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Pediatric Perioperative Clinical Pharmacy Practice: Clinical Considerations and Management: An Opinion of the Pediatrics and Perioperative Care Practice and Research Networks of the American College of Clinical Pharmacy

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Pediatric perioperative clinical pharmacists are uniquely positioned to provide therapeutic and medication management expertise at a particularly vulnerable transition of care from the preoperative space, through surgery, and postoperative setting. There are many direct-patient care activities that are included in the role of the pediatric perioperative pharmacist, as well as many opportunities to develop effective, optimized, and safe medication use processes. This article outlines many of the areas in which a pediatric perioperative clinical pharmacist may intervene.

ABBREVIATIONS ASHP, American Society of Health-System Pharmacists; CAPD, Cornell Assessment of Pediatric Delirium; CHSPS, Children's Hospitals Solutions for Patient Safety; DOAC, direct oral anticoagulant; ERP, enhanced recovery pathway; FFP, fresh frozen plasma; INR, international normalized ratio; ISMP, Institute for Safe Medication Practices; KIDs List, Key Potentially Inappropriate Drugs in Pediatrics; LAST, local anesthetics systemic toxicity; LMWH, low-molecular-weight heparin; LP, lumbar puncture; NSAID, non-steroidal anti-inflammatory medication; PCA, patient-controlled analgesia; pCAM-ICU, pediatric Confusion Assessment Method for the Intensive Care Unit; PCC, prothrombin complex concentrate; PONV, postoperative nausea and vomiting; POVOC, postoperative vomiting in children; PPA, Pediatric Pharmacy Association; rFVIIa, recombinant activated factor VII; UFH, unfractionated heparin; VTE, venous thromboembolism; VWD, von Willebrand disease; VWF, von Willebrand factor

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Introduction

Clinical pharmacy practice within pediatric perioperative care is an evolving subspecialty. Advancement of invasive and minimally invasive surgical techniques and materials, coupled with strategies to decrease operative stress and improve multidisciplinary perioperative care coordination, has contributed to improved outcomes in children.[1] Pharmacists are poised to provide critical recommendations and serve as drug therapy and medication safety experts to this vulnerable population throughout the surgical continuum. Pediatric perioperative clinical pharmacists may participate in a variety of team activities, such as stewardship for fluids, antimicrobial agents, blood factor products, postoperative nausea and vomiting (PONV) prevention and treatment, and assessment of pain and analgesic response. All of these activities can contribute to improved clinical outcomes and cost savings to the patient and the health system.[2,3]

General Pediatric Pharmacy Principles in Perioperative Care

Providing medical care to children requires appreciation of the role that growth and development play not only in physical attributes and cognition, but also in normal physiologic functions. Heart rate, respiratory rate, and blood pressure in children differ from the normal values of adults. Notably higher heart rates and respiratory rates are observed in neonates and infants, and these values reach adult heart and respiratory rates by adolescence. Hypotension is typically defined as a systolic blood pressure below the fifth percentile for age or as <60 mm Hg for term neonates, <70 mm Hg for infants, <70 mm Hg + (2 × age in years) for children 1 to 10 years of age, and <90 mm Hg for children older than 10 years.[4] Values are even lower for premature neonates.

The pharmaceutical care of children goes beyond providing fractional doses for the smaller sized patient.[5] Drug pharmacokinetics, dosing, and medication delivery

and safety considerations in children differ across the age continuum from adult patients.

Pharmacokinetic properties of drugs continue to change, and the child's organ and biotransformation systems continue to develop after birth.[6] Volume of distribution changes over time, with neonates and infants having relatively high total body water spaces and larger extracellular fluid compartments. This volume of distribution coupled with lower circulating plasma proteins may increase the free fraction of drugs in the neonate and young infant. Total body water and body fat in children approximate adult values typically in the second decade of life. The capacity of drug metabolism varies by age as well. Phase I and II metabolizing enzymes develop at different rates in children. The neonate and infant are most susceptible to prolonged half-life of certain medications owing to delayed biotransformation. Glomerular filtration and tubular secretion are also delayed at birth, but approach adult capacity by the first year of life, and at times may exceed adults in the first decade of life.[6] Glomerular hyperfiltration or augmented renal clearance is also a phenomenon reported in critically ill children.[7]

Drug dosing in children is most often calculated as weight based (milligram per kilogram) up to the maximum adult dose (typically >40 kg). Pediatric patients often require the use of enteral liquid formulations owing to the small doses required and a lack of esophageal coordination to swallow tablets and capsules, which necessitates thoughtful formulary management in order to provide medication for children of all ages.[8] Additionally, intravenous products often need further dilution in order to provide a measurable dose. The Standardize4Safety Initiative, led by American Society of Health-System Pharmacists (ASHP), was a US Food and Drug Administration–funded medication safety project to develop and implement standard concentrations and dosing units of measure for intravenous continuous infusions and extemporaneously compounded oral liquids for pediatric patients.[9] Similarly, the Institute for Safe Medication Practices (ISMP) provides best practices for using smart infusion pump and automated dispensing cabinet technology that are applicable in centers caring for children.[10,11] Moreover, the ASHP–Pediatric Pharmacy Association (PPA) guidelines for providing pediatric pharmacy services in health systems outlines safe and effective means for satisfying the special needs of pediatric patients.[12] Pediatric perioperative clinical pharmacists use these recommendations from ISMP, ASHP, and PPA to assist in creating a safer medication use system for children in the perioperative space.

Enhanced Recovery Pathways

Enhanced recovery pathways (ERPs) are evidence-based strategies that combine many interventions throughout the perioperative period (pre-, intra-, and post-operative phases) to improve surgical outcomes, such as reduction in complications, length of stay, cost, and improvements in quality of life.[13] ERPs have been widely used in adult patients in recent decades, and their application to pediatric surgery is more nascent.[14] The most common adult surgeries for ERP implementation include colorectal, orthopedic, and cardiac, and additional pediatric procedures, such as neonatal surgery, are being explored.[15] Common elements of ERP include minimization of fasting, avoidance of hyperosmolar bowel preparation and routine placement of nasogastric tubes, early mobilization, and the implementation of multimodal, opioid-sparing analgesia.[14,16] Research on the contribution of other pharmacotherapy elements, such as prophylaxis for surgical site infections, venous thromboembolism (VTE), and PONV has been proposed.[17] Protocol implementation is best accomplished through a step-wise multidisciplinary quality improvement methodology.[13,14] The pediatric perioperative clinical pharmacist can advocate for evidence-based medication use throughout the different phases of ERP and encourage expansion of pediatric-specific ERP at their practice site.

Fluids and Electrolytes

The management of fluids and electrolytes is important for maintaining homeostasis in the pediatric patient, especially to prevent fluid overload in the preoperative and early postoperative periods.[18] The body's natural mechanisms for maintaining intravascular volume are often inadequate in the surgical patient owing to increased blood, renal, gastrointestinal, and insensible water losses. Goal-directed fluid management strategies facilitate correction of electrolyte deficits, prevent hypoglycemia and hyperglycemia, and ensure adequate intravascular volume to maintain cardiac output and tissue oxygen delivery.[19]

For minor procedures (i.e., those not requiring general anesthesia), a short fasting period will likely not require intravenous fluids for most healthy children. A major exception includes neonates who will require dextrose-containing fluids (most commonly Dextrose 10%) with electrolytes to prevent hypoglycemia if the fasting period is longer than the usual feeding interval (most commonly every 2 to 4 hours). Children undergoing longer and more complicated procedures will require intravenous fluids before, during, and after surgery. The fasting period prior to surgery may vary between centers and by surgery type, but is usually 6 hours for solid food, 4 to 6 hours for formula/breast milk in infants, and 2 hours for clear liquids. The most recent Cochrane review[20] concluded that in children with a normal aspiration/regurgitation risk, there was no apparent benefit to withholding clear oral fluids at 2 hours preoperatively compared with 6 hours or more, so clear oral liquids are often encouraged to reduce discomfort from hunger or thirst.

Maintenance fluid rates may be calculated a number of ways, including estimating calorie expenditure

Table 1. Holliday-Segar Formula[21]*

Body Weight, kg	Calculation
1–10	4 mL/kg/hr
10–20	40 mL/hr + 2 mL/kg/hr for each kg above 10 kg
>20	60 mL/hr + 1 mL/kg/hr for each kg above 20 kg

* This formula calculates the maintenance need for water in pediatric patients.

and body surface area. One of the most common and simplest methods is the Holliday-Segar method, also known as the "4-2-1 rule."[21] This calculation is shown in Table 1.

Neonates younger than 44 weeks' postmenstrual age will have differing fluid requirements based on age and other chronic conditions, with maintenance fluid requirements often ranging from 60 to 100 mL/kg/day in the first few days of life, up to 120 to 150 mL/kg/day or more thereafter.[22]

In addition to maintenance fluids, replacement of intravascular volume losses during surgery is required. This often ranges from 1 to 15 mL/kg/hr depending on the type of surgery, but may even be as high as 50 mL/kg/hr, for example, in premature neonates undergoing surgery for necrotizing enterocolitis due to significant trauma and ischemic bowel.[22,23] Maximal allowable blood loss for any surgery is calculated by using the following equation:

$$\text{Maximal allowable blood loss} = \left(\left(\text{Hb initial} - \text{Hb low}\right) \div \text{Hb initial}\right) \times \text{EBV},$$

in which "Hb initial" is starting hemoglobin, "Hb low" is the lowest acceptable hemoglobin threshold without red cell transfusion, and "EBV" is the patient's estimated circulating blood volume. Table 2 lists the estimated circulating blood volume by patient age. Surgeries associated with higher blood volume loss in children include cardiac, liver transplant, scoliosis, craniosynostosis, and trauma-related surgeries. In general for children, 1 mL of blood loss is replaced with 1 mL of colloid or 1.5 mL of crystalloid.[22]

Fluid selection is important for maintaining fluid, electrolyte, and glucose homeostasis. As mentioned previously, neonates and young infants will require generally Dextrose 10% or greater to prevent hypoglycemia. Older pediatric patients at high risk for hypoglycemia include those who have parenteral nutrition-dependence, certain endocrine disorders, low body weight, or longer surgery durations. In older infants and children, Dextrose 5% is appropriate in those with adequate nutritional status. Non-dextrose containing fluids (such as Lactated Ringer) or lower dextrose concentrations

Table 2. Estimated Circulating Blood Volume in Infants and Children[24]

Patient Age	Estimated Circulating Blood Volume, mL/kg
Preterm neonate	90–100
Term neonate	80
Infant > 3 mo	70

may be used intraoperatively to prevent hyperglycemia; however, dextrose-containing solutions should be used postoperatively to prevent hypoglycemia.[22,25] With regard to electrolytes, the American Academy of Pediatrics recommends that maintenance fluids for patients aged 28 days to 18 years be isotonic to prevent hyponatremia and include potassium and dextrose (for example, Dextrose 5% with 0.9% sodium chloride and potassium chloride 20 mEq/L).[19] Neonates may require hypotonic fluids (such as Dextrose 10% with 0.2% sodium chloride) owing to the immaturity of their kidneys and large free water needs. A reasonable approach for a neonate who is already stable on maintenance fluids would be to continue this fluid during surgery and add a balanced salt solution, colloid, or blood product when needed for replacement of fluid losses.

Overall, an awareness of the unique needs of pediatric and neonatal patients to maintain intravascular volume, euglycemia, and prevent electrolyte derangements is important for the pediatric perioperative clinical pharmacist to ensure optimal outcomes for patients.

Antimicrobials

The pediatric perioperative clinical pharmacist can play an active role in antimicrobial stewardship through recommendations and optimal dosing and timing of perioperative antibiotics. In 2013, ASHP, the Infectious Diseases Society of America, Surgical Infection Society, and Society of Healthcare Epidemiology of America published a clinical practice guideline for antimicrobial prophylaxis in surgery, with cefazolin as the preferred prophylaxis agent in most cases.[26] The guidelines offer drug selection and dosing in adults (>18 years of age) and pediatric patients aged 1 to 18 years. From a stewardship perspective, Laituri and Arnold[27] provide a cogent summary of antibiotic prophylaxis in surgical neonates. Special consideration for this patient population includes the higher volume of distribution of water-soluble antimicrobials and the potential for altered elimination and prolonged half-lives from immature renal and hepatic routes. However, the same administration principles apply to children of all ages: the antimicrobial agent should be initiated within 60 minutes of surgical incision; additional intraoperative dosing is indicated if the procedure duration exceeds 2 half-lives of the antibiotic or there is significant blood loss.[26]

Table 3. Risk Factors for PONV in Pediatric Patients[29]

Factor
Surgery lasting more than 30 min
Age greater than 3 yr
Strabismus surgery, adenotonsillectomy, hernia repair, orchiopexy, and penile surgery
History of or a relative with PONV

PONV, postoperative nausea and vomiting

Postoperative Nausea and Vomiting

In 2020, an updated consensus guideline for the management of PONV was released. This version updated existing recommendations for risk stratification, multimodal PONV prevention and treatment strategies for both adults and children, but also offers guidance of PONV within recovery pathways.[28] Risk factors for PONV in pediatric patients are listed in Table 3. On average, children have twice the risk of developing PONV when compared with adults. The added risk for each additional PONV risk factor is 10%, 30%, 55%, and 70%, respectively.[29] Avoiding or minimizing exposure to volatile anesthetics, anticholinesterases, and postoperative opioids may reduce baseline risk, with the pediatric perioperative clinical pharmacist playing an integral role of recommending non-opioid and opioid multimodal analgesic therapy options. Liberal fluid therapy (e.g., 30 mL/kg Lactated Ringer injection) may also reduce baseline risk of PONV.[28] Antiemetic prophylaxis is recommended at all risk stratifications, but multimodal therapy with a $5HT_3$-antagonist and dexamethasone is recommended for medium and high-risk patients. Rescue treatment in the guideline includes droperidol, promethazine, and metoclopramide. However, the ISMP in the Targeted Medication Safety Best Practices from 2018–2019 recommended to eliminate injectable promethazine from hospitals.[10] Promethazine injection has a black box warning for fatal respiratory depression in children younger than 2 years, and additionally can cause chemical irritation and severe tissue injury from perivascular extravasation or if given via intra-arterial injection. Moreover, dopamine antagonists (metoclopramide and promethazine) were featured in the *Key Potentially Inappropriate Drugs in Pediatrics* (KIDs List) with the recommendation to avoid intravenous use of these agents in infants and use caution in children owing to increased risk of respiratory depression, extravasation, and death.[30] The pediatric perioperative clinical pharmacist can aid in the selection of patient-specific prophylactic PONV therapies by using the postoperative vomiting in children (POVOC) score and developing a risk mitigation and monitoring strategy for patients at high risk.[29] Rescue antiemetics in children would include a $5HT_3$-antagonist (e.g., ondansetron, granisetron, or dolasetron), an antihistamine (e.g., dimenhydrinate), or low-dose droperidol, if not administered previously.

Table 4. Examples of Pain Assessment Tools for Assessing Neonatal and Pediatric Patients

Tool	Patient Criteria
Premature Infant Pain Profile (PIPP)[35]	Preterm and term neonates, up to 12 mo
Crying, Requires increased oxygen administration, Increased vital signs, Expression, Sleeplessness Scale (CRIES)[36]	Preterm 32 wks gestation to term neonates, up to 6 mo
Neonatal Pain, Agitation, and Sedation Scale (NPASS)[37]	Preterm and term neonates 23–40 wks gestation
Neonatal Infant Pain Scale (NIPS)[38]	Newborn and infants, up to 12 mo
Revised Faces, Legs, Activity, Cry, Consolability (r-FLACC) tool[39]	Birth to 7 years of age; may be used in those who are cognitively impaired
Wong Baker Faces Pain Rating Scale (WBFPRS)[40]	3 to 4 yr or older, must understand pictures or colors
Faces Pain Scale–Revised (FPS-R)[41]	
Visual Analog Scale (VAS)[42]	> 8 yrs, must understand numbers
Numerical Rating Scale	

Pain and Analgesia

A major responsibility of those who care for children is eliminating or minimizing pain, when possible. Effective pain management involves an interdisciplinary team and includes pharmacologic, cognitive-behavioral, psychologic, and physical treatments.[31] Early effective pain treatment in postsurgical patients is safer and more efficacious than delayed treatment and reduces discomfort and possibly total analgesic exposure. Pediatric perioperative clinical pharmacists are uniquely poised to assist with drug selection to maximize efficacy and minimize adverse effects.

There are several unique considerations for perioperative pain management in pediatric patients including differences in how to assess pain and an inability for younger or cognitively impaired patients to vocalize pain. Additionally, emergence delirium, a transient state of marked irritation and disassociation after the discontinuation of anesthesia, is 3 to 8 times more likely in the pediatric postsurgical patient than in adults.[32] Anticholinergics, benzodiazepines, and opioids may precipitate emergence delirium. Often lasting 30 to 45 minutes after emergence, delirium complicates patient assess-

ment for adequate pain control and comfort. Generally, non-pharmacologic measures should be used to help reorient the child to their surroundings, and inclusion of the caregivers in this process can be helpful. Once the child is making purposeful movements, responding appropriately to their caregivers, and speaking appropriately (if able to assess, based on the patient's age), the ability to accurately assess pain control increases. Those patients who are refractory to non-pharmacologic measures can be treated with either typical or atypical antipsychotics, such as intravenous haloperidol or oral quetiapine.[33] The use of delirium scoring systems such as the pediatric Confusion Assessment Method for the Intensive Care Unit (pCAM-ICU) or Cornell Assessment of Pediatric Delirium (CAPD) may minimize exposure to antipsychotic agents.[34]

Pain Assessment. The appropriate scale to assess pain should be determined on the basis of the child's age, development, and institutional practice. There are numerous scales that exist to assess pain in neonatal and pediatrics patients (see Table 4).

Pharmacologic Treatments Based on Pain Severity. Plans for postoperative pain management should be discussed with the family/caregivers prior to surgery, including anticipated type, route, and duration of pharmacologic treatment.[31] Non-pharmacologic measures should be used in all patients when able because this may reduce the need for medications. Major classes of pharmacologic agents include opioids and non-opioid analgesics. Non-opioid analgesics, such as oral acetaminophen or oral ibuprofen, are likely adequate for procedures likely to produce only mild pain. Ibuprofen and other non-steroidal anti-inflammatory medications (NSAIDs) are generally used with caution in children younger than 3 to 6 months owing to an increased risk of renal toxicity, especially in patients with short postoperative monitoring periods or quickly discharged home. While data are limited, newer evidence has been published supporting the safety of ibuprofen in infants as young as 3 months who weigh at least 5 kg.[43,44] Ketorolac has been used safely in a variety of postoperative settings.[45] Data supporting ketorolac use in post–cardiac surgery pediatric patients demonstrate safety and efficacy in full-term infants as young as 14 days of life, although data in premature infants are more limited.[46–48] NSAIDs are associated with risk of gastrointestinal bleeding, renal toxicity, and reversible platelet inhibition. Maintenance of adequate hydration, avoidance of other nephrotoxins, and caution with thrombocytopenia is recommended. There is also concern for delayed bone healing in orthopedic surgery patients due to decreasing prostaglandins, which promote bone healing, as well as anastomotic leak and dehiscence in gastrointestinal surgeries. While some data demonstrate this risk in adult patients, these risks have not been demonstrated in pediatric patients, although studies are limited.[49,50]

In addition to use in mild pain, non-opioid analgesics should be routinely recommended when not contraindicated to reduce opioid exposure in those with surgeries resulting in moderate or severe pain.[31] These may be initiated in the preoperative or intraoperative periods. In addition to acetaminophen and NSAIDs, other non-opioids have also been studied in children for this indication with some success, including ketamine, dexmedetomidine, clonidine, and dexamethasone.[51] Enhanced recovery programs often include multimodal pain management strategies that could lead to duplicate indications for as-needed pain medications. The Joint Commission and Centers for Medicare and Medicaid Services recommend against therapeutic duplication, that is, use of 2 or more medications for the same indication. It is important for the pharmacist to keep in mind these standards of practice and intervene to avoid duplicate indications where more than 1 as-needed medication is prescribed for the same pain level score.

Common opioids used for moderate or severe pain include hydrocodone, morphine, fentanyl, and hydromorphone. Codeine, tramadol, and meperidine are not recommended for the postsurgical pediatric patient, as all 3 medications appear on KIDs List with concerns for respiratory depression.[30,52,53] Codeine and tramadol are specifically contraindicated in those younger than 12 years for postoperative pain management or children younger than 18 years following tonsillectomy and/or adenoidectomy. Oral options are preferred in moderate pain, when tolerated, and should start with the smallest effective dose with titration in small increments as necessary. Intravenous use is likely indicated in severe pain when regional analgesia is not appropriate or available. The most invasive surgeries will likely require continuous intravenous opioid infusions with additional intermittent opioid dosing. Careful attention should be paid to the dosing of opioids in children as well as the duration of effect, because this will affect the frequency of re-dosing. The ability to measure smaller doses in infants and young children can also be problematic, often requiring dilutions for younger patients or preference of one agent to another owing to the ability to measure doses. For example, a small volume of hydromorphone is typically required to administer an equi-effective dose owing to a higher concentration and potency, so morphine may be preferred in infants and small children owing to ease of measuring.

Adverse effects of each medication class should be anticipated and treated appropriately. These include assessment for pruritus and ensuring an adequate bowel regimen. Often combinations of polyethylene glycol 3350, sennasoids, and stool softeners are necessary to maintain bowel movements every 48 hours for those receiving opioid therapy. Observation of serious side effects, such as kidney injury from NSAIDs and respiratory depression from opioids, is also paramount. Intravenous naloxone should be readily available, such as in emergency carts or automated dispensing cabinets.[54]

Table 5. Summary of Safety Concerns and Potential Solutions for PCA in Postoperative Children[59]

Safety Concern	Possible Solution
Programming errors	• Smart pumps with barcode scanning • Computer provider order entry • Establishing reporting system • Regular audits
Programming protocol	• Standardization of protocol • Patient evaluation • Risk stratification • Staff education
Patient monitoring	• Assessment of sedation level • Smart pumps with oximetry and capnography
PCA by proxy (e.g., by caregiver)	• Radiofrequency thumb tags • Patient and family education
PCA with continuous infusion	• Establish pediatric pain services

PCA, patient controlled-analgesia

Dosing for naloxone will vary depending on whether full or partial reversal for respiratory depression is needed. Typically, full opioid reversal (naloxone 0.1 mg/kg/dose up to 2 mg) is less preferred in the postoperative setting for patients with symptoms of respiratory depression, because this will lead to uncontrolled pain after administration. A smaller dose for reversal of respiratory depression (0.001 to 0.005 mg/kg/dose up to 0.08 mg) with re-dosing every 2 to 3 minutes allows for titration to effect and decreases complete opioid blockade.[4,55]

Patient-Controlled Analgesia. Opioids also may be given by patient-controlled analgesia (PCA) in children and adolescents who are able to reliably assess their own pain and properly activate the PCA device. The most common opioids given by PCA include fentanyl, morphine, and hydromorphone. PCA use after surgery has been shown to decrease pain intensity and improve patient satisfaction.[56] Typically, 7 years is the youngest age for which PCA would be considered. PCA by proxy (i.e., parent or nurse-driven) analgesia in younger patients or those with cognitive impairment is controversial. It should only be used after significant education and institutional policies have been put in place to prevent inadvertent harm, including significant respiratory depression.[54,57] In addition, pediatric capnography can be implemented as an additional layer of safety in the pediatric patient setting when using PCA.[58]

The settings of a PCA include the drug used, bolus dose, lockout interval, hourly maximum dose, and, optionally, the basal rate. Basal rate infusions are not routinely used and should be reserved only for children who are opioid tolerant or with severe pain in intensive care units. Ensuring safe PCA use is important to reduce side effects, and pediatric perioperative clinical pharmacists should be involved in the development of standardized practices and policies to prevent errors. A summary of safety concerns and potential solutions can be found in Table 5.

Local Anesthesia Nerve Blocks. Regional anesthesia, including neuraxial (e.g., peripheral, caudal, and spinal) nerve blocks and lumbar and thoracic epidurals, is an increasingly used modality in pediatric patients. Neuraxial nerve blocks are typically placed under general anesthesia to improve intra- and post-operative pain control; however, the increase of ultrasound-guided placement has expanded the use of this modality into other spaces (e.g., emergency department, procedural units). Peripheral nerve blocks can be placed as a single injection or given as a continuous infusion through a catheter to the nerve site. The choice of agent and concentration required depends on the type and location of the block being performed. Guidelines on dosing and product choice for various blocks in pediatric patients have recently been published.[60] Local anesthetics can cause systemic toxicity (LAST) to the cardiac and central nervous systems. Signs of LAST include altered mental status, seizures, tremor, tachyarrhythmia, and cardiovascular collapse. Long-acting local anesthetics, such as bupivacaine and ropivacaine, have a greater propensity to cause systemic toxicity than lidocaine, and are a greater risk in infants younger than 6 months.[61] Management of LAST is largely supportive and often warrants activation of emergency code response. In neurologic or cardiovascular emergencies, intravenous lipid emulsion boluses (1–1.5 mL/kg over 1 minute every 3 minutes up to 3 mL/kg) and continuous infusions (0.25 mg/kg/min of lipid emulsion 20% titrated to blood pressure) can be given to help bind the local anesthetic.[62] Pharmacists working in perioperative spaces should collaborate with their anesthesia providers to determine when intravenous lipid emulsion should be administered and where it should be stored for emergent situations so that these clinical scenarios are safely managed immediately.

Table 6. Recommendations for Anticoagulant Holding Prior to Lumbar Puncture and Anticoagulant Reversal Strategy[65–67]

Medication	Elimination Half-Life	Planned Reversal Strategy	Emergent Reversal Strategy	Hold Prior to LP	First Dose After LP
LMWHs	4.5–7 hr	Hold 24 hr prior to surgery	1 mg protamine sulfate per 1 mg LMWH	Prophylaxis: 12 hr Treatment: 24 hr	4 hr (hold treatment dose 24 hr if traumatic LP)
Unfractionated heparin	1–2 hr	Hold 4–6 hr prior to surgery	Protamine sulfate (dose dependent on time since heparin administration)	4–6 hr	1 hr
Warfarin	Highly variable (20–60 hr), duration of effect 2–5 days	Hold 5 days before surgery, bridge with LMWH	Immediate: FFP or PCC* Long term: Vitamin K	5 days or until INR ≤1.4	12 hr
DOACs	9–24 hr	Hold 1–2 days before surgery, bridge based on expert opinion	FFP, PCC*, idarucizumab† (dabigatran), andexanet alfa‡ (apixaban and rivaroxaban)	1–2 days	6 hr
Aspirin	4–6 hr (platelet inhibition lasts 7–10 days)	Hold 7–10 days prior to surgery	Administer platelets	Continue	N/A
Clopidogrel	6 hr (platelet aggregation inhibited ~5 days)	Hold 5 days before surgery	Administer platelets	7 days	6 hr

DOAC, direct oral anticoagulant; FFP, fresh frozen plasma; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LP, lumbar puncture; N/A, not applicable; PCC, prothrombin complex concentrate

* Dosing of PCC in children is based on available adult data because pediatric data are limited. Use caution and dose at lower end of dosing range.
† There is no pediatric literature available to describe the dosing, and safety and efficacy, of idarucizumab in children.
‡ There is no pediatric literature available to describe the dosing, and safety and efficacy, of andexanet alfa in children.

Anticoagulation

Anticoagulation needs of pediatric patients are diverse, thus the expertise of the pediatric perioperative clinical pharmacist is warranted. Some surgeries, such as those requiring cardiopulmonary bypass, require intraoperative anticoagulation. For patients maintained on anticoagulation before surgery, careful consideration must be made to balance the risks of bleeding during surgery with the risk of VTE. This requires withholding anticoagulants for the appropriate duration of time prior to surgery, and if this is not possible, use of emergent reversal of anticoagulation with 4-factor prothrombin complex concentrate (PCC) infusion during surgery. Finally, prevention of VTE after surgery is an important consideration for all patients, and patients may require at-home anticoagulation for up to 28 days (usually 7–10 days), especially after cancer surgery.[63]

Perioperative Anticoagulation Management. Data and recommendations for perioperative management of systemic anticoagulation for pediatric patients are sparse, and most relevant data are found in cardiology and solid organ transplant. When managing pediatric patients, the pediatric perioperative clinical pharmacist must take into consideration adult literature and pediatric pharmacokinetics of various agents. For patients maintained on antithrombotic therapy, preoperative management depends on the elimination half-life of the anticoagulant and the reason for anticoagulation. The risk of thrombosis with the underlying condition must be considered when making the decision to withhold or bridge anticoagulation. The risk of bleeding, associated with the surgical procedure and any use of epidural anesthesia during or after the procedure, is the largest consideration when making the decision on bleeding risk. Bleeding risk is considered lowest with dermatologic procedures, biopsies, endoscopy, and dental surgeries and highest in those surgeries where bleeding in an enclosed space will cause significant morbidity, such as intracranial and spinal procedures.[64] A list of commonly used anticoagulant and antiplatelet agents, their duration of effect, and approach to management can be found in Table 6. For patients receiving lumbar puncture (LP) in conjunction with surgery, it is important to consider

Table 7. Venous Thromboembolism Risk Factors and Pharmacologic Contraindications[77,79]

VTE Risk Factors
• Age >12 yr
• Hospitalization >72 hr
• Obesity (BMI > 95th percentile)
• Altered mobility status
• Thrombophilia
• ICU admission
• Active cancer
• Recent surgery within the past 30 days
• Estrogen therapy
• Acute systemic inflammation/infection
• Major trauma requiring ICU admission
• Major burn
• Severe dehydration
• Protein-losing disorder
• Cyanotic heart disease or low-flow states
• Family history of VTE in a first-degree relative
Contraindications to Pharmacologic Prophylaxis
• Allergy to UFH or enoxaparin
• Intracranial hemorrhage
• Acute stroke or brain ischemia
• Ongoing and uncontrolled bleeding
• Uncorrected coagulopathy
• Incomplete spinal cord injury with suspected or known paraspinal hematoma
• Platelet count <50,000 per mcL
• Epidural anesthesia
• The patient is likely to require an invasive procedure within 24 hr of starting anticoagulation
• Congenital bleeding disorder
• Uncontrolled severe hypertension or intracranial mass

BMI, body mass index; ICU, intensive care unit; UFH, unfractionated heparin; VTE, venous thromboembolism

the timing of LP and, if applicable, catheter removal in relation to anticoagulation. See Table 6 for the recommended time between anticoagulant dosing and LP or epidural catheter insertion or removal.[65]

For patients receiving warfarin, bridging with an agent with a shorter half-life, such as low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH), may be necessary. The need for bridging depends on the risk of thrombosis in the absence of antithrombotic therapy. For minor procedures, anticoagulation may be able to be continued without cessation, while for most major procedures bridging is necessary. The CHEST guidelines recommend stopping warfarin 5 days before the planned procedure, and restarting therapy 12 to 24 hours after hemostasis is obtained post procedure.[66] Given their shorter duration of effect, perioperative management of UFH and LMWH is accomplished by withholding the agent for the appropriate duration before and after surgery without need to bridge. It is recommended to withhold UFH for 4 to 6 hours before surgery, and restart it after hemostasis is obtained.[66]

The use of direct oral anticoagulants (DOACs) in pediatric patients remains uncommon, although use in older adolescents, in sickle cell anemia, or in clinical trial participants is taking place in clinical practice.[68] A pharmacokinetic approach to management of DOACs in the perioperative setting suggests they should be withheld for 1 to 2 days prior to surgery and restarted the day after surgery.[69] For pediatric patients, adherence to clinical trial recommendations or consultation with a pediatric hematologist should be considered.

Antiplatelet agents in pediatric patients are mainly used in the cardiac population and thus procedural management is often specific to the procedure and underlying reason for antiplatelet therapy. The need to withhold antiplatelet therapy depends on the risk of thrombosis in the absence of therapy and the risk of bleeding with the procedure. The most commonly used antiplatelet agents in pediatric patients are aspirin and clopidogrel, both of which bind irreversibly to their respective targets and, thus, have a much longer duration of effect than the drug's elimination half-life. In most cases, aspirin can be safely continued; however, clinically relevant, non-major bleeding has been observed in patients undergoing cardiac surgery.[64,66] For patients for whom aspirin can be safely withheld, it should be stopped 7 to 10 days before the procedure.[64,66] For patients on clopidogrel, it should be stopped 5 days before the procedure.[64,66]

Emergent Reversal. For elective surgeries, reversal of anticoagulation typically can be accomplished by withholding anticoagulants for an appropriate duration as described above. However, in emergent situations, pharmacologic reversal of anticoagulation may be necessary. Reversal of anticoagulation is not without risk as it can be associated with a higher risk of thrombosis because of the inducement of a hypercoagulable state. Reversal of heparin-based anticoagulants is accomplished with protamine sulfate at a dose of 1 mg per 1 mg of enoxaparin or 100 units of heparin.[70] Only heparin given in the past few hours should be neutralized, and dosing tables exist to calculate the amount of protamine needed given the time since heparin administration.[70] The reversal agent of choice for warfarin depends on the immediacy of surgery and the threat of bleeding. For patients with elevated international normalized ratio (INR >8) without significant bleeding, reversal may be accomplished with parenteral vitamin K.[71] When warfarin reversal is needed immediately, fresh frozen plasma (FFP) or PCC can be used.67 Guidance and data on reversal of DOACs are limited to the adult population. DOAC reversal can be accomplished with PCC, FFP, or drug-specific reversal agents: idarucizumab for dabigatran reversal and andexanet alfa for reversal of apixaban and rivaroxaban.[72] Guidance on reversal of antiplatelet agents is less well defined. The most commonly used antiplatelet agents, aspirin and clopidogrel, bind irreversibly to platelets, so exogenous platelet administration may be necessary in patients with significant bleeding.[67]

Table 8. Recommended Factor Concentration in the Perioperative Period[82]

	% Factor Activity*, range				
	Preoperative	**Intraoperative**	**POD 1-3**	**POD 4-6**	**POD 7-14**
Major surgery					
Hemophilia A	80–100	80–100	60–80	40–60	30–50
Hemophilia B	60–80	60–80	40–60	30–50	20–40
Minor surgery					
Hemophilia A	40–80	40–80	20–50	20–50	N/A
Hemophilia B	40–80	40–80	20–50	20–50	N/A

N/A, not applicable; POD, postoperative day

* Units may vary based on laboratory reporting of blood factors. Factor activity as % is equivalent to a concentration reported as international units per deciliter (IU/dL).

Prevention of Venous Thromboembolism. In post-surgical patients, VTE is a well-known complication. In 2008, the US Surgeon General released a call-to-action to prevent VTE; however, application in pediatric patients has been slow, limited by a scarcity of quality data.[73] Since this publication, the incidence of hospital-acquired VTE in children has increased, with surgery recognized as an important risk factor, and is estimated at 0.1% of the pediatric surgical population.[74–76] While the incidence of VTE in children is markedly lower than in adults, it remains the second largest cause of preventable harm in pediatric patients.[77] The cost of hospital-acquired VTE in pediatric patients is estimated to be approximately USD $30,000 per episode and is driven by increased length of stay, laboratory testing, and increased drug costs.[78] Institutions caring for children should have a standardized way of assessing VTE risk and providing appropriate prophylaxis. The Children's Hospitals Solutions for Patient Safety (CHSPS) recommends VTE risk in children be assessed at a minimum on admission, pre- and post-operatively, and upon transfer to a different level of care, highlighting the importance of this topic in perioperative care.[77] For children 12 years or older who are undergoing an hour or more of general anesthesia, the CHSPS recommends the use of mechanical prophylaxis intraoperatively.[77] Currently, the use of a risk-stratified approach dividing children into low, moderate, or high risk of VTE is the standard of care for determination of VTE prophylaxis strategies perioperatively[77,79,80] Table 7 provides a list of VTE risk factors and pharmacologic considerations when assessing risk and VTE in children. While which risk factors convey low, moderate, and high risk of VTE in pediatric patients differs among published guidelines, most recommend early ambulation for all pediatric patients, compression stockings for those with moderate or high VTE risk, and additional pharmacologic prophylaxis for high-risk patients.[77,79–81] Pediatric perioperative clinical pharmacists should advocate for the creation and maintenance of institutional guidelines for VTE prevention. Reminders to reassess the need for VTE prophylaxis should be built into perioperative transitions of care as well.

Unique Hematologic Considerations. ***Bleeding Disorders***. The presence of inherited bleeding disorders is a challenge in the perioperative setting. The most common genetic disorders of bleeding are hemophilia A, caused by deficiency in factor VIII; hemophilia B, caused by deficiency in factor IX; and von Willebrand disease (VWD), caused by missing or defective von Willebrand factor (VWF). The pediatric perioperative clinical pharmacist caring for these patients should be familiar with hematologic management and ideally co-manage these patients with a hematologist. Management of these patients should be done at facilities with sufficient laboratory and blood bank support to monitor during procedures. The World Federation of Hemophilia recommends that procedures for patients with hemophilia take place early in the day so that maximal laboratory and supportive care staff are available in the immediate postoperative setting.[82] Pharmacists must take particular care to ensure adequate inventories of relevant factor products while balancing the financial aspects of care. One strategy that may assist in balancing the financial aspect is using the patient's own medication supply in the perioperative setting when possible. The presence of a genetic bleeding disorder with adequate treatment is not an absolute contraindication to postoperative pharmacologic VTE prophylaxis and is a factor to consider when balancing the risks of bleeding and VTE development.

In patients with hemophilia who are undergoing surgery, it is important to consider the severity of hemophilia, home factor regimen, and history of inhibitor formation when developing a perioperative factor replacement plan. Hemophilia severity is classified according to baseline factor activity level: mild (5%–40%), moderate (1%–5%), or severe (<1%). While only patients with severe hemophilia are at risk of spontaneous bleeding and are likely to be maintained on prophylactic factor treatment in the absence of trauma, all patients with hemophilia are at risk of developing bleeding after surgery and should be treated with factor products.[82–84] See Table 8 for recommended factor level ranges. In general, 1 international unit/kg of factor VIII raises activity level by 2%, while 1 unit/kg of factor IX raises activity level

by 1%; however, dosing should be confirmed by using the product-specific package insert.[84] If bleeding risk is high in the immediate postoperative period, continuous infusion of factor may be necessary to maintain levels high enough to prevent bleeding or expansion of a hematoma. For patients with inhibitors, the use of bypassing agents may be necessary for prophylaxis and treatment of bleeding. Activated prothrombin complex concentrate and recombinant activated factor VII (rFVIIa) can be used for hemophilia A with inhibitors, and rFVIIa is used for hemophilia B with inhibitors.[84] Factor VIII and factor IX activity can be monitored directly; however, turnaround time for these tests is usually at least 1 to 2 hours. In patients with hemophilia with low factor activity, activated partial thromboplastin time and activated clotting time are also prolonged, which may provide a more immediate assessment of clotting ability.

Perioperative management of patients with VWD is less well defined. There are multiple subtypes of VWD. Type 1 is caused by partial quantitative deficiency of VWF, type 2 by qualitative deficiency of VWF, and type 3 by total deficiency of VWF. Patients with VWD may have lower concentrations of factor VIII because VWF is necessary to stabilize factor VIII in plasma. This decrease in factor VIII is most severe in VWD type 3. Intravenous or intranasal desmopressin can be used prior to an invasive procedure to transiently correct VWF and factor VIII concentrations in patients with type 1 and some patients with type 2 disease by inducing release of VWF from endothelial cells. Types 2B and type 3 VWD are typically unresponsive to desmopressin.[85] Use of desmopressin to manage VWD is typically not recommended in patients with underlying heart disease. Fluid restriction to avoid hyponatremia may be warranted, and close monitoring of electrolytes with supplementation should be performed in all patients receiving desmopressin.[85] Desmopressin is typically administered for no more than 5 days. In all patients receiving major surgery and those undergoing minor surgery who have VWD types unresponsive to desmopressin, VWF concentrates should be used. It is important to note that available VWF concentrates have varied levels of factor VIII relative to VWF, and both must be considered when providing factor replacement.[85,86] Care must be taken not to oversupplement factor VII relative to VWF because factor VIII concentrations over 150% increase risk of thrombosis.[85] Careful monitoring of VWF and factor VIII is recommended.

Religious Refusal of Blood Transfusions. Some religious faiths, such as Jehovah's Witnesses, oppose the use of blood transfusions, which can make blood loss in the perioperative setting challenging to manage. Except in emergencies, parental consent to transfuse pediatric patients is required, and in patients with postsurgical blood loss, this can present an ethical challenge. In situations where the life of the child is at risk, the medical team can act together with the court to transfuse the child without the parents' permission, but this type of action should be avoided whenever possible.[87] With careful planning, even pediatric cardiac surgeries requiring cardiopulmonary bypass have been performed without the use of blood products.[88–90] Care of these patients in accordance with their religious belief involves minimizing blood loss during surgery, enhancing erythropoiesis, and correcting coagulation defects and promoting hemostasis.[91] Patients with religious objections to blood transfusion should be screened for anemia at least 4 weeks prior to surgery and treated according to the underlying cause. Optimization of iron status, as well as supplementation with vitamin C, folate, and vitamin B12, are all recommended. The use of erythropoietin-stimulating agents in both the pre- and post-surgical settings to increase erythropoiesis has been used successfully; however, data are largely limited to case reports and small case series.[89,90,92,93] Olshove et al[89] reported a preoperative regimen of erythropoietin 500 units/kg twice a week, along with multivitamin, supplemental iron, vitamin C, vitamin D, thiamine, and folic acid, which achieved a preoperative hematocrit of 46.1%, as effective in preventing transfusion in 5 pediatric congenital heart patients. Optimal dosing and duration of erythropoietin, as well as recommended presurgical hemoglobin and hematocrit targets, have not been established for pediatric patients; however, a hemoglobin concentration lower than 13 g/dL has been used as a marker for preoperative anemia for adults. Erythropoietin management should be performed by the pediatric perioperative clinical pharmacist in conjunction with pediatric hematology, based on the most recent evidence. Minimizing blood loss by optimizing coagulation is necessary to limit need for transfusion. The pediatric perioperative pharmacist should recommend cessation of any drugs that can potentiate bleeding such as NSAIDs, anticoagulants, antiplatelets, and herbal remedies (especially garlic-, ginkgo-, green tea extract–, and ginger-containing products) before surgery, when possible. The use of tranexamic acid and replacement of specific clotting factors, using recombinant products, has been recommended for adult patients and use in pediatric patients has been reported.[91,94]

Special Populations

There are many additional unique considerations in various pediatric surgery types that are not specifically addressed in the prior sections. While not fully comprehensive, a list of some medication-specific considerations for the most common pediatric surgery types can be found in Table 9.

Conclusion

The pediatric perioperative clinical pharmacist is uniquely poised to provide pharmacotherapy and medication use expertise across the perioperative continuum of care. This review provides a general summary of considerations and recommendations for the pediatric perioperative pharmacist concerning enhanced recovery

Table 9. Special Pediatric Perioperative Medication Considerations

Pediatric Surgery Population	Special Perioperative Medication Considerations
Cardiac	• Intraoperative methylprednisolone is common at the initiation of pediatric cardiopulmonary bypass, but an additional dose given preoperatively to neonatal cardiac surgery patients has been associated with preoperative adrenal insufficiency.[95–97] The STRESS study is currently underway to provide safety and efficacy data for perioperative steroids in infants undergoing cardiac surgery with cardiopulmonary bypass.[98] • Intraoperative tranexamic acid may reduce postoperative blood loss following pediatric cardiac surgery, but may be associated with increased seizure risk.[99,100] • Dexmedetomidine may play a role in stabilizing the postinfusion heart rate while also decreasing the incidence of tachyarrhythmia in the postoperative setting.[101,102] • Use of vasoactive agents pre- and post-operatively depend on patient physiology and the need to provide inotropic, chronotropic support or preload or afterload augmentation.
CDH	• CDH is the most common indication for neonates with respiratory failure receiving ECLS.[103] • Institutions should develop guidelines for medications needed at initiation of and during ECLS (e.g., cannulation, sedation, anticoagulation). • Guidelines should take into account differences in sedation and anticoagulation requirements for neonates, infants, and young children (e.g., lower endogenous antithrombin concentrations requiring larger heparin doses). • Avoid aggressive fluid resuscitation, because fluid overload is associated with poor outcomes.[104] • Care includes the management of PH after birth and when weaning off of ECLS includes the following: o iNO is often considered for PH; however, the benefits are inconclusive (and iNO should be avoided with left ventricular dysfunction).[105] o Milrinone may be beneficial if there is left ventricular dysfunction.[104] o Prostaglandin E1 may be used to maintain patency of the ductus arteriosus in the presence of right ventricular failure.[104] o Additional pulmonary vasodilators may be considered (e.g., phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and prostaglandins). • For surgical repair of CDH while on ECLS, optimal management of anticoagulation is required to prevent bleeding complications. • Anticoagulation management during repair frequently includes lowering anticoagulation targets during the perioperative period and use of aminocaproic acid or tranexamic infusion.
Gastrointestinal	• Perioperative antibiotic coverage is typically expanded to include both Gram-negative and anaerobic organisms (e.g., ampicillin + gentamicin + metronidazole in neonates; and ceftriaxone + metronidazole or piperacillin/tazobactam in infants and children).[106] • Parenteral nutrition should be used in pediatric patients with anticipated longer durations of inability to take enteral feeds. ASPEN recommends 1–3 days for infants and 4–5 days for older children and adolescents.[107] • If portions of the gastrointestinal tract are removed or bypassed (e.g., jejunostomy), this may affect the ability to use certain medications, based on the site of absorption. Medication regimens should be reviewed postoperatively to ensure adequate absorption and adjusted as appropriate. • Removal of large segments of bowel may result in short-bowel syndrome. Postoperative and longer-term management frequently include the following: o Parenteral nutrition o Antibiotics for intestinal bacterial overgrowth o Antimotility or other agents to reduce excessive stool output o Antacids for increased gastric acid output
Neurosurgical	• Use of perioperative gabapentin has been shown to improve pain in the immediate postoperative period for spinal surgery patients.[108] • Use of dexamethasone to manage cerebral edema is common in the perioperative period.[109] Dose and duration vary significantly among providers.[110] • Hypopituitarism is a severe complication of some brain surgery, usually involving tumor removal near the pituitary. It requires prompt pharmacologic management. Patients can experience deficiency in growth hormone, adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropins, and vasopressin.[111] • Patients undergoing neurosurgical procedures are at risk for sodium disorders such as SIADH, central diabetes insipidus, and cerebral salt wasting.[112]

(Table cont. on page 501)

Table 9. Special Pediatric Perioperative Medication Considerations *(cont.)*

Orthopedic	• Use of aspirin as chemoprophylaxis for VTE in pediatric patients is common.[113] Data supporting this practice in children are lacking, and data in adult patients are conflicting.[114] • Use of regional anesthesia and multimodal analgesia for pain management is the standard of care.[50]
Solid organ transplant	• Induction of immunosuppression is dependent on a number of patient and organ-specific risk factors, and typically begins on the day of transplant often with corticosteroids (i.e., methylprednisolone) and/or a lymphocyte-depleting agent (i.e., antithymocyte globulin, alemtuzumab) or IL-2 receptor antagonist (i.e., basiliximab). • Maintenance immunosuppression with calcineurin inhibitor (e.g., tacrolimus or cyclosporine) and antiproliferative agent (e.g., mycophenolate or azathioprine) is the backbone of most solid organ transplant regimens in children, and the agent selected and time to initiation after transplant is dependent on the induction therapy used.[115,116] • ABO-incompatible transplants may use plasmapheresis, IVIG, and/or rituximab to help mitigate allograft rejection.[117]
Trauma	• The use of tranexamic acid in pediatric trauma patients in the perioperative setting reduces transfusion requirements in children.[118] • Vaccination with *Haemophilus influenzae* type B, pneumococcal conjugate and polysaccharide, meningococcal conjugate vaccines should be considered in postsplenectomy patients. Tetanus and/or tetanus toxoid should be considered on the basis of wound type and history of past adsorbed tetanus toxoid doses in pediatric trauma and burn patients. Patients with skull fractures and CSF leak should be offered a pneumococcal vaccine.[119,120] • Children with burn injury benefit from fluid resuscitation in the first 24 hr after injury, typically using the Parkland formula.[121,122] • Attenuation of hypermetabolic activity may be achieved with propranolol, and oxandrolone may mitigate muscle wasting and improve rehabilitation in children with burn injuries.[122–124]

ASPEN, American Society for Parenteral and Enteral Nutrition; CDH, congenital diaphragmatic hernia; CSF, cerebral spinal fluid; ECLS, extracorporeal life support; IL-2, interleukin-2 X; iNO, inhaled nitric oxide; IVIG, intravenous immune globulin; PH, pulmonary hypertension; SIADH, syndrome of inappropriate antidiuretic hormone; VTE, venous thromboembolism

pathways, fluids and electrolytes, antimicrobials, PONV, pain and analgesia, anticoagulation, and selected surgery types. Pediatric perioperative clinical pharmacists should ensure they have adequate knowledge of these specific pediatric physiologic and pharmacotherapeutic considerations and are able to apply and extrapolate evidence-based medicine in children to ensure the safety and best possible outcomes of the pediatric surgical patient.

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