Safety Considerations for the Inpatient Medication-Use Process in **Pediatric and Neonatal Patients**

By **Rowan Elkeshawi**, BPS[◇§], **Katherine K. Maddox**, BPS, BS[◇§], **Andriana T. Xenophontos**, BPS, BS[◇§] & **Kyle Hampson**, PharmD[◆◇†§]

DOI: 10.33940/pediatrics/2022.1.3
Submitted: June 30, 2021 / Accepted: November 10, 2021

[◆]Corresponding author
[◇]Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University
[†]Department of Pharmacotherapy Services, The Brooklyn Hospital Center
[§]Authors contributed equally to this work
Disclosure: The authors declare that they have no relevant or material financial interests.

The delivery of safe and effective healthcare to pediatric and neonatal patients presents unique challenges to the medication-use system. The diversity of patients within this population and the consequences of ontogeny on pharmacokinetics and pharmacodynamics directly impact the safe use of medications in children and increase the risk of adverse drug events.[1] This review will explore the medication-use system for hospitalized children and neonates, discuss vulnerabilities within this system, and provide examples of advancements made to improve the pediatric medication-use system.

Keywords: *pediatric, neonatal, medication safety, medication use process, formulary, medication reconciliation, administration, ordering, dispensing, computerized physician order entry (CPOE)*

Introduction

The medication-use process within healthcare institutions involves several steps: medication procurement and formulary management, medication reconciliation, ordering, preparation and dispensing, administration, and monitoring.[2,3] While all steps of this process are prone to medication errors[2], some steps may be more error-prone than others. An analysis of over 25,000 medication safety incidents reported during a nine-year period in neonatal intensive care units (NICUs) and pediatric intensive care units (PICUs) in England and Wales found that ordering and administration were the most error-prone steps (accounting for 29% and 53.5% of errors, respectively).[4]

This study also highlighted the vulnerability of our smallest patients to flaws in the medication-use system. Forty-eight percent of all medication incidents occurred in neonates (aged $\leq$ 28 days old) and 36.5% of incidents occurred in patients 1 month to 1 year old. Furthermore, while only 12% of incidents went on to cause patient harm, over 50% of these incidents occurred in neonates.[4] This aligns with a previous study that postulated that dosing errors due to rapid changes in weight and the use of specialized compounds predisposed patients in the NICU to medication errors with potential for harm.[5]

The Medication-Use System in Pediatric and Neonatal Patients

Despite the frequency of medication-related safety events in the pediatric and neonatal populations, children's hospitals have reported limited medication safety resources. A survey of children's hospitals found that only two-thirds of hospitals had a medication safety pharmacist. A similar amount of respondents reported that nursing spent at least half of a full-time equivalent working on medication safety activities. Additional medication support services came from physicians (30.8% of respondents), a medication safety and informatics coordinator, data analyst, and an industrial engineer.[3]

The increased risk of medication errors in pediatric and neonatal patients and inconsistent medication safety resources in institutions underscore the importance that all clinicians play an active role in strengthening medication-use system safety. As medication therapy experts, pediatric pharmacists play an important role on the pediatric care team. One study conducted at an 84-bed pediatric teaching hospital showed that pediatric pharmacists were able to reduce medication errors from reaching patients.[6] Through participation in medical rounds and order verification, pediatric pharmacists identified 1,315 interventions over the course of a two-month period. The most common interventions were "drug therapy recommendations" (46%), where pharmacists recommended to change medication selection due to a change in the patient's clinical status (i.e., culture results) or allergies. "Errors" (24.5%) were the second most common intervention type, of which over 68% were prescribing errors.[6] While this study underrepresented errors in medication administration, it highlights that pharmacists can reduce medication errors in collaboration with the care team.

Medication Procurement and Formulary Management

The medication-use system for pediatric patients begins with the procurement and management of the hospital formulary. Providing pharmacotherapy to pediatric and neonatal patients may require the use of unique medications and for medications to be used in a different manner compared to adult patients. Because of the intricacies of medication use in this patient population, pediatric clinicians should play an active role in formulary decisions for an institution.[2] Timely clinical data is typically used to inform institutional formulary decisions; however, this may not be readily available for pediatric and neonatal populations, and clinicians may extrapolate safety and efficacy data from adult studies.[7] Pediatric clinicians can aid in formulary decision-making, especially given the frequent "off-label" use of medications in this patient population.[2,7] When possible, it is suggested that a formulary specific to pediatric patients be implemented to limit concentrations and standardize dosages of high-risk and frequently used medications.[8]

Many commercially available medications are not designed for pediatric use. Pharmacies often use commercially available oral and intravenous products to engineer products that are suitable for children (i.e., oral liquid preparations or specific concentrations of intravenous medications).[7] If unstandardized processes or multistep dilutions are utilized to compound specialized medications for use in pediatrics, the risk of a medication error increases.[2]

Medication Reconciliation

Medication reconciliation can play a key role in prospectively identifying errors with medications. A single-center, prospective, observational study of children admitted to a university hospital in Spain found that 41% of pediatric patients admitted had a discrepancy between their best possible medication history and their prescribed treatment on admission.[9] It is crucial that clinicians conducting medication reconciliation are familiar not only with the medications used to treat pediatric patients, but also the dosing regimens and formulations. While clinicians prescribe medications in terms of milligrams, grams, and other standardized units, family members may only know the volume of the medication that they are to administer. Since many medications used to treat children are available in varying concentrations, this can create confusion regarding the dose being delivered to the child. For example, amoxicillin-clavulanate is available in varying concentrations. Although the medication is dosed based on the amoxicillin component, the strengths are not interchangeable due to differing ratios of amoxicillin and clavulanic acid. (See **Table 1**.)

In addition to confusion regarding commercially available products, extemporaneously compounded products are commonly prescribed when treating children and pose unique challenges for medication safety. Compounded medication formulas are not standardized and some formulations have not been extensively studied. Additionally, universal adoption of studied formulas has not been embraced widely within the pharmacy community, and individual compounding pharmacies may develop their own formula. To address and correct these differences, the American Society of Health-System Pharmacists in collaboration with the Food and Drug Administration (FDA), The Joint Commission, and the Institute for Safe Medication Practices began the Standardize 4 Safety initiative. This program aims to regulate concentrations of oral and intravenous medications to decrease medication errors,

Table 1. Amoxicillin-Clavulanic Acid Ratios[10]

Concentration of Amoxicillin (per 5 mL)	Concentration of Clavulanic acid (per 5 mL)	Ratio
125 mg	31.25 mg	4:1
200 mg	28.5 mg	7:1
250 mg	62.5 mg	4:1
400 mg	57 mg	7:1
600 mg	42.9 mg	14:1

primarily around transitions of care where medication reconciliation is taking place. In addition to improving the accuracy of medication reconciliation, standardization can benefit other areas of the medication-use process as well.[11] Some organizations, like the Michigan Pediatric Safety Collaboration, have launched a statewide coalition to standardize the compounding of oral medications used in pediatrics and publishes validated compounding formulas online (www.mipedscompounds.org). Nationwide Children's Hospital in Columbus, Ohio, has also published validated compounding formulas online (www.nationwidechildrens.org/specialties/pharmacy-services/compounding-formulas).

Medication Ordering

The medication ordering step of the medication-use process is highly vulnerable to medication errors. The cause of this is multifactorial; however, calculation errors, lack of FDA-approved dosing guidelines, and inconsistent units for dosing regimens likely contribute to the risk of errors in pediatric populations.[2] Most established doses in pediatric and neonatal patients are weight-based, which may increase risk of calculation errors. These dosing regimens may be reported in a variety of ways, such as milligram/kilogram/dose versus milligram/kilogram/day. This is also seen in critical care settings with the use of continuous infusions (milligram/kilogram/minute vs. milligram/kilogram/hour). Inconsistencies among ordering may lead to discrepancies further along the medication-use process, and careful attention must be paid to units when orders are placed.[2]

Given that pediatric and neonatal dosing recommendations are typically provided in terms of body weight or body surface area, errors in obtaining anthropometric data are a frequent cause of medication errors. Recording accurate anthropometric information is essential in preventing these errors. One study that measured medication errors in children who presented to the emergency room found that 31% of weight errors included the substitution of weight in pounds for the weight in kilograms and 6% of weight errors included decimal place errors.[21] Furthermore, this study highlighted that this risk is compounded when the weight is used for multiple medication orders. Forty-three percent of weight errors that were involved in a medication error caused more than one medication error.[21] An accurate patient height is critical to calculating creatinine clearance for renal function assessment and for calculating body surface area, which is used when dosing certain medications. According to the Pennsylvania Patient Safety Reporting System (PA-PSRS), 679 reports have been identified in relation to an inaccurate patient height.[12] The most common transcription errors were the use of the wrong unit of measurement, the substitution of another measurement with height, and typographical errors. These inaccurate patient heights most often led to errors in calculation of medication doses or the input of certain laboratory values.[12]

One method used to improve patient safety and standardize ordering practices is the use of computerized physician order entry (CPOE) systems. CPOE systems should be capable of ordering medications based on weight for pediatric and neonatal orders, and should only use one unit of weight to prevent the need for unit conversion.[13] A 2016 survey of pediatric hospitalist programs reported that 90.6% of programs used order sets or CPOE orders with pediatric weight-based dosing, 79.7% review pediatric medication safety events or concerns, 58.7% were aware that their hospital had defined or documented maximum doses on orders, and 50% had milligram-per-kilogram dosing required to be in the order.[13]

Implementation of CPOE systems eliminates paper transcription in hospital settings and allows for the implementation of clinical decision support (CDS), which are computerized prompts that aid healthcare providers in the implementation of clinical guidelines, and the addition of hard and soft stops when prescribing in real-time. It also streamlines the transcription process, as physicians and pharmacists have access to the same interface. The implementation of CPOE systems, specifically those with CDS systems, in hospitals have shown a decrease in potentially harmful medication errors.[13] While CPOE and CDS systems have the potential to improve safety, they may also have unintended consequences. One study reported barriers in communication between members of the medical team and between the medical team and patients as a result of CPOE implementation.[22] Given the advantages in safety that these systems afford, healthcare professions must collaborate to overcome potential communication issues to enhance patient safety.

CPOE in Parenteral Nutrition

Parenteral nutrition (PN) is the most complicated intravenous (IV) solution ordered in hospitals. Given the multitude of components of PN, the ordering process is highly error-prone. CPOE has been shown to reduce ordering errors for PN. MacKay and colleagues evaluated the rates of medication errors in PN prescription, transcription, preparation, and administration after implementing the CPOE system.[14] The CPOE program was compliant with standards from the American Society for Parenteral and Enteral Nutrition (ASPEN) and integrated hard and soft stops. After seven years, researchers found that there were statistically significant cost reductions and lower error rates (2.7/1000 PN) than the national average (15.6/1000 PN).[14]

CPOE systems also allow for increased interdisciplinary management strategies, such as the automatic data transmission including electronic health records (EHR) between all healthcare professionals. The integration of CDS, including the implementation of appropriate hard and soft stops, minimizes potential errors.

Neonatal-Specific CPOE Systems

While the implementation of CPOE systems has led to an overall decrease in medication errors, many systems do not have the proper interfaces to allow for pediatric- and neonatal-specific prescription entries. Integrated CDS alerts also do not take into account this population, and many adult-focused dosing alerts must be overridden, increasing the time to medication administration. The introduction of pediatric- and neonatal-specific CPOE systems may be beneficial in the prescribing process.

A study published in 2020 designed and developed a neonatal-specific CPOE and investigated the efficacy in medication error reduction. In comparison to handwritten orders, the neonatal-specific CPOE reduced neonatal medication prescription errors, time for dose calculation, and electronic documentation of medical records.[15]

Medication Preparation and Dispensing

Pediatric and neonatal patients require personalized care, which includes utilizing weight-based dosing for medication dosing and extemporaneous compounds. Many commercially available dosage forms are designed for adult use and may not be appropriate for use in children based on their size or comorbidities. The commercially available standard adult concentration of some intravenous medications may be too dilute for use in neonates and children who have restrictions on their daily fluid volume.[2] Additionally, commercially available dosage forms may require manipulation to obtain a weight-based dose for a child.[6] For example, tablets or suppositories may need to be cut to deliver a smaller dose, capsules may be opened and mixed with food or beverage prior to administration, or medications manufactured for IV use may be given orally.[2] While these practices may not be avoidable, they are often not validated, may lead to alterations in the bioavailability of the medication, and have unknown beyond use dating.[2]

Compounding parenteral solutions for children often includes an increased risk of error in comparison to compounding for their adult counterparts. Parenteral solutions designed for pediatric and neonatal patients may involve more calculations, dilutions (i.e., aliquots), and manipulation of commercially available products to achieve the desired dose or concentration. One advancement in IV compounding safety that may be utilized is IV workflow management systems. These systems are designed to automate the preparation and verification of compounded sterile products.[23] By automating calculations, utilizing barcode scanning for each ingredient prior to mixing, and employing gravimetric analysis to confirm the accuracy of the components included in the solution, IV workflow management systems reduce human error in compounding.[23] While not available at all pediatric hospitals, these systems can be used to improve the safety and accuracy of compounding processes, and are becoming more popular among pediatric institutions.

With a variety of products and concentrations used for treating pediatric and neonatal patients, a risk of error is present when dispensing medications. The use of a color-coded medication safety system in a community pediatric emergency setting was shown to decrease medication delay and improved nursing accuracy.[16] During a simulated emergency resuscitation, the use of pre-filled, color-coded syringes led to a reduction in dosing errors.[16]

Administration

As described previously, one study showed that errors in medication administration account for over 50% of medication errors in the NICU and PICU.[4] Further characterizing these errors, another study from Turkey found that the most common types of error in medication administration were time errors or dose errors, with a majority of factors leading to the errors being system-based.[25]

Other studies have emphasized the drug class as being related to the risk of error, with opiate, antibiotic, and sedative drugs being the most likely to be involved in medication administration errors.[26] While the cause of medication-administration errors is multifactorial, proper safeguards and technology should be put into place to reduce the risk of errors.

Despite the risk of error in medication administration, advances in healthcare technology have improved the safety of this process. Bedside barcode scanning is used to validate that the right medication is given to the right patient at the right time. Infusion pumps and syringe pumps can deliver small doses of medications with high accuracy and have programmable soft and hard stops that can catch administration errors.[1,17] While these technologies have helped to make medication administration safer for pediatric and neonatal patients, they require development and maintenance of barcode and infusion pump libraries.

While the use of syringe pumps and their libraries has improved the safe infusion of medications, risk of inconsistent medication delivery for pediatric and neonatal patients is still present. A 2016 FDA Safety Communication details a risk of poor flow continuity (defined as an inconsistent rate of delivery) at low infusion rates (especially with flow rates less than 0.5–5 mL/hr).[24] These rates are commonly used for medication administration in neonates and smaller pediatric patients, especially when titratable medications are used (e.g., fentanyl, midazolam, dopamine, epinephrine). Lack of flow continuity can lead to a delay of therapy, over- or underinfusion, and adverse effects.[24] To mitigate these risks, the FDA recommends using the smallest size of syringe that is compatible with the syringe pump, using the shortest length of small-bore or microbore tubing possible, minimizing dead space from inline filters, and limiting the number of connection sites in the line.[24] Electronic priming of the syringe pump before starting the infusion or after replacing a near-empty syringe and keeping the syringe pump level with the distal tip of the catheter should be done whenever possible.[24]

Specialized administration sets have recently been developed to reduce the administration of medications by the incorrect route. Aerosolized medications can be given through Aerogen tubing, which is colored blue.[18] The EnFit system is used to administer enteral nutrition and medications through special tubing, which is colored purple. These systems enhance the safety of administration because they are incompatible with tubing and syringes designed for intravenous use.[19]

Monitoring

Pediatric and neonatal patients require thorough, consistent pharmacovigilance monitoring because of their vulnerability to adverse effects of medications and the complexities of the medication-use system. Pediatric pharmacists work with the pediatric care team to ensure safe medication use and monitor response to therapy. Pediatric pharmacists have also been shown to decrease the incidences of medication errors in inpatient pediatric settings, including intensive care units. The Pediatrics Practice and Research Network (PRN) of the American College of Clinical Pharmacy (ACCP) and the Pediatric Pharmacy Association (PPA) advocate for the expansion of qualified clinical pharmacists as a member of the multidisciplinary team for the benefit of pediatric patients.[20]

Conclusion

The complexity of providing care to pediatric and neonatal patients leaves them vulnerable to medication errors within the medication-use system. These young patients are managed differently because they require specialized dosage forms and utilize weight-based dosing. Advances in patient safety like standardizing extemporaneous medication preparation, CPOE, and EnFit can help to make the medication-use system safer. Clinicians caring for these patients, including pharmacists, can help improve the medication-use system and make a difference in providing safe care for these patients.

References

1. Greenberg R, Smith P, Bose C, et al. National Survey of Neonatal Intensive Care Unit Medication Safety Practices. *Am J Perinatol*. 2018;35(14):1419-1422.

2. Kennedy AR and Massey LR. Pediatric Medication Safety Considerations for Pharmacists in an Adult Hospital Setting. *Am J Health Syst Pharm*. 2019;76(19):1481-91.

3. Nelson KL, Morvay S, Neidecker M, et al. Evaluation of Medication Safety Resources in Pediatric Hospitals. *Am J Health Syst Pharm*. 2020;77(3):S78-86.

4. Alghamdi AA, Keers RN, Sutherland A, et. al. A Mixed-Methods Analysis of Medication Safety Incidents Reported in Neonatal and Children's Intensive Care. *Paediatr Drugs*. 2021;23(3):287-297.

5. Kaushal R, Bates DW, Landrigan C, et al. Medication Errors and Adverse Drug Events in Pediatric Inpatients. *JAMA* 2001;286(16):2114-20.

6. Cunningham KJ. Analysis of Clinical Interventions and the Impact of Pediatric Pharmacists on Medication Error Prevention in a Teaching Hospital. *J Pediatr Pharmacol Ther*. 2012;17(4):365-373.

7. Potts AL. *Medication Safety* in *Pediatric Pharmacotherapy*. Benavides S and Nahata MC Ed. American College of Clinical Pharmacy. 2013. Pp.48-60.

8. Benjamin L, Frush K, Shaw K, et. al. Pediatric Medication Safety in the Emergency Department. *Pediatrics*. 2018;141(3):e20174066.

9. Fuentes DPI, Martin-Aragon S, and Vendrell MCM. Medication Reconciliation Upon Admission in Pediatric Hospital Setting: Prelimiary Data. *Int J Clin Pharm*. 220;42:209-16.

10. Amoxicillin-Clavulanic Acid. Lexicomp. Wolters Kluwer 2021. Updated June 29, 2021.

11. American Society of Health System Pharmacists. Standardize 4 Safety. ASHP website. https://www.ashp.org/Pharmacy-Practice/Standardize-4-Safety-Initiative?loginreturnUrl=SSOCheckOnly. Accessed June 24, 2021.

12. Kukielka E. Challenges With Measurement and Transcription of Patient Height: An Analysis of Patient Safety Events in Pennsylvania Related to Inaccurate Patient Height. *Patient Saf.* 2021;3(1):48–57. https://doi.org/10.33940/data/2021.3.5

13. Alvarez F, Ismail L, Marksowsky A. Pediatric Medication Safety in Adult Community Hospital Settings: A Glimpse Into Nationwide Practice. *Hosp Pediatr*. 2016;6(12):744–749.

14. MacKay M, et al. Frequency and Severity of Parenteral Nutrition Medication Errors at a Large Children's Hospital After Implementation of Electronic Ordering and Compounding. *Nutr Clin Pract*. 2016;31(2):195-206.

15. Daher A, et al. Impact of Computerized Prescription on Medication Errors and Workflow Efficiency in Neonatal Intensive Care Units: A Quasi-Experimental Three-Phase Study. *Methods Inf Med*. 2020;59(4-05):140-150.

16. Feleke R, Kalynych CJ, Lundblom B, et. al. Color Coded Medication Safety System Reduces Community Pediatric Emergency Nursing Medication errors. *J Patient Saf*. 2009;5(2):79-85.

17. Melton KR, Timmons K, Walsh KE, et. al. Smart Pumps Improve Medication Safety But Increase Alert Burden in Neonatal Care. *BMC Medical Inform Decis Mak*. 2019;19(1). doi:10.1186/s12911-019-0945-2

18. Aerogen. Discover Aerogen Continuous Nebulization. Aerogen website. https://www.aerogen.com/continuous-nebulization-tube-set/. Accessed June 7, 2021.

19. Guenter P and Lyman B. Safer Enteral Nutrition Syringes. *Patient Saf*. 2020;2(4): 58-61. https://doi.org/10.33940/med/2020.12.4.

20. Bhatt-Mehta V, Buck ML, Chung AM, et. al. Recommendations for Meeting the Pediatric Patient's Need for a Clinical Pharmacist. *J Pediat Pharmacol Ther*. 2012;17(3):281-91.

21. Hirata KM, Kang AH, Ramirez GV, et. al. Pediatric Weight Errors and Resultant Medication Dosing Errors in the Emergency Department. *Pediatr Emerg Care*. 2019;35:637-42.

22. Dykstra R. Computerized Physician Order Entry and Communication: Reciprocal Impacts. *Proc AMIA Symp*. 2002;230-4.

23. Institute for Safe Medication Practices. Maximize Benefits of IV Workflow Management Systems by Addressing Workarounds and Errors. ISMP website. https://www.ismp.org/resources/maximize-benefits-iv-workflow-management-systems-addressing-workarounds-and-errors. Published September 7, 2017. Accessed October 12, 2021.

24. Food and Drug Administration. Syringe Pump Problems with Fluid Flow Continuity at Low Infusion Rates Can Result in Serious Clinical Consequences. FDA Safety Communications. https://www.fdanews.com/ext/resources/files/2016/08/08-25-16-pumpsafetynotice.pdf?1480880246#:~:text=The%20FDA%20is%20informing%20health,can%20result%20in%20serious%20clinical. Published August 25, 2016. Accessed October 14, 2021.

25. Ozkan S, Kocaman G, Ozturk C, et. al. Frequency of Pediatric Medication Administration Errors and Contributing Factors. *J Nurs Care Qual*. 2011;26(2):136-43.

26. Gonzales K. Medication Administration Errors and the Pediatric Population: A Systematic Search of the Literature. *J Pediat Nurs*. 2010;25:555-65.

About the Authors

Kyle Hampson (kyle.hampson@liu.edu) is an assistant professor of Pharmacy Practice at the Arnold & Marie Schwartz College of Pharmacy and Health Sciences (Long Island University Pharmacy) in Brooklyn, New York. He earned his Doctor of Pharmacy at Duquesne University in Pittsburgh, Pennsylvania, and completed both pharmacy practice and nutrition support pharmacy residencies at Emory University Hospital in Atlanta, Georgia. He has 10 years of clinical pharmacy experience in nutrition support and pediatrics and is a board-certified nutrition support pharmacist (BCNSP), board-certified pediatric pharmacy specialist (BCPPS), and a certified nutrition support clinician (CNSC).

Katherine Maddox is a pharmacy student in her final year at the Arnold & Marie Schwartz College of Pharmacy and Health Sciences (Long Island University Pharmacy) in Brooklyn, New York, where she also pursues her master's in public health. She previously earned a Bachelor of Science in biology from the University of North Carolina Wilmington and a Bachelor of Professional Studies from Long Island University Brooklyn. Upon graduation, she is pursuing residency training and has a special interest in ambulatory care.

Rowan Elkeshawi is a pharmacy student in her final year at the Arnold and Marie Schwartz College of Pharmacy and Health Sciences at Long Island University in Brooklyn, New York. She previously earned a Bachelor of Professional Studies from Long Island University - Brooklyn. Upon graduation, she is pursuing residency training and hopes to work in ambulatory care.

Andriana Xenophontos is a pharmacy student in her final year at the Arnold & Marie Schwartz College of Pharmacy and Health Sciences (Long Island University Pharmacy) in Brooklyn, New York. She previously earned her bachelor's degree from the New York Institute of Technology with a focus on life sciences and premedical studies, and a Bachelor of Professional Studies from Long Island University Brooklyn. Upon graduation, she is pursuing employment at CVS Health as a community pharmacist. As an immunizer, she has administered hundreds of vaccines, including COVID-19 and influenza, throughout different clinics and pharmacies. Her research interests include pharmacist impacts on neurological disorders like migraines and seizures. Xenophontos also enjoys spending time with her fiancé and family, cooking, traveling, and watching *The Office*.