong-Baker FACES scale, can be used in any age- and developmentally appropriate child (Table 1-3). Children as young as 6 years may reliably use the "FACES" assessment, and children older than 8 years can typically rate their pain on a numeric scale (McGrath 2013). Observational pain assessments may also be used, but these are not preferred to self-assessment scales. Observational pain scales are used in sedated patients or those who are too young or cognitively inappropriate to describe pain. Examples of observational pain scales include the Neonatal Pain, Agitation, and Sedation Scale (N-PASS); Face, Legs, Activity, Cry, and Consolability scale (FLACC); and Nonverbal Pain Scale. Observational scales best identify the presence of pain rather than its intensity because pain-induced behaviors and physiological responses are not linked to pain intensity (Wells 2008).

In addition to quantifying or qualifying pain with a subjective or behavioral scoring tool, other elements must be included in the assessment. Having the patient or caregiver describe the onset, location, quality, and intensity of pain is as important as clarifying the factors that aggravate or relieve pain and the previous treatments that have been successful or unsuccessful. Setting the expectation of pain relief is imperative because achieving a "zero" pain score may not be possible in some cases, and attempts to attain this goal may lead to medication overuse and adverse effects. Timing of assessments should be based on the analgesic administered and the expected achievement and duration of effects. The frequency of assessment will be patient-dependent, considering the source of pain, adequacy of initial pain relief with medication, and medication adverse effects (Chou 2016). Documenting pain assessment in hospitalized children improves pain management (McGrath 2013).

PROCEDURAL SEDATION

Procedural sedation is used for various reasons, including ensuring patient safety by modifying patient behavior or movement to allow for completion of procedures, control of anxiety, curtailment of psychological trauma, and minimization of physical pain and discomfort. If the disposition allows, the goal of procedural sedation is to return the child to a state in which discharge from medical care is safe. Medications with short duration and few post-procedure sequelae are ideal to accomplish a safe discharge. Historically, anesthesia providers have performed procedural sedation. More recently, credentialing of practitioners such as emergency medicine physicians and intensivists to manage airways, ventilation, and cardiovascular adverse events has increased the number of procedures that can be performed. Procedural sedation is now often performed in clinic areas, sedation suites, ED, and treatment rooms instead of the operating theater. Providing these services is not without risks to the patient; however, the AAP has guidelines for monitoring and treating pediatric patients undergoing procedures (Coté 2016).

Pediatric patients undergoing painful or prolonged procedures may benefit from a medication that contains both sedative and analgesic properties. When choosing an agent for sedation, the route of administration, onset of action,

Table 1-3. Comparison of Pain Assessment Instruments

Instrument	Population	Validated Pain State	Type of Assessment	Type of Scale
FLACC	Children, all ages	Acute, surgical	Observational	Behavioral, physiological
FPS-R	≥ 4 yr	Acute, surgical	Self	Pictorial
N-PASS	Neonates	Acute, surgical	Observational	Behavioral, physiological
NVPS	Children, all ages	Acute, surgical	Observational	Behavioral, physiological
NRS	≥ 6 yr	Acute, surgical, chronic	Self	Numeric
VAS	≥ 6 yr	Acute, surgical, chronic	Self	Numeric
Wong-Baker FACES	≥ 4 yr	Acute, surgical	Self	Pictorial

FLACC = Face, Legs, Activity, Cry, and Consolability scale; FPS-R = Faces Pain Scale Revised; N-PASS = Neonatal Pain, Agitation, and Sedation Scale; NRS = numeric rating scale; NVPS = Nonverbal Pain Scale; VAS = visual analog scale.

Table 1-4. Levels of Sedation

Level of Sedation	Stimulus Response	Airway Patency	Ventilation	Hemodynamics
Minimal ("anxiolysis")	Verbal and tactile	Unaffected	Unaffected	Maintained
Moderate ("conscious sedation")	Verbal and tactile	Unaffected	Unaffected	Maintained
Deep	Noxious tactile	Affected	Affected	Maintained
General anesthesia	None	Affected	Affected	Impaired

duration of action, and adverse effect profile must be considered. The level of sedation desired is another important element in agent selection (Table 1-4).

Indications for Use

Rapid Sequence Intubation

Rapid sequence intubation originated in the ED as a way to handle the airway of a patient in extremis with an unknown aspiration risk. The goal is to induce unresponsiveness and muscular relaxation as quickly as possible in order to control the airway (Bledsoe 2004). Benzodiazepines, ketamine, etomidate, quick-acting opioids (e.g. fentanyl), and rapid-acting neuromuscular blocking agents are preferred because of their favorable pharmacodynamic profiles of quick onset and short duration of action. Hemodynamic stability will contribute to the selection of agents, and the agents with cardiovascular neutrality (e.g., ketamine, etomidate, fentanyl) will likely be preferred for a patient with compromised hemodynamics. The NEAR III investigators reported the intubation practices in children younger than 16 years and described etomidate (64%) and succinylcholine (53%) as the most common induction agent and paralytic used, though there was a trend toward not using a neuromuscular blocking agent in children younger than 2 years (39%). Premedication with the intubation adjuvants atropine or lidocaine had decreased from previous years (Pallin 2016).

Although little evidence supports adjuvants to blunt hemodynamic response with intubation, these adjuvants may be used in some institutions and in certain patient populations. Use of intravenous atropine during intubation conserves the heart rate by antagonizing acetylcholine in the sinoatrial node, which helps combat the vagal-mediated bradycardia that can be induced by inserting a laryngoscope or using succinylcholine. The anticholinergic effects of atropine can help curtail secretions from succinylcholine or ketamine (Bledsoe 2004). The expert opinion from the pediatric shock group recommends using ketamine with adjuvant atropine for intubation of critically ill children (Brierley 2009). More recently, in a study of over 300 neonatal and pediatric intubations, fewer bradyarrhythmias were noted with atropine administration (OR 0.14; 95% CI, 0.06–0.35; p<0.05). Lack of atropine administration resulted in more-frequent arrhythmias, suggesting that atropine administration provides a safer intubation environment (Jones 2013). Intravenous lidocaine is used as an adjuvant in intubating a patient with neurological injury. Intravenous lidocaine is thought to blunt the sympathomimetic response from intubation and preserve cerebral perfusion. A systematic review has shown equivocal results when comparing intravenous lidocaine-pretreated and lidocaine-untreated patients with traumatic brain injury in hemodynamics, ICP reduction, or overall neurological outcome (Bucher 2015). At this time, no data support intravenous lidocaine as an intubation adjuvant in a neurologically injured patient.

Non-painful Procedures

Procedural sedation is used for non-painful procedures such as radiologic imaging, echocardiograms, and auditory testing. Previously, agents such as benzodiazepines and barbiturates were the only available medication, leading to delayed recovery periods. With the introduction of dexmedetomidine and propofol, recovery time has been shortened.

Because imaging is being pushed to the outpatient areas, children undergoing these procedures most likely do not have an artificial airway for mechanical ventilation; therefore, using an agent that allows spontaneous respirations such as dexmedetomidine is a favorable choice for sedation. A 2015 meta-analysis compared dexmedetomidine with propofol for procedural sedation in 337 children undergoing MRIs. Children who received dexmedetomidine had a longer mean recovery time with a pooled mean difference of 10.7 minutes between the groups (95% CI, 4.26–17.13; p<0.05). The dexmedetomidine group had a delayed discharge time weighted mean difference of 12.7 minutes (95% CI, 8.1–17.37; p<0.05) compared with the propofol group. However, despite the delays in the dexmedetomidine group, both groups had similar duration of sedation for the procedure. As for effects on the respiratory and cardiovascular system, minimum heart rate did not differ between the two groups, but the dexmedetomidine group had higher minimum mean arterial pressure and respiratory rates (Fang 2015). Concurrent use of dexmedetomidine and midazolam was compared with propofol for maintaining anesthesia in a small group of children (n=40) undergoing an MRI. Dexmedetomidine/midazolam resulted in a delayed time to full responsiveness compared with propofol

alone (44 vs. 29 minutes; p<0.05). Similarly, the time to discharge from the hospital was delayed in the combination group (95 vs. 79 minutes; p<0.05). The dexmedetomidine/midazolam group had lower heart rates and higher systolic blood pressures (p<0.05), but respiratory rates or respiratory events did not differ between the two groups (Heard 2008).

As more procedures are being completed in the ambulatory setting, intravenous access may be limited. Therefore, alternative routes of administration such as oral or intranasal may be more feasible. In 2015, a systematic review investigated non-intravenous routes of sedation for children younger than 19 years undergoing imaging. Intranasal midazolam was studied for procedural use in children during CT. Intranasal midazolam 0.5 mg/kg with intranasal ketamine 5 mg/kg had 83% achievement of desired sedation level. Monotherapy with 0.4 mg/kg of intranasal midazolam achieved sedation in 75% of the tested population. Comparing 0.2 mg/kg of intranasal midazolam with oral chloral hydrate showed that chloral hydrate achieved the desired level of sedation more often than a single dose of intranasal midazolam, likely because of the less-than-optimal midazolam dose (93% vs. 40%, p<0.05) (Thomas 2015). In a study comparing intranasal dexmedetomidine with oral midazolam in children younger than 5 years undergoing a CT scan, the dexmedetomidine group met the sedation goal 67% of the time, compared with 24% in the oral midazolam group (p<0.05). The scan times were similar in both groups, and no adverse events were reported with either therapy. Both groups had similar sedation scores 10 and 20 minutes after administration, but the dexmedetomidine group had a higher sedation score at the time of the CT scan, which is consistent with the half-life and duration of action of dexmedetomidine. The lower level of sedation in the midazolam group may explain the larger number of rescue ketamine doses given compared with the dexmedetomidine group (22 vs. 10 doses, p<0.01). Parental satisfaction was more favorable in the intranasal dexmedetomidine group but did not achieve statistical significance (Ghai 2016). When comparing oral midazolam with oral chloral hydrate for sedated transthoracic echocardiograms, midazolam offered a 40-minute faster recovery than chloral hydrate (p<0.05). However, chloral hydrate provided a deeper level of sedation so that a more comprehensive evaluation could be completed. No hemodynamic compromise was noted in this study (Thomas 2015). Similarly, two different doses of intranasal dexmedetomidine (2 mcg/kg and 3 mcg/kg) were compared with oral chloral hydrate for sedation during transthoracic echocardiograms in children younger than 3 years. Rescue medication was rarely needed, with 4% or less of the patients receiving additional sedation medications. Heart rate was decreased in all groups, with a 22% decrease in the chloral hydrate group, a 27% decrease in the 2-mcg/kg dexmedetomidine group, and a 23% decrease in the 3-mcg/kg dexmedetomidine group (p=0.21). The mean time to discharge did not differ between the groups (p=0.18) (Miller 2016).

Painful Procedures

Procedural sedation for painful procedures has created a use for ketamine because of its analgesic properties and favorable pharmacodynamics. The Pediatric Sedation Research Consortium published an observational review of 22,000 children younger than 21 years who received ketamine for procedural sedation outside the operating room. Intravenous ketamine was used 92% of the time, and intramuscular ketamine was used 5.6% of the time. Almost 70% of the procedures were classified as painful. Although no analgesic therapy was captured in the study, other sedatives were co-administered (anticholinergics 19.8%, benzodiazepines 57.9%, propofol 35.4%). Adverse events were reported in 7.3% of patients, with severe adverse events occurring in 1.7% of the study group. Severe adverse events were defined as airway obstruction, laryngospasm, emergency airway intervention, aspiration, or cardiac arrest. Evaluation through logistic regression revealed that the physical location of the procedure appeared to be an independent risk factor for adverse events, with the ED having the lowest odds (OR 0.71; 95% CI, 0.57–0.88) and dental suites having the highest odds (OR 3.75; 95% CI, 1.74–8.06) of an adverse event. A primary cardiac diagnosis also increased the odds of having any adverse event (OR 2.38; 95% CI, 1.64–3.46). Both propofol and anticholinergic use were independent risk factors for severe adverse events (propofol 5.36; 95% CI, 4.08–7.05; anticholinergics 2.92; 95% CI, 2.35–3.63) (Grunwell 2016).

Ketamine has been compared with other procedural sedatives. Ketamine was prospectively compared with ketamine/propofol for children with isolated orthopedic injuries undergoing procedural sedation. Monotherapy with ketamine had a prolonged median sedation time (16 minutes vs. 13 minutes) and a median recovery time (12 minutes vs. 10 minutes), as well as more adverse effects (49% vs. 25%) than ketamine/propofol. However, the ketamine monotherapy group received 1 mg/kg of ketamine, whereas the ketamine/propofol group received 0.5 mg/kg of each drug, which may have contributed to the incongruent results (Shah 2011). Ketamine/midazolam has also been prospectively evaluated against midazolam/fentanyl for procedural sedation and analgesia in pediatric orthopedic emergencies. The ketamine/midazolam group had less hypoxia (45.2% vs. 76.6%, p<0.05), shorter hypoxic episodes, and lower pain scores than the midazolam/fentanyl group. However, the ketamine/midazolam group had a higher incidence of adverse effects (51.6% vs. 6.7%, p<0.05) (Cevik 2013). A study of pediatric burn patients who were randomized to receive either ketamine/propofol or ketamine/dexmedetomidine showed no difference in sedation scores, Sao_2 values, and diastolic blood pressures. Systolic blood pressures were increased in the ketamine/dexmedetomidine group (p<0.05), and respiratory depression was noted in the ketamine/propofol group but not the ketamine/dexmedetomidine group (13.3% vs. 0%, p<0.05). In addition, recovery took longer in the ketamine/dexmedetomidine group (36 vs. 27 minutes, p<0.05)

(Canpolat 2012). Fentanyl/etomidate versus ketamine/midazolam was studied for procedural sedation and analgesia in children undergoing orthopedic reductions. Etomidate/fentanyl produced higher distress and pain scores, according to parental and physician observations ($p<0.05$). However, etomidate/fentanyl had shorter sedation time (49 vs. 77 minutes, $p<0.05$) and recovery time (24 vs. 61 minutes, $p<0.05$) than ketamine/midazolam. More adverse drug events (e.g., pain at injection site, myoclonus) and respiratory events occurred in the etomidate/fentanyl group (Jayaram 2010).

Propofol has been studied in many combinations for procedural sedation in children. One study randomized children undergoing procedural sedation in the interventional radiology suite to receive either propofol/fentanyl or propofol/fentanyl plus ketamine. Adding ketamine to the propofol/fentanyl group led to fewer propofol boluses to maintain sedation ($p<0.05$) and fewer oxygen desaturations ($p=0.05$) (Erden 2009). In children with acute lymphoblastic leukemia, similar desired levels of sedation and analgesia were achieved in both the propofol/alfentanil and the propofol/ketamine groups. In contrast, the propofol/alfentanil group had a significant increase in cardiorespiratory adverse effects compared with the propofol/ketamine group, perhaps because of opioid exposure ($p<0.05$) (Chiaretti 2010). Monotherapy with propofol resulted in more oxygen desaturations ($p=0.05$), more hypotensive episodes ($p<0.05$), and increased propofol exposure ($p<0.05$) when concomitant ketamine was not given (Chiaretti 2011).

In 2015, the Pediatric Sedation Research Consortium explored propofol use for pediatric procedural sedation performed by pediatric intensivists. Of the 91,189 propofol procedures conducted in children, 52% of the population used propofol boluses alone, and almost 41% used a propofol bolus plus an infusion. Concurrent medications included lidocaine (35%), opioids (23%), benzodiazepines (16%), and ketamine (4%). The adverse event rate was 5%, and the severe adverse event rate was 2.2%, with most adverse events being airway patency and ventilation events. The multivariable logistical regression showed that lower respiratory tract infections (OR 2.8; 95% CI, 2.39–3.28) and the physical location of the procedure were independent risk factors for adverse events. The most adverse events were found in dental suites with an odds ratio of 8.46 (95% CI, 4.1–17.49), followed by cardiac catheterization units (OR 2.62; 95% CI, 1.57–4.36), with the pediatric ICU (PICU) (OR 1.38; 95% CI, 1.20–1.58) and EDs (OR 1.01; 95% CI, 0.44–2.29) having the lowest odds for adverse events. In addition, using propofol plus four other medications increased the risk of adverse events by 3 times that of patients receiving propofol plus three or fewer medications (propofol plus four medications OR 5.83; propofol + three medications or less OR 1.17–1.76, $p<0.05$). Painful procedures appeared to be protective, with an odds ratio of 0.73 (95% CI, 0.68–0.78). It was hypothesized that the lack of analgesic effect of propofol allowed the presence of pain to stimulate the respiratory drive of the patient, thus avoiding the respiratory adverse events often associated with propofol use (Kamat 2015).

Assessment and Monitoring

Monitoring of patients receiving procedural sedation should be focused on maintaining the patient's airway, breathing, and circulation. The AAP has published guidelines for equipment and personnel requirements according to the level of sedation obtained. Monitoring should always include pulse oximetry, telemetry, and blood pressure measurement at designated intervals intra- and post-procedure. Capnography is recommended in moderate sedation and required in deep sedation. Rescue carts stocked with age- and size-appropriate airway equipment and medications are required to be available. Patients should be observed by trained personnel (i.e., anesthesiologist, trained physician, or advanced practice provider) who can perform interventions to keep the airway patent and address hypoventilation and hemodynamic instability. In addition, patients should be observed before and after they emerge from sedation for drug-related adverse effects and should receive treatment accordingly (Coté 2016).

PROLONGED SEDATION

Critically ill children often require prolonged sedation to meet therapeutic goals and to enhance healing. Sedation, like analgesia, can decrease the physiological stress response and decrease the body's metabolic demand. In addition, prolonged sedation decreases physiological stress by inducing amnesia, alleviating agitation, and reducing consciousness. Adequate sedation creates a safe environment for patient and caregiver, permits ventilator synchrony, and allows for other therapeutic interventions and monitoring. Selection of agents for prolonged sedation should consider the duration of expected sedation, goal level of sedation (e.g., light vs. deep sedation), clinical status, organ function of the patient, and anticipated adverse effects.

Data supporting preferred agents for prolonged use in children are lacking. According to a 2014 international survey, practice varies greatly across the globe. In mechanically ventilated children, fentanyl was the most prescribed opioid infusion (66%), and midazolam was the first-line sedative (86%). Propofol and dexmedetomidine were commonly associated with administration restrictions because of their potential for severe adverse effects and elevated drug cost, respectively (Kudchadkar 2014).

A systematic review of PICU prolonged sedation practices found 39 studies with fairly poor quality evidence, each with a different sedation regimen. Heterogeneity of measured sedation end points, non-standardized dosing, and lack of safety end points were identified. Midazolam was the most studied of the sedatives, with an increased interest in dexmedetomidine (Hartman 2009). Most agents used in prolonged sedation are typically given as continuous infusions. However, a 1999

study showed the successful transition of midazolam infusions to scheduled enteral lorazepam to achieve adequate sedation of mechanically ventilated children. This study found that 80% of the midazolam infusions were discontinued within 3 days of initiating lorazepam, with remaining patients having the infusion rate reduced by over 50%. A cost savings over $42,000 occurred with benzodiazepine transition in this 15-month investigation. This study is significant because it shows the effect of capitalizing on drug pharmacokinetics to achieve the desired goal (Lugo 1999).

Sedation Strategies

Unlike the adult population, the pediatric critically ill population has no comprehensive pain and sedation guideline to consult. The relative paucity of data likely contributes to the absence of recommendations. The adult PAD guidelines do not specifically address practice standards of managing sedation, analgesia, and delirium in critically ill children. The guidelines may be used as a resource to stimulate pediatric PAD research, assist in creating pediatric protocols to treat pain and agitation, and prevent and treat delirium (Barr 2013).

One institution has published its experience with a PICU nurse-driven sedation protocol. The length of PICU stay decreased by a median of 1 day, total sedation days decreased by 2 days, and lorazepam infusions for sedation were almost eliminated compared with the observation group (Deeter 2011). Although initially successful, a review of practice 4 years after protocol implementation showed an increase in PICU length of stay and sedation days. An increased use of dexmedetomidine was noted, and use of benzodiazepines remained similar to use at implementation levels (Yaghmai 2016).

The RESTORE study addressed gaps in the literature regarding prolonged sedation in children. This is the largest pediatric sedation study to date, enrolling almost 2500 patients with acute respiratory failure between 17 intervention institutions and 14 control institutions. The study objective was to compare a nurse-driven, goal-oriented, sedation protocol with standard of care. The protocol was very complex and considered pain, sedation, and withdrawal assessments as well as scheduled arousal assessments (e.g., sedation "holiday") and extubation readiness tests, when deemed appropriate. The primary objective of decreasing the days on

Patient Care Scenario

M.N., a 5-year-old boy (height 43 inches [108 cm], weight 60 kg) with uncontrolled severe persistent asthma, is admitted to the PICU with a severe acute asthma exacerbation. He is receiving continuous inhaled albuterol at 10 mg/hour and methylprednisolone 60 mg intravenously daily. He still has retractions of accessory muscles, prolonged expiratory phase, and decreased air movement at the bases of both lungs. A dose of magnesium sulfate (2000 mg intravenously × 1) is given and initiated on noninvasive positive pressure ventilation with heliox. Despite all of the interventions, his oxygenation and ventilation is compromised; hence, the decision is made to place an endotracheal tube and initiate mechanical ventilation. Rapid sequence intubation is initiated with fentanyl, etomidate, and succinylcholine, and an endotracheal tube is successfully placed. What would be an appropriate continuous infusion regimen to provide analgesia and sedation for this child receiving mechanical ventilation?

ANSWER

Several options can be used for analgesia and sedation in this child. However, morphine should be avoided. Morphine should not be used because of the potential for histamine release exacerbating airway bronchospasm. Fentanyl or hydromorphone would be reasonable options for analgesia in a patient with asthma. Fentanyl might be the best choice because of its shorter half-life, but its high volume of distribution and lipophilicity may not be desirable in this child with obesity. As for sedatives, dexmedetomidine, midazolam, ketamine, and propofol are all reasonable options. Ketamine is the only drug with data to support its use for sedating patients with asthma. One retrospective study reported that intravenous ketamine given at 2 mg/kg × 1, followed by an infusion at 20–60 mcg/kg/minute, improved ventilation (e.g., improved partial pressure of oxygen/fraction of inspired oxygen ratio, lung compliance). Ketamine has bronchodilator properties, which would explain its success in patients with asthma. Dexmedetomidine, because of its lack of interference with the respiratory drive, may prove advantageous as a sedative in a patient with asthma and allowance for native respiratory drive to stay intact. Midazolam and propofol would be options in this child as well because they would provide titratable sedation (e.g., from light to deep) if the situation continued to deteriorate (e.g., continuous neuromuscular blockade is introduced). Midazolam and propofol are not without risks; both adversely affect the cardiorespiratory system, and propofol has the risk of PRIS with high doses and long durations of use. One other layer of complexity in this sedation conundrum is the dosing of these agents in a child with obesity. Ketamine, dexmedetomidine, and midazolam should be dosed on ideal body weight, whereas fentanyl uses an adjusted body weight for dosing.

1. Youssef-Ahmed MZ, Silver P, Nimkoff L, et al. Continuous infusion of ketamine in mechanically ventilated children with refractory bronchospasm. Intensive Care Med 1996;22:972-6.
2. Ross EL, Heizer J, Mixon MA, et al. Development of recommendations for dosing of commonly prescribed medications in critically ill obese children. Am J Health Syst Pharm 2015;72:542-56.

mechanical ventilation in the intervention group was unmet (median 6.5 vs. 6.5 days, p=0.61). However, the intervention group did have fewer opioid days (9 vs. 10 days, p<0.05) and less exposure to different sedative classes (two vs. three classes, p<0.05) than the standard-of-care patients. In addition, the intervention group spent more time awake and calm than the control group (86% vs. 75% of the day, p<0.05). The intervention group reported more days of pain scores at or above 4 (50% vs. 23%, p<0.05) and more agitation (60% vs. 40%, p<0.05) than the standard-of-care group. The authors concluded that alertness resulted in more reported pain and agitation, but also reaffirmed that having an arousable and calm, critically ill, mechanically ventilated child is achievable (Curley 2015).

A secondary analysis of this RESTORE data set investigated the role of dexmedetomidine in sedating critically ill children. Almost 50% of the control group (n=596) received dexmedetomidine, with 11% (n=138) receiving dexmedetomidine as the primary sedative agent, 23% (n=280) as a secondary agent, and 15% (n=178) as a peri-extubation agent. In the intervention group, 23% of the population (n=287) received dexmedetomidine, with only 55 of the subjects receiving it per protocol as a peri-extubation agent. Increasing the use of dexmedetomidine as a primary and secondary agent was a general trend during the study. Children in the control group who received dexmedetomidine as a peri-extubation agent had the shortest duration of mechanical ventilation (median 4.4 days) compared with when dexmedetomidine was used as the primary agent (median 5 days) and secondary agent (median 9.9 days). This discrepancy may be explained by the secondary agent group having higher severity of illness scores and more severe lung disease. The dexmedetomidine for peri-extubation and primary agent groups had similar median opioid and benzodiazepine cumulative drug exposure (opioids: 12.5 vs. 12.8 mg/kg; benzodiazepines: 13.1 vs. 9.7 mg/kg). However, the secondary group had a markedly higher median exposure of opioids (53.2 mg/kg) and benzodiazepines (42.3 mg/kg). The authors concluded that peri-extubation dexmedetomidine helps facilitate ventilator weaning. In addition, dexmedetomidine as a primary agent is better used in the less critically ill patient than in the severely critically ill patient. Secondary use of dexmedetomidine did not offer much clinical benefit, according to the results of this subanalysis (Grant 2016).

Another sedation strategy in its infancy is analgosedation. This analgesia-based sedation is aligned with the adult PAD guidelines, which recommend minimizing sedatives such as benzodiazepines to help decrease the risk of delirium. Untreated or undertreated pain in critically ill adults has been identified as a cause of agitation, and optimizing comfort with an analgesic seems appropriate. Although the evidence is of moderate quality in adults, analgosedation is a compelling sedative-sparing strategy as more data analyses show the negative impact of sedative-hypnotic regimens on clinical outcomes and patient quality of life (Barr 2013). However, no pediatric analgosedation studies have been published to date; therefore, this strategy for prolonged sedation should not be considered standard of practice in children.

Monitoring and Assessment

Similar to monitoring analgesia, observing for drug toxicities and adverse events as well as assessing the efficacy of therapy is imperative in monitoring prolonged sedation. Heart rate, heart rhythm, respiratory rate, blood pressure, and oxyhemoglobin saturations must be monitored continuously or often. Further monitoring with laboratory values such as blood gases, serum electrolyte panels, and hepatic or renal function tests may be needed, depending on the sedatives being used.

Many assessment tools are available to evaluate the level of consciousness in a sedated patient. Several of the pediatric assessment tools for sedation are borrowed from adult versions, but with additional age- and development-appropriate anchor points (Table 1-5). All sedation scales assess the level of consciousness through a series of questions, observations, and exposure to noxious and non-noxious stimuli at dedicated time intervals. The Ramsay scale is a 6-point scoring system designed as a test of arousal and responsiveness in adults, though it has not been validated in children (Ramsay 1974). The University of Michigan Sedation Scale is a five-level observational tool validated for short, procedural-related observations with limited applicability in prolonged sedation scenarios (Malviya 2002). The Richmond Agitation-Sedation Scale (RASS) is 10-point scoring tool commonly used in pediatric patients, but until recently, it had been validated only in critically ill adults (Kerson 2016; Ely 2003; Sessler 2002). The RASS, favored for its clear and easily navigated assessment, encompasses the entire spectrum of consciousness from deeply sedated to very agitated (Kerson 2016). The State Behavioral Scale (SBS) is an eight-dimension assessment tool that provides up to five levels to each dimension assessment (Curley 2006). The COMFORT scale, a five-level, nine-dimension tool that evaluates distress in PICU patients, has come under scrutiny because of the physiological variables included in the assessment (Ambuel 1992). The COMFORT-behavior scale was created to remove the physiological variables (heart rate, blood pressure) that were previously included in the COMFORT assessment. Heart rate and blood pressure were removed because they poorly correlated with the behavioral assessment, especially in a hemodynamically unstable patient receiving vasoactive infusions (Ista 2005). These assessments all have an observational component of the scoring tool, but some introduce an intervention before the observation. This progressive stimulus is necessary to complete

Table 1-5. Comparison of Sedation Scales

	Validated Population		Domains for Assessment			
Name of Instrument	Age	Patient Variables	Consciousness	Agitation	Respiratory	Pain
COMFORT	Newborn – 17 yr	+ ventilator	X	X	X	X
COMFORT-B	Newborn – 18 yr	± ventilator ± sedatives	X	X	X	X
Ramsay	Adults	± ventilator + sedatives	X	X		
RASS	Adults 2 mo – 21 yr	± ventilator ± sedatives	X	X	X	
SBS	6 wk – 6 yr	+ ventilator + sedatives	X	X	X	
UMSS	4 mo – 5 yr	+ sedatives	X	X		

COMFORT-B = COMFORT-behavior; RASS = Richmond Agitation-Sedation Scale; SBS = State Behavioral Scale; UMSS = University of Michigan Sedation Scale.

the evaluation for the Ramsay scale and SBS. However, the provocation may not be desirable, especially if assessing an already agitated or hemodynamically tenuous patient.

UNTOWARD EFFECTS OF ANALGESIA AND SEDATION

When recalling the untoward effects of analgesia and sedation, hemodynamic compromise, respiratory depression, opioid-induced constipation, and nausea and vomiting come to mind. Iatrogenic withdrawal syndrome is also of concern with prolonged, continuous exposure to these agents (e.g., opioids, benzodiazepines, barbiturates, and dexmedetomidine). Abrupt discontinuation after such exposure may activate this withdrawal syndrome. Other chapters in this series will examine iatrogenic withdrawal syndrome. Other than acute adverse drug events and withdrawal, exposure to analgesics and sedatives has many protracted effects.

Hyperalgesia

Opioid-induced hyperalgesia has been described in both human and animal models with various types of pain. Hyperalgesia is an increased sensitivity to pain, and in opioid-induced hyperalgesia, opioids are thought to worsen pain through a paradoxical response to painful stimuli (Roeckel 2016). The mechanism is theorized to be from sensitization of the primary afferent neurons, enhanced glutamate release at the primary afferent neurons, hyperexcitability of the neurons, and release of excitatory neurotransmitters (Anand 2010). Hyperalgesia is a clinical diagnosis of increased pain perception despite increasing opioid exposure. Opioid-induced hyperalgesia differs from opioid tolerance, given that tolerance has a decreasing clinical effect with prolonged exposure. In addition, opioid-induced hyperalgesia differs from allodynia because allodynia describes a painful response induced by normally innocuous stimuli (Roeckel 2016). There is only one published report of opioid-induced hyperalgesia in a child. The patient with polyarticular juvenile idiopathic arthritis was experiencing refractory pain with escalating opioid doses and allodynia. With a taper and eventual discontinuation of the opioids, pain alleviation was reported (Vijayan 2012).

Prevention and treatment of hyperalgesia is not well understood. Some approaches to relieve symptoms have been documented in case reports. Removing the offending opioid, rotating to a different opioid, and using a longer-acting opioid have been executed with success. Adding low-dose ketamine (0.25–5 mg/kg), an *N*-methyl-d-aspartate (glutamate) receptor antagonist, has also been successful in some cases (Anand 2010). With the paucity of pediatric hyperalgesia literature, this phenomenon is not currently recognized as an issue in pediatric patients. However, with its increased recognition in adult patients and the changing landscape for analgesia and analgosedation, the conversation about opioid-induced hyperalgesia will likely increase.

Delirium

Delirium is acute brain dysfunction manifested by changes and fluctuations in cognition and attention. Symptoms manifest as hyperactive (e.g., restless, agitated, emotional liability), hypoactive (e.g., somnolence, withdrawal from environment), or mixed delirium. Delirium is recognized as an adverse consequence of critical illness in adults and children alike. The

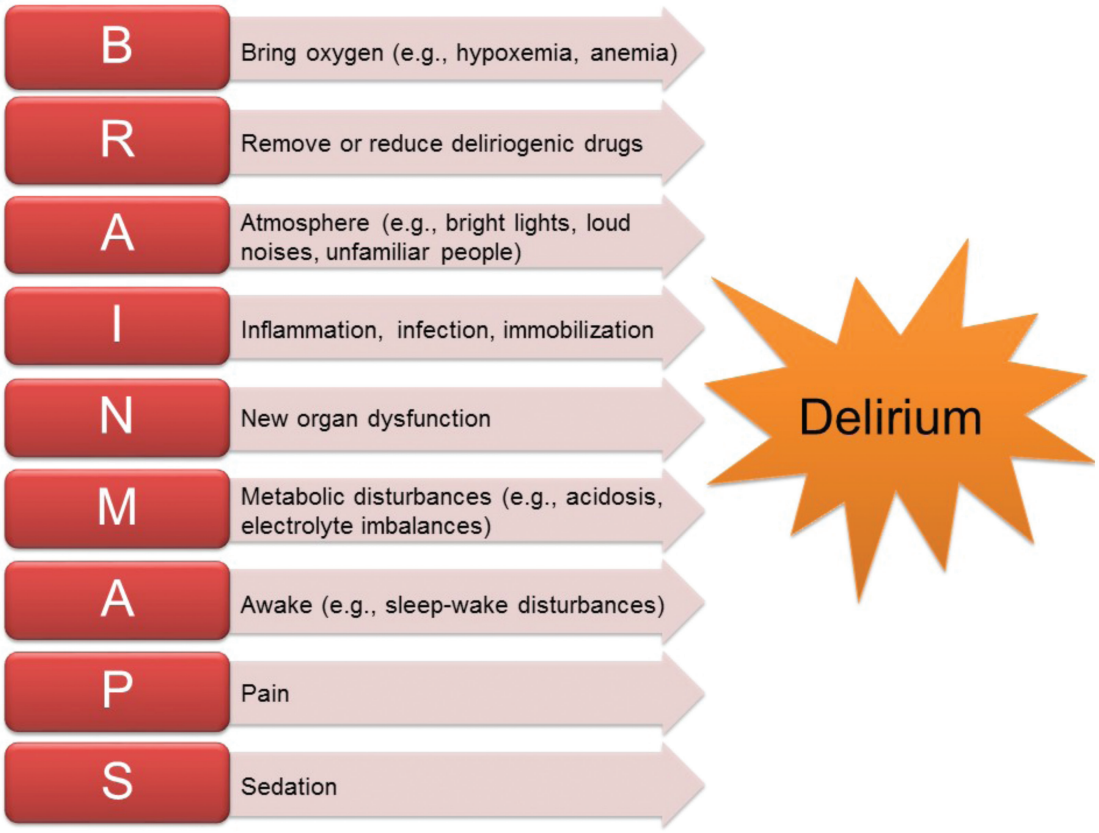

Figure 1-1. Evaluation of potential explanations for delirium.

Information from Pediatric Road Map.

largest pediatric delirium study had a point prevalence of 25% across all studied institutions and a median institutional prevalence of 23.3% (interquartile ratio 20%–35.4%, p=0.038) (Traube 2017). Several risk factors have been identified (e.g., severity of illness, exposure to certain medications, and disruption of sleep-wake cycles) (Silver 2015) (Figure 1-1). In the point prevalence study, medications appeared to contribute to delirium, with narcotics, benzodiazepines, and antiepileptic drugs identified. Age younger than 2 years (adjusted OR 0.7; 95% CI, 0.5–1), use of physical restraints (adjusted OR 4; 95% CI, 2–7.7), and use of vasopressors (adjusted OR 2.4; 95% CI, 1.5–3.8) were also identified as contributing factors. After 5 days in the PICU, prevalence increased from 20% to 37% (p<0.001) (Traube 2017).

Adult delirium data analyses have shown negative long-term consequences in critical care survivors resulting in cognitive dysfunction, increased length of stay, and even mortality, as well as an increased financial burden to the health care system (Barr 2013). In a recent study, total costs of a PICU stay were higher in children who had delirium at any time during admission than in those who did not (median $18,831 vs. $4802; p<0.05), with the daily PICU cost reflecting this trend as well (median $2645 vs. $1701; p<0.05) (Traube 2016). Delirium significantly affects the health care system.

To prevent or treat delirium, a clinician must be able to recognize the signs and symptoms. The gold standard for diagnosing delirium is an evaluation completed by a psychiatrist. However, psychiatry resources are not available in all locations at all times. Therefore, bedside tools were developed to allow non-psychiatry clinicians to complete the delirium assessment (Table 1-6). The Delirium Rating Scale, 1988 (DRS-88) was the first tool for hospitalized patients to detect hyperactive delirium symptoms (Trzepacz 1988). This scale was revised in 1998 to help discern between delirium and psychiatric disorders (Trzepacz 2001). The Pediatric Anesthesia Emergence Delirium (PAED) tool was created to detect postoperative emergence delirium in children but was not applied to other hospitalized children (Sikich 2004). In 2008, the adult confusion assessment method for ICU (CAM-ICU) tool was adapted for critically ill pediatric patients and renamed the pediatric confusion assessment method for ICU (pCAM-ICU). This was the first pediatric bedside tool that could detect symptoms of delirium in patients 5 years

Table 1-6. Comparison of Pediatric Delirium Screening Tools

	DRS-88	DRS-R-98	PAED	pCAM-ICU	psCAM-ICU	CAPD
PICU population (n)	Med/surg (154)	Med/surg (154)	Med/surg[a] (154)	Med/surg, cardiac (68)	Med/surg, cardiac (300)	General (111)
Age (yr)	1–17	1–17	1–17	≥ 5	0.5–5	Birth – 21 yr
Include mechanical ventilation?	No	No	No	Yes	Yes	Yes
Include developmental delay?	No	No	No	No	No	Yes
Type of delirium	Hyperactive	Hyperactive	Hyperactive	Hyperactive Hypoactive	Hyperactive Hypoactive	Hyperactive Hypoactive
No. of questions or domains	10	16	5	4	4	8
Administering provider	Psychiatrist	Psychiatrist	Anesthesia	Bedside[b]	Bedside[b]	Bedside[b]

[a]Included postoperative patients, not PICU patients.

[b]Bedside provider includes nurse, advanced practice provider, and physician.

CAPD = Cornell Assessment of Pediatric Delirium; DRS-88 = Delirium Rating Scale, 1988; DRS-R-98 = Delirium Rating Scale, Revised, 1998; IRR = interrater reliability; PAED = Pediatric Anesthesia Emergence Delirium; pCAM-ICU = pediatric confusion assessment method for the ICU; psCAM-ICU = preschool confusion assessment method for the ICU.

and older (Smith 2011). To fill the age gap left by the first version of the pCAM-ICU, the preschool confusion assessment tool for ICU (psCAM-ICU) was validated in children 6 months to 5 years of age (Smith 2016). The Cornell Assessment of Pediatric Delirium (CAPD) is an adaption of the PAED with additional questions to detect hypoactive delirium. The CAPD includes developmental anchor points for all ages, negating an age limitation (Traube 2014). A recent publication showed much overlap in the symptoms of delirium and iatrogenic drug withdrawal syndrome in children. Although these screening tools help assign objectivity to the assessment, the syndromes are not mutually exclusive, and the authors warn providers not to overlook the clinical context (Madden 2017).

Prevention and treatment of delirium are evolving. The adult PAD guidelines recommend normalizing patient environments, promoting sleep, and performing early mobilization. One center showed that the incidence of delirium in the PICU decreased from 19.3% to 11.8% with the successive rollout of delirium screening, sedation, and early-mobilization protocols (Simone 2017). The PAD guidelines recommend against pharmacologic therapy for preventing or treating delirium because data are sparse to support medication use (Barr 2013). Prevention of delirium has been investigated in the pediatric anesthesia literature with respect to anesthesia emergence, as well in the adult critically ill population with dexmedetomidine use. Treating the symptoms of delirium with typical antipsychotics (e.g., haloperidol) and atypical antipsychotics (e.g., risperidone, quetiapine, olanzapine) has been reported in both the adult and the pediatric delirium literature; however, well-designed, well-controlled trials are lacking to support the safe and effective use of these agents. These medications are not without acute risk, most notably QT prolongation, dystonic reactions, and neuroleptic malignant syndrome. Therefore, if pharmacologic treatment of a pediatric patient for delirium becomes an intention, this decision should be entered into thoughtfully and with a specific monitoring plan outlined.

Neurodevelopmental Outcomes

Currently, neurodevelopmental outcomes of children exposed to short- and long-term analgesics and sedatives are unknown. A growing body of literature aims to describe the effect of drug exposure on a child's motor and cognition development. In a study of infants younger than 8 weeks with perioperative analgesia and sedation exposure, drug exposure was not associated with negative neurodevelopmental outcomes 2 years after cardiac surgery (Guerra 2011). Mechanically ventilated preterm infants with a median gestational age of 29 weeks who received morphine had a decreased IQ early in life, but by 5 years of age, this effect had disappeared (de Graaf 2011). In a neuropsychological follow-up study of childhood meningococcal survivors exposed to analgesia and sedation in the PICU, the children had poor test outcomes at least 4 years after admission. Full-scale IQ, verbal and vocabulary IQ, and visual attention and executive functioning were all adversely affected ($p<0.05$). A multivariate analysis showed that opioids were associated with the poor cognitive outcomes after controlling for many confounding factors (van Zellem 2014).

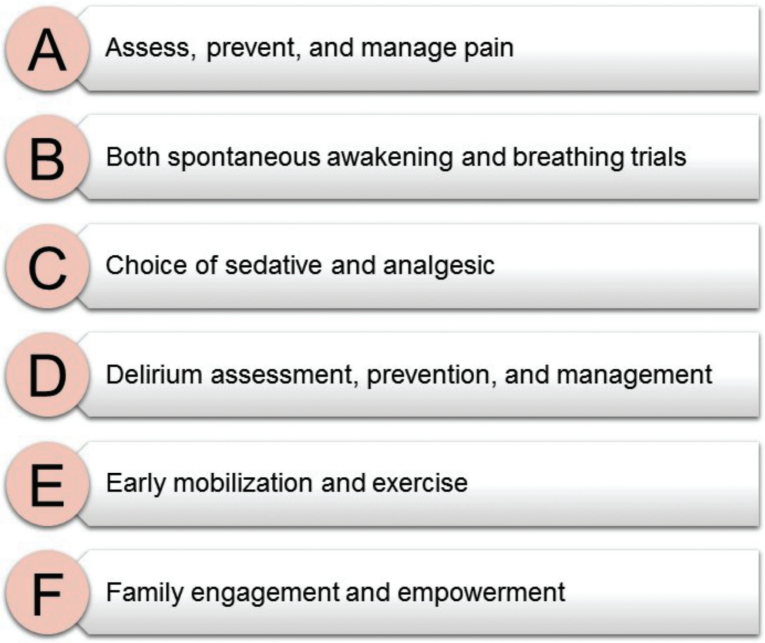

Figure 1-2. The ABCDEF care bundle.

One limitation to studying neurocognitive outcomes is the heterogeneity of the pediatric population, which may preclude classifying patients into homogeneous groups for more in-depth investigation. In addition, follow-up may be more difficult because many childhood hospitalizations are acute and limited and do not require recurring care. There is a growing interest in the pediatric critical care discipline to address the unanswered questions of growth and development after critical illness and interventions, including prolonged analgesia and sedation. Some children's hospitals are responding to this need by creating longitudinal clinics to assist with follow-up.

Another initiative that is growing to address neurocognitive patient outcomes is the development of the ABCDEF care bundle in the ICU setting (Figure 1-2). Each arm of bundle can help to reduce and prevent delirium, and enhance rehabilitation of the adult ICU patient. The combination of all the arms of ABCDEF care bundle is thought to optimize the climate for successful ICU liberation. Pediatric centers are actively working to implement similar bundles; therefore, pediatric data supporting ABCDEF care bundles are forthcoming.

CONCLUSION

Providing hospitalized children with safe, effective, and appropriate analgesia and sedation is complex. However, provision of analgesia and sedation is necessary to meet the expectations of the patient and caregiver in pain relief and level of sedation as well as to optimize the healing environment. Challenges with providing this care include understanding the ontogeny of the disposition and clearance mechanisms in pediatric patients as well as how obesity and other illnesses contribute to medication pharmacokinetics. Analgesics and sedatives carry a high risk of patient harm

Practice Points

- **Each analgesic and sedative medication has a unique pharmacokinetic profile. The agent-specific adverse events with administration (e.g., fentanyl and rigid chest syndrome, propofol and PRIS) and the ways in which to alleviate and avoid them must be understood and appreciated.**
- **Appreciation of the developmental changes in children is important in order to optimize analgesia and sedation and avoid toxicities that may lead to serious adverse effects.**
- **Obesity complicates drug dosing of these high-risk medications; thus, dosing on the basis of ideal, adjusted, or total body weight must be considered.**
- **Combination or multimodal analgesic therapy is preferred for postoperative analgesia.**
- **Self-reported pain assessment is preferred to observational pain assessment tools.**
- **When choosing sedatives for procedural sedation, onset and duration of action are important, as are the adverse effects on the cardiorespiratory system. If there is a potential to adversely affect hemodynamics, respiratory drive, or airway patency, patients must be sedated in a safe environment with appropriate rescue equipment and providers who are skilled in managing cardiorespiratory emergencies.**
- **Sedation and delirium assessments are available for children. Practitioners must understand the limitations of these tools to make appropriate assessments.**

if used inappropriately. Pharmacists must be the health care providers to create the analgesic and sedation plan because of their extensive training in pharmacology and medication safety management.

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Self-Assessment Questions

1. A 14-year-old boy presents to the pediatric ED after being ejected from a motor vehicle during a crash. There is concern for traumatic brain injury and suspected elevated intracranial pressure. The patient's Glasgow Coma Scale score is 8. Vital signs are heart rate 102 beats/minute, blood pressure 82/46 mm Hg, and respiratory rate 6 breaths/minute. Rapid sequence intubation will be performed. Which one of the following is the best sedative to recommend for this patient?

   A. Etomidate
   B. Lidocaine
   C. Midazolam
   D. Propofol

2. A 6-year-old girl with medulloblastoma is undergoing an MRI of the head today in the outpatient radiology suite. She is hemodynamically stable, with no signs or symptoms of infection, and has her tunneled central venous line in place. Her allergies include eggs and peanuts. The family says that she has high anxiety in closed, dark spaces and is requesting medication to alleviate her anxiety. The sedation team physician wants this patient to remain extubated during the procedure. Which one of the following is best to recommend for this patient?

   A. Propofol 250-mcg/kg/minute intravenous infusion
   B. Midazolam 0.2 mg/kg intranasally
   C. Midazolam 0.5 mg/kg intranasally plus ketamine 5 mg/kg intranasally
   D. Midazolam 0.1 mg/kg intravenously plus dexmedetomidine 0.5 mcg/kg/hour intravenous infusion.

3. An 18-month-old boy is admitted to the pediatric ICU (PICU) with a metabolic crisis of a known fatty acid oxidation disorder. He is hemodynamically unstable and receiving a dopamine infusion through a peripheral venous line. A central venous line will be placed by the PICU team. Which one of the following is the best option for procedural sedation in this patient?

   A. Etomidate
   B. Ketamine
   C. Midazolam
   D. Propofol

4. A 14-month-old boy is admitted to the PICU with respiratory syncytial virus bronchiolitis and acute respiratory failure. He is placed on mechanical ventilation and remains hemodynamically stable without the need for vasoactive support. Because of ventilation issues, this patient needs to be initiated on a continuous neuromuscular blockade infusion to facilitate ventilator synchrony. Which one of the following sedatives is best for this patient?

   A. Morphine
   B. Fentanyl
   C. Midazolam
   D. Dexmedetomidine

5. One pediatric intensivist is adamant about using atropine as a pretreatment for intubating all infants. Which one of the following statements best supports the consensus of the validity of this practice?

   A. Evidence does not support the use of atropine in any situation.
   B. Atropine decreases bradycardic events with intubation.
   C. No increase in arrhythmias was noted in the untreated atropine group.
   D. Adverse effects of atropine outweigh the benefit of using it during intubation.

6. A 5-year-old girl (height 47 inches [120 cm], weight 40 kg) is admitted to the PICU after cardiac arrest at home. She is noted to have seizure activity after return of spontaneous circulation. Her seizures are refractory to first- and second-line therapies, so she is going to be initiated on pentobarbital to induce burst suppression on the electroencephalogram. The medical team asks which weight to use to dose her pentobarbital. The usual starting pentobarbital dose is a bolus of 5 mg/kg, followed by infusion at 1 mg/kg/hour. Which one of the following is the most appropriate pentobarbital dose for this patient?

   A. 90 mg × 1, followed by 18-mg/hour infusion
   B. 120 mg × 1, followed by 24-mg/hour infusion
   C. 150 mg × 1, followed by 30-mg/hour infusion
   D. 200 mg × 1, followed by 40-mg/hour infusion

7. A 5-month-old infant (weight 6 kg) with trisomy 21 presents after an atrioventricular canal repair. He transitioned out of the operating room on a 2-mcg/kg/hour fentanyl infusion. The nurse reports that he is very agitated and irritable and moving all of his extremities on the current fentanyl dose. He is receiving a low dose of milrinone but no other vasoactive agents. He remains tachycardic, but his vital signs are otherwise within normal range. The medical team would like to extubate him in 24 hours but would like to offer additional sedation in the interim. Which one of the following infusions is best to recommend for this patient?

   A. Increased fentanyl
   B. Dexmedetomidine
   C. Midazolam
   D. Pentobarbital

8. A 13-year-old female adolescent was admitted with septic shock and acute respiratory failure and is now off vasopressors. She is being transitioned off fentanyl and dexmedetomidine infusions after being sedated and on the ventilator for 4 days. Which one of the following most increases this patient's risk of delirium?

   A. Age
   B. Dexmedetomidine infusion
   C. Duration of stay
   D. Use of vasopressors

9. A 9-year-old girl is transitioning off a fentanyl infusion after being sedated and on the ventilator for 8 days. Methadone has been initiated for withdrawal attenuation. Other pertinent medications include oral ciprofloxacin for treatment of a UTI, intravenous famotidine for stress-related mucosal disease, and intravenous ondansetron as needed for nausea and vomiting (one dose in 24 hours). She is awake in the evenings, asleep throughout the daytime, and less engaged with her environment and her family. She becomes combative with the bedside caregivers at times. The medical team is concerned for delirium. Which one of the following is best to recommend for this patient?

   A. Provide an atypical antipsychotic
   B. Institute day- and nighttime activity schedule
   C. Add a dexmedetomidine infusion
   D. Add lorazepam intravenously as needed

10. A patient has opioid-induced pruritus with intravenous morphine for postoperative pain management. Which one of the following is best for this patient?

    A. Initiate diphenhydramine
    B. Change to intravenous fentanyl
    C. Change to enteral morphine
    D. Initiate a dexmedetomidine infusion

11. A 16-year-old male adolescent is admitted to the PICU after a motor vehicle crash with a traumatic brain injury. He is 24 hours into sedation with propofol so that frequent neurological examinations can be done. Which one of the following monitoring values would be most appropriate to detect the life-threatening adverse event of propofol-related infusion syndrome at this time?

    A. Serum phosphorus
    B. Arterial blood gas
    C. Creatine phosphokinase
    D. Serum triglycerides

12. An 8-year-old boy with acute myeloid leukemia presents to the ED with febrile neutropenia, septic shock, and respiratory failure. The decision is made to intubate this patient and place him on mechanical ventilation. The boy is intubated with rapid sequence intubation using fentanyl, etomidate, and succinylcholine. Which one of the following adverse effects would be most likely after this patient's rapid sequence intubation drug exposures?

    A. Tachycardia
    B. Hypertension
    C. Adrenal suppression
    D. Hyperventilation

Questions 13–15 pertain to the following case.

J.M. is an 8-year-old, mechanically ventilated boy with trisomy 21. He is admitted to the PICU with acute respiratory failure. The nurse reports increased agitation despite escalating continuous infusion of both the opioid and the benzodiazepine, with extra bolus doses given of each.

13. J.M.'s medical team has high suspicion for delirium. Which delirium screening tool would be most appropriate for J.M.?

    A. PAED (Pediatric Anesthesia Emergence Delirium)
    B. Cornell Assessment of Pediatric Delirium (CAPD)
    C. Preschool confusion assessment method for ICU (psCAM-ICU)
    D. Delirium Rating Scale, 1988 (DRS-88)

14. Which one of the following pain scales would be most appropriate for J.M.?

    A. VAS
    B. FACES
    C. N-PASS
    D. FLACC

15. Which one of the following sedation scales would be most appropriate for J.M.?

    A. University of Michigan Sedation Scale
    B. Richmond Agitation-Sedation Scale (RASS)
    C. State Behavioral Scale (SBS)
    D. N-PASS