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collaboration, advocacy, research, and education

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JPPT | 2025 KIDs List

Pediatric Pharmacy Association 2025 KIDs List of Key Potentially Inappropriate Drugs in Pediatrics

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OBJECTIVE The objective was to update the KIDs List, a list of drugs and excipients that are potentially inappropriate for use in pediatric patients, accounting for emerging pharmacologic agents and published evidence.

METHODS A panel of 12 pediatric pharmacists from the Pediatric Pharmacy Association (PPA) evaluated primary, secondary, and tertiary literature; FDA Pediatric Safety Communications; the UpToDate Lexidrug database; and product information for drugs that may be considered potentially inappropriate for use in pediatric patients. A PubMed search identified new publications from October 1, 2017, to November 1, 2023. All agents included in the previous publication and those anecdotally identified as candidates for the list by the authors or PPA members were evaluated. Evidence was reviewed by all authors. The draft list underwent a 30-day public comment period prior to being finalized.

RESULTS A PubMed search yielded 917 unique titles of which 17 were deemed relevant for full review. Sixty-seven drugs and/or drug classes and 10 excipients from the original publication were also reviewed. Author and PPA member recommendations highlighted an additional 25 drugs or drug classes. The UpToDate Lexidrug database extraction yielded 1470 drugs, which were filtered to 145 agents for author review. After critical analysis and reorganization, the second edition of the KIDs List contains 39 drugs and/or drug classes and 10 excipients.

CONCLUSIONS This article updates the initial list of drugs and excipients that are potentially inappropriate for prescribing in all or a select subgroup of pediatric patients. The second edition should stimulate novel research to inform future updates.

ABBREVIATIONS AAP, American Academy of Pediatrics; ADR, adverse drug reaction; BPCA, Best Pharmaceuticals for Children Act; ED, emergency department; FDA, US Food and Drug Administration; MeSH, Medical Subject Headings; NSAIDs, nonsteroidal anti-inflammatory drugs; PPA, Pediatric Pharmacy Association; PREA, Pediatric Research Equity Act; WHO, World Health Organization

KEYWORDS adverse drug event; adverse drug reaction; excipients; medications; pediatrics; potentially inappropriate medication list

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Introduction

Adverse drug reactions (ADRs) represent a significant health care burden. Every year, 6 of every 1000 adults will visit the emergency department (ED) for an ADR.[1] Nearly 40% of these visits prompt hospitalization, a setting in which serious ADRs occur in 6.7% of patients with a fatality rate of 0.32%, representing a top-10 cause of death.[2] Specific subpopulations experience higher risk, including those at the extremes of the age spectrum.[3] Serious ADRs account for up to 4% of pediatric hospitalizations and occur in up to 18% of hospitalized pediatric patients.[4–6]

While some ADRs are iatrogenic and unpredictable, others are unintended but expected based on the pharmacology of the drug. Regardless of etiology, these ADRs are most likely preventable. In addition to harm, preventable ADRs add unnecessary burden to the patient and caregivers as well as additional cost to the health care system. It has been documented that up to half of ADRs in hospitalized pediatric patients are preventable.[7]

Multiple underlying reasons for higher rates of ADRs in the pediatric population exist, including frequent off-label drug usage, the need for individualized dose

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calculations, and age-related differences in drug disposition and effect. Currently more than 4400 medications are available in the United States, with approximately 50 new medications being approved each year by the US Food and Drug Administration (FDA).[8] The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) have stimulated significant research on medications in children.[9] However, 64% of new drugs and biologics lack pediatric prescribing information within 5 years of FDA approval.[10] Additionally, indications for 40% of ordered medications in hospitalized pediatric patients and more than 50% in neonates remain off-label.[11,12] In the outpatient setting, approximately 20% of pediatric and more than 80% of neonatal visits result in 1 or more off-label drug prescriptions.[13] Although lack of FDA labeling does not preclude high-quality, evidence-guided therapy, the high frequency of off-label medication use in the pediatric population is mainly due to the use of older, generic drugs, which did not benefit from the research requirements of PREA and BPCA. The use of many of these older drugs may rely on data from case reports, anecdotal observational experience, and historical dogma to inform prescribing patterns in pediatrics.

An important contributing factor leading to an increased rate of ADRs in the pediatric population is the rapid ontogeny of organs involved in the absorption, metabolism, and elimination of systemic drugs.[14] Specific risk points include a thinner stratum corneum in neonates, enhancing percutaneous absorption of topically administered drugs; immature hepatic enzyme systems in infancy, decreasing metabolism; and incomplete renal glomeruli and tubules for the first year after birth, affecting elimination of drugs and/or metabolites. The complexity and timing of the development of each of these organ systems have the potential to increase ADRs from drugs that have a comparatively lower risk of toxicity in adults.

In the early 1990s, geriatrician Mark Beers led a Delphi study to formulate a list of drugs that are potentially inappropriate for use in patients 65 years and older residing in nursing homes.[15] The "Beers Criteria" have since been updated 6 times, expanded to include all adults older than 65 years, endorsed by the American Geriatrics Society, and integrated into a trademarked software application.[16] The Beers Criteria represent a standard of care that has improved safe prescribing and use of drugs in older adults.[17] A comparable evidence-based list of drugs was published in 2020 that sought to bring a similar focus to unintended and preventable ADRs in the pediatric population, namely the Key Potentially Inappropriate Drugs in Pediatrics, or "KIDs List."[18]

The KIDs List has improved medication safety in pediatric patients through dissemination of evidence-based information, incorporation into information systems, and quality improvement initiatives. Clinician-scientists have used the KIDs List to identify medications associated with a high risk for ADRs at pediatric hospitals and health systems caring for pediatric patients.[19–23] Additionally, the KIDs List has catalyzed vital research in the pediatric population, supporting dialogue among interprofessional practitioners, pediatric institutions, and the public.[24–26] To continue this work, the Pediatric Pharmacy Association (PPA) commissioned an expanded group of pediatric pharmacists to evaluate the medical literature and update the list of drugs that should be "avoided" or "used with caution" in all or a subset of the pediatric population.

Materials and Methods

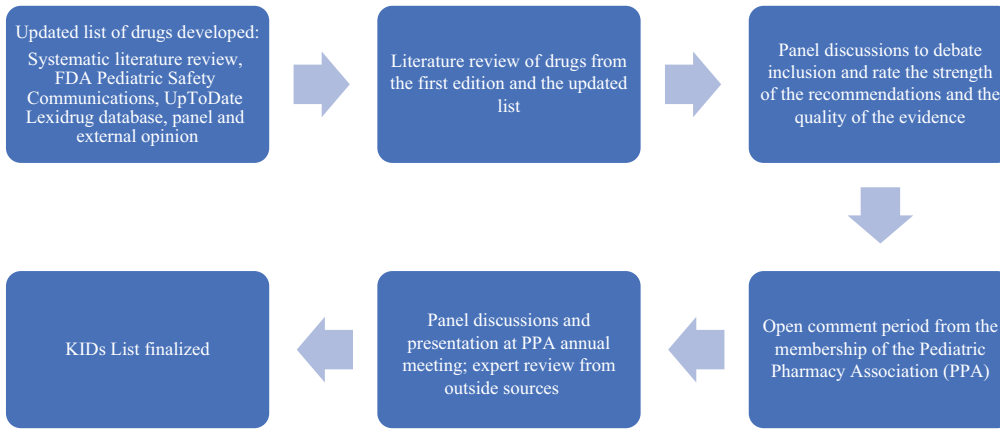
Panel Selection and Composition. The PPA Board of Directors solicited revision of the first edition of the KIDs List on June 20, 2023. All panel members completed a conflict-of-interest disclosure form at the beginning of the process and reaffirmed disclosure at each panel meeting. No panel member had a conflict of interest that precluded participation.

Literature Search and Review. Electronic databases, published communications, FDA product labeling, clinical practice guidelines, panel member expertise, and external reviewers were used to ensure consideration of novel candidate drugs and excipients. The process is described in Figure 1. Published sources were collected, screened, and assessed for eligibility, using the PRISMA strategy.[27]

PubMed. A PubMed search was conducted to identify articles published after data screening for the first KIDs List edition, using a date range of October 1, 2017, to November 1, 2023. The search terms were *adverse drug events* and *adverse drug reactions* as Medical Subject Headings (MeSH) with filters of "English," "Child: birth-18 years," "Humans," and "Case reports," "Observational study," or "Clinical trial." Abstracts were reviewed by 2 panel members. If one of those individuals concluded that the drug or excipient warranted further consideration, the full text was reviewed based on area of subspecialty pediatric expertise and presented to the full panel for consideration.

UpToDate Lexidrug. An UpToDate Lexidrug staff member searched the Lexi-Drugs and Pediatric and Neonatal Lexi-Drugs databases on February 6, 2024. The fields "Warnings: Additional Pediatric Considerations," "Adverse Drug Reaction (Significant) Considerations," "Warnings/Precautions," "Special Alerts List," and "Alert: U.S. Boxed Warnings" were searched by using the following terms: "children" OR "pediatric" OR "neonate" OR "infant" OR "child" OR "adolescent." Two panel members narrowed the list as described in Supplemental Material 1. The list of potential candidate monographs was reviewed by the entire panel with literature searches conducted at the request of any member. Each literature search was conducted by a single panel member, based on area of subspecialty pediatric expertise and presented to the full panel for consideration.

Figure 1. Methods for development of the updated KIDs list.



FDA, US Food and Drug Administration; PPA, Pediatric Pharmacy Association.

FDA Communications. FDA Pediatric Safety Communications (https://www.fda.gov/science-research/pediatrics/fda-pediatric-safety-communications) were searched by 1 panel member. Communications released between January 2019 and March 2024 were reviewed for relevancy for inclusion in the KIDs List.

Anecdotal Observation. Panel members suggested drugs and excipients that were thought to be potentially harmful in pediatric patients. Additionally, the original panel members compiled emails from colleagues regarding exclusions from the first edition. A PubMed search was conducted on each drug. A summary of available evidence was prepared by 2 panelists chosen on the basis of area of subspecialty pediatric expertise. Summaries were reviewed by the full panel.

First-Edition Drugs and Excipients. A PubMed search on each drug was conducted and a summary of available evidence was prepared by 2 panelists chosen on the basis of area of subspecialty pediatric expertise. Summaries were reviewed by the full panel.

External Review. The draft tables were submitted to the members of PPA for review via an electronic communication. Comments were accepted from February 7, 2025, through March 7, 2025. The panel researched all comments for discussion, consensus, and revision to the manuscript, if appropriate.

Operational Definitions. *ADR.* The panel adopted the World Health Organization (WHO) description of an ADR as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man."[28]

Potentially Inappropriate Medication. Potentially inappropriate medications were defined as "medications or medication classes that should generally be avoided in persons 18 years or younger because they pose a higher risk of one or more significant ADRs for children than adults and a safer alternative is available." This list is meant to serve as a clinical tool and is not meant to replace clinical judgment or be used in a punitive manner. Needs of an individual patient, disease(s) management, or unique situations may outweigh the recommendations found in this list. The choice of appropriate medications for pediatric patients should be made by an interprofessional health care team, should include individualized dosing and appropriate monitoring, and should consider the values and preferences of the child and caregivers.

Recommendation (Avoid Versus Caution). Two recommendations were used: avoid and caution. Avoid was used when the authors deemed that evidence of clinical benefit did not outweigh the potential adverse effect based on any of the following: the severity of the adverse effect, the quality of evidence supporting clinical utility, and/or the presence of alternative therapies. Caution was used to describe drugs in which benefit in specific clinical scenarios may warrant use despite evidence demonstrating a higher risk of adverse effect(s) in children than adults.

Strength of Recommendation (Strong or Weak). This assessment reflected a classification by the panel describing the seriousness of an ADR, the extent to which the clinician can confidently conclude that the undesirable effect(s) of the intervention outweighs the desirable effect(s). A "strong" recommendation is predicated on the belief that most informed clinicians would choose the recommended course of action. A strong recommendation implies that a clinician presented with information about a specific ADR would choose to avoid or use the drug cautiously in lieu of assuming the risk of the ADR. A strong recommendation allows clinicians to have confidence in their interactions with patients and to structure discussions accordingly. Conversely, a weak recommendation is

consistent with significant variability in the clinician's decision when presented with information about a specific ADR. The clinician must carefully examine specific treatment decisions in this context because these decisions may vary according to the caregivers' and patients' values and preferences.

Quality of Evidence. The quality of evidence reflects the aggregate of published information. The quality of evidence definitions used for the "KIDs List: Second Edition" were based on those from the GRADE recommendations and the Beers Criteria.[29,30] An assessment of "high" quality indicates that further published information or research is very unlikely to alter our confidence in the recommendation or estimate of ADR effect. "Moderate" quality suggests that further research may have a significant impact on our confidence because it may influence or change the evidence regarding a recommendation. "Low" quality implies that further published information or research is likely to affect our confidence in the estimate of effect and may change the conclusion. The KIDs List panel elected to use a "very low" classification of evidence given the paucity of high-quality data on ADRs in pediatrics. "Very low" quality implies that any estimate of effect is very uncertain.

Scope. This list should serve as a useful resource for clinicians and institutions caring for pediatric patients and provide a basis for allocation of resources and additional research to improve drug safety in the pediatric population. During the review process, only those drugs approved for use in the United States, regardless of FDA-labeled age, were considered. Hence, application of this list for pediatric patients in countries other than the United States may be incomplete. It should be noted that some drugs included on this list are also on the WHO Model List of Essential Medicines for Children.[31] Acceptable therapeutic alternatives readily available in the United States (for the same indication) played a role in the expert panel's determination to include a drug in the KIDs List. The KIDs List is not intended to supersede recommendations for drugs found in the WHO Model List of Essential Medicines for Children. Use of these drugs outside the United States for certain clinical conditions may be warranted.

Intent and Audience. The intent of the KIDs List is to improve the safety of medication use in pediatric patients, educate clinicians, and serve as a quality improvement tool. The primary target audience of this publication is health care professionals caring for patients 18 years of age or younger regardless of setting. The KIDs List is intended to be an evidence-based guide to supplement clinical decision-making. The recommendations do not suggest absolute contraindication of any drug in any pediatric patient. As in all medical cases, the entire clinical picture of the patient must be assessed and evaluated by the health care professionals directly involved in the patient's care. Treatment with drugs on this list may be warranted depending on the clinical situation. The KIDs List is not a substitute for clinical judgment. There may be specific populations or diseases for which treatment with any of these drugs is warranted.

Results

Between September 2023 and October 2024, the panel held monthly virtual meetings; live meetings occurred on May 2 and May 3, 2024. A summary of the systematic review and identification of included drugs and excipients is outlined in Figure 2. The initial PubMed search yielded 917 unique titles. Panel members identified 17 articles for full-text review. A search of all 4149 drugs included in the 2 UpToDate Lexidrug databases yielded 1470 unique drugs of which 145 were included for consideration by the full panel (Supplemental Material 1). No relevant FDA Pediatric Safety Communications from the period since the original KIDs List were identified. Twenty-five drugs or drug classes were evaluated on the basis of anecdotal observation. Sixty-seven drugs and/or drug classes and 10 excipients were evaluated on the basis of their inclusion in the first edition.

The final KIDs List contains 39 drugs or drug classes (Table 1). There was sufficient evidence to classify 18 drugs/drug classes as "avoid" in all or a subgroup of pediatric patients; 19 are classified as "use with caution"; 2 drugs were included owing to dosing or concentration limits specific to pediatric patients. Sixty-seven percent of drugs classified as "avoid" had a combination of strength of recommendation plus quality of evidence as either "strong" and "high" or "strong" and "moderate."

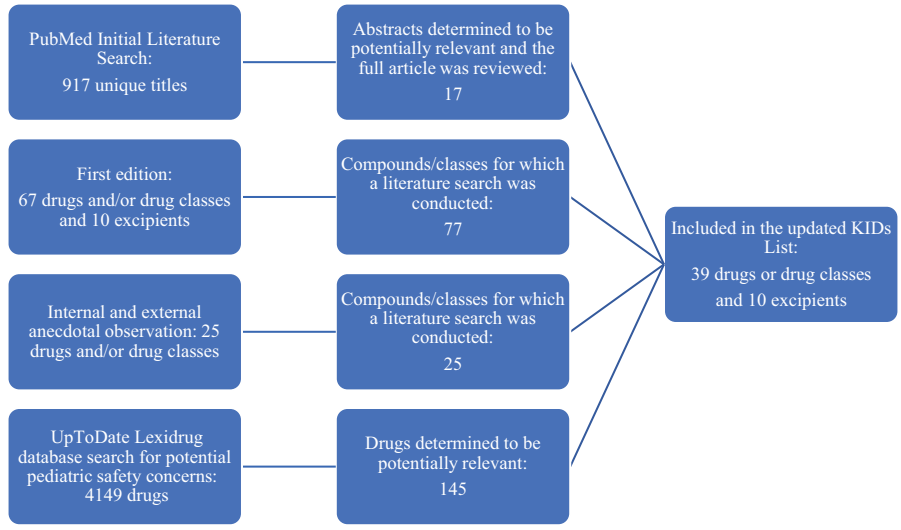
Drugs removed from or added to the KIDs List are outlined in Supplemental Material 2. Among the 5 drugs removed from the list, 3 were removed owing to lack of commercial availability in the United States, while 2 were removed owing to emerging evidence. All drugs added to the KIDs List occurred in the setting of low or very low quality of evidence, primarily consisting of product labeling.

Ten excipients were identified (Table 2). All 4 "avoid" recommendations were conditional, with 3 as dose limitations and 1 contingent upon newborn genetic screening. Moderate- or high-quality evidence drove most recommendations (70%).

Discussion

Lack of an updated evidence-based reference prompted the first edition of the KIDs List.[18] The current publication is an update of the list of potentially inappropriate drugs in pediatrics, reflecting the most current information. Refining the initial process and expanding the author panel led to a carefully compiled list of 39 drugs or drug classes and 10 excipients warranting avoidance or caution in some or all pediatric patients. Notably, these figures represent relative

Figure 2. Results of literature search, expert opinions, FDA Pediatric Safety Communications, and UpToDate Lexidrug database search.



FDA, US Food and Drug Administration.

equilibrium with the first edition, with specific attention paid to highlighting class effects, when supported by evidence. Several debates occurred during roughly 20 hours of panel meetings to produce simple, concise, consensus recommendations, ranging from ancient debates about tetracyclines and teeth to emerging controversies regarding the safety and efficacy of neuropsychiatric medications in children. We have highlighted the rationale behind some of the committee's recommendations below.

Tetracyclines. The impact of tetracycline on teeth has been acknowledged for well over 60 years.[32] Emerging evidence since the first publication of the KIDs List allowed a closer examination of the tetracycline antibiotics as a class. A strong recommendation is now being made to caution against the use of several additional tetracyclines owing to tooth discoloration. It is likely that additional research will further inform the strength of this recommendation. While tetracyclines are known to bind to calcium and are incorporated into teeth and bone to some extent with bone remodeling in persons of all ages, tooth discoloration is most prominent when tetracyclines are administered before mineralization of the succedaneous teeth is completed by 8 years of age, excluding third molars.[33] Although tetracyclines should be avoided in children younger than 8 years, their use may be necessary in some children. Of note, while doxycycline has a similar molecular structure to tetracycline, *in vivo* reports of tooth discoloration, enamel hypoplasia, and bone growth retardation are largely lacking. Therefore, its use in young children is recommended as first-line for the short-term treatment (21 days or less) of susceptible infections, such as rickettsial disease, Lyme disease, vibriosis, and anthrax, where equally effective alternatives are not available.[34]

Antipsychotics. Pediatric mental health has strained the global health system with many clinical considerations informing the use of antipsychotics in youth.[35] Youth are at an increased risk for acute dystonic reactions and hyperprolactinemia with the use of first-generation antipsychotics (e.g., haloperidol) given sensitivity to their potent D_2 blockade within the nigrostriatal and tuberoinfundibular dopamine pathways.[36–40] While first-generation antipsychotics are sometimes used in clinical practice, particularly for the management of acute agitation or aggression, the panel agreed that alternative agents (e.g., olanzapine) are available with a reduced risk for adverse effects. This recommendation is in alignment with updated pediatric treatment guidelines and literature.[41–43]

While second-generation antipsychotics are a reasonable alternative to first-generation antipsychotics in some instances, the panel also considered their many pediatric-specific adverse effects. Metabolic risk is of critical importance in this age group, considering that youth are at an increased risk for developing weight gain, metabolic syndrome, dyslipidemia, and/or type 2 diabetes with second-generation antipsychotic use.[44] The panel acknowledged that their long-term use cannot be avoided in youth with a severe mental illness (i.e., schizophrenia spectrum, bipolar mood disorders), but there are many evidence-based medication alternatives for other indications (e.g., stimulants for impulsive aggression in the setting of attention-deficit/hyperactivity

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Angiotensin receptor blockers[66–69] Azilsartan Candesartan Irbesartan Losartan Olmesartan Telmisartan Valsartan	Renal tubular dysgenesis	Caution in younger than 1 mo	Weak	Very low
Atazanavir[70,71]	Kernicterus	Caution in younger than 3 mo unless pharmacogenetic testing is used	Weak	Very low
Camphor, topical[72–74]	Seizures	Caution in 18 yr of age and younger	Weak	Very low
Carbinoxamine[75]	Death	Avoid in younger than 2 yr	Strong	Low
Ceftriaxone[76–79]	Kernicterus	Caution in younger than 3 wk except for one-time doses for gonococcal treatment	Weak	Very low
Chloramphenicol[80]	Gray baby syndrome	Avoid in younger than 1 mo unless serum concentration monitoring is used	Strong	High
Chlorhexidine, topical[81–83]	Chemical burn	Caution with concentrations >0.5% in less than 7 days old and less than 34 weeks' gestation Caution with concentrations ≥2% in younger than 1 mo	Weak	Low
Corticosteroids, topical (medium, high, and very high potency)[84]	Cushing syndrome, adrenal suppression	Avoid in younger than 2 yr for diaper dermatitis	Strong	Low
Darunavir[85]	Seizures, death	Avoid in younger than 3 yr or ≤10 kg	Strong	Very low
Dicloxacillin[86]	Kernicterus	Caution in younger than 1 mo	Weak	Very low
Dicyclomine[87,88]	Apnea	Avoid in younger than 6 mo	Strong	Low
Difluprednate[89,90]	Increased intraocular pressure	Caution in 18 yr of age and younger	Weak	Low

(Table cont. on page 428)

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition *(cont.)*

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Diphenoxylate and atropine[91,92]	Respiratory failure, death	Avoid in younger than 6 yr	Strong	Moderate
Dopamine antagonists				
First-generation antipsychotics[36–40] Chlorpromazine Droperidol Fluphenazine Haloperidol Loxapine Perphenazine Pimozide Thiothixene Thioridazine Trifluoperazine	Acute dystonic reactions (e.g., oculogyric crisis, torticollis)	Avoid in 18 yr of age and younger	Strong	High
	Hyperprolactinemia		Weak	High
Prochlorperazine[93–95]	Acute dystonic reactions (e.g., oculogyric crisis, torticollis)	Avoid in younger than 2 yr Caution in 2–18 years of age	Strong	Moderate
Second-generation antipsychotics[36,37,44,46,47] Aripiprazole Asenapine Brexpiprazole Cariprazine Clozapine Iloperidone Lurasidone Lumateperone Olanzapine Paliperidone Quetiapine Risperidone Ziprasidone	Withdrawal emergent dystonia/ dyskinesia	Avoid rapid discontinuation in 18 yr of age and younger	Strong	High
	Type 2 diabetes, weight gain, dyslipidemia, and/or metabolic syndrome (risk greater for clozapine ≥ olanzapine > quetiapine > risperidone, paliperidone, iloperidone > asenapine > aripiprazole, brexpiprazole > lurasidone, cariprazine > ziprasidone, lumateperone)	Avoid use of olanzapine for a duration of >12 wk in 18 yr of age and younger Caution in 18 yr of age and younger	Strong	High
	Hyperprolactinemia (risk greater for paliperidone > risperidone > olanzapine)	Caution in 18 yr of age and younger	Strong	High
Metoclopramide[93,96,97]	Acute dystonic reactions (e.g., oculogyric crisis, torticollis)	Avoid in younger than 1 yr Caution in 1–18 yr of age	Strong	High

(Table cont. on page 429)

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition *(cont.)*

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Promethazine[98,99]	Respiratory failure, death Acute dystonic reactions (e.g., oculogyric crisis, torticollis)	Avoid in younger than 2 yr Caution in 2–18 yr of age	Strong	Moderate
Trimethobenzamide[100,101]	Acute dystonic reactions (e.g., oculogyric crisis, torticollis)	Avoid in 18 yr of age and younger	Strong	Low
Ester local anesthetics				
Benzocaine, topical[102]	Methemoglobinemia	Avoid oral application in younger than 2 yr	Strong	High
Lidocaine viscous, topical[103,104]	Central nervous system depression, seizures, arrhythmia, death	Avoid oral application in younger than 2 yr	Strong	High
Gentamicin ophthalmic ointment[105–107]	Severe ocular reactions	Avoid in younger than 1 mo	Strong	High
Guanylate cyclase-C agonists				
Linaclotide[108]	Death from dehydration	Caution in younger than 2 yr	Weak	Very low
Plecanatide[109]	Death from dehydration	Caution in 18 yr of age and younger	Weak	Very low
Lamotrigine[37,110,111]	Skin rashes ranging in severity from benign to life-threatening	Caution in 18 yr of age and younger; slow dose titration required	Strong	High
Loperamide[112]	Ileus, lethargy	Avoid in younger than 3 yr for acute infectious diarrhea	Strong	High
Macrolides[34,113–115] Azithromycin Erythromycin	Hypertrophic pyloric stenosis (risk greater for erythromycin > azithromycin)	Avoid in younger than 1 mo except for *Bordetella pertussis* (azithromycin) or *Chlamydia trachomatis* pneumonia (azithromycin and erythromycin). Caution in younger than 1 mo for *Ureaplasma* (azithromycin).	Strong	High

(Table cont. on page 430)

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition *(cont.)*

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Malathion, topical[116,117]	Organophosphate poisoning	Caution in younger than 2 yr	Weak	Very low
Midazolam[118,119]	Severe intraventricular hemorrhage, periventricular leukomalacia, or death	Caution in patients weighing less than 1500 g	Weak	Low
Mineral oil[120]	Lipid pneumonitis	Avoid in younger than 1 yr	Strong	Low
Mirabegron[121]	Increased blood pressure	Caution in younger than 3 yr	Weak	Very low
Molnupiravir[122]	Bone and cartilage toxicity	Caution in 18 yr of age and younger	Weak	Very low
Montelukast[123]	Sleep disturbances	Caution in 18 yr of age and younger	Weak	Very low
Naloxone[124]	Seizures	Avoid in neonates for postpartum resuscitation	Strong	High
Nitrofurantoin[125]	Hemolytic anemia	Avoid in younger than 1 mo	Weak	Very low
Opioids				
Codeine[126–130]	Respiratory failure, death	Avoid in younger than 12 yr Avoid in 12–18 yr of age after surgery to remove tonsils and/or adenoids Caution in 12–18 yr of age Recommend pharmacogenetic testing	Strong	High
Meperidine[131,132]	Acute neurotoxicity (agitation, myoclonus, hyperreflexia, tremors, delirium, seizures)	Avoid in younger than 1 mo Caution in 18 yr of age and younger	Strong	High
Opium tincture[133]	Respiratory failure	Avoid in younger than 1 mo Caution in 18 yr of age and younger	Weak	Low

(Table cont. on page 431)

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition *(cont.)*

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Tramadol[129,130,134]	Respiratory failure, death	Avoid in younger than 12 yr Avoid in 12–18 yr of age after surgery to remove tonsils and/or adenoids Caution in 12–18 yr of age Recommend pharmacogenetic testing	Weak	Low
Propofol[135–137]	Propofol-related infusion syndrome	Avoid doses >4 mg/kg/hr for greater than 48 hr in 18 yr of age and younger	Strong	Moderate
Ribavirin (oral inhalation)[138]	Sudden respiratory deterioration	Caution in younger than 2 yr	Strong	Low
Salicylates[139,140] Aspirin Bismuth Subsalicylate Salicylic Acid (topical) Salsalate	Reye syndrome	Caution in 18 yr of age and younger with suspicion of viral illness (influenza and varicella)	Weak	Very low
Sodium phosphate solution enema, rectal[141,142]	Electrolyte abnormalities, acute kidney injury, arrhythmia, death	Avoid in younger than 2 yr	Strong	High
Sodium polystyrene sulfonate[143,144]	Colonic perforation	Caution in patients weighing less than 1500 g	Weak	Low
Sulfonamides[145] Silver sulfadiazine, topical Sulfadiazine Sulfamethoxazole	Kernicterus	Caution in younger than 1 mo	Weak	Very low

(Table cont. on page 432)

disorder). While metabolic risk is a class effect, it is important to acknowledge that olanzapine is the only agent that has a manufacturer-specific recommendation to avoid its use first-line in youth given its high risk for metabolic adverse effects.[45] When clinically necessary to use a second-generation antipsychotic, agents with a lower metabolic risk should be considered (see Table 1 for risk delineation). Withdrawal-emergent dystonia/dyskinesia and hyperprolactinemia were also included as important considerations with second-generation antipsychotics, based on updated literature to support pediatric-specific risk.[36,37,44,46,47]

Montelukast. An enhanced focus on pediatric mental health has contributed to novel concerns regarding widely used medications. Montelukast has played a prominent role in the treatment of asthma and allergic conditions in children since its approval in 1998. In 2020, the FDA released a boxed warning about serious neuropsychiatric adverse effects with montelukast.[48] These effects include irritability, aggression,

Table 1. Key Potentially Inappropriate Drugs in Pediatrics (KIDs) List: Second Edition *(cont.)*

Drug (Systemic Administration Unless Otherwise Noted)	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Tetracyclines[33,146–150] Demeclocycline Eravacycline Minocycline Omadacycline Sarecycline Tetracycline Tigecycline	Tooth discoloration	Caution in younger than 8 yr	Strong	High (demeclocycline, tetracycline) Low (minocycline, sarecycline, tigecycline) Very low (eravacycline, omadacycline)
	Enamel hypoplasia (tetracycline)	Caution in younger than 8 yr	Strong	High
	Retardation of skeletal development and bone growth (tetracycline)	Caution in younger than 1 mo	Strong	Moderate
Tricyclic antidepressants[37,151–153] Desipramine Imipramine	Sudden cardiac death	Avoid in 18 yr of age and younger	Strong	High (desipramine) Moderate (imipramine)
Valproic acid and derivatives[37,154–156]	Pancreatitis, fatal hepatotoxicity	Avoid in younger than 2 yr Caution in 2–6 yr	Strong	High
Verapamil[157–159]	Cardiovascular collapse	Caution in younger than 1 yr	Weak	Low

anxiety, and mood disorders and have been reported in both adults and children with similar frequencies. Sleep disturbances such as nightmares have been shown to occur more commonly in children.[49–52] Thus, the KIDs List recommendation is to use caution in children 18 years and younger. While the level of evidence for this recommendation is very low, clinicians should consider the overall risk of neuropsychiatric effects in each individual patient. The KIDs List recommendation is based on the evidence of an increase in sleep disturbances in children. Current evidence does not indicate an overall increased risk in children compared with adults, thus precluding a higher-level warning with montelukast in the KIDs List. Use of montelukast in children should be limited to patients who will benefit and who can be closely monitored for neuropsychiatric effects.

Dopamine Receptor Antagonists. Evidence regarding dopamine receptor antagonists and their therapeutic competitors challenged the authors, given their prevalent adverse effects contrasted against clear therapeutic niches. An increased prevalence or recognition of migraines in pediatric patients has stressed EDs nationwide.[53] Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and triptans are guideline-recommended treatment options for pediatric migraines.[54] Emerging literature has suggested that the pathophysiology of pediatric migraines may differ from that of adults.[55] In fact, several studies evaluating triptans for the treatment of pediatric migraine have not demonstrated greater efficacy than placebo. The guidance on medication selection in the ED after NSAIDs, acetaminophen, and/or triptan failure remains limited; however, the development of a standardized migraine protocol that incorporated non-opioid analgesia and a dopamine receptor antagonist was associated with improved patient outcomes.[56] While caution is certainly warranted in pediatric patients, prochlorperazine has demonstrated efficacy for the treatment of acute pediatric migraines; coadministration with diphenhydramine is a reasonable precaution given the risks of developing acute dystonic reactions.[57,58] Metoclopramide may be less effective than prochlorperazine but is a sensible alternative if prochlorperazine is not available or on shortage.[59] Further research is necessary to fully

Table 2. Excipients With Known or Potential Harms When Used in Pediatric Patients

Excipient (Systemic Administration Unless Otherwise Specified)	Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Benzyl alcohol, sodium benzoate, benzoic acid[63,160,161]	Gasping syndrome	Avoid exposure of >99 mg/kg/day in younger than 1 mo (with the exception of sodium phenylacetate/sodium benzoate used for the treatment of urea cycle disorders)	Strong	High
Ethanol/ethyl alcohol[19,63–65] **(excluding ethanol lock)**	CNS depression, hypoglycemia	Caution in younger than 6 yr: maximum 0.5% v/v ethanol with clinician supervision Caution in younger than 12 yr: maximum of 5% v/v ethanol with clinician supervision	Strong	Moderate
Isopropyl alcohol, topical[162,163]	Chemical burn	Caution in patients weighing less than 1500 g	Weak	Low
Methylparaben, propylparaben[164]	Kernicterus	Caution in younger than 2 mo	Weak	Very low
Phenylalanine[165]	Cognitive and behavioral problems	Avoid in 18 yr of age and younger with an unknown phenylketonuria test	Strong	High
Polysorbate 80[166–168]	Vasculopathic hepatotoxicity (E-Ferol syndrome)	Avoid exposure of ≥72 mg/kg/day in younger than 1 mo Caution exposure of >1.4 mg/day in younger than 1 mo	Strong	High
Propylene glycol[169]	Lactic acidosis, CNS depression, hypoglycemia, hemolysis, seizure	Avoid >1 mg/kg/day in younger than 1 mo Avoid >50 mg/kg/day in 1 mo of age or older to younger than 5 yr	Strong	Moderate

CNS, central nervous system

elucidate the optimal abortive regimen for children presenting to the ED for migraines, particularly after failure of guideline-recommended regimens.

Daptomycin. Important limitations of the KIDs List highlight gaps in knowledge that continue to affect the safety of pharmacotherapy in pediatric patients. As an example, daptomycin was included in the first edition of the KIDs List and subsequently removed in this iteration. The citation in the first edition was the package insert, which continues to state, "Daptomycin for Injection is not recommended in pediatric patients younger than one year of age due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs."[60] The recommendation of caution in the first edition was appropriately classified as weak on the basis of very low-quality evidence. Emerging evidence highlights essential and safe use of daptomycin in infants younger than 1 year.[61,62] Although published evidence represents a small number of infants and ongoing evidence-generation is warranted, human data were given greater weight in our analyses than animal or *in vitro* data. In contrast to daptomycin, many drugs remain on the KIDs List, based on animal or *in vitro* data in the absence of formal human study.

Diphenoxylate/Atropine. Panel members were challenged by clear manufacturer recommendations from product labeling without corresponding supporting data published in peer-reviewed journals. Owing to reported cases of severe respiratory depression and coma, diphenoxylate and atropine should not be administered to patients younger than 2 years. The tablet formulation, specifically, is contraindicated in children younger than 6 years (and recommended for ≥13 years of age). The panel did not change the recommendation from the previous edition and recognizes the challenge for clinicians now that the liquid

product has been discontinued from the market. As more safety data emerge in the pediatric population, the recommendation will be reevaluated. Labeled dosing and warnings will be scrutinized for inclusion and exclusion.

Excipients – Ethanol. Excipients represent a unique challenge to clinicians serving pediatric patients and similarly challenged the authors. Ethanol is commonly used as an excipient to enhance solubility of drugs in solution and prevent microbial growth. Its use in liquid medications for children, both intravenous and oral, has been a cause for concern for decades.[63,64] In 1984, the American Academy of Pediatrics (AAP) published recommendations on limits for alcohol concentrations in over-the-counter medications, and the FDA has similar recommendations published in the Federal Register.[64,65] Despite the recommendations from the AAP and FDA on limits for over-the-counter medications, no recommendations exist for prescription products. In a study published in 2024, seven medications used in pediatric patients were shown to have the potential to increase blood alcohol concentrations above 2.5 mg/dL, which is approximately equivalent to the concentration an adult would experience upon consumption of 10 mL of wine.[19] While the clinical implications of increased blood alcohol concentrations in infants and children remain theoretical, the high concentrations found in some medications for children remain a concern. The current KIDs List recommendation mirrors the limits from the FDA for over-the-counter products, but more data on its risks would help provide clarity on safe limits. Notably, no complete list of drugs containing benzyl alcohol, ethanol, propylene glycol, and other excipients exists. We considered excipients individually and included available information, with a specific focus on thresholds for toxicity. Clinicians must remain diligent in identifying the presence and concentration of these excipients in drugs prescribed to pediatric patients.

Conclusions

An extensive review of primary literature and tertiary references, followed by a robust panel discussion of pediatric pharmacotherapy specialists, facilitated an updated list of drugs and excipients that should generally be avoided or used with caution in all or select subgroups of pediatric patients. The first edition of the KIDs List has served as a valuable tool to improve drug safety for children, functioning as an evidence-based reference of the risks associated with relatively contraindicated drugs in the pediatric population. The list also has served as a reference to combat historical dogma, accurately reflecting the rationale and level of evidence supporting contraindications and highlighting knowledge gaps in the published literature. Recommendations have been revised from the 2020 publication, based on novel research and robust feedback from the community of health care professionals serving pediatric patients. Knowledge of pediatric pharmacology has expanded at an encouraging pace to inform the second edition of the KIDs List. However, significant gaps in knowledge still exist and justify the promotion of both prospective and retrospective safety studies of pediatric pharmacotherapy. This list represents a single step in the ongoing work of clinicians and researchers to continuously improve drug safety for children.

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JPPT | Invited Review

Under the Influence: Cognitive Effects of Medical Marijuana on Developing Minds

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Cannabis is a highly discussed topic in medicine today. From therapeutic applications in conditions such as chronic pain, multiple sclerosis, epilepsy, chemotherapy-induced nausea and vomiting, and inflammatory bowel disease to the growing prevalence of recreational use, cannabis remains at the forefront of medical and societal conversations. In this review, we will explore the history of marijuana use in medicine, examine the current evidence supporting its pharmacological benefits, and delve into its impact on the developing brain. Additionally, we will highlight the pivotal role pharmacists play in this evolving landscape and guide you through the latest research findings.

ABBREVIATIONS 5-HT, serotonin; AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians and Gynecologists; AMA, American Medical Association; ASCO, American Society of Clinical Oncology; CB1, cannabinoid-1; CB2, cannabinoid-2; CBD, cannabidiol; CD, Crohn disease; CDC, Centers for Disease Control and Prevention; CINV, chemotherapy-induced nausea and vomiting; CSA, Controlled Substances Act; DEA, Drug Enforcement Administration; DOJ, US Department of Justice; FAAH, fatty acid amide hydrolase; FDA, US Food and Drug Administration; GABA, gamma-aminobutyric acid; GI, gastrointestinal; GPR55, G-protein coupled receptor 55; HCP, health care provider; HEC, highly emetogenic chemotherapy; HHS, US Department of Health and Human Services; IASP, International Association for the Study of Pain; IBD, irritable bowel disease; IQ, intelligence quotient; JAMA, Journal of the American Medical Association; MEC, moderately emetogenic chemotherapy; M/P, milk-to-plasma ratio; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSCA, McCarthy Scales of Children's Abilities; NICU, neonatal intensive care unit; THC, delta-9-tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid 1; TSC, tuberous sclerosis complex, USP, US Pharmacopeia; WHO, World Health Organization.

KEYWORDS cannabinoids; cannabis; epilepsy; fetal development; marijuana

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Introduction

In May 2024, the US Department of Health and Human Services (HHS) and Department of Justice (DOJ) requested that the Drug Enforcement Administration (DEA) reschedule marijuana to schedule III from schedule I under the Controlled Substances Act (CSA). According to the CSA, a drug in schedule I is a drug with a high potential for abuse, no currently accepted medical use, and a lack of accepted safety for use under medical supervision. Drugs in schedule III on the other hand, have a lower potential for abuse, have accepted medical use, and moderate or low propensity for physical dependence or high psychological dependence.[1] Rescheduling marijuana to schedule III will not only decriminalize it, but it will open the doors to facilitating research on pharmaceutical cannabinoids.

Brief History of Use

The earliest documented consumption for medicinal purposes is 4000 BC, when cannabis was used as medicine by the Chinese for a range of women's health conditions including dysmenorrhea, dysuria, and hyperemesis gravidarum.[2,3] In 2000 BC, cannabis plants were used as food, medicine, and clothing all over the world. Flash forward to the Victorian era, where Indian cannabis was used by neurologists for the treatment of epilepsy. Later in 1851, the US Pharmacopeia (USP) classified marijuana as a treatment for epilepsy, chronic migraines, and pain. The Great Depression also brought a great shift in perspective with marijuana use. Marijuana use was perceived to promote crime and adverse social consequences. At this point, medical marijuana did not require a prescription. The Marihuana Tax Act of 1937 imposed tax on the sale of cannabis, hemp, or marijuana. In 1941, despite opposition from the American Medical Association (AMA) and physicians who believed in the medical efficacy of marijuana, all cannabis preparations were removed from the USP and National Formulary. The Controlled Substances Act (CSA) was passed in 1970 and classified cannabis as a schedule I drug, making it illegal for any use.[4]

Current State

Marijuana has become a hot topic over the last few years, and increasingly popular in use for medicinal and non-medicinal reasons. Its medicinal use affects nearly all body systems. There are over 100 phytocannabinoids derived from the genus Cannabis plant. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the 2 most common and work on cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors. It is a partial agonist in both CB1 and CB2 receptors and achieves its psychoactive properties through modulation of gamma-aminobutyric acid (GABA) and glutamate. Unlike CBD, THC is a proconvulsant while CBD is an anticonvulsant. CBD does not appear to bind to either CB1 or CB2 but does possess neuroprotective and anti-inflammatory effects. Although both have the same chemical formula, $C_{21}H_{30}O_2$, THC has a cyclic ring while CBD has a hydroxyl group.[5] CB1 receptors are located throughout the wall of the gut and peripheral nervous system. Acute stimulation of CB1 receptors causes a reduction of motility and secretion of the gastrointestinal (GI) system, mediated by motor, secretory, and sensory afferent neurons. Located on immune cells and other neurons in the epithelium and gut wall, CB2 receptors are upregulated in inflammatory states. Stimulation of CB2 receptors is anti-inflammatory and activates the immune system.[6] THC is known for supplying the user with the traditional "high" as it has more psychotropic effects.

In December of 2018, the 2018 Farm Bill was signed into law. It removed hemp, defined as cannabis (*Cannabis sativa* L.) and derivatives of cannabis with no more than 0.3% THC on a dry weight basis, from the definition of marijuana in the CSA. This meant that CBD and THC can be sold over the counter in all dosage forms including gummy candies, dabs, vapes, tinctures, oils, and more as long as the products contained no more than 0.3% of THC. Over the counter, delta-8-tetrahydrocannabinol, synthetic variations, and other blends have gained popularity. Little research has been done on the long-term effects, efficacy, and dosing of these products. Behind the counter, prescription-only US Food and Drug Administration (FDA) approved products include dronabinol and nabilone, which are both THC derived products and cannabidiol, which is a CBD-derived product.[7] The body of literature for the efficacy of medical marijuana for various disease states increase on a daily basis. As of April 2024, over 70% of the United States has legalized marijuana for recreational and medical use.[8] What does that mean? Marijuana use may increase both recreationally and medically. What else does that mean? More research needs to be done to assess its effects on the pediatric brain, from in utero to adolescence. In this review, we will review the history of marijuana use in medicine, discuss the current evidence supporting its pharmacological use in chemotherapy-induced nausea and vomiting (CINV), multiple sclerosis (MS), irritable bowel disease (IBD), epilepsy, and chronic pain, and outline the effects marijuana has on the developing brain.

Cannabinoids, Cannabis, and Marijuana

Before we delve in, we should focus on some key definitions.

Cannabis: all products derived from the plant *Cannabis sativa*.

Cannabinoids: group of substances found in the cannabis plant. The 2 main cannabinoids are CBD and THC.

Marijuana: parts of or products from the plant *Cannabis sativa* that contain substantial amounts of THC.[9]

All 3 of these words will be used in this review; however, they cannot be used interchangeably (Table).

Pharmacotherapeutic Uses

Pain. Chronic pain, characterized by persistent or recurrent discomfort lasting more than 3 months, is a prevalent issue among children. A systematic review from The Journal of International Association for the Study of Pain (IASP) assessed the prevalence of chronic pain in children and adolescents. These authors reported a rate of 20.8%, signifying approximately 1 in 5 young individuals experiencing persistent pain.[11] Children with chronic pain often report significant physical disability, emotional distress, anxiety and depression, and sleep disturbances, compared with peers without this condition.[12,13] The World Health Organization (WHO) guidelines on the management of chronic pain highlight that an interdisciplinary and multimodal approach should be tailored to the unique needs of the child and caregivers. This strategy incorporates multiple modalities to effectively

Table. Pharmacokinetics of Inhaled vs Enteral Cannabis[6,10]

Parameter	Inhaled Cannabis	Enteral Cannabis
Onset	Seconds to minutes	2 hr
Duration	1–2 hr	2–4 hr
Bioavailability	Readily absorbed	THC: 5%–20% CBD: 6%–19%
Half life	THC: 30 hr; CBD: 9–32 hr	
Metabolism	Metabolized by and potent inhibitor of CYP2C19 and CYP3A4	
Tolerance	Downregulation of CB1 receptors	
Plasma protein binding	Highly protein bound	

CB1, cannabinoid-1; CBD, cannabidiol; THC, delta-9-tetrahydrocannabinol

address chronic pain management including physical, psychological, or pharmacological interventions.[14] Several case reports highlight pediatric patients with conditions such as neuropathic pain, cancer pain, spasticity-related pain, and chronic pain syndromes, where traditional treatments were insufficient, leading to the consideration of medical marijuana as an alternative option for symptom relief.

The American Academy of Pediatrics (AAP) opposes the use of medical marijuana outside the regulatory framework of the FDA.[15] However, there is acknowledgement that marijuana may be considered an option for children with life-limiting or severely debilitating conditions when current therapies are unable to provide sufficient relief. Medical marijuana plays a promising role in pediatric palliative care, particularly in its potential to alleviate symptoms and maximize quality of life for children with unpleasant or intolerable pain. Compared with opioid regimens, marijuana possibly offers benefits by supporting refractory pain management and reducing polypharmacy, often with fewer or milder adverse effects.[16]

A 15-year-old with hypoxic brain injury and spastic quadriplegia used medical marijuana to manage refractory spasticity and pain unresponsive to baclofen, botulinum toxin injections, and nerve blocks. After starting 3 times daily 1:1 THC:CBD regimen (unknown formulation and dose), she experienced significant pain relief, improved facial muscle function, and progress in therapy. Following spinal fusion and an oxycodone wean, her marijuana use became irregular due to increased drowsiness and limited product availability. When her supply ran out, a noticeable decline in quality of life occurred, which improved upon resumption of therapy.[17]

An 11-year-old with relapsed rhabdomyosarcoma was prescribed an oil-based tincture in a 1:1 THC:CBD ratio (dose in milligrams is not specified). Drops were administered 3 times daily to manage treatment-resistant nausea, appetite loss, anxiety, and pain. The regimen resulted in significant symptom improvement, allowing discontinuation of multiple medications, including acetaminophen and gabapentin. After 8 months, the THC:CBD was temporarily discontinued to investigate a fever, which was later determined to be caused by typhlitis rather than the THC:CBD tincture. During the pause, the patient experienced increased anxiety and pain, which resolved upon reinitiating both marijuana and gabapentin.[17]

Epilepsy. According to the Centers for Disease Control and Prevention (CDC), 1% of children have epilepsy in the United States and it is the most frequent chronic neurologic condition in childhood.[18] While the precise mechanisms by which CBD exerts its anticonvulsant effects in epilepsy are not yet fully elucidated, growing evidence suggests that it works by decreasing neuronal hyperexcitability through a combination of actions. CBD appears to antagonize G-protein coupled receptor 55 (GPR55) receptors at excitatory synapses, desensitize transient receptor potential vanilloid 1 (TRPV1) channel, and inhibit adenosine reuptake, all of which may contribute to its ability to control seizures.[19]

The largest clinical trials to date examining plant-derived, highly purified cannabidiol use in children with epilepsy were trial 1/NCT02224560, trial 2/NCT02224690, trial 3/NCT02091375, and trial 4/NCT02091375, which collectively involved 550 patients ranging in age from 2 to 55 years old with Lennox-Gastaut or Dravet syndromes and were conducted at 58 sites across Europe and the United States. These trials provided critical evidence supporting the efficacy and safety of cannabidiol (Epidiolex), contributing to its status as one of the most well-researched and widely used CBD treatments for pediatric epilepsy.[20] Key findings from trials 1 and 2 included a 44% reduction ($p = 0.01$) in drop seizures and in trial 3 a 39% reduction ($p = 0.01$) in convulsive seizures in at a dose of 20 mg/kg/day of Epidiolex.[21–23] Although these studies only looked at seizures associated with Dravet syndrome and Lennox-Gastaut syndrome, its efficacy has been widespread throughout many epilepsy syndromes, with the newest FDA approval in 2020 for seizures associated with tuberous sclerosis complex (TSC). Key findings from the study in TSC patients aged 1 to 56 years old included a 30.1% reduction from baseline seizures in the 25 mg/kg/day group and a 28.5% reduction in the 50 mg/kg/day group. The most common side effects across all studies included diarrhea, appetite suppression, and somnolence.[24]

It is crucial for health care providers (HCPs) to emphasize the difference between Epidiolex and other cannabidiol products when counseling caregivers. A recent guideline on optimizing Epidiolex treatment highlights the importance of discussing the varying concentrations found in non-FDA-approved cannabidiol products, as these can differ significantly from the standardized formulation of Epidiolex. Another misconception is the belief that Epidiolex, due to its clinical trials and documented side effects, has more adverse effects than non-FDA-approved cannabidiol products. Non-FDA approved CBD products have not undergone the same rigorous testing, meaning their side effect profiles are less well understood and most likely are not as well characterized, thoroughly evaluated or documented than FDA-approved products.[25]

Multiple Sclerosis. Although relatively rare in pediatrics, approximately 2% to 10% of individuals with MS are diagnosed before their 18th birthday. MS is an immune disease that leads to neurodegeneration, chronic inflammation, and demyelination of the central nervous system.[26] In Canada and multiple European countries, nabiximols, an oromucosal spray containing an ~1:1 ratio of THC to CBD, is a medication

approved for the treatment of adult patients with spasticity from MS. Nabiximols are in phase 3 of FDA trials in the United States for adults, with no clinical studies in pediatric patients.[27]

The American Academy of Neurology recently published guidelines on the use of cannabinoids for MS, citing numerous studies that demonstrate its effectiveness in alleviating symptoms such as spasticity, muscle spasms, pain, and bladder retention. It is hypothesized that cannabinoids inhibit the progression of MS and provide neuroprotection in animal models through the reduction in the proliferation and number of T cells, which impacted and reduced the degree of demyelination of neurons.[28,29] However, it is important to note that these studies have not included pediatric populations, and therefore the safety and efficacy of cannabinoids for children with MS remain unclear.[30,31] Additionally, several small studies have reported impaired cognition in pediatric patients with MS after long-term cannabinoid use, which correlated with reduced tissue volume in subcortical, medial temporal, and prefrontal regions.[32] Although some of the research in adults has shown promising results, more studies in pediatric patients need to be done in order to assess long-term effects of cannabinoids.[33]

Chemotherapy-Induced Nausea/Vomiting. Nausea and vomiting are among the most challenging complications of chemotherapy, severely affecting a patient's overall well-being and jeopardizing adherence to life-saving treatment regimens. It is estimated that CINV occurs in up to 70% of the pediatric population undergoing intensive chemotherapy.[34] Pharmacologic treatment is crucial in this indication as it prevents complications such as malnutrition, reduces physical and emotional distress, and significantly improves a child's overall quality of life during therapy. Medical marijuana has surfaced as a promising adjunctive treatment for the management of CINV, particularly for patients inadequately relieved from conventional antiemetic regimens.

The mechanism by which cannabinoids alleviate CINV is multifaceted, involving both central and peripheral pathways of attenuation. Studies highlight that cannabinoid agonists influence GI function by engaging peripheral CB1 receptors, which play a key role in slowing intestinal movement.[35] The central antiemetic effects of CBD appear to be mediated by multiple mechanisms involving serotonin (5-HT) pathways. Activation of somatodendritic auto receptors, specifically 5-HT1A receptors, leads to a decreased firing rate of serotonin neurons. This reduction in neuronal activity subsequently lowers the release of serotonin in the forebrain, a key mediator of nausea and vomiting.[36] Additionally, recent findings suggest that CBD may also function as an allosteric modulator of the 5-HT3 receptor, similarly resulting in reduced serotonin signaling.[37] Given their ability to reduce vomiting through distinct mechanisms, THC and CBD both hold potential value in effectively managing CINV.

The current recommendation from the American Society of Clinical Oncology (ASCO) Focused Guideline highlights 2 FDA-approved cannabinoid products, dronabinol (Marinol) and nabilone (Cesamet), for the treatment of nausea and vomiting unresponsive to traditional antiemetic medications. Despite recent advancements in medical marijuana research, ASCO states that existing evidence remains insufficient to recommend medical marijuana for this indication. ASCO likely considers the evidence insufficient due to the lack of standardized dosing, robust clinical trials, and consistent outcomes in studies on medical marijuana for CINV, particularly when compared with FDA-approved treatments like dronabinol and nabilone; as such, ASCO remains cautious about recommending medical marijuana until higher-quality, large-scale, randomized controlled trials can provide more definitive and reliable evidence.[38] Although data on medical marijuana use in pediatric oncology remain limited, clinical trials have assessed the safety and efficacy of FDA-approved synthetic cannabinoids in the pediatric cohort.

To highlight the use of cannabinoids in CINV, a 10-year retrospective chart review analyzed 55 pediatric patients ranging in age from 0 to 18 years old receiving moderately or highly emetogenic chemotherapy (MEC or HEC) and at least 1 dose of dronabinol.[39] The response to dronabinol, based on the frequency of emesis events, was categorized as good, fair, or poor. Patients received a median of 3.5 doses per hospital visit (range: 1–129). Across all emetogenic risk levels, 60% of patients reported a good response, 13% had a fair response, and 27% were classified as poor responders. Tolerability, indirectly assessed by the continuation of therapy as outpatients, was noted in 62% of patients.

Irritable Bowel Disease. It is estimated that 1 in 1299 children aged 2 to 17 are affected by IBD.[40,41] Patients with IBD have been found to exhibit genetic polymorphisms in cannabinoid receptors. One example is fatty acid amide hydrolase (FAAH), which degrades endocannabinoids like anandamide and 2-arachidonoylglycerol, leading to increased activation of cannabinoid receptors (e.g., CB1), influencing GI motility. CBD inhibits FAAH, potentially raising endocannabinoid concentrations in the gut, which may improve motility and homeostasis. Additionally, CBD interacts with 5-HT1A serotonin receptors, which regulate GI function through antidepressant and antiemetic effects. Further research is needed to fully elucidate these interactions and their therapeutic potential.[42]

Between 18% and 61.2% of pediatric patients with IBD were reported to use cannabinoids for symptom control.[43–45] Patients report that marijuana improves nausea, vomiting, appetite, diarrhea, coping, pain, and delayed motility for patients with IBD. A retrospective case-control study of 615 adults with Crohn disease

(CD), which analyzed data from the Healthcare Cost and Utilization Project-National Inpatient Sample found that patients who used marijuana for symptom control had lower rates of fistulizing disease, lower total parenteral nutrition requirements, and underwent fewer colonic surgical resections.[46] To date, there has not been a randomized controlled trial studying marijuana as a treatment for pediatric IBD. The body of literature consists primarily of retrospective case studies and surveys; therefore, cannabinoid use in pediatric IBD is not widely recommended in clinical practice, and more rigorous studies are needed to determine the efficacy and safety of these treatments in children with IBD. From a clinicians perspective, for refractory patients who have exhausted all FDA-approved treatments, medical marijuana may serve as a promising alternative as long as there are no drug-drug, drug-food, drug-disease, and drug-genetic interactions.

Effects During Pregnancy. Despite the American College of Obstetricians and Gynecologists (ACOG) recommendations against marijuana use during pregnancy,[47,48] data from 2007–2012 National Surveys on Drug Use and Health, a cross-sectional nationally representative survey, found that 16.2% of pregnant women in the United States used marijuana daily. Women report using cannabinoids in pregnancy to help with common ailments such as morning sickness, sleep, stress, depression, and pain. Since this survey, marijuana legalization has expanded substantially across the United States, therefore prevalence is likely much higher. THC is found to cross the placenta. Fetal plasma THC concentrations were approximately 10% of maternal values after acute exposure and were significantly higher after repeated exposure.[49] THC binds to the cannabinoid receptors of the placenta. Binding to the cannabinoid receptors inhibits the migration of the epithelial layer of human placental amnion tissue. It disrupts endogenous cannabinoid signaling and estrogen signaling. As a result, it affects the development and function of the placenta.[50–52] What does this do to the fetus? Studies have shown that in utero exposure to marijuana disrupts normal brain development and function leading to impaired cognition, increased sensitivity to polysubstance abuse, decreased attention span, behavioral problems impaired visual problem solving, motor coordination, and analysis.[53–59] There is currently no literature to support the association between perinatal marijuana use and fetal mortality, however the risk of stillbirth is slightly increased.[60] These data strongly advise against the use of maternal marijuana during pregnancy.

What about the pregnant woman? How does marijuana use affect her? Young-Wolff et al[61] performed a population-based retrospective cohort study of 250,221 pregnant women in California who reported prenatal marijuana use. They found that prenatal marijuana use increased the risk of gestational hypertension, preeclampsia, and placental abruption. On the other hand, there was a decreased risk of gestational diabetes. The study concluded there was no association with placenta previa, placenta accreta, or maternal morbidity.[61] Due to the potential risks to both the mother and fetus, the lack of standardized formulations, and inconsistent dosing, prenatal marijuana use is not recommended. Pharmacists play a crucial role in supporting expectant mothers by offering non-punitive, compassionate guidance to help them make informed decisions about discontinuing marijuana use and not using the drug during their pregnancy. By providing evidence-based, FDA-approved therapeutic alternatives, pharmacists can help ensure the health and safety of both the mother and the developing infant.

Effects During Lactation. The use of marijuana during lactation raises significant concerns due to the potential transfer of cannabinoids through breast milk and its subsequent effects on the lactating infant. THC is the primary psychoactive component of marijuana, driving both its effects on the mind and associated therapeutic properties. THC is a highly lipid soluble compound with rapid uptake and accumulation in adipose tissue.[62] Additionally, THC's low molecular weight further contributes to its pharmacokinetic profile, facilitating its effective transfer into human breast milk. A prospective, observational pharmacokinetic study conducted by Wymore et al[63] established a milk:plasma partition coefficient for THC of approximately 6:1. A milk-to-plasma (M/P) ratio of less than 1.0 indicates that minimal concentrations of a compound are transferred into breast milk, classifying these drugs as low risk for breastfeeding infants.[63] Therefore, an M/P ratio of 6:1 indicates significantly higher concentrations of THC in breast milk compared with maternal plasma, suggesting high risk of exposure to the infant. Furthermore, studies have shown that THC can linger in breast milk for varying durations, with detectable concentrations ranging from as little as 6 days to over 6 weeks.[64] Wymore et al[63] demonstrated that THC was detectable in the breast milk of all participants for the entire 6-week duration of their study, enrolling 25 breastfeeding mothers who reported marijuana use. Seven women participating in this study abstained from cannabis use for more than 5 weeks. Despite this termination of use, the estimated mean THC half-life in their breast milk was 17 days. This prolonged period highlights the potential for sustained infant exposure even after maternal cessation.

Data are sparse on the relationship between THC transfer into breast milk and factors such as the potency of marijuana and maternal usage frequency. Additional components such as the method of consumption (e.g., smoking, vaping, edibles), and the timing of breastfeeding relative to cannabis use may influence the amount of THC transferred through lactation. The variability in these factors complicates the ability to predict infant exposure

accurately and highlights the need for further research to better understand these dynamics and their potential impact on infant health. While THC's effects during lactation are a major consideration, CBD also warrants attention, especially regarding its presence in breast milk. A physiologically based pharmacokinetic model was developed using data from 181 mothers who donated 200 breast milk samples. Interestingly, 42% of these samples had CBD concentrations below the level of quantification. The study found that CBD levels in breast milk were higher when the mother ingested it through oil or pipe, compared to other forms such as joints, blunts, or edibles. The estimated dose for fully breastfed infants was projected to result in exposure of less than 1% of what children aged 4 to 10 years might receive if taking CBD therapeutically for seizures. Despite these findings, the FDA continues to strongly advise against the use of CBD, THC, or marijuana in any form during pregnancy and breastfeeding due to potential risks.

Effects During Infancy/Childhood. Prenatal cannabinoid use has been linked to lower birth weight, impaired cognitive functioning, and an increased risk of psychological issues in infants and children. A meta-analysis published in Journal of the American Medical Association (JAMA) in 2022 found that among 16 studies including 59,138 patients, there were significant increases in risk of birth weight less than 2500 g (RR, 2.06 [95% CI, 1.25–3.42]; $p=0.005$), small for gestational age (RR, 1.61 [95% CI, 1.44–1.79]; $p<0.001$), preterm delivery (RR, 1.28 [95% CI, 1.16–1.42]; $p<0.001$), neonatal intensive care unit (NICU) admission (RR, 1.38 [95% CI, 1.18–1.62]; $p<0.001$), decreased mean birth weight (mean difference, −112.30 [95% CI, −167.19 to −57.41] g; $p<0.001$), Apgar score at 1 minute (mean difference, −0.26 [95% CI, −0.43 to −0.09]; $p=0.002$), and infant head circumference (mean difference, −0.34 [95% CI, −0.63 to −0.06] cm; $p=0.02$).[65] Beyond the first 28 days of life, 2 studies utilized the McCarthy Scales of Children's Abilities (MSCA) to measure the cognitive functioning of infants and children who were exposed to cannabis prenatally. They found a dose-dependent relationship between frequency of cannabis use during pregnancy and infants' verbal memory, motor development and intelligence quotient (IQ) at 36 and 48 months. Interestingly, the same frequency was not found at 60 or 72 months.[66–68]

Prenatal cannabinoid use altered caudate functional connectivity with cerebellum, occipital fusiform, and anterior insula with cerebellum. These alterations contribute to deficits in motor and visual-spatial activity, integration and coordination, attention, and social-emotional stability.[65] The ABCD Study looked at 655 children aged 9 to 11 years of age who were exposed to cannabis prenatally. They found that infants exposed to cannabis before and after maternal knowledge of pregnancy were associated with a higher incidence of psychotic like experiences (internalizing, externalizing, attention, thought and, social problems), sleep problems, and body mass index, as well as lower cognition and gray matter volume in childhood.[69] Goldschmidt et al[70] found daily cannabis use in any trimester was associated with lower IQ in childhood. Daily cannabis use in the second and third trimesters predicted poor performance on tests assessing memory and quantitative reasoning among 6-year-old children. Published studies show a causal link between prenatal cannabinoid use and adverse outcomes for infants and children. As noted above and further substantiated by these later studies, cannabis use by mothers planning or anytime during pregnancy should be strongly discouraged through compassionate, non-punitive approaches from using cannabis during these susceptible phases.

Effects During Adolescence. It is estimated that 78% of first-time cannabinoid users are children 12 to 20 years old.[71] By age 18, about 45% of youth have reported using cannabis. According to the Monitoring the Future Study which looks at trends in illicit and legal drug use in adolescents found that the perceived risk of cannabis compared with other drugs has decreased substantially, resulting in increased cannabinoid use rates.[72,73] In fact, in 2022, the CDC reported 6% of 12th graders utilize cannabis daily.[74] With increased use comes increased risk as many teens choose smoking cannabis over drinking alcohol[75] recognizing alcohol abuse has its own well-defined health risks.

Since cannabis is derived from the dried flowers and leaves of the cannabis sativa plant, many adolescents perceive them as "natural" and therefore safer to use. However, research shows a very different story—cannabis can have significant and potentially harmful effects on developing adolescent brains. Adolescent brains are developing until about age 25, therefore early cannabinoid use affects the brain's ability to focus, remember, solve problems, regulate addiction and coordinate body movements.[76] Chronic cannabinoid use has been associated with the downregulation of CB1 receptors, leading to disrupted reward signaling and reduced reward sensitivity. This disruption can manifest as depressive symptoms such as anhedonia, low mood, and decreased motivation, ultimately increasing the risk for addiction, psychosis, and depression.[77] Adolescents who use cannabis daily are 4 times as likely to develop cannabis dependence within 2 years after use onset.[78] Long-lasting mental health issues associated with cannabinoid use include social anxiety and schizophrenia.[79]

Early onset use of cannabis has also been linked with causing more impairments in daily functioning. Studies have shown that cannabinoid use impairs attention, processing speed, verbal learning and memory, and executive functioning.[80] Even when used for a short period of time, longitudinal studies found that these effects last well into adulthood.[81] Additionally, adolescents with early onset use of cannabis had the greatest reductions in IQ (i.e., from "average"

in childhood to "low-average" in adulthood). These reductions persisted into adulthood despite early discontinuation of cannabinoids.[82] In 2021, Albaugh et al[83] analyzed 1598 magnetic resonance imaging (MRI) images from 799 adolescents aged 14to 19 years old and found that cannabis use over 5 years was associated with dose-dependent thinning of the left and right prefrontal cortices, areas critical for decision-making and impulse control. These neuroanatomical changes, linked to CB1 receptor activity, suggest that cannabis use during adolescence may alter normal brain development, particularly in regions undergoing significant age-related changes.[83] Recreational cannabinoid use is not recommended due to its potential risks to the developing adolescent brain. Pharmacists play a vital role in supporting adolescents by providing compassionate, non-judgmental guidance to help them make informed decisions about discontinuing marijuana use when it is not medically necessary. If an adolescent believes they may need marijuana for medical reasons, pharmacists can also facilitate a referral to a registered HCP for further evaluation and appropriate care. Over the counter CBD products are not as heavily regulated as medical marijuana prescribed by a HCP, therefore use is not recommended.

DEA Rescheduling: A New Era for Cannabis Innovation

On May 16, 2024, the DEA issued a notice of proposed rulemaking to explore moving cannabis from schedule I to schedule III, following a recommendation from the HHS after reviewing its medical applications and scientific evidence.[84] The investigation into rescheduling cannabis represents a pivotal moment in drug policy reform, with the potential to transform the landscape of medical cannabis research and access. By aligning policy with evolving scientific understanding, this shift could facilitate more comprehensive studies and broaden the scope of therapeutic applications. Changing cannabis to a schedule III substance could simplify the research process by reducing regulatory challenges and barriers. This transition would lower security demands, minimize storage needs, and decrease federal reporting duties, making studies more cost-effective and adaptable.

In 2023, the National Institutes of Health dedicated 74% of its $95 million in cannabis research funding to areas unrelated to therapeutic use, including its largest share (45%) to the National Institute on Drug Abuse for studying abuse potential and safety.[84] The National Institutes of Health's emphasis on funding cannabis research focused primarily on abuse potential and safety often overlooks its promising therapeutic applications. Redirecting a greater proportion of resources toward exploring the medical benefits of cannabis could pave the way for new treatments, offering significant advancements in patient care and scientific discovery. Rescheduling cannabis, alongside a balanced focus on both safety and therapeutic potential, could have significant implications for the future of clinical practice, offering new opportunities for providers and patients alike.

Conclusion

Advancements in medicine and evolving legislation have significantly highlighted the role of cannabinoids in health care. Cannabinoids have proven their utility as treatments for disease states such as CINV, MS, IBD, epilepsy, and chronic pain. While cannabinoids have proven valuable in clinical practice, the recent rescheduling from schedule I to schedule III underscores the need for further research including active compound content, health/physiologic effects, if any, from the other many components found in marijuana or other non-single-compound products, individual compound dose, and amount and duration of use supports expanded clinical trials to optimize their therapeutic potential. While cannabinoids are recommended for certain medical uses, studies have highlighted their negative impact on pregnant mothers, infants, children, and adolescents. Pharmacists play a critical role in counseling individuals seeking safer therapeutic alternatives or discontinuing cannabinoid use altogether. By providing education and raising awareness, pharmacists can help address this public health concern and promote healthier outcomes.

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JPPT | Systematic Review

Daptomycin Experience in the Pediatric and Neonatal Population: A Systematic Review

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ABBREVIATIONS AEs, adverse effects; BMT, bone marrow transplantation; CCPD, continuous cycling peritoneal dialysis; CHD, congenital heart disease; Clin, clinical; CoNS, coagulase-negative staphylococcus; CPK, creatine phosphokinase; CR, case report; CRBSI, catheter-related bloodstream infection; CS, case series; cSSTI, complicated skin and skin structure infection; CVC, central venous catheter; DAP, daptomycin; E, elevated; FDA, US Food and Drug Administration; GA, gestational age; GP, Gram positive; GPC, Gram positive cocci; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplant; IA, intra–abdominal; ITT, intention to treat; lab, laboratory; LZD, linezolid; micro, microbiological; mITT, modified intention to treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NR, not reported; NS, not significant; PDA, patent ductus arteriosus; PFA, patent foramen ovale; PNA, pneumonia; PP, per protocol; PS, prospective study; RA, retrospective analysis; RCT, randomized controlled trial; SOC, standard of care; SA, *Staphylococcus aureus*; SE, *Staphylococcus epidermidis*; SSI, surgical site infection; ST398, Sequence Type 398 (MRSA); ST80, Sequence Type 80 (MRSA); TEC, teicoplanin; TOC, test of cure; Tx, treatment; ULN, upper limit of normal; VAN, vancomycin; VISE, vancomycin-intermediate *Staphylococcus epidermidis*; VRE, vancomycin-resistant *Enterococcus*; VP, ventriculoperitoneal; WNL, within normal limits

KEYWORDS daptomycin; infant; neonatal; pediatric; systematic review

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This review examines the use of daptomycin in pediatric patients, including infants and neonates. A systematic review was conducted including articles containing safety and efficacy outcomes along with dosing information in pediatric patients receiving daptomycin. Randomized controlled trials (RCTs), prospective studies, retrospective analyses (RA), cohort studies, case reports or case series in patients less than 18 years of age were included. The review summarizes 41 articles between 2006 and 2024 (3 randomized controlled trials, 2 prospective studies, 9 retrospective reviews, and 27 case reports). Mean efficacy documented by either clinical improvement, clinical cure or microbiological cure in all prospective studies and retrospective reviews was 79.4% (range: 36.7%–100%). Dosing ranged from 4 to 12 mg/kg/day with 12 mg/kg/day administered in 2 divided doses being the most commonly used regimen in neonates and infants. There were few adverse effects reported or defined; primarily CPK elevations with no significant differences observed compared with standard of care treatments, although the quality of evidence was limited. Future prospective trials in the infant and neonatal population are warranted to determine a standard approach to treatment. This review highlights the growing body of evidence supporting the use of daptomycin in pediatrics, offering valuable insights for clinicians, particularly when faced with limited treatment options due to standard treatment failure and antimicrobial resistance.

Introduction

Daptomycin is a cyclic lipopeptide antibiotic approved in 2003 for the treatment of infections caused by Gram-positive organisms.[1] Its mechanism of action is unique compared with other antimicrobial agents. The daptomycin structure encourages the formation of complexes which interact with the negatively charged bacterial cell membrane. This leads to a conformational change in the cell membrane which causes a flow of potassium (K^+) ions out of the cell, resulting in cell death.[2] Gram-positive bacteria exhibit complex resistance, presenting challenges in health care facilities and community settings. *Staphylococcus aureus,* a common Gram-positive bacterium, can cause a range of infections from minor skin infections to severe conditions like pneumonia, bacteremia, endocarditis and osteomyelitis. Methicillin-resistant *Staphylococcus aureus* (MRSA), carries the Staphylococcal chromosomal cassette (SCC*mec*) and exhibits resistance to several classes of antimicrobial agents, significantly limiting treatment choices and emphasizing the critical need for innovative antimicrobial approaches.[3]

Guidelines endorsed by the American Academy of Pediatrics (AAP) including those from the Infectious

Disease Society of America's (IDSA) Guidelines for Treatment of MRSA in Adults and Children and the Guidelines for Management of Acute Hematogenous Osteomyelitis recommend vancomycin as a first-line agent for invasive multidrug resistant Gram-positive infections, including coagulase-negative *Staphylococcus* species (CoNS) and methicillin-resistant *Staphylococcus aureus* (MRSA), depending on infection severity, cultures and sensitivities.[4,5] In the event of vancomycin resistance, such as strains of vancomycin-resistant *Enterococcus* (VRE), adverse effects or treatment failure, alternative options include ceftaroline and linezolid, both of which have indications approved by the US Food and Drug Administration (FDA) in children.[4–6] While daptomycin is an alternative agent included in IDSA and AAP recommendations, providers may be reluctant to use it due to lack of pediatric data and differences in clearance and volume of distribution demonstrated in prior pharmacodynamic (PD) and pharmacokinetic (PK) trials in children.[7–9]

Daptomycin, originally marketed in the United States as Cubicin (Merck & Co, Inc, Rahway, NJ), is FDA-approved for complicated skin and skin structure infections (cSSTIs) and *S aureus* bacteremia in adults and pediatric patients 1 year or older. It is also approved for bloodstream infections with right-sided infective endocarditis, specifically in adults.[1] Evidence from pharmacokinetic (PK) studies in children demonstrate varying pharmacokinetics from that of adults, particularly in neonates, infants and children under 6 years of age.[9] Within the FDA-approved label, daptomycin dosing in pediatrics varies significantly from adults and is based on infection type and age. Dosing ranges from 5 mg/kg every 24 hours in adolescents with cSSTIs up to 12 mg/kg every 24 hours in children 1 to 6 years of age with *S aureus* bacteremia. Children 1 to 6 years of age should receive a 60-minute daptomycin infusion per the labelling, as opposed to the standard 30-minute infusion time in adults and older children (see Discussion). The prescribing information states it is not recommended in pediatric patients younger than 1 year of age due to risk of potential adverse effects to the muscular, neuromuscular, and nervous systems. Daptomycin is known to possibly increase blood creatinine phosphokinase (CPK) concentrations; whether this is linked to adverse events is worth investigation.[1] Several articles have reviewed pediatric daptomycin literature in the past; the most recent review by Karageorgos et al,[10] which reviewed data up until its publishing in 2016, expressed a need for additional data in infants and neonates. Since then, there has been an increase of daptomycin publications in pediatric patients. This review seeks to collect and evaluate the updated literature on the efficacy and safety of daptomycin in pediatric treatments, with a focus on children younger than 1 year of age.

Methods

Literature Review. A literature search was conducted on PubMed MEDLINE (1987–March 2024) using the search terms "daptomycin and pediatrics," "daptomycin and children," "cubicin and children," and "cubicin and pediatrics." Studies included in the review were limited to those available or translated in English and including patients from birth to 18 years of age. Articles were included if they contained patient data on receiving daptomycin, were randomized controlled trials (RCTs), retrospective analyses (RA), cohort studies, case reports or case series, and patients were less than 18 years of age. Studies performed in vitro or missing dosage information were excluded. A second search was also conducted in Clinicaltrials.gov using the search term "daptomycin," filtering for subjects 0 to 17 years and completed trials. Article bibliographies from the resulted searches were also reviewed for additional pertinent literature. Assessments of titles, abstracts, and full texts were conducted independently by 2 investigators. Authors worked independently and no automation tools were used. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to identify, screen and select articles.[11] See Supplemental Figure.

Data Extraction. Primary outcome measures of either clinical cure, clinical improvement or microbiological cure were reviewed. Clinical cure was defined based on each study or report's definition for clinical cure or improvement and was not defined universally or consistently across all studies. Laboratory markers including C-reactive protein (CRP), white blood cells (WBCs), temperature or fever monitoring, and clinical signs and symptoms of infection were all possible factors included in the reported clinical cure. Microbiological cure was defined as the absence of the original microorganism in follow-up cultures or negative cultures. Safety outcomes were also assessed based on the percentage of treatment-related adverse events reported. Laboratory markers such as creatine phosphokinase (CPK) were included if reported. Elevations in CPK due to daptomycin were defined per study. Pharmacokinetic data, dosing and infusion durations were included if provided.

Statistical Analysis. Data were collected and analyzed using descriptive statistics. For continuous variables, medians, means and ranges were reported where appropriate. Binary variables were described using frequencies and average percentages to show how common each category was reported. Missing data was not included in statistical calculations.

Results

Of the 196 articles reviewed from the MEDLINE search, 11 from bibliography searches, and 6 from clinicaltrials.gov, 172 were excluded. Duplicate articles

were removed. Reviews, susceptibility trials and animal studies were some of the most common reasons for exclusion. Other reasons for exclusion included pharmacokinetic-specific studies, studies assessing single-dose pharmacokinetics, lack of pediatric-specific data, lack of dosing information, lack of daptomycin-specific information or lack of translation available in English. Articles initially screened for inclusion may have been excluded later in the review process for multiple reasons (i.e., article did not have specific dosing information AND was not available in English). We identified a total of 41 articles (5 prospective studies, 9 retrospective analyses or case series and 27 case reports) which met inclusion for our review. Table 1 summarizes prospective studies and retrospective analyses.[12–25] Table 2 includes all case reports.[26–52] All articles included in this review were published between 2006 and March 2024.

Trials and Retrospective Reviews. Three randomized controlled trials (RCTs), 2 prospective observational studies, and nine retrospective analyses were included in the review.[12–16] The 3 RCTs compared daptomycin with standard of care (SOC) treatment, most commonly vancomycin.[12–14] As neonatal and infant studies were of particular interest, we identified 7 studies that included children under 1 year of age, 4 of which included neonates.[16–22] Age was typically reported as postnatal age (PNA), with a median age for all studies and case series of 6.5 years. Asfour et al[18] and Mohzari et al[19] were the 2 studies that reported gestational age (GA), of which the median for both studies was 27 weeks.

MRSA and MSSA were the most common organisms with bacteremia and cSSTIs as the most frequently reported types of infection. Other less frequently reported types of infection included bone and joint infections and endocarditis. Dosing ranged from 4 mg/kg/day up to 12 mg/kg/day (including 6 mg/kg/dose twice daily). Dosing varied by age, with most dosing categorized by age similar to FDA-approved prescribing information.[1] While infusion durations were infrequently reported, 4 studies specified infusions consistent with the prescribing information.[1,13–15,18] Tedeschi et al[16] reported using a 3-minute rapid infusion for the 12 patients who received daptomycin. The median duration documented was 12.5 days (range: 1–44 days). Efficacy documented by either improvement or cure across all studies and reviews varied substantially, with a mean of 79.4% (range: 36.7%–100%).

In Bradley et al[12] evaluating the safety and efficacy of daptomycin vs SOC in children with acute hematogenous osteomyelitis, power was not met due to low enrollment to detect noninferiority of clinical improvement by day 5. The RCT by Arrieta et al[13] evaluated the safety and efficacy of daptomycin vs SOC for children with Staphylococcal bacteremia with safety as the primary outcome. The article by Bradley et al[14] evaluated daptomycin compared with SOC for treatment of cSSTIs. Outcomes were reported for the intention-to-treat (ITT), modified intention-to-treat (mITT), and the clinically evaluable (CE) population.[14] Articles by Arrieta et al[13] and Bradley et al[14] were both designed with safety as the primary outcome, however these studies were not powered for efficacy or safety.

Of the RCTs reviewed, 87% of patients treated with daptomycin met clinical and/or microbiological cure in the modified intention to treat (mITT) analyses (as defined per study) with a difference in cure rates compared with SOC ranging from −7.9% to 11%. There was no statistically significant difference in efficacy found between daptomycin and the comparator groups among the 3 RCTs.[12–14] Confidence intervals of 95% were reported for primary and secondary outcomes.

Safety data were analyzed descriptively in all 3 studies.[12–14] Treatment-related adverse events were reported with an average of 28.8% with daptomycin and 37% in the SOC comparator studies (8.25% difference). In the RCT by Bradley et al[12] comparing safety of daptomycin (n = 74 patients) with SOC (n = 72 patients) in pediatric patients with osteomyelitis, patients with treatment-related adverse events occurred 6.8% in the daptomycin group vs 18.1% in the comparator group. Patients who discontinued treatment due to at least 1 adverse effect were 1.4% in the daptomycin group vs 9.7% in the SOC group. There were no serious treatment-related adverse effects in the daptomycin group, while 4.2% of the comparator group experienced serious adverse effects such as pyrexia, drug reaction with eosinophilia and systemic symptoms (DRESS) and red man syndrome.[12] Arrieta et al[13] reported an increase in blood CPK concentrations above the normal range (reported as 39 to 308 U/L) in 7.3% of patients receiving daptomycin (n = 55) vs no increase in CPK concentrations in the SOC (n = 27) group (values ranged from 19 to 545 U/L) however, it was deemed that only 2 cases (3.6%) were attributed to daptomycin therapy. Bradley et al[14] reported increased serum CPK concentrations in 14 (5.5% of daptomycin patients) and 7 (5.3% of the SOC patients). Only 1 case of elevated serum CPK concentration was deemed to be related to daptomycin. In Bradley et al[12] increases in CPK blood concentrations following treatment were reported in 7 (11%) daptomycin patients and 4 (6%) SOC patients, however all were less than or equal to 2.5 times the upper limit of normal and resolved during or following treatment.

In summary of all prospective and retrospective studies, treatment-related or possible adverse effects were reported in 13 of the 14 articles. Adverse effects occurred in an average of 10.2% (range: 0%–65.5%) of patients. Whereas 7 of the 8 studies that included infants (n = 7) and/or neonates (n = 4) reported an average of 4.2% of treatment-related adverse events (range: 0%–11.1%). A significant increase in CPK concentrations as defined per study, was reported an average

Table 1. Daptomycin Pediatric Prospective and Retrospective Studies

First Author	Study Design (Comparator)	DAP Patients, n (Total Patients)	Median Age (IQR)	Population	Infection Type	Organism	DAP Dose (by age)	Tx Duration*, Days (range)	Measure of Treatment Success	% Patients Successful Treatment (Outcome Difference, 95% CI)	Tx-Related AEs†	Elevated CPK
RCTs												
Bradley[12]	RCT (SOC) mITT	74 (149)	9.75 yr (1.2–17.3)	Children	Bone/joint	GP	7 mg/kg/day (12–17 yr) 9 mg/kg/day (7–11 yr) 12 mg/kg/day (1–6 yr)	8 (1–42)	Clin improvement by day 5, Clin cure at end of Tx	77.5% vs 82.9% SOC (–6.1%, –19.4 to 7.4) 83.1% vs 89.9% SOC (–7.9, –19.8 to 4)	6.8% vs 18.1% SOC	4%
Arrieta[13]	RCT (SOC) mITT	55 (81)	9.6 yr (2–16.9)	Children	Bacteremia, cSSTI, IA, Bone/joint	MRSA, CoNS, MSSA	7 mg/kg/day (12–17 yr) 9 mg/kg/day (7–11 yr) 12 mg/kg/day (1–6 yr)	11 (1–44)	Clin and micro resolution	88% vs 77% SOC (11%, –9 to 31%)	65.5% vs 76.9% SOC	7.3% vs 0% SOC
Bradley[14]	RCT (SOC) mITT	257 (389)	NR	Children	cSSTI	GP (35% MRSA)	5 mg/kg/day (12–17 yr) 7 mg/kg/day (7–11 yr) 9 mg/kg/day (2–6 yr) 10 mg/kg/day (12–23 mo)	NR (1–10)	Clin improvement	90.9% vs 86.7% SOC (4.2%, –3.3 to 11.8)	14% vs 17% SOC	5.5% vs 5.3% SOC
Prospective studies												
Iwata[15]	PS	18	7 yr (1–15 yr)	Children	cSSTI, Bacteremia	GP	10mg/kg/day (1 to < 2 yr) 9 mg/kg/day (2–6 yr) 7 mg/kg/day (7–11 yr) 5 mg/kg/day (12–17 yr)	6 (5–14)	Clin and micro resolution	83.30%	11.1%	0%

(*Table cont. on page 454*)

Table 1. Daptomycin Pediatric Prospective and Retrospective Studies *(cont.)*

First Author	Study Design (Comparator)	DAP Patients, n (Total Patients)	Median Age (IQR)	Population	Infection Type	Organism	DAP Dose (by age)	Tx Duration*, Days (range)	Measure of Treatment Success	% Patients Successful Treatment (Outcome Difference, 95% CI)	Tx-Related AEs†	Elevated CPK
Tedeschi[16]	PS	12	192 days (14 days–7 yr)	Neonates, infants	Bacteremia, cSSTI	CoNS	8 mg/kg/day	14	Micro resolution	100%	0	0%
Retrospective studies												
Vonasek[17]	RA	147	3 yr (0.75–8 yr)	Infants, children	Bacteremia, SSTI, SSI, IA, empiric, others	CoNS, *Enterococci,* MRSA, MSSA, others	4–12 mg/kg/day in divided doses	8.5, median (IQR 6–15)	Clin improvement	36.7%	1.4%	2%
Asfour[18]	CS	10	39 days (14–62 days)	Neonates, preterm infants	CoNS Bacteremia	CoNS	6 mg/kg every 12 hr or 10 mg/kg/day	24 (1–44)	Clin and micro resolution	50%	0	0
Mohzari[19]	RA	21	5 days (2–26 days)	Neonates, preterm infants	Endocarditis, sepsis, bacteremia	CoNS	6 mg/kg/dose BID (n = 8) or 10 mg/kg/day (n = 8)	22 (4–43)	Clin improvement	61.90%	9.5%	0
Rosanova[20]	RA	28	45.5 mo (12–117 mo)	Infants	Endocarditis, sepsis, bacteremia, others	GP	10 mg/kg/day (Range: 6–12 mg/kg/day)	19 (IQR 7–42)	Clin and micro resolution	78.50%	11%	7%
Namtu[21]	RA	109	12 yr (2.5 mo –24 yr)	Infants, children	CRBSI, bacteremia, cSSTI, Bone/joint	CoNS, *Enterococci* MSSA, MRSA, *Bacillus sp,* others	Children's Hospital dosing protocol: 10 mg/kg/day (≤ 6 yr) 8 mg/kg/day (> 6 to < 12 yr) 6 mg/kg/day (≥ 12 yr)	16 (3–121) 12, median	Clin or lab evidence of resolution	98%	NR	4%

(*Table cont. on page 455*)

Table 1. Daptomycin Pediatric Prospective and Retrospective Studies *(cont.)*

First Author	Study Design (Comparator)	DAP Patients, n (Total Patients)	Median Age (IQR)	Population	Infection Type	Organism	DAP Dose (by age)	Tx Duration*, Days (range)	Measure of Treatment Success	% Patients Successful Treatment (Outcome Difference, 95% CI)	Tx-Related AEs†	Elevated CPK
Syrogiannopoulos[22]	RA	128	2.8 (8 days–14 yr)	Neonates, infants	cSSTI	SA	10 mg/kg/day	10 (IQR 7–14)	Clin and micro resolution	96.1%	0	7%
Garazzino[23]	RA	46	8.7 (2.6–14.5 yr)	Children	CVC–related sepsis, osteomyelitis, cSSTI, endocarditis	MRSA, CoNS MSSA, *Enterococci*	6 mg/kg/day (6–8 IQR)	14 (IQR 10–26.5)	Clin improvement	70.4%	6.5%	0
Syriopoulou[24]	RA	81	13 (8–16 yr)	Infants, Children	Bone/joint, cSSTI, bacteremia, endocarditis, others	GP: MRSA, MSSA, CoNS, *Enterococci*	6 mg/kg/day (4–10 mg/kg/day)	12.5 (IQR 7–25)	Clin and micro resolution	92.5%	7.4%	1.2%
Ardura[25]	RA	16	6.5 yr	NR	Bacteremia, cSSTI, others	MRSA, MSSA, VRE	4–6 mg/kg/day	10 (6–34)	Micro resolution	88%	0	0

AE, adverse effects; CCPD, continuous cycling peritoneal dialysis; Clin, Clinical; CoNS, coagulase–negative Staphylococcus; CPK, creatine phosphokinase; CR, case report; CRBSI, catheter–related bloodstream infection; CS, case series; cSSTI, complicated skin and skin structure infection; CVC, central venous catheter; GP, Gram positive; GPC, Gram positive cocci; IA, intra–abdominal; ITT, intention to treat; Micro, microbiological; mITT, modified intention to treat; MRSA, methicillin–resistant Staphylococcus aureus; MSSA, methicillin–sensitive Staphylococcus aureus; NR, not reported; PP, per protocol; PS, prospective study; RA, retrospective analysis; RCT, randomized controlled trial; SA, Staphylococcus aureus; SE, Staphylococcus epidermidis; SSI, surgical site infection; ST398, Sequence Type 398 (MRSA); TOC, test of cure; Tx, treatment; ULN, upper limit of normal; VAN, vancomycin; VRE, vancomycin–resistant Enterococcus

* Mean values used unless otherwise specified.

† AEs during Tx include neurologic or nerve conduction abnormalities, musculoskeletal (weakness, myalgia), CPK elevations, rise in SCr not correlated with other causes, elevated other markers.

Table 2. Daptomycin Pediatric and Neonatal Case Reports

First Author	Age at Tx	PMH	Infection Type	Organism (Resistance)	DAP dose (mg/kg/day)	Tx Duration (days)	Measure of Improvement	Time to Improvement (days)	Reason for switch to DAP	AE[¶]	CPK	Clin Cure (Y/N)
Infant and neonatal reports												
Heger[26]	13 days	Premature, 30-wk GA	CRBSI Bacteremia	MRSA	12* 6 mg/kg every 12 hr	59	Negative culture	6	Less invasive monitoring	Y	E‡	Y
Kang[27]	6 mo	Heart-lung transplant	Bacteremia, cSSTI	VRE	10	14	Negative culture	2	C&S showing resistance	NR	NR	Y
Minotti[28]	34 days	Premature, 24-wk 5-day GA	Endocarditis	CoNS VISE	12* 6 mg/kg every 12 hr	NR	Negative Culture, CRP	3	Clin & micro failure	Y#	WNL	Y
Shigeta[29]	36 days	Premature, 23-wk GA, PDA, PFO	Endocarditis	CoNS	7.8	58	Negative Culture	2	Micro failure	N	WNL	Y
Chan[30]	15 days	Premature, 28- wk 1-day GA	Endocarditis	MRSA	12* 6 mg/kg every 12 hr	40	Clinical/ lab	18	Micro failure	N	WNL	Y
Sahin[31]	2.5 mo	Meningomyelocele hydrocephalus	Meningitis	VRE	8	15	Lab, negative culture	5	Clin & micro failure	N	WNL	Y
Sanchez[32]	8 mo	NS	Pericarditis, cSSTI	MRSA	6	5	Clinical/lab	NR	Clin failure; VAN not therapeutic	NR	NR	Y
Gawronski[33]	25 days	Premature, 24-wk 1 day GA, renal impairment	Bacteremia	MRSE	12* 6 mg/kg every 12 hr	15	Negative culture	1	Micro failure, therapeutic VAN Tx	N	WNL	Y
Tsironi[34]	28 days	NS	SSTI	MRSA (PVL+ ST80)	12	42	Clinical/lab	10	Initial Tx	N	WNL	Y
Hussain[35]	23 days	Premature, 27-wk 4 day, PDA	Bacteremia	MRSA (VISA)	10 15† Infused over 40 min	14	NR	NR	C&S data showing resistance	N	WNL	Y
Porter[36]	106 days	Premature, 25-wk GA, NEC, VP shunt	CNS	CoNS (VRSE)	6	28	Negative culture	3	Micro failure, developed VAN resistance	NR	NR	Y

(*Table cont. on page 457*)

Table 2. Daptomycin Pediatric and Neonatal Case Reports *(cont.)*

First Author	Age at Tx	PMH	Infection Type	Organism (Resistance)	DAP dose (mg/kg/day)	Tx Duration (days)	Measure of Improvement	Time to Improvement (days)	Reason for switch to DAP	AE[¶]	CPK	Clin Cure (Y/N)
Sarafidis[37]	38 days	Premature, 27-wk 3 day GA RDS	Bacteremia	CoNS *E. faecium* (day 23)	12* 6 mg/kg every 12 hr	17	Negative culture, clinical	2	Micro failure	N	WNL	Y
Beneri[38]	2 mo	Full term, CHD	Bacteremia	VRE	6[†]	56	Negative culture	7*	Micro failure	N	WNL	Y
Child and adolescent reports												
Kinoshita[39]	13 yr	NS	UTI	CoNS (Mec A)	6.5	13	Clinical/lab	NR	AE to prior Tx	N	WNL	Y
Yozgat[40]	16 yr	NS	Endocarditis	MSSA	8	3	Negative culture, clinical	5	NR	N	WNL	Y
Hall[41]	12 yr	NS	Bacteremia, cSSTI	MRSA	10	42	Negative culture, clinical/ lab	8	Clin & micro failure	NR	NR	Y
Morris[42]	8 yr	CHD	Bacteremia	MRSE	8 mg/kg every 48 hr	19	Negative culture, clinical/ lab	2	Potentially resistant to VAN/TEC	N	WNL	Y
Buyukcam[43]	3 yr	AML, Down syndrome	CRBSI Bacteremia	VRE	8	35	NR	NR	Clin & micro failure	N	WNL	Y
Prabhudesai[44]	3.5 yr	Renal failure, coagulopathy	Endocarditis + CRBSI	MRSA	12	56	Negative culture, clinical/ lab	3	Clin & micro failure	N	WNL	Y
Billups[45]	8 yr	Recurrent MRSA SSTI	Bone/joint	MRSA	8	35	Clinical/lab	1	Clin failure	N	WNL	Y
Jalal[46]	12 yr	CHD	Bacteremia, endocarditis	MRSA	10	28	Negative culture, clinical/ lab	3	C&S data showing resistance	N	WNL	Y
Mutschler[47]	10 yr	Trauma/ hemipelvectomy	Bacteremia, cSSTI	VRE (van-b) (LZD-resistant)	8	17	NR	NR	Micro failure (LZD resistant)	NR	NR	Y
Erturan[48]	16 yr	NS	Bacteremia, osteomyelitis,	MRSA - PVL+ST80	8	21	Negative culture, clinical/ lab	10	Clin failure	NR	NR	Y

(*Table cont. on page 458*)

Table 2. Daptomycin Pediatric and Neonatal Case Reports *(cont.)*

First Author	Age at Tx	PMH	Infection Type	Organism (Resistance)	DAP dose (mg/kg/day)	Tx Duration (days)	Measure of Improvement	Time to Improvement (days)	Reason for switch to DAP	AE[¶]	CPK	Clin Cure (Y/N)
Fossati[49]	11 yr	Post-HSCT	Bacteremia	VRE VanA PCR Positive	4	9	Negative culture, clinical/ lab	N	C&S data showing resistance	NR	NR	N
Jaspan[50]	21 mo	Leukemia	Bacteremia, Meningitis	VRE (CC17, LZD-resistant)	4 mg/kg every 12 h[§]	56	Negative culture	14	Clin & micro failure	NR	NR	Y
Jacobson[51]	15 yr	Burns	CRBSI Bacteremia	MRSA	6	7	Negative culture, clinical	N	AE to prior Tx	NR	NR	N
Akins[52]	13 yr	GVHD, aplastic anemia, BMT	Endocarditis	VRE	8	8	Negative culture	NR	C&S data showing resistance	N	WNL	Y

AEs, adverse effects; BMT, bone marrow transplantation; CCPD, continuous cycling peritoneal dialysis; CHD, congenital heart disease; Clin, clinical; CoNS, coagulase-negative Staphylococcus; CPK, creatine phosphokinase; CR, case report; CRBSI, catheter-related bloodstream infection; CS, case series; cSSTI, complicated skin and skin structure infection; CVC, central venous catheter; DAP, daptomycin; E, elevated; GA, gestational age; GP, Gram positive; GPC, Gram positive cocci; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplant; ITT, intention to treat; lab, laboratory; LZD, linezolid; Micro, microbiological; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive Staphylococcus aureus; MRSE, methicillin-resistant Staphylococcus epidermidis; NR, not reported; NS, not significant; PDA, patent ductus arteriosus; PFA, patent foramen ovale; PNA, pneumonia; PP, per protocol; SA, Staphylococcus aureus; SE, Staphylococcus epidermidis; ST398, Sequence Type 398 (MRSA); ST80, Sequence Type 80 (MRSA); TEC, teicoplanin; TOC, test of cure; Tx, treatment; VAN, vancomycin; VISE, vancomycin-intermediate Staphylococcus epidermidis; VRE, vancomycin-resistant Enterococcus; VP, ventriculoperitoneal; WNL, within normal limits; Y, yes

* Daily dose was divided q 12 hr.
† Dose was adjusted during treatment course.
‡ CPK became elevated on Tx day 45 to 70 units/L, then 304 units/L on Tx day 67.
§ Daptomycin was concomitantly administered intraventricularly as 2.5 mg in 5 mL normal saline via the ventriculostomy tube daily and locked for 30 minutes, then opened for CSF drainage.
¶ AEs during Tx include neurologic or nerve conduction abnormalities, musculoskeletal (weakness, myalgia), CPK elevations, rise in serum creatinine not correlated with other causes, elevated other markers.
# Daptomycin was discontinued after patient developed eosinophilic pneumonia while on treatment. Pneumonia and infection resolved.

of 2.8%. Significant increases in CPK varied per study from greater than 1 to greater than 2.5 times the upper limit of normal (ULN) from baseline during daptomycin therapy. A rise in CPK was not confirmed to be caused by daptomycin in any of the patients.[12–25]

Case Reports. Twenty-seven case reports (Table 2) were identified for this review.[26–33,36–52] Of the 27 published case reports, 13 (48%) were of children under 1 year of age. The median age reported was 1.73 years (range 13 days–16 years). If GA was reported, it was included within Table 2. The most common organisms identified were MRSA (n = 11), VRE (n = 8) and CoNS (n = 7), specifically *S epidermidis* (n = 5) and the most treated infections were bacteremia (n = 16), endocarditis (n = 7), and cSSTIs (n = 5). Median daptomycin dosing used was 10 mg/kg/day (range: 4–15 mg/kg/day). In the subset of children less than 1 year of age, the most common dose of daptomycin was 12 mg/kg/day, typically divided into 6 mg/kg IV every 12 hours (n = 5). Infusion durations were only reported in 1 case report of a neonate who received up to 15 mg/kg as a 40-minute intravenous infusion.[35] The median duration of daptomycin therapy was 21 days (range: 3–59 days). Time to clinical improvement was noted to be an average of 6.2 days (1–18 days) with a median of 4 days and clinical cure was reported in 25 of the 27 case reports (92.5%).

Safety was reported in 18 of the 27 case reports.[26,28–31,33–36,38–41,43–46,52] Of the 18 reports, 1 patient developed eosinophilia and daptomycin was discontinued, although the cause of the eosinophilia was not determined.[28] One patient started with a baseline CPK of 29 U/L measured on day of life 25 (DAP treatment day 12) which increased to 405 U/L on day of life 53 (DAP treatment day 40 and LZD treatment day 8).[26] Daptomycin was not discontinued in this case and continued through day 72. The last follow-up CPK concentration was 308 on day 67 of therapy with no mention of adverse effects. The remaining 17 case reports reported CPK concentrations within normal limits.

The most common prior antibiotics used were vancomycin (n = 20) and linezolid (n = 8). The majority (n = 17) of patients had overlap of antibiotics during daptomycin treatment with linezolid (n = 6), rifampin (n = 5), and gentamicin (n = 4) overlapping most frequently. Most frequently reported reasons for switch to daptomycin included clinical and microbiological failure on prior treatment (n = 6), microbiological failure (n = 7), and documented culture and sensitivity data showing resistance (n = 5). Antimicrobial resistance data was infrequently reported. PVL-positive ST80 MRSA phenotypic resistance was reported in 2 cases.[35,48] Of the VRE strains, CC17-ST412 clonal complex was reported in 1 case report.[50] Susceptibilities to daptomycin were reported in 19 of the 27 case reports with a median MIC of 1 mcg/mL (range: 0.064–2 mcg/mL) across a range of Gram-positive bacteria.[26,28,30,31,33–35,37–39,41–44,46,49–52] Pharmacokinetic data were infrequently reported and, therefore, not included within Table 2. Three case reports (aged 15 days, 28 days and roughly 2 months of age) reported daptomycin serum peak concentrations using a dosing strategy of 6 mg/kg every 12 hours ranging from 27.26 mcg/mL to 51.9 mcg/mL.[30,34,38]

Discussion

Daptomycin Treatment Success and Rational for Daptomycin Use. Since the most recent review in pediatrics, 3 RCTs have been added to the literature on the use of daptomycin in pediatrics.[10] There has also been an increase in studies, case reports, including use in neonates and infants. Of the 3 RCTs published, clinical success of daptomycin was reported as an average of 85.5%, with an overall success of 79.4% within the retrospective analyses, prospective studies and RCTs combined. As the RCTs did not meet power for efficacy nor were they designed to prove efficacy, noninferiority or superiority as the primary outcome, no inferences on the results compared with SOC can be made. Pooled data indicate that daptomycin achieved clinical success in most patients. Among the RCTs there was no significant difference in defining clinical success, clinical cure, or test-of-cure.

In summary of the case reports, clinical cure was achieved in 92.5% of the reports. Case reports indicated switches to daptomycin due to clinical or microbiological failure, adverse event to prior treatment, less invasive monitoring, and subtherapeutic vancomycin troughs. These factors emphasize daptomycin's role in therapy, particularly once first-line agents fail or with documented or suspected antimicrobial resistance. Active surveillance for increasing vancomycin resistance patterns such as those associated with sequence type (ST) 80 MRSA and clonal complex (CC) 17-ST412 VRE can be used to support an early switch to daptomycin to prevent treatment failure.[55] There was no significant difference in defining clinical success or clinical cure between the case reports.

Dosing and Pharmacokinetic Considerations. This review also aimed to explore dosing strategies used in neonates and infants. For infants and neonates, the most common dose of daptomycin was 6 mg/kg IV every 12 hours (12 mg/kg/day). Within the case report by Gawronski et al[33] dosing and pharmacokinetic parameters for several case reports were summarized. In preterm neonates with normal renal function between 27 and 80 days post-natal age, daptomycin 6 mg/kg/dose every 12 hours yielded peaks ranging from 22.9 to 41.7 mg/dL, compared with older full-term neonates which yielded lower peaks ranging from 10.9 to 17.7 mg/dL, yet similar troughs as preterm neonates.[23] This suggests a highly variable and inverse relationship with distribution and clearance in preterm neonates vs term infants in line with what was also summarized in a previous review article reporting on

pharmacokinetics of 11 studies, including infants and neonates.[10] In the case of a full-term infant, pharmacokinetic monitoring was used to adjust daptomycin dosing from 4 mg/kg to 6 mg/kg every 36 hours based on a low daptomycin serum peak (6.19 mcg/mL). Following dosage adjustment, blood cultures became negative.[39] Doses as high as 15 mg/kg daily over 40 minutes in a 23-day-old neonate were reported with pharmacokinetic and safety monitoring and no reported adverse effects.[35]

Concentration-dependent nerve toxicity was observed in preclinical trials in juvenile dogs, providing rationale for using prolonged infusion times for young children in clinical trials, and the basis for the infusion recommendations in the daptomycin prescribing information. Nerve toxicity was observed at significantly lower daptomycin peak concentrations in juvenile dogs compared with adults and therefore, longer infusion times were used in children up to 6 years of age in pediatric studies to theoretically reduce peak concentrations while not affecting the overall AUC.[1,8,56] In the prospective observational study by Tedeschi et al,[16] a 3-minute daptomycin rapid infusion of 8 mg/kg was administered to 12 patients with no adverse effects. This is the only study that reported an infusion duration in neonates and infants although it is unclear how many patients were less than 1 year of age.[16] In a phase 1 single-dose pharmacokinetic safety study by Bradley et al,[56] daptomycin was administered over 30 minutes at 4 mg/kg in patients 3 to 12 months and 6 mg/kg in patients 13 to 24 months with no significant adverse effects. Given limited reports in the literature and no published studies directly comparing daptomycin infusion durations with adverse effects in pediatric patients, clinicians should consider daptomycin pharmacokinetics, weighing the risks and benefits of a shorter infusion until more evidence is available.

Safdar et al[53] reported in previous PK/PD analysis that peak to MIC and 24-hour AUC to MIC ratios best correlated with daptomycin efficacy. Mean daptomycin AUC to MIC ratios reported for 1-log killing were 666 for *Staphylococcus aureus* and 4.14 to 33.8 for *E faecium*. Mean peak to MIC ratios reported for 1-log bactericidal activity against *S aureus* were 129 +/− 24.1 with a range of 86 to 184 and 0.62 to 5.05 for tested *E faecium* isolates.[53] Based on Monte Carlo PK simulations conducted in a study by Wei et al,[54] higher dosing of 8 to 12 mg/kg in infants and children, specifically 12 mg/kg/day in infants 3 to 12 months was affirmed as being necessary to achieve probable responses to infections caused by *S aureus* and *E faecium*. Achieving desired peak to MIC and AUC to MIC concentrations with higher doses is something to consider in overcoming treatment failure due to suboptimal pharmacokinetics and dosing.

Daptomycin Treatment Success and Rational for Daptomycin Use. Of the 3 RCTs published, clinical success of daptomycin was reported as an average of 87%, with an overall success of 78% within the retrospective analyses and RCTs combined. As the RCTs did not meet power for efficacy nor were they designed to prove efficacy noninferiority or superiority as the primary outcome, no inferences on the results compared to SOC can be made. Pooled data indicate that daptomycin achieved clinical success in most patients.

Of the case reports, clinical cure was achieved in 92.5% of the reports. Case reports indicated switches to daptomycin due to clinical or microbiological failure, adverse event to prior treatment, less invasive monitoring, and subtherapeutic vancomycin trough concentrations. These factors emphasize daptomycin's role in therapy, particularly once first-line agents fail or exhibit resistance. Active surveillance for increasing vancomycin resistance patterns such as those associated with sequence type (ST) 80 MRSA and clonal complex (CC) 17-ST412 VRE can be used to support an early switch to daptomycin to prevent treatment failure.[55]

Genotyping and Resistance. This review highlights 2 significant MRSA cases with documented resistance.[34,48] The first, by Erturan et al,[48] was associated with osteomyelitis, while the second by Tsironi et al,[34] was an ophthalmic infection. Both infections were caused by Panton-Valentine Leucocidin (PVL) positive strains belonging to the ST80 lineage.[34,48] These cases demonstrated clinical success after treatment with daptomycin compared to the standard anti-MRSA regimen. This suggests that daptomycin may be a promising treatment option for MRSA infections, especially those caused by PVL-positive ST80 strains. Overall, these findings underscore the importance of considering alternative treatments such as daptomycin for managing MRSA infections, particularly when dealing with strains that exhibit unique genotypic characteristics like PVL positivity and specific clonal types.

Adverse Effects. Of the 3 RCTs included in the review, treatment-related adverse events occurred 8.3% less often than with SOC, although we cannot confirm statistical significance due to lack of power and statistical reporting. Only 1 case report cited substantially elevated CPK concentrations during daptomycin therapy. Elevated CPK concentrations reported in the daptomycin prescribing information were based on Bradley et al,[14] studying daptomycin for cSSTIs in children. CPK was elevated in 5.5% of patients in the daptomycin group vs 5.3% in the comparator group.[1,14] Bradley et al[12] found no serious treatment-related adverse effects in pediatric patients with osteomyelitis treated with daptomycin. Eight of the studies included in this review were conducted in infants or neonates, showing not only use of daptomycin in this population, but a low percentage of adverse effects (4.2%). Significant CPK elevations were only reported an average of 2.8% across all studies and retrospective analysis. Among the 27 pediatric case reports using

daptomycin, only 2 noted adverse effects, with more than half (63%) of cases monitoring and confirming normal CPK concentrations.[26,28] In a population with limited high-quality evidence, the currently summarized observations in this review demonstrate use with little to no reported toxicity compared to what is reported in the product labelling.[1]

Limitations

This review is limited by publication bias, as treatment failures may have not been published. There is limited high-quality evidence, only 3 RCTs, none of which met power for outcomes. Significant heterogeneity amongst studies and reports exists. There is also variance in definitions of clinical success, clinical cure, and treatment-related adverse effects.

Conclusions

Daptomycin may be a promising alternative for treating Gram-positive infections in pediatric patients, including neonates and infants, when other antibiotics are deemed ineffective or inappropriate. Higher dosing was used in infants and children with limited reported adverse effects. Future prospective trials in the infant and neonatal population are warranted to determine a standard approach to treatment. Exploring daptomycin efficacy compared to SOC in specific resistance patterns is another area of interest. This review provides use of daptomycin in the pediatric population over the last 15 to 20 years, specifically highlighting a significant increase in articles published after the last systematic review and those in infants and neonates. It offers valuable insights for clinicians considering daptomycin therapy in pediatric patients, particularly when faced with limited treatment options due to antimicrobial resistance or potential concern of increased adverse effects when needing to utilize higher dosing strategies in younger patients.

Article Information

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JPPT | Multicenter Retrospective Study

Impact of a Procalcitonin Guided Antibiotic Management Strategy in Pediatric Sickle Cell Patients With Fever

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OBJECTIVE This study assessed the relationship between antibiotic durations and the use of procalcitonin (PCT) in febrile pediatric patients with sickle cell disease (SCD), including those diagnosed with acute chest syndrome (ACS) and/or vaso-occlusive crisis (VOC).

METHODS This multicenter, retrospective cohort study compared antibiotic durations in febrile pediatric SCD patients between 2 cohorts, 1 utilizing PCT (PCT cohort) and 1 not utilizing PCT (no-PCT cohort). Secondary endpoints compared the impact of PCT on antibiotic durations in those also diagnosed with ACS and/or VOC.

RESULTS A total of 258 patient encounters were included. The overall mean antibiotic duration in the PCT cohort was 4.2 days (SD 2.6) vs 4.7 days (SD 3.6) (p = 0.991). For those diagnosed with ACS (n = 17), the mean antibiotic duration was 6 days (SD 2.2) in the PCT cohort vs 9.7 days (SD 3.5) (p = 0.037; n = 7). Those diagnosed with both VOC and ACS (n = 40) averaged 5.6 days (SD 1.9) in the PCT cohort vs 9.3 days (SD 3.2) (p = 0.002; n = 9). Regression analyses revealed an increased odds of longer antibiotic duration in the no-PCT cohort for those with ACS (OR 1.51, 95% CI 1.07–2.13, p = 0.019), and for those with both VOC and ACS (OR 1.72, 95% CI 1.22–2.42, p = 0.002).

CONCLUSIONS There was not a significant difference in overall antibiotic durations between cohorts. However, in the PCT cohort there was a significant reduction of antibiotic durations seen in patients diagnosed with ACS or VOC and ACS, averaging 3.7 fewer days of antibiotics.

ABBREVIATIONS ACS, acute chest syndrome; AKI, acute kidney injury; ALT, alanine aminotransferase; CRP, C-reactive protein; LCL, lower control limit; PCT, procalcitonin; SCD, sickle cell disease; UCL, upper control limit; VOC, vaso-occlusive crisis; WBC, white blood cell

KEYWORDS acute chest syndrome; antibiotics; infection; pediatrics; procalcitonin; sickle cell disease; vaso-occlusive crisis

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Introduction

Patients with sickle cell disease (SCD) are at increased risk of infection due to functional asplenia and consequently, bacterial infections remain the leading cause of death in children with SCD worldwide.[1] Therefore, the presentation with fever is considered a potential medical emergency in SCD patients which frequently leads to the initiation of empiric antibiotics. However, fever often occurs in vaso-occlusive crisis (VOC) and acute chest syndrome (ACS) with non-bacterial etiologies such as viruses, fat emboli from bone marrow infarction, or vaso-occlusion in the vasculature of the lungs.[2] The potential for fevers to occur in this population from non-infectious etiologies poses a diagnostic challenge, which may lead to the use of unwarranted antibiotics and increased antimicrobial resistance. Therefore, there is a need for guidance on when to continue or discontinue empiric antibiotics within this population. While C-reactive protein (CRP) and the white blood cell (WBC) count are non-specific inflammatory markers, procalcitonin (PCT) is a more specific infectious biomarker validated in the general population.[3] Also, WBC counts and CRP levels can be affected by acute inflammation which can occur due to a VOC; whereas PCT concentrations appear to not be affected.[4] There is limited data with utilizing PCT in pediatric patients with SCD with fever in general. Therefore, this study intends to assess the relationship between antibiotic durations and the use of PCT in febrile pediatric patients with SCD, including those diagnosed with secondary complications such as ACS and/or VOC.

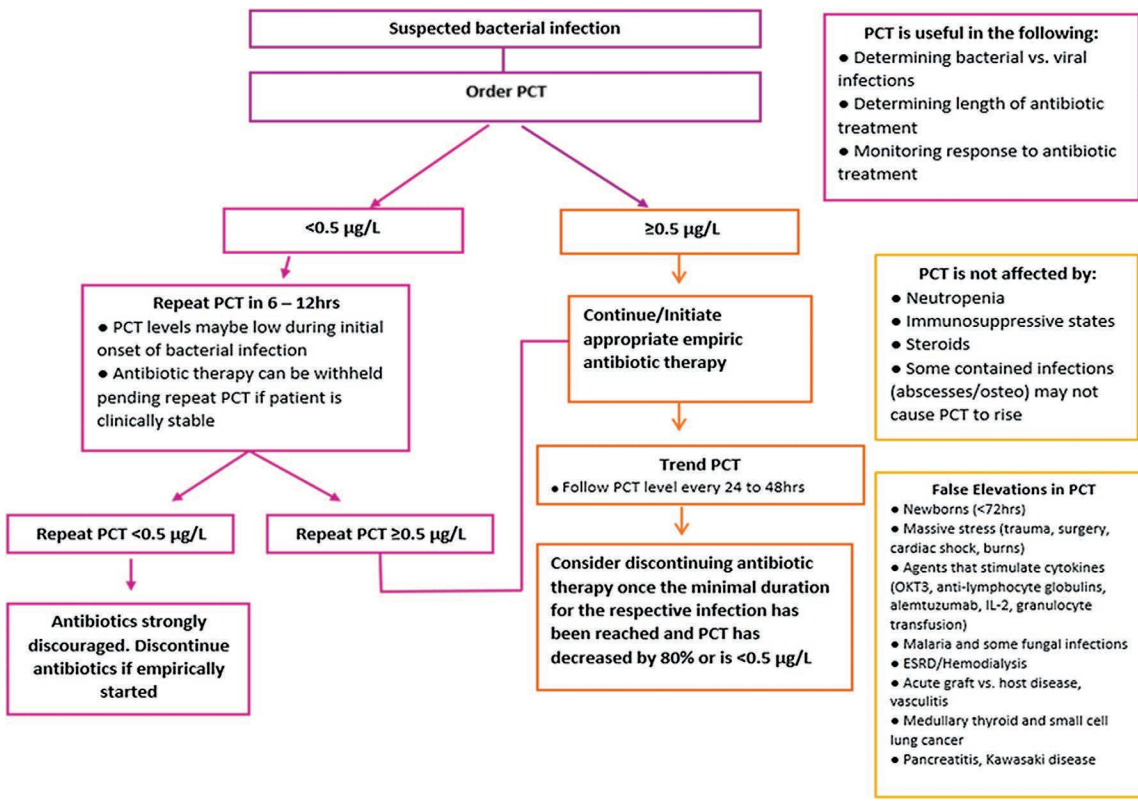
Materials and Methods

This was a multicenter, retrospective, observational cohort study conducted at Prisma Health Children's

Hospital–Midlands (Midlands) and Prisma Health Children's Hospital–Upstate (Upstate) from March 1, 2021–October 31, 2022. The study population included all pediatric sickle cell patients with a fever (≥ 100.4°F or 38°C who required hospitalization and were initiated on empiric antibiotics. Patients requiring prolonged durations of antibiotic therapy are typically diagnosed with complicated infections in which blood PCT concentrations may have no clear role or are not supported by current guidelines (i.e., osteomyelitis, endocarditis, mycobacterial infections, or infections requiring multiple surgical interventions for source control). Therefore, patients receiving >15 days of antibiotic therapy were excluded. Cohorts were divided based on patients with PCT concentrations (PCT cohort) and those without (no-PCT cohort). Our institution developed a PCT protocol which utilized PCT concentrations of ≥ 0.5 µ/L to suggest that a bacterial infection is probable in which antibiotics should be continued. While 2 PCT concentrations of <0.5 µ/L likely suggested a non-bacterial etiology in which antibiotics could be discontinued (see Figure).

The primary endpoint compared antibiotic durations between both cohorts. Secondary endpoints included proportional differences between cohorts. Specifically, antibiotic durations for patients who were also diagnosed with VOC, ACS, or VOC and ACS. Other comparisons between cohorts included confirmed bacterial infections, re-initiation of antibiotics for a suspected infection within 30 days of discontinuation, antibiotic associated complications (i.e., rash, neutropenia, thrombocytopenia, *C difficile* infection, acute kidney injury [AKI], or hepatotoxicity), hospital length of stay; protocol adherence, and 30-day mortality. A diagnosis of VOC or ACS was determined by clinician interpretation and empiric antibiotic selections were determined by the primary clinician as well. Confirmed bacterial infection was defined as any positive culture results (including blood, sputum, wound, urine, and cerebrospinal fluid cultures). AKI was defined as an increase in serum creatinine > 0.3 mg/dL or > 1.5-fold from baseline, or urine output < 0.5 mL/kg/hr for more than 6 hours.[5] Hepatotoxicity was defined as > 2-fold increase in ALT. Protocol adherence was defined as 100% compliance with the institution specific protocol (see Figure).

Figure. Procalcitonin (PCT) protocol.



Blood PCT concentrations were obtained on the first day of admission if being admitted for fevers and concerns for a bacterial infection. If already admitted, blood PCT concentrations were obtained on the first day of fevers. Repeat PCT were recommended to be obtained every 24 to 48 hr per protocol.

Table 1. Patient, Clinical, and Outcome Characteristics by Patient Cohort, PCT vs no-PCT

Characteristic	PCT Cohort (n = 190)	No-PCT Cohort (n = 68)	Total (N = 258)	p value
Age (yr), mean ± SD	10.3 ± 6.4	10.2 ± 6.2	10.2 ± 6.4	0.910
Weight (kg), mean ± SD	38.2 ± 24.2	39.9 ± 28.6	38.6 ± 25.4	0.985
Sex, n (%)				
Female	82 (43.2)	32 (47.1)	114 (44.2)	0.578
Male	108 (56.8)	36 (52.9)	144 (55.8)	
SCD genotype, n (%)				
HgbSC	30 (15.8)	6 (8.8)	36 (14.0)	0.314
HgbSS	129 (67.9)	48 (70.6)	177 (68.6)	
Other	31 (16.3)	14 (20.6)	45 (17.4)	
Immunizations current (yes), n (%)	178 (93.7)	66 (97.1)	244 (94.6)	0.367
100% adherent to PCT protocol,* n (%)	67 (35.3)	n/a	n/a	n/a
Prisma Health Children's Hospital, n (%)				
Midlands	170 (89.5)	18 (26.5)	188 (72.8)	<0.001
Upstate	20 (10.5)	50 (73.5)	70 (27.2)	
Admitted to ICU or Floor, n (%)				
Floor	172 (90.5)	64 (94.1)	236 (91.4)	0.363
ICU	18 (9.5)	4 (5.9)	22 (8.6)	
Patient on hydroxyurea (yes), n (%)	98 (51.6)	46 (67.7)	144 (55.8)	0.022
Secondary SCD complication, n (%)				
VOC	68 (35.8)	33 (48.5)	101 (39.2)	0.222
ACS	17 (9.0)	7 (10.3)	24 (9.3)	
VOC & ACS	40 (21.1)	9 (13.2)	49 (18.9)	
Neither	65 (34.2)	19 (27.9)	84 (32.6)	
Viral panel results (yes), n (%)				
RSV +	4 (2.1)	0 (0)	4 (1.6)	0.576
Covid +	17 (9.0)	7 (10.3)	24 (9.3)	0.743
Influenza +	4 (2.1)	1 (1.5)	5 (2.0)	1.000
Rhino/enterovirus +	11 (5.8)	13 (19.1)	24 (9.3)	0.001
Adenovirus +	4 (2.1)	0 (0)	4 (1.6)	0.576
Viral panel negative	140 (73.7)	40 (58.8)	180 (69.8)	0.022
Other	15 (7.9)	7 (10.3)	22 (8.5)	0.543
Chest X-ray interpretation, n (%)				
Chest involvement	70 (36.8)	21 (30.9)	91 (35.3)	0.670
No chest X-ray obtained	32 (16.8)	12 (17.7)	44 (17.0)	
No chest involvement	88 (46.3)	35 (51.5)	123 (47.7)	
Antibiotic used, n (%)				
Ceftriaxone	169 (89.0)	60 (88.2)	229 (88.8)	0.873
Ampicillin/sulbactam	9 (4.7)	2 (2.9)	11 (4.3)	0.733
Amoxicillin/clavulanate	19 (10.0)	3 (4.4)	22 (8.6)	0.157
Azithromycin	67 (35.3)	20 (29.4)	87 (33.7)	0.381
Levofloxacin	13 (6.8)	2 (2.9)	15 (5.8)	0.367
Other	50 (26.3)	21 (30.9)	71 (27.5)	0.469
Appropriate ABX dosing per institutional protocol (yes), n (%)	166 (87.4)	49 (72.1)	215 (83.3)	0.004
ABX for bacterial infection reinitiated w/in 30 days (yes), n (%)	18 (9.5)	6 (8.8)	24 (9.3)	0.874

(*Table cont. on page 467*)

Table 1. Patient, Clinical, and Outcome Characteristics by Patient Cohort, PCT vs no-PCT *(cont.)*

Characteristic	PCT Cohort (n = 190)	No-PCT Cohort (n = 68)	Total (N = 258)	p value
Antibiotic Duration by infection type, mean ± SD				
VOC	3.4 ± 2.2	2.9 ± 1.6	3.2 ± 2.0	<0.001†
ACS	6.0 ± 2.2	9.7 ± 3.5	7.1 ± 3.1	
VOC & ACS	5.6 ± 1.9	9.3 ± 3.2	6.3 ± 2.6	
Neither	3.7 ± 2.9	3.9 ± 2.7	3.7 ± 2.9	
Suspected ABX complications, n (%)				
Rash	0 (0)	0 (0)	0 (0)	—
Neutropenia	1 (0.5)	0 (0)	1 (0.4)	1.000
Thrombocytopenia	0 (0)	0 (0)	0 (0)	—
C difficile infection	0 (0)	0 (0)	0 (0)	—
Acute kidney injury	2 (1.1)	0 (0)	2 (0.8)	1.000
Hepatotoxicity	1 (0.5)	2 (2.9)	3 (1.1)	0.171
No complications suspected	187 (98.4)	66 (97.1)	253 (98.1)	0.610
Bacterial infection confirmed by culture, n (%)	8 (4.2)	1 (1.5)	9 (3.5)	0.291
Blood culture, n (%)				
Staphylococcus epidermidis	2 (1.1)	0 (0)	2 (0.8)	1.000
Staphylococcus hominis	1 (0.5)	0 (0)	1 (0.4)	
Streptococcus pneumoniae	2 (1.1)	0 (0)	2 (0.8)	
Negative	180 (97.3)	65 (100)	245 (95)	
Not obtained = 8				
Urine culture, n (%)				
Escherichia coli	2 (5.9)	1 (8.3)	3 (1.2)	1.000
Escherichia coli ESBL positive	1 (2.9)	0 (0)	1 (0.4)	
Proteus mirabilis	1 (2.9)	0 (0)	1 (0.4)	
Negative	30 (88.2)	11 (91.7)	41 (15.8)	
Not obtained = 213				
Respiratory culture (negative), n (%)	3 (100)	1 (100)	4 (1.6)	—
Not obtained = 254				
30-day mortality (# deceased), n (%)	4 (2.1)	0 (0)	4 (0.01)	0.576

ABX, antibiotic(s); ACS, acute chest syndrome; ICU, intensive care unit; PCT, procalcitonin; RSV, respiratory syncytial virus; SCD, sickle cell disease; VOC, vaso-occlusive crisis

*The "Upstate" Children's hospital utilizes PCT without a standardized protocol.
†P value represents differences in ABX duration by infection type for all patients ("Total" column).
—Statistic could not be calculated.

Descriptive statistics were used to summarize patient demographics, clinical data, and outcomes data. Mean (SD) or median (IQR) are reported for continuous variables, as appropriate, while counts and proportions are reported for categorical variables. For continuous data, differences by PCT and no-PCT protocols were evaluated using the Wilcoxon rank sum test. For other continuous data, either the Wilcoxon rank sum or the Kruskal-Wallis tests were used, depending on the number of levels for the classification variable. Normality was evaluated using the Shapiro-Wilk test and visual inspection of histogram plots with a normal curve overlay. A significant Wilcoxon rank sum test, which is based on ranks, indicates that either mean or median values tended to be larger (or smaller) for 1 group compared with the other. For categorical variables, the χ^2 test or Fisher exact test was used to evaluate differences between cohorts. Logistic regression was used to obtain ORs with 95% CIs for PCT status with other factors. All data were analyzed in SAS Enterprise Guide v8.3 with statistical significance based on resulting p-values ($p < 0.05$).

Results

A total of 648 encounters were screened for inclusion. After applying exclusion criteria, a total of 258 encounters were included in the final analysis, with 190 encounters in the PCT cohort and 68 encounters in the no-PCT cohort. Reasons for exclusion were patients being afebrile during hospitalization (n = 327), patients being admitted to an adult hospital within this health

Table 2. Association of PCT and ABX duration by Secondary Diagnosis

Characteristic	Antibiotic Duration			
	Mean ± SD			OR (95% CI)†
	PCT	no-PCT	p value*	(ref = PCT)
ABX Duration (all data)	4.2 ± 2.6	4.7 ± 3.6	0.991	1.12 (1.01–1.24)‡
VOC, ABX duration	3.4 ± 2.2	2.9 ± 1.6	0.307	0.88 (0.69–1.11)
ACS, ABX duration	6.0 ± 2.2	9.7 ± 3.5	0.037	1.51 (1.07–2.13)
VOC & ACS, ABX duration	5.6 ± 1.9	9.3 ± 3.2	0.002	1.72 (1.22–2.42)
Other, ABX duration	3.7 ± 2.9	3.9 ± 2.7	0.548	1.02 (0.86–1.22)

ABX, antibiotic(s); ACS, acute chest syndrome; PCT, procalcitonin; SCD, sickle cell disease; VOC, vaso-occlusive crisis

*P value for mean durations based on Wilcoxon rank sum test.
†Logistic regression: OR and 95% CI.
‡OR and 95% CI *after controlling for type of secondary diagnosis*.

system (n = 48), being febrile without the initiation of antibiotics (n = 7) or receiving antibiotics for >15 days (n = 8). The patients who received antibiotics for >15 days included 6 patients diagnosed with osteomyelitis and 2 patients diagnosed with necrotizing pneumonia which required repeated surgical interventions.

Demographic, clinical, and outcome characteristics are shown in Table 1. The distribution of patients by age, weight, and sex did not differ between cohorts. The mean age of the PCT cohort was 10.3 years (SD 6.4) and 10.2 years (SD 6.2) in the no-PCT cohort (p = 0.91). The PCT cohort was composed of 108 (56.8%) males and 82 (43.2%) females, while the no-PCT cohort had 36 (52.9%) males and 32 (47.1%) females (p = 0.578). Regarding sickle cell disease genotypes between the cohorts, the PCT cohort included 30 (15.8%) patients with HgbSC, 129 (67.9%) patients with HgbSS, and 31 (16.3%) patients with other genotypes, while the no-PCT cohort was composed of 6 (8.8%), 48 (70.6%), and 14 (20.6%), respectively (p = 0.314). In the PCT cohort, 17 (9%) of patients were diagnosed with ACS only, 40 (21.1%) with ACS and VOC, 68 (35.8%) with VOC only, and 65 (34.2%) diagnosed with neither. While the no-PCT cohort included 7 (10.3%) patients with ACS only, 9 (13.2%) with ACS and VOC, 33 (48.5%) with VOC only, and 33 (48.5%) diagnosed with neither (p = 0.222). There was a lower percentage of patients on baseline hydroxyurea in the PCT cohort (98/190, 51.6%) vs the no-PCT cohort (46/68, 67.7%), (p = 0.022). The percentage of negative respiratory pathogen panel results was higher in the PCT cohort (140/190, 73.7%) vs the no-PCT cohort (40/68, 58.8%), (p = 0.022). There were more patients in the PCT cohort at the "Midlands" facility (170/190, 89.5%) vs the "Upstate" facility (20/190, 10.5%), (p < 0.001). Appropriate antibiotic dosing per institutional protocol was higher in the PCT cohort (166/190, 87.4%) vs the no-PCT cohort (49/68, 72.1%) (p = 0.004). There were 8 patients (4.2%) in the PCT cohort with confirmed bacterial infections vs 1 patient (1.5%) in the no-PCT cohort (p = 0.291). Confirmed bacterial infections consisted of bacteremia (n = 5 PCT vs n = 0 no-PCT, p = 1.000) and urinary tract infections (n = 4 PCT vs n = 1 no-PCT p = 1.000). There were no differences with antibiotic associated complications between cohorts and documented complications were rarely seen. There were also no differences in re-initiation of antibiotics (p = 0.874) or 30-day mortality (p = 0.576) between both cohorts.

Comparisons of antibiotic duration use by patient cohort and by secondary diagnosis are shown in Table 2. The overall mean antibiotic duration in the PCT cohort was 4.2 days (SD 2.6) compared with 4.7 days (SD 3.6) in the no-PCT cohort (p = 0.991). Antibiotic duration in the PCT vs no-PCT cohort was similar amongst patients with VOC alone, 3.4 (SD 2.2) vs 2.9 (SD 1.6) days (p = 0.307). For patients with an ACS diagnosis alone, the mean antibiotic duration was 6 days (SD 2.2) in the PCT cohort compared with a higher antibiotic duration of 9.7 days (SD 3.5) in the no-PCT cohort (p = 0.037). Patients with both a VOC and ACS diagnosis averaged 5.6 days (SD 1.9) on antibiotics in the PCT cohort which was significantly lower than the 9.3 days (SD 3.2) in the no-PCT cohort (p = 0.002).

Outcomes were further evaluated with logistic regression models to assess risk for increased antibiotic duration by patient cohort ("PCT cohort" was the reference value). (Regression results are also shown in Table 2.) Antibiotic duration by PCT cohort was significant after controlling for secondary diagnosis (i.e., ACS and/or VOC). For every 1-day increase in antibiotic duration, patients had 12% greater odds of being in the no-PCT cohort (OR 1.12, 95% CI 1.01–1.24). Stratified results by secondary diagnosis showed no difference in antibiotic duration between cohorts for patients diagnosed with

VOC (OR 0.88, 95% CI 0.69–1.11), however significant differences were found for patients diagnosed with ACS only (OR 1.51, 95% CI 1.07–2.13) and for those diagnosed with both ACS and VOC (OR 1.72, 95% CI 1.22–2.42).

Discussion

The above findings demonstrate no significant difference in overall antibiotic exposures (crude association) when utilizing a procalcitonin guided antibiotic management strategy in pediatric sickle cell patients with fever. However, there were significant antibiotic exposure reductions that were observed in patients who were also diagnosed with ACS or VOC & ACS, averaging 3.7 fewer days of antibiotics in the PCT cohort.

Adult studies have demonstrated the ability for blood PCT concentrations to predict rates of bacterial infections and reduce antibiotic durations of therapy, but there is a lack of data within the pediatric population.[6] Patel et al[7] evaluated the utility of PCT as an early biomarker of bacterial infections, within 6 hours of presentation, in adult patients with SCD with VOC and signs of sepsis. They concluded a blood PCT concentration <0.5 μ/L was associated with a low risk of bacterial infections and that those patients may be managed with just monitoring and supportive care.[7] Similarly another study identified significantly higher PCT concentrations (mean = 8.99 μ/L, range = 0.03–78.36 μ/L) in confirmed bacterial infections within adult patients presenting to the emergency department with SCD, VOC, and fever compared with viral infections or VOC only. They defined confirmed bacterial infections as a positive bacterial culture (blood, body fluid, urine, respiratory or cerebrospinal fluid) or *C difficile* toxin assay. The most common organisms detected in that study were *E coli, C difficile,* Staphylococcus species and Enterobacter species. They concluded that a PCT level >0.5 μ/L demonstrated an 81% sensitivity and 85% specificity for predicting confirmed bacterial infections within this population.[8] Therefore, our PCT protocol utilized the PCT value of >0.5 μ/L to guide our clinicians to either continue or initiate appropriate empiric antibiotics.

While PCT does have the ability to identify bacterial infections, it also can impact antibiotic exposures. Razazi et al[3] evaluated if a PCT based antibiotic prescribing regimen would reduce antibiotic exposure without increasing risk of adverse effects in adult patients with ACS. Results demonstrated more patients, diagnosed with ACS episodes (n = 103), received ≤ 3 days of antibiotics in the PCT-guided cohort (31% vs 9%; p < 0.01) with no infection relapse or pulmonary superinfection seen in the entire cohort.[3] The current study demonstrated that pediatric sickle cell patients with fever and diagnosed with ACS received 3.7 fewer days of antibiotics when a procalcitonin protocol was utilized (6 days vs 9.7 days; p = 0.037). This study also identified shorter antibiotic durations in the PCT cohort in patients diagnosed with both ACS and VOC (5.6 days vs 9.3 days; p = 0.002). There were also very few antibiotic associated complications across both cohorts. Most antibiotic re-initiations were due to the patient being readmitted for another fever or concern for a viral infection (empiric antibiotics were initiated upon admission prior to determining a viral etiology by utilizing a respiratory pathogen polymerase chain reaction assay). We did not identify that any antibiotic re-initiations were due to an actual confirmed bacterial infection (i.e., a positive blood culture). However, a multicenter retrospective cohort study including 35,548 encounters representing 11,181 individual patients with sickle cell disease from thirty-six children's hospitals who presented to the emergency department with fevers noted that bacteremia was uncommon (1.1%).[9]

Limitations of Study

There were limitations in this study, including that the institution specific PCT protocol was not fully implemented during the entire study period (35.3% had PCT protocol adherence). This may have contributed to the low adherence rates to the PCT protocol. Common reasons for PCT protocol non-adherence included only a single PCT being obtained without a repeat value, or antibiotics being continued with repeat PCT values <0.5 μ/L. This may have resulted in no significant difference in overall antibiotic durations between cohorts. However, even with the low adherence, statistical significance was still met in certain circumstances, showing lower antibiotic exposures when utilizing PCTs in patients diagnosed with ACS or VOC and ACS. Uneven cohorts did exist due to clinical practice differences observed among sites as well as with the differences in the size of SCD populations between hospital locations within the state.

Conclusions

In conclusion, this study provides evidence for implementing a PCT guided antibiotic management protocol in pediatric sickle cell patients with fever (see Figure). Although the overall impact on reduced antibiotic durations was not significant between procalcitonin cohorts, reduced antibiotic durations were seen for patients with certain comorbid conditions. Specifically, shorter antibiotic durations were seen in febrile pediatric patients with SCD and other complications, such as ACS or VOC and ACS. Therefore, the addition of utilizing a PCT algorithm may be beneficial in not only assisting with the inpatient infectious work-up but by reducing antibiotic durations in pediatric patients with SCD presenting with fever who are also diagnosed with ACS or VOC and ACS.

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Ethical Approval and Informed Consent. This study was approved by the institutional review board at Prisma Health on October 13, 2022 (1963099-1). Given the nature of this study, informed consent was not required.

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JPPT | Single-Center Retrospective Study

Impact of Pharmacist-To-Dose Enoxaparin in Pediatric Patients

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OBJECTIVE Variations in pharmacokinetics necessitate monitoring anti-Xa concentrations for optimal anticoagulation in pediatric patients receiving enoxaparin for the prophylaxis or treatment of venous thromboembolism. Pharmacists play an essential role through pharmacist-to-dose (PTD) protocols. This study aims to assess the impact of pharmacist involvement by comparing rates of achieving target anti-Xa concentrations before and after implementation of the PTD protocol in a pediatric population.

METHODS Medical records were queried for patients 18 years old and younger who received enoxaparin as an inpatient at West Virginia University Medicine Children's Hospital from January 2016 to September 2023. Indication, dosing, and administration of enoxaparin were assessed. Anti-Xa concentrations were evaluated for appropriate timing and goal range. Secondary outcomes included the number of anti-Xa concentrations drawn, the number of enoxaparin dose adjustments, the rate of accurately drawn anti-Xa concentrations, the rate of following guideline recommended enoxaparin dosing on initiation, and the time to goal anti-Xa concentration.

RESULTS There was no difference in the rate of anti-Xa concentrations that were in goal before and after the implementation of a pharmacist-led enoxaparin dosing protocol. The frequency of concentrations drawn appropriately was higher, and the time to goal was shorter after the implementation of the PTD protocol, although this difference was not statistically significant.

CONCLUSIONS There was no difference in the rate of anti-Xa concentrations that were in goal between groups. This likely stemmed from the use of the same dose adjustment guideline among both groups. This underscores the equal quality of care provided by pharmacists in achieving optimal anticoagulation and positive outcomes.

ABBREVIATIONS eGFR, estimated glomerular filtration rate; PTD, pharmacist-to-dose; VTE, venous thromboembolism

KEYWORDS anticoagulation; enoxaparin; pediatrics; pharmacist; protocol; venous thromboembolism

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Introduction

It is estimated that the annual incidence of venous thromboembolism (VTE) is 0.07–0.14 per 10,000 healthy children and 5.3 per 10,000 pediatric hospital admissions.[1] Enoxaparin is a low-molecular-weight-heparin that is indicated for the prophylaxis and treatment of venous thromboembolism in pediatric patients. The use of enoxaparin has increased, replacing unfractionated heparin as a more common choice for parenteral anticoagulation. Enoxaparin boasts a longer half-life, elevated subcutaneous bioavailability, and a reduced risk of heparin-induced thrombocytopenia in contrast to unfractionated heparin.[2]

The 2012 American College of CHEST Physicians guideline recommends dosing enoxaparin based on pediatric patients' weight and age.[3] Compared with adults, pediatric patients exhibit a larger volume of distribution and more rapid clearance of low-molecular-weight-heparin, accompanied by decreased plasma concentrations of antithrombin. These differences can lead to escalated dose requirements. Consequently, anti-Xa concentrations are recommended to be drawn to monitor for optimal anticoagulation in the pediatric population.[2] The CHEST guideline recommends using a target range of 0.5–1 IU/mL for anti-Xa monitoring in patients receiving therapeutic low-molecular-weight-heparin. The goal anti-Xa concentration for prophylaxis with enoxaparin is less defined, but the range of 0.1–0.3 IU/mL is cited from its use in the literature.[3]

With the role of pharmacists in the clinical care setting progressively expanding, a 2023 survey involving critical care pharmacists in adult hospitals in the United States revealed that 41% of institutions had adopted pharmacist-driven protocols for dose adjustments of

enoxaparin.[4] This practice is also extending to pediatric hospitals, where pharmacists are involved in enoxaparin dosing and monitoring. Currently, a significant portion of the literature surrounding pharmacist-to-dose (PTD) protocols for enoxaparin focuses on the efficacy of these protocols. The additional monitoring and dose adjustments that are required in the pediatric population are clinical contributions that pharmacists can make through PTD protocols; however, the literature on the impact that pharmacists have on clinical outcomes through PTD protocols remains limited.[5–6]

In 2019, West Virginia University Medicine Children's Hospital implemented a PTD protocol for enoxaparin dosing. This protocol empowered pharmacists to dose enoxaparin upon initiation, order anti-Xa plasma concentrations, and adjust dosages in accordance with a set guideline. While this guideline had existed before the implementation of the PTD protocol, its administration was predominantly overseen by physicians, with pharmacists providing recommendations as needed. Prior data collected at the institution focused on the efficacy of this guideline. This study aims to continue the investigation in this space by focusing on the impact of pharmacists, assessing rates of achieving goal anti-Xa concentrations before and after the implementation of a PTD protocol in pediatric patients.

Materials and Methods

Study Design. This retrospective, single-center chart review was conducted at West Virginia University Medicine Children's Hospital. The electronic medical record was queried for patients aged 18 years and younger who received enoxaparin while inpatient from January 2016 to September 2023. Patients were included if they had at least 1 anti-Xa concentration drawn. Patients were excluded if they met any of the following criteria: no PTD order after implementation, known coagulation disorder, estimated glomerular filtration rate (eGFR) < 10 mL/min/1.73m^2, continuation of enoxaparin from home or outside facility, received a maximum prophylactic dose of enoxaparin (30 mg every 12 hours or 40 mg every 24 hours) and did not require monitoring, or received less than 2 doses of enoxaparin (see the definitions section for additional details). Each anti-Xa concentration was considered an individual data point for analysis. Anti-Xa concentrations that were collected outside the timeframe of 4–6 hours (±30 minutes) postdose were excluded. A 30-minute buffer was allotted to account for nursing workflow. Anti-Xa concentrations drawn from January 1, 2016, to October 31, 2019, were assigned to the pre-PTD group, while concentrations drawn from January 2, 2020, to September 30, 2023, were assigned to the post-PTD group. Anti-Xa concentrations drawn from November 1, 2019, to January 1, 2020, were also excluded from the analysis to allow for a washout period before and after the implementation of the PTD protocol. Chromogenic anti-Xa assays on ACL TOP were used to measure concentrations.

Data collection. Data collection of patient demographics included age, sex assigned at birth, weight, body mass index, and eGFR. Indication, dosing, and timing of enoxaparin administration were collected. Appropriateness of the time of anti-Xa concentration collection was assessed. Anti-Xa concentrations were then categorized as being subtherapeutic, therapeutic, or supratherapeutic based on our institution-specific guideline. Finally, dose adjustments were recorded, including any notable discrepancies from the guideline.

Outcomes. The primary outcome was the rate of anti-Xa concentrations in the goal range before and after implementing a pharmacist-led enoxaparin-dosing protocol. Secondary outcomes included the number of anti-Xa concentrations drawn, the number of dose adjustments, the rate of accurately drawn anti-Xa concentrations, the rate of following the initial dose according to the guidelines, and the time to achieve the goal anti-Xa concentration before and after implementing a pharmacist-led enoxaparin-dosing protocol.

Definitions. The goal prophylaxis anti-Xa concentration was defined as 0.1–0.3 ± 0.02 IU/mL, and the goal treatment anti-Xa concentration was defined as 0.5–1 ± 0.05 IU/mL. Any other patient-specific treatment concentrations determined by the treatment team were granted ±0.05 IU/mL to account for laboratory variation. Premature neonates were defined as children 1 month of age or younger who were born before 37 weeks gestation. Coagulation disorders were defined as any disorder mentioned in the patient's history and physical that affects the blood's ability to clot and include, but are not limited to, hemophilia, Von Willebrand disease, and other clotting factor deficiencies. eGFR was calculated by the 2009 bedside Schwartz equation.

Statistical Analysis. Each laboratory concentration drawn was included individually for statistical analysis. After implementing the PTD protocol, an estimated 79% of concentrations were found to be in goal based on previous data collected at our institution. For the sample size calculation, a difference of 15% was considered statistically significant. A sample size of 300 anti-Xa concentrations (150 anti-Xa concentrations pre-PTD and 150 anti-Xa concentrations post-PTD) was required to meet a power of 80%. Alpha was set at 0.05. The data were analyzed using a X^2 analysis.

Results

A total of 106 patients were included, with 55 patients in the pre-PTD group and 51 in the post-PTD group. Patients in both groups had similar characteristics in terms of weight, body mass index, eGFR, and age (Table 1). There were more patients in the

Table 1. Characteristics of Patients Who Received Enoxaparin

	Pre-PTD (n = 55)	Post-PTD (n = 51)	p value
Weight, mean ± SD, kg	51.6 ± 37.1	51.6 ± 37.6	0.99
BMI, mean ± SD, kg/m^2	26.5 ± 9.0	24.7 ± 10.2	0.37
eGFR, mean ± SD, mL/min/1.73m^2	86.2 ± 26.2	92.7 ± 25.3	0.18
Age, mean ± SD, yr	10.8 ± 6.8	10.5 ± 6.1	0.82

PTD, pharmacist-to-dose; BMI, body mass index; eGFR, estimated glomerular filtration rate

Table 2. Patient Age Groups by Indication for Enoxaparin

	Pre-PTD (n = 55)	Post-PTD (n = 51)	p value
Prophylaxis, n (%)	23 (42)	24 (47)	0.59
0–1 mo, n (%)	1 (4)	0	0.99
≥2 mo–18 yr, n (%)	22 (96)	24 (100)	0.46
Treatment, n (%)	32 (58)	27 (53)	0.59
Premature neonate, n (%)	3 (9)	0	0.24
1–2 months, n (%)	3 (9)	1 (4)	0.62
3 mo–1 yr, n (%)	4 (13)	4 (8)	0.99
2–4 yr, n (%)	0	8 (16)	0.002
5–18 yr, n (%)	22 (69)	14 (27)	0.17

PTD, pharmacist-to-dose

pre-PTD treatment group aged 5–18 years (p = 0.17), while there were more patients in the post-PTD treatment group aged 2–4 years (p = 0.002). There were 3 (9%) premature neonates included in the pre-PTD group compared with none in the post-PTD group (p = 0.24) (Table 2).

In the pre-PTD group, 233 concentrations were drawn. Of those, 200 (85.8%) were drawn appropriately, and 140 (70%) were in the goal range. In the post-PTD group, 227 concentrations were drawn. Of those, 200 (88.1%) were drawn appropriately, and 140 (70%) were in the goal range (Table 3).

The rate of appropriateness of the first dose of enoxaparin was similar across both groups. There was a total of 12 instances, 4 in the pre-PTD group and 8 in the post-PTD group, where first doses were rounded to the nearest available syringe size for administration. This rounding caused doses to lie beyond 10% of the dose recommended by the guideline. Of the 12 other instances where initial doses fell outside of the guideline, 5 were recommendations from the hematology/oncology team. The time to reach the goal anti-Xa concentration was 2.25 days in the pre-PTD group compared with 1.02 days in the post-PTD group. There was no statistical difference in the number of dose adjustments between the 2 groups (Table 4). A higher number of dose adjustments occurred in the pre-PTD group due to the provider choice compared with the post-PTD group (13 versus 4, respectively). Additional dose adjustments in the post-PTD group were based on changes in clinical status in patients who were receiving prophylaxis dosing and transitioned to treatment dosing (n = 2) and dose adjustments for ease of administration, either during the inpatient admission or for outpatient use (n = 2) (Table 5).

Discussion

There was no difference in the rate of anti-Xa concentrations in the goal range before and after implementing a pharmacist-led enoxaparin dosing protocol. The same dosing guideline for initiating and adjusting enoxaparin dosing based on concentrations was used both before and after implementing the PTD protocol. Using the same institutional dosing guideline may have contributed to the similar rates of anti-Xa concentrations that were in goal. In the post-PTD group, there were fewer provider-driven dose adjustments (8% vs 21.3%; p = 0.03). There also were more concentrations that were drawn appropriately (88.1 vs 85.8%; p = 0.47), although this was not statistically significant. This highlights the crucial role pharmacists can play in managing anticoagulation in pediatric patients through effective monitoring and dose adjustments.

Table 3. Anti-Xa Concentrations

	Pre-PTD Concentrations	Post-PTD Concentrations	p value
Total concentrations drawn, n	233	227	
Concentrations drawn after dose adjustments, n (%)	63 (27)	48 (21)	0.14
Concentrations drawn appropriately, n (%)	200 (86)	200 (88)	0.47
Concentrations drawn appropriately, not in goal, n (%)	60 (30)	60 (30)	0.87
Concentrations drawn appropriately, in goal, n (%)	140 (70)	140 (70)	0.73

PTD, pharmacist-to-dose

Table 4. Evaluation of Initial Dosing of Enoxaparin

	Pre-PTD	Post-PTD	p value
First dose appropriate, n (%)	43 (78)	39 (76)	0.84
First dose not appropriate: rounding, n (%)	4 (7)	8 (16)	0.17
First dose not appropriate: other, n (%)	8 (15)	4 (8)	0.28
Time to goal anti-Xa in days, mean ± SD	2.25 ± 5.21	1.02 ± 0.69	0.12
Number of dose adjustments, n (%)	63 (32)	48 (24)	0.14

PTD, pharmacist-to-dose

Table 5. Reasons for Dose Adjustments of Enoxaparin

	Pre-PTD Dose Adjustments (63)	Post-PTD Dose Adjustments (48)	p value
Provider choice, n (%)	13 (21)	4 (8)	0.03
Protocol guidance, n (%)	46 (73)	40 (83)	0.56
Change in clinical status, n (%)	0	2 (4)	0.15
Other, n (%)	4 (6)	2 (4)	0.43

PTD, pharmacist-to-dose

All patients followed the previously defined goal range except for 1 patient who spanned both groups. This patient required an increase in the therapeutic anti-Xa range due to the continued development of clots while targeting the conventional 0.5–1 IU/mL range.

Although the difference in time to goal was not statistically significant between the 2 groups, it suggests the value that pharmacists may bring in achieving anti-Xa goal concentrations sooner. Patients in the post-PTD group achieved therapeutic anti-Xa concentrations 1.23 days earlier, which could potentially be a clinically significant difference. This difference in time to goal may have been influenced by 2 patients in the pre-PTD group with a longer time to goal (33.36 and 15.17 days). Although these patients were outside of the defined goal range, they remained clinically stable, and the medical team decided to maintain the same enoxaparin dose. It required additional concentrations to be drawn within the goal range of 0.5–1 ± 0.05 IU/mL, as defined in the Methods section, for these patients to achieve their goal.

The existing literature on enoxaparin dosing in pediatric patients primarily focuses on investigating the safety and efficacy of various dosing strategies, as well as subsequent monitoring protocols.[5–8] Wiltrout et al[5] investigated the implementation of a pharmacist-driven protocol with initial doses of therapeutic enoxaparin differing from our institution (1.5 mg/kg/dose for infants < 2 months of age and 1 mg/kg per dose for children ≥ 2 months). The same dose adjustment guidance was used. Their findings revealed that 56% of patients achieved initial anti-Xa values within the goal range, and thrombus resolution was associated with achieving anti-Xa concentrations within the therapeutic goal range. Fung et al[6] conducted a retrospective chart review of a freestanding children's hospital to determine enoxaparin dosage requirements across various age groups and concluded that the existing dosing schemes in place were inadequate to achieve the initial goal anti-Xa concentrations. Similarly, Bennett et al[9] investigated the clinical outcomes of pediatric patients who received prophylactic enoxaparin using a pharmacist-led protocol, noting lower instances of VTE in patients who achieved the goal range of 0.2–0.5 IU/mL. Although the guidance differed slightly from our institution in both initial dosing and monitoring, this literature highlights the importance of promptly and consistently obtaining prophylactic or therapeutic anti-Xa concentrations. These studies used pharmacist-led protocols; however, none compared the crucial role that pharmacists play in directing dose adjustments to achieve target anti-Xa concentrations efficiently by analyzing data before and after the implementation of these protocols. The results of this study show that pharmacist-led protocols yield similar rates of achieving goal anti-Xa concentrations while potentially reducing the time required for patients to reach these concentrations compared with the same protocols led by physicians. Although the length of stay was not assessed by this study, reducing the time to goal may result in shorter admissions.

Limitations of this research project include its retrospective nature and single-center design. The frequency and significance of bleeding and thrombotic events were not evaluated. The reliance on a patient's history

and physical to identify coagulation disorders may be a limitation if these disorders are not appropriately documented. Patients in the pre-PTD group that were included spanned approximately 33 months, and the same number of concentrations obtained in the post-PTD group was achieved in approximately 18 months. This discrepancy was not due to an increased frequency of monitoring, as the number of patients was similar in both groups; however, it may have stemmed from increased usage of enoxaparin. Physicians and pharmacists may have become more comfortable with dose adjustments as the use of enoxaparin in pediatrics has increased in recent years, and nursing staff may have become more familiar with obtaining the correct concentrations. It is challenging to determine the extent to which the increased frequency of enoxaparin use would have impacted the results of this study. However, the rising need for monitoring accompanying the prescribing of enoxaparin presents more opportunities for pharmacists to be involved in clinical care.

Conclusion

There was no difference in the rate of anti-Xa concentrations that were in the goal range before and after the implementation of a pharmacist-led enoxaparin dosing protocol. This likely stemmed from the use of the same dosing guideline among both groups. PTD protocols will enable physicians to focus on other aspects of clinical care while pharmacists oversee the dosing and monitoring of enoxaparin to achieve optimal anticoagulation and positive outcomes. These findings indicate that PTD protocols can and should be implemented.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution.

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JPPT | Quality Improvement

Optimization of Medication Workflows to Improve Timely Medication Administration on a Pediatric Hospital Unit: A Quality Improvement Project

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OBJECTIVE Medication workflows are important to improve patient safety and provide timely lifesaving medical care. When operating efficiently, they can also decrease medication and labor waste. The objective of this quality improvement project is to compare missing dose request rates before and after improvements in medication workflows, specifically, decreases in medication and labor waste and the financial implications of these improvements.

METHODS The study evaluated the rate of medication missing dose requests on a 24-bed medical surgical unit in a standalone pediatric hospital from May 2022 to October 2022. Medication workflows were evaluated by pharmacy and nursing team members, and interventions were identified and implemented with the Model for Improvement methodology. Outcomes of missing dose requests per 100 medication doses dispensed were tracked weekly, as were staff time and costs of medications.

RESULTS The missing dose requests per 100 medication doses dispensed decreased from 3.8 to 1.03 during the 6-month initiative. This improvement estimated that 988 missing medication doses were prevented, leading to an estimated $61,038.64 in waste savings. The average cost of the medication and materials (excluding labor) to replace a single missing dose of medication was $61.78. The median cost was $54.71 (IQR, 11.91–4,213.11). Pharmacist, pharmacy technician, and nurse time saved per missing dose were estimated to be 6, 14, and 17 minutes, respectively.

CONCLUSION Multimodal improvements in inpatient medication workflow reduce missed medication errors and improve cost and labor efficiencies.

ABBREVIATIONS ADC, automated dispensing cabinet; EHR, electronic health record; IV, intravenous; PDSA, plan-do-study-act

KEYWORDS medical waste; medication waste; patient safety; pediatric pharmacy; pharmacy practice; quality improvement

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Introduction

Medication errors are a common source of pediatric health care harm. Per the US Pharmacopeia, pediatric patients experience significantly more medication errors than adult patients (31% vs 13%, respectively).[1] It has been estimated that in the United States, 7.5 million preventable pediatric medication errors occur each year.[2] Literature has shown that 0.24% of medication errors in pediatric patients lead to harm, including 7000 patient deaths annually.[2,3] This increased risk of harm is due to the lack of available pediatric dosage forms (e.g., oral liquid suspensions, solid dosage forms in appropriate dosages)—the standard for weight-based dosing in pediatric patients—and the need to use nonstandard dosages to ensure pediatric patients can receive the medication at the proper dose.

Medication errors for hospitalized children result from failure of 1 or more of the 5 key steps in the medication pathway: ordering, transcribing, dispensing, administering, and monitoring. Patient-specific doses are prepared in hospital pharmacies and delivered to inpatient units. Once these doses are delivered to inpatient units, they are subsequently administered by a nurse at their ordered administration time. This process falters when the nurse cannot locate these doses to administer to the patient, which results in system inefficiency. These inefficiencies include medication waste, lost labor from attempts by pharmacy and nursing to locate the dose, compounding a new dose, and

delivering the new dose. In addition to these sources of waste, delays in patient care also result from the medication being unavailable to administer when needed. Untimely administration of medication can cause direct harm to pediatric patients.[4] Furthermore, the time and energy invested in locating a missing medication dose or re-preparing it can result in time away from other patient care needs, indirectly contributing to additional patient harm.[5]

Internal baseline data showed that 3.8% of the medications dispensed by pharmacy are reported missing (3.8 missing medication requests per 100 doses dispensed). If nursing cannot find the medication when they are scheduled to administer it, they will contact pharmacy by phone or by the *medication message* function within the Epic electronic health record (EHR) (Verona, WI). Pharmacy staff will confirm the location of the medication or prepare an additional dose of medication and deliver it for administration.

This quality improvement study compared missing dose requests per 100 medication dispenses pre and post intervention to enhance the efficiency in the medication dispensing and administration domains. The goal of this initiative was to reduce missing dose request dispenses on a single multispecialty medical/surgical inpatient unit and quantify the efficiency improvements achieved in both time and costs.

Methods

Setting. This study was conducted at a large freestanding quaternary children's hospital system in the Midwestern United States with more than 440 inpatient beds. The inpatient pharmacy dispenses at least 30,000 inpatient medication doses to inpatient units per month. These doses are primarily patient-specific enteral liquid and intravenous (IV) medications. Pharmacy staff transport these doses to inpatient units by hand or via a pneumatic tube system. A 24-bed medical surgical unit, serving primarily adolescent children, was selected to evaluate the missing medication dispense rate and contributing causes. The patient to nurse ratio on this unit is on average 5:1. The improvement project spanned from May 2022 to November 2022 with subsequent sustainability monitoring through July 2023.

The pharmacy department standardly delivers medications by hand directly to the unit medication room at prespecified times where they are stocked in a patient-specific bin or in an automated dispensing cabinet (ADC) (Omnicell, Mountain View, CA) for general access for commonly administered medications. The first dose following the verification of a new medication order is typically delivered via our pneumatic tube system. Controlled substances and hazardous medications cannot be delivered via the pneumatic tube system per policy and are delivered by hand. Prior to this project, there was no standard process in place for pharmacy and nursing to locate medications that were not available on the unit.

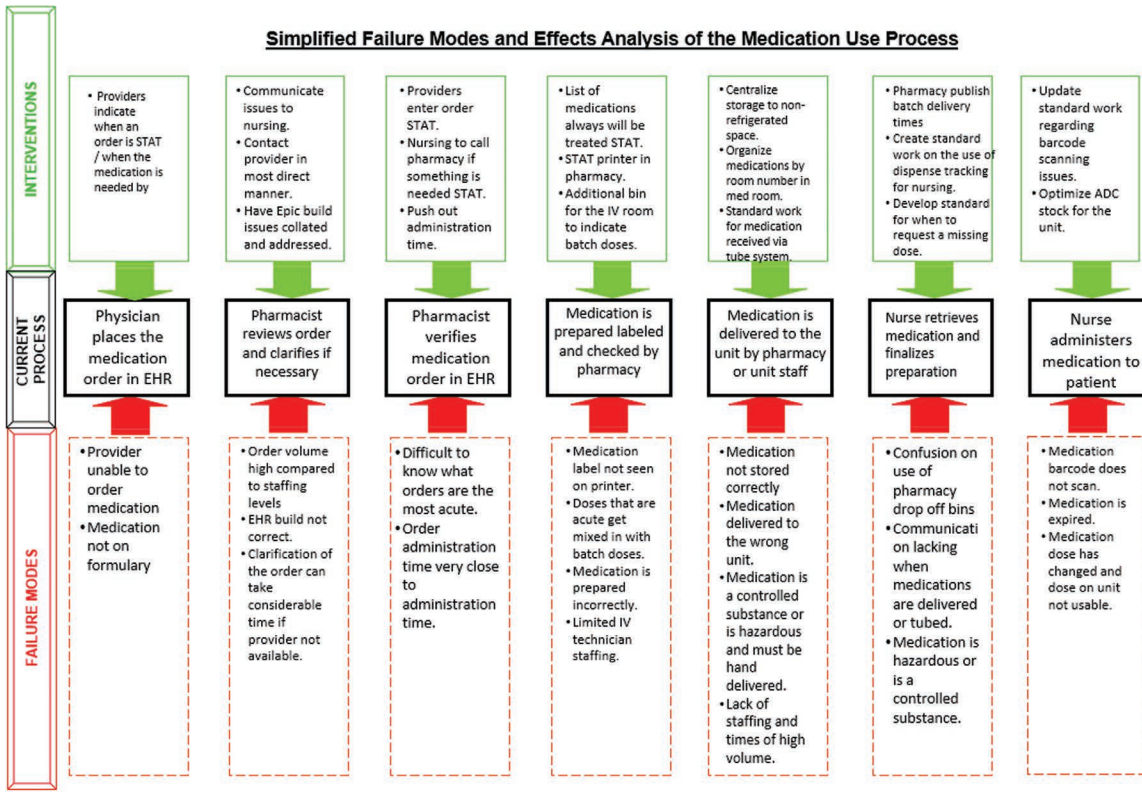
Quality Improvement Overview. This improvement project was completed by using the Model for Improvement methodology.[6] A multidisciplinary team was created that included 3 clinical care nurses, a nurse educator, a respiratory therapist, a unit secretary, and 2 pharmacists. *Ad hoc* input from resident physicians was included to assist with understanding parts of their workflow that affect medication order verification. Key improvement tools included a key driver diagram, process mapping, U charts, Pareto charts, simplified failure modes and effects analysis (Figure 1), and plan-do-study-act (PDSA) cycle testing.

Intervention Development. An analysis of the missing dose requests from the previous 6 months to see which medications, dispense types, delivery locations, and delivery methods had the most missing dose requests was completed to assist in identifying types of medication dispenses most associated with a missing dose request. Baseline missing dose request dispenses were established by averaging the missing dose request dispenses from March and April 2022. A key driver diagram (Figure 2) was created from the simplified failure modes and effects analysis, and missing dose analysis was developed to highlight key drivers and potential interventions to focus improvement efforts. Five key drivers were prioritized by a simple majority of the multidisciplinary improvement team; they informed the intervention development and were tested in a PDSA fashion: 1) improve communication between pharmacy, nursing, and ordering providers; 2) increase awareness of where medications are stored; 3) optimize ADC inventory; 4) increase time to prepare and administer the drug by the assigned administration time; and 5) streamline order entry process to indicate when a medication is needed.

To improve communication between pharmacy, nursing, and order providers, a set of clear and precise standard ordering instructions were developed for the use of dispense tracking technology within the EHR (see Supplemental Table S1), and for the process pharmacists should use to communicate with providers to clarify medication orders in question. Standard work instructions for the use of dispense tracking technology allowed nurses to be trained on how to use this technology to see where in the dispensing process the medication was, if it was delivered, and how it was delivered. This information was previously found through phone calls or messages in the Epic EHR, or not available at all.

To improve awareness of where medications were stored, standard work instructions were developed to guide handling of medications delivered through the pneumatic tube system (see Supplemental Table S2). Previously, doses of medications were taken from the pneumatic tube system to a variety of final delivery

Figure 1. Simplified failure modes and effects analysis.



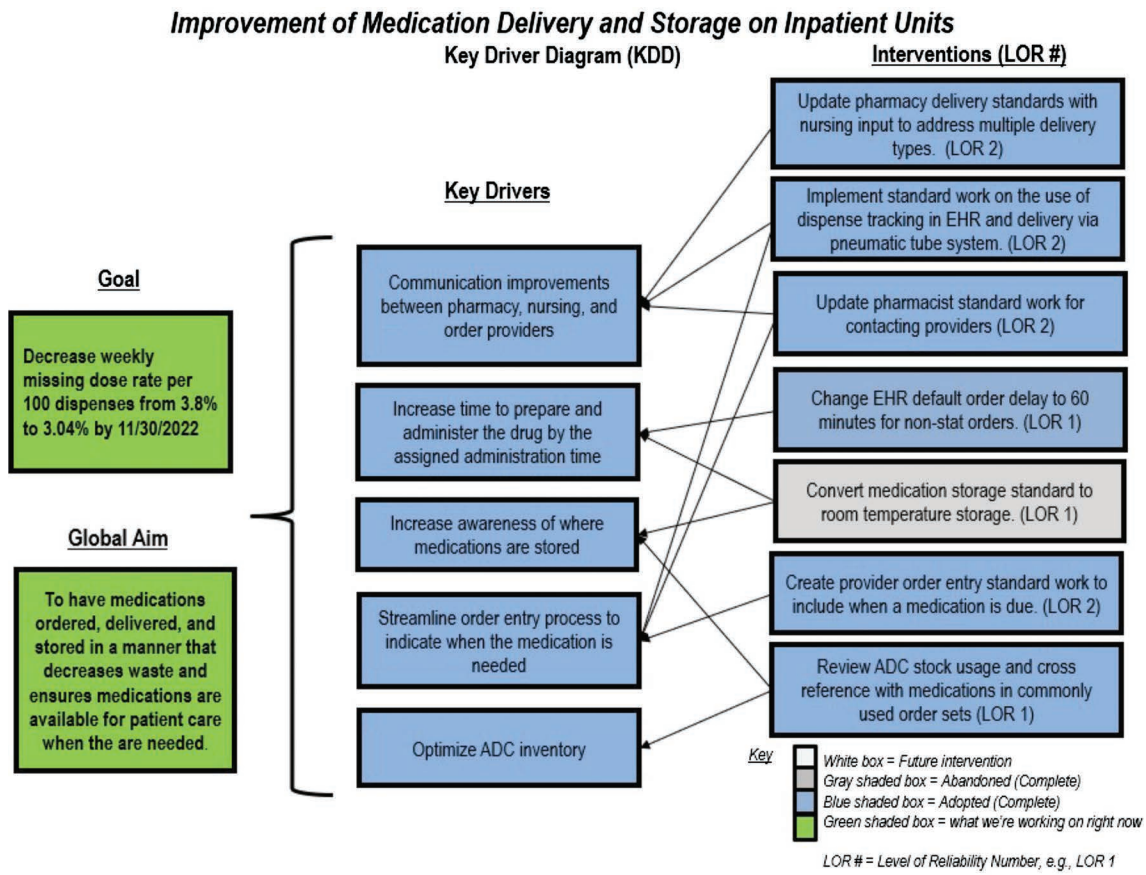
ADC, automated dispensing cabinet; EHR, electronic health record; IV, intravenous

locations, making the dose difficult to locate. The new process requires that all doses of medication delivered through the pneumatic tube system be taken to the unit medication room to decrease resources used in looking for the medication. The 2 interventions combined were designed to make it clear where medications were located.

Optimizing the inventory in the ADC on the unit was also identified as a critical intervention, based on the review of all missing dose requests that identified what medications, dispense types (e.g., sterile products, oral liquids, unit dose tablets), delivery locations (e.g., room temperature storage, refrigerated storage, ADCs), and delivery methods (hand delivered vs pneumatic tube system) were most frequently missing. Most missing medications were not stored in the ADC, were frequently used medications, medications from commonly used order sets, or medications stocked in the ADC that had insufficient inventory based on usage. The pharmacy team revised the inventory in the ADC to match usage of identified medications.

Optimization of the EHR medication order process increased time to prepare and administer the drug by the assigned administration time and streamlined the order entry process to indicate when a medication is needed. The team identified the following areas for improvement: 1) medication order default start times are too close to the time of order verification to allow the pharmacy time to prepare and deliver the medication; 2) nursing is required to administer a dose of medication within an hour before or after the scheduled due time, leading to urgency to acquire the medication; and 3) pharmacy is rarely aware of when medication orders are needed immediately, owing to the lack of provider notification during medication order entry. The Information Services team facilitated EHR build improvements by modifying the default medication start time interval in the EHR. The default medication start time interval at discovery was to round up the administration time to the next 30-minute interval but was revised to round up to the next 60-minute interval. This allowed pharmacy adequate time to verify the medication order, prepare the medication, and deliver it to the unit before the dose is needed by nursing. The next intervention was to address streamlining of the order entry process to indicate when a dose is needed. The team discovered an ordering provider knowledge gap in their ability to change the start time for that order, indicate the order was needed

Figure 2. Key driver diagram.



ADC, automated dispensing cabinet; EHR, electronic health record

urgently, or see when the first administration would be due while entering the order. With the help of the resident physicians (common ordering providers), we were able to develop education on how to recognize and change the start time of an order and indicate if it was needed urgently during order entry. By knowing when the medication is needed, pharmacy can better prioritize which medication order should be verified and dispensed first.

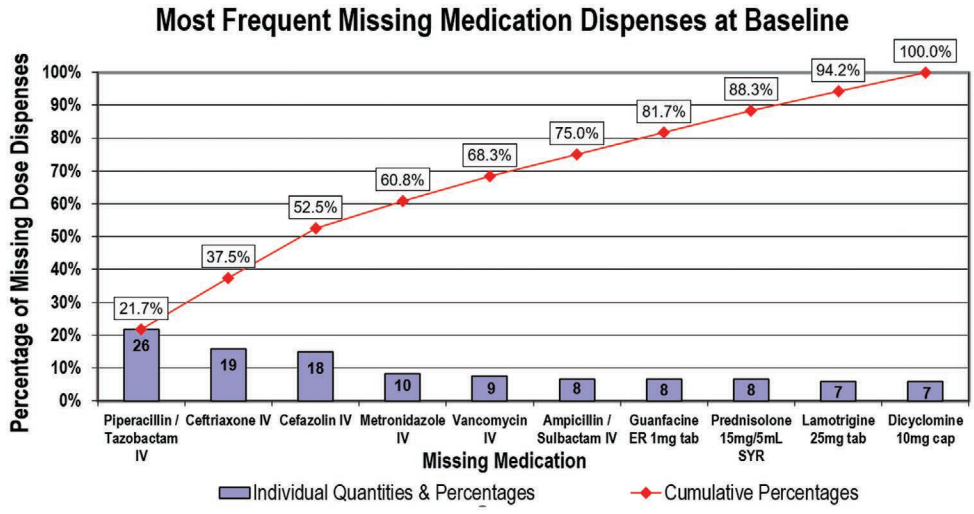
Measurements and Reporting. The primary measure was missing medication dose request rate per 100 medication doses dispensed. The data were collected prospectively from May 2022 through November 2022 by the primary investigator (JCS). These data were measured weekly by quantifying all electronic missing dose requests dispensed divided by the total number of medication doses dispensed. These data were acquired though EHR reporting. Descriptive statistics were used to describe quantitative and percentage change in the missing dose rate per 100 doses dispensed from baseline, average costs, average time expenditures, and median values of medication costs. The secondary measures captured included nursing and pharmacy time spent addressing missing dose requests and the amount of medication waste, in dollars, that was accumulated from having to re-dispense a medication. This was measured by observing 100 missing dose request medication dispenses. The time measured from these 100 observations was averaged. To quantify the total amount of time spent, this average time was multiplied by the total number of missing medication doses dispensed. Drug waste was averaged in a similar fashion over these 100 dispenses to establish an average medication cost per missing dose request dispense. Final accumulations of time and medication waste were based on the percentage decrease of missing dose request dispenses from baseline at the final weekly measurement prior to November 30, 2022. A balancing measure documented was the total quantity of expired medications retrieved from the unit ADC to monitor for an increase in expired medications due to an increase in medication inventory in our ADC machines.

Results

Baseline measurement of the primary outcome was 3.8 missing medication dose request dispenses per 100 medication doses dispensed. The Pareto charts for the most frequently missing medications are outlined in Figures 3 and 4. The most frequent missing dose requests were for first-dose IV antibiotics that were dispensed from pharmacy. When excluding first-dose IV antibiotics, the next most frequent category was oral unit dose medications that were included in commonly used order sets on the unit and were not stocked in the ADC.

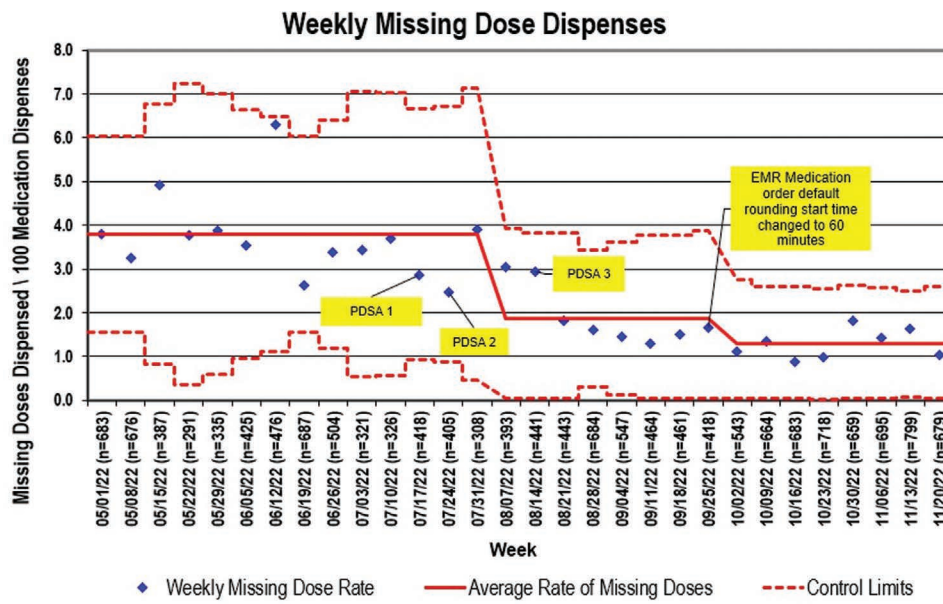
The primary measure of missing medication dose requests dispenses per 100 medication doses dispensed decreased from a baseline of 3.8/100 (3.8%) to 1.03/100 (1.03%) (Figure 5). This marked a decrease of 271% in missing dose request dispenses from baseline from

Figure 3. Pareto chart—most frequently missing medications at baseline.



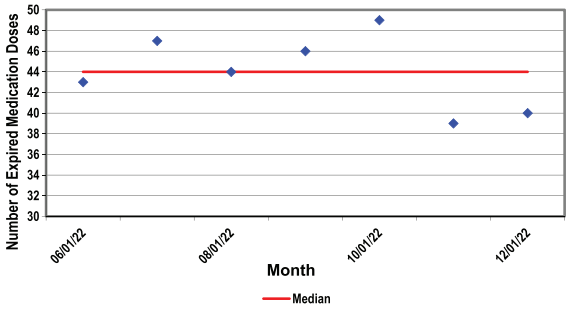
cap, capsule; ER, extended release; IV, intravenous; SYR, oral syringe; tab, tablet

Figure 4. U chart—weekly missing medication dose dispenses per 100 medication doses dispensed.



EMR, electronic medication record; PDSA, plan-do-study-act

Figure 5. Monthly total of medications wasted from ADC machines.



ADC, automated dispensing cabinet

May 2022 through November 2022. This resulted in 19 total weekly missing medication doses avoided following implementation of all interventions. The secondary outcome of time and medication waste savings can be seen in the Table. Based on 100 direct observations, the measured time for each missing dose request medication dispense resulted in a loss of 6 minutes of pharmacist time, 14 minutes of pharmacy technician time, and 17 minutes of nursing time. The average cost of the medication and materials (excluding labor) to replace a single missing dose of medication was $61.78. The median cost was $54.71 (IQR, 11.91–4213.11). With our improvement from baseline, this would equate to an annual cost savings of $61,038.64 based on the average cost to replace a single missing dose. The balancing measure of the quantity of expired medications retrieved from the unit ADC was no different from baseline through the completion of this project. This was measured to see if there was an increase in expired medications due to increased medication inventory being stored in the ADC.

Table. Labor and Pharmaceutical Waste Savings

Labor Savings		
Role	**Time Spent Per Missing Dose, min**	**Estimated Annual Labor Time Savings, min**
Pharmacist	6	5928
Pharmacy technician	14	13,832
Nurse	17	16,796
Pharmaceutical Waste Savings		
Medication Cost Per Missing Dose	**Missing Doses Prevented**	**Estimated Annual Pharmaceutical Waste Savings**
$61.78	988	$61,038.64

Discussion

Other studies and review articles have investigated reducing missing medications and waste. These studies primarily focused on internal pharmacy workflow optimization[7–9] use of computer model estimates or simulations,[7,10,11] and/or implementation of technology.[11,12] In contrast, this study prospectively evaluated missing dose data by a multidisciplinary team that focused on workflows that carried across disciplines in addition to internal workflows. All members of the team evaluated the workflow from start to finish to identify areas that affect the rate of missing doses along with medication and labor wastes.

Our primary outcome showed a better-than-expected decrease in missing dose requests per 100 doses dispensed from 3.8 to 1.03, a 271% improvement. Pharmacist, pharmacy technician, and nursing labor time saved, based on this decrease, was 6, 14, and 17 minutes, per dose, respectively. There was no difference in medication waste from the unit ADC following changes to its medication inventory. Efficiency and cost saving can be realized with focused improvement efforts.

This project addresses both financial and operational efficiency. With health care systems across the country pressured to find ways to optimize efficiency of current resources and reduce waste, this is an example of how both objectives can be achieved. This project occurred on just 1 inpatient unit and yielded 100 minutes of staff time per shift. If this were spread to all patient care areas, the impact could be even greater across a health care system. To achieve this time efficiency, the most significant intervention was aligning drugs included in commonly used order sets with the medication inventory in ADC cabinets. Inventory optimization did not cover all medications ordered. When the standard start time for medication orders was extended to 60 minutes, this helped give the pharmacy time to prepare and deliver the medications not in the ADC and allowed nursing to give the medications at their ordered due time. These 2 interventions in combination appeared to have a synergistic effect on decreasing the missed medication requests. A surprising finding was the average cost of the medication doses that were re-dispensed ($61.78/dose). Pharmaceutical expenditures have been increasing rapidly during the past 20 years, largely due to the increased cost of new and current therapies.[13] With medications becoming more costly, the expected average cost per dose was anticipated to be higher. However, the frequency of missed dosing requests with re-dispensing demonstrates that even at $61.78/dose, the aggregate financial impact of avoiding re-dispensing is material ($61,038.16 estimated annual savings). These interventions on inpatient care areas that administer more high-cost medications would produce a larger financial savings.

These results show that improvement in the medication ordering, preparing, and administration workflow

can significantly affect quality and safety. Optimizing patient care is also core to the mission for all health care systems. Medication delays threaten optimal care, as evidenced by the designation of medication delays as a National Patient Safety Agency goal.[14] Not only does timely medication delivery improve care, but also nursing distraction can negatively affect patient safety.[15,16] The hunt for missing medications and the time consumed negotiating and receiving a new medication are indisputable distractions. Pharmacists are also affected by these distractions, leading to increased errors.[17,18]

One of the most beneficial learnings from this improvement project is the newfound understanding and knowledge regarding interdepartmental workflows. Prior to this multidisciplinary improvement team formation, many assumptions about how pharmacy and nursing workflows functioned were not accurate. A key strategy to understand the workflows was observation on the clinical units and in the pharmacy. Through these observations, the assumptions regarding pharmacy and nursing workflows were proven inaccurate, allowing for collaboration and improvements to be made. Many improvement projects can succeed through small team or secular improvement, but this project demonstrates the necessity and value of cross-functioning teams to identify and drive improvement interventions. Physical observation or "Gemba walks" have been shown to provide a better understanding of workflows and allow those in the workflow to help identify and solve problems.[19] This allowed our team to gain knowledge on the issues affecting the groups outside of their professional discipline and communicate better across disciplines.[20]

With the improvements we made in reducing missing dose requests, medication waste, and labor waste, we also identified other ways for improvement. First, we did not evaluate our daily batch schedule within the pharmacy. Deliveries that occur close to common administration times can increase missing dose requests because of the limited time between medication delivery and medication administration. Increasing the number of batches you complete a day can decrease waste by preventing doses from being made that were either discontinued or are meant for a discharged patient, but it also increases the labor needed to deliver the additional batch doses to patient care units. Second, education of new employees on the updated medication workflows needs to occur to maintain these results. We have identified that including a medication workflow section into new employee onboarding is vital to continue this success. Third, this study was conducted on a single inpatient medical surgical unit. The opportunity to spread these improvements to other units will greatly decrease missing medication requests, medication waste, and labor waste across the whole health system.

There are several limitations to this study. First, this is a local study at a standalone children's hospital focused on an individual unit. Adult or pediatric systems still should be able to apply the process used in this study, but their individual interventions and impacts may be different. Second, this project took place in a medical surgical unit, whereas an intensive care unit or emergency department may have different needs. These interventions will need to be validated in these patient care areas. The interventions may also have a larger impact on a unit that has higher-cost medications. Third, while the team did calculate the time saved from distractions from missing doses, there was no measurement of what was done with the time saved. Fourth, this study involved solely pediatric patients. This may underestimate the impact of a similar quality improvement initiative at an adult center where standard dosage forms are much more common and are more easily dispensed from an ADC. Fifth, the balancing measure of waste from ADC-stocked medications is a lagging indicator because it will take time for medications to expire. However, new medications added were used frequently and thus should be used well ahead of expiration. Additionally, there are other strategies in place to improve prioritization and efficiency of medication dispensing (e.g., STAT bins, label indicators). Staffing was deemed adequate for both pharmacy and nursing during this period.

Conclusions

This improvement study demonstrates a multidisciplinary team's successful reduction in missed medication dosing requests with a measurable impact on efficiency and waste reduction. Keys to this successful improvement included medication dispensing and delivery standard work establishment, medication standardization in the ADC, and use of EHR constraints around medication order to administration times. Future work will allow local system-wide spread, though this could represent a substantial improvement opportunity for many health care institutions.

Article Information

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JPPT | Single-Center Retrospective Study

Use of Intrapleural Alteplase in the Treatment of Parapneumonic Effusion in Children: A Report of a 10-year Experience

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OBJECTIVES Intrapleural alteplase is used in children with parapneumonic effusion (PPE) with variable dosing strategies. We compared the outcomes of a lower (≤2 mg) and a higher (>2 mg) alteplase dose in children with PPE.

METHODS A retrospective study was conducted among admitted patients younger than 18 years who received at least 1 intrapleural alteplase dose from July 2014 to May 2023. The primary outcome was the treatment failure rate. Secondary outcomes included chest tube output and duration of placement and hospital and pediatric intensive care unit (PICU) length of stays.

RESULTS Seventy-two patients were included (lower dose: 62.5% vs higher dose: 37.5%) with a median age of 5 years (IQR, 1–8 years). The median alteplase dose was 2 mg (IQR, 2–4 mg). Treatment failure occurred in 10 (14%) patients. The lower dose group had a similar failure rate compared with the higher dose group (lower dose: 9% vs higher dose: 22%; p = 0.161), despite a statistically significant higher median chest tube output in the higher dose group (346 [IQR, 256–466] vs 175 [IQR, 70–358] mL/24h; p = 0.002). However, after adjusting for weight, both groups had a similar output (12 mL/kg/24h). Alteplase instillation after primary video-assisted thoracoscopic surgery (VATS) was associated with a significant reduction in the duration of chest tube placement and hospital and PICU stays.

CONCLUSIONS Lower alteplase doses (≤2 mg) were effective for most children with PPE. Alteplase combined with primary VATS might be associated with better outcomes.

ABBREVIATIONS LOS, length of stay; PICU, pediatric intensive care unit; PPE, parapneumonic effusion; VATS, video-assisted thoracoscopic surgery

KEYWORDS alteplase; chest tube; children; empyema; parapneumonic effusion; VATS

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Introduction

Pneumonia is associated with significant morbidity and mortality worldwide, particularly among children younger than 5 years of age.[1] While patients typically recover with the use of antimicrobials and supportive care, some patients develop complications.[2] While the incidence of parapneumonic effusion (PPE) and empyema in children in the United States has decreased after the introduction of the pneumococcal vaccines,[3] the overall incidence appears to be increasing globally over the past decade.[4–8] Approximately 40% to 50% of children admitted with pneumonia develop a PPE, and many of them require additional therapy, including surgical intervention.[9,10]

Current practice guidelines recommend 2 strategies for the initial management of complicated PPE as follows: chest tube drainage with intrapleural fibrinolytic therapy and video-assisted thoracoscopic surgery (VATS).[11–13] Two systematic reviews of randomized trials demonstrated similar rates of treatment failure and mortality between the 2 strategies.[14,15] However, there were inconsistent findings regarding the differences in hospital length of stay (LOS) and cost.[14–17] An economic analysis found that chest tube drainage with fibrinolytic therapy was the more cost-effective strategy for children with PPE, based on limited outdated data.[16] Furthermore, a recent report that included nearly 3500 children with PPE showed that patients treated with primary VATS had a shorter hospital and pediatric intensive care unit (PICU) LOS and reduced use of health care resources, including radiographic studies and mechanical ventilation, which could reduce overall hospitalization costs.[17]

Older fibrinolytic agents, such as streptokinase and urokinase, were initially evaluated for the treatment of

patients with PPE yielding positive outcomes.[18] However, their use has been replaced by alteplase (tissue plasminogen activator) for safety reasons. Alteplase has been used frequently with variable dosing strategies for children with PPE.[12] The 2011 Pediatric Infectious Diseases Society and the Infectious Diseases Society of America pediatric pneumonia guidelines recommend 2 dosing regimens based on the results of 2 prospective studies: a fixed dose (4 mg) daily for 3 days and a weight-based dose (0.1 mg/kg, maximum 3 mg) every 8 hours for 3 days.[11,19,20] However, observational studies have reported various dosing strategies, ranging from 0.5 to 10 mg, given as a fixed,[21–24] weight-based,[25–27] or ultrasound-grade-based[28,29] regimen, with positive overall outcomes.

Given the variability in alteplase dosing among children with PPE in the available literature, more evidence is needed to help define an optimal dosing regimen. This study reports outcomes associated with a 10-year experience of children treated with intrapleural alteplase for PPE, aiming to evaluate the clinical outcomes of lower alteplase doses (≤2 mg) compared with higher doses (>2 mg).

Materials and Methods

Participants. This study was a single-center, retrospective chart review conducted at an academic children's hospital between July 2014 and May 2023. All children younger than 18 years of age who received at least 1 dose of intrapleural alteplase for the treatment of a thoracic effusion were included. Patients who received alteplase through a peritoneal tube for intra-abdominal infections were excluded. Thoracic effusion was defined as a PPE associated with any etiology.

Treatment. The treatment approach for PPE in children at our institution is not standardized, and each patient is managed differently, primarily based on physician preference. Chest tube placement is the usual first-line strategy with or without fibrinolytic therapy. Alteplase therapy initiation and discontinuation are mostly guided by chest tube output along with clinical assessment. The alteplase dose regimen varies depending on the patient's age and clinical situation; doses used in patients in our analysis ranged from 0.5 to 15 mg.

Surgical evaluation is performed at various intervals. While VATS is usually deferred until the patient is not improving with chest tube drainage and fibrinolytic therapy, some patients are treated initially with VATS, followed by alteplase therapy, which is initiated on postoperative day 1 or 2. This approach is justified as appropriate by the surgery team, as the patient is likely to require surgery eventually due to the severity of the PPE.

Outcomes. The primary outcome for our analysis was the rate of composite treatment failure, defined as a need for VATS following chest tube placement and alteplase therapy and/or the development of recurrence within 6 months of the index dose. The secondary outcomes evaluated were chest tube output, expressed as milliliters per 24 hours and milliliters per kilogram per 24 hours following alteplase administration, duration of chest tube placement, hospital LOS, PICU LOS, and all-cause 6-month mortality. Chest tube output was recorded after each alteplase instillation, and the average output for each patient was used to estimate the median output of the dose group. The duration of chest tube placement, hospital LOS, and PICU LOS were calculated starting from the chest tube insertion date.

Data Collection. A list of patients who received intrapleural alteplase was retrieved using our institution's electronic health record. Data were collected from the patient's electronic health records and included demographic data (age, sex, race, weight, and height); comorbidities; reason for admission; indication for chest tube insertion; dates of chest tube insertion and removal; dates of hospital admission and discharge; dates of PICU admission and discharge; baseline temperature and supplemental oxygen requirements; baseline and after alteplase laboratory results; baseline and after alteplase chest tube output; baseline chest X-ray impression; microbiological culture results; antimicrobials administered; alteplase doses and volumes; thoracic surgeries; and clinical outcomes (treatment failure, recurrence, and mortality). For children younger than 2 years of age, obesity was defined as a weight-for-length percentile above the 95th percentile using the World Health Organization growth charts.[30] For children older than 2 years, obesity was defined as a body mass index above the 95th percentile using the Centers for Disease Control and Prevention body mass index–for-age growth charts.[31]

Statistical Analysis. Formal sample size calculation was not performed, as all eligible patients were included. Descriptive statistical analysis was conducted using Microsoft Excel software, Version 16.81 (Redmond, WA). Proportions (frequencies) were used for categorical variables. Continuous variables were summarized as median (IQR). IBM SPSS Statistics, Version 29.0 (IBM Corp., Armonk, NY) was used for inferential analysis. The difference in treatment failure between the lower (≤2 mg) and the higher (>2 mg) alteplase dose groups was assessed using the χ^2 or Fisher's Exact test. The Mann-Whitney *U* test was used for continuous data. All p values were 2 tailed, and a value of 0.05 or less was considered significant.

Post-hoc analyses for the primary and secondary outcomes were performed for the following 3 groups: (1) patients who received initial therapy with alteplase alone vs those who received alteplase with primary VATS; (2) patients with PPE caused by pneumonia; and (3) children younger than 3 months of age.

Results

Seventy-six patients were screened; 72 were included in the final analysis. Four patients were excluded because they received alteplase for effusions associated with intra-abdominal infections through a peritoneal tube or abdominal drainage device.

Baseline Characteristics. Table 1 summarizes the baseline characteristics of the included patients. The median age was 5 years (IQR, 1–8 years), with a similar proportion of males and females (50% each). All the included patients had variable degrees of PPE secondary to various etiologies, with pneumonia being the most common etiology (75%); 2 patients with pericardial effusion had an associated PPE. Alteplase was administered as intrapleural for all included patients. There were considerable differences between the 2 dose groups. The lower dose group was younger (2.2 [IQR, 0.7–6] years vs 8 [IQR, 5–14] years), had fewer obese patients (18% vs 37%), and had lower supplemental oxygen requirements (40% vs 63%).

Approximately 50% of patients had a positive culture result at some time during their hospitalization. The most common isolate was methicillin-resistant *Staphylococcus aureus* (n = 10). The median duration of antibiotic therapy was 22 days (IQR, 18–26 days). Table 2 summarizes infectious disease characteristics.

Intrapleural Alteplase Therapy. Overall, the median alteplase dose was 2 mg (IQR, 2–4 mg); most patients (n = 19; 26%) received three doses. Most patients received no more than 1 dose per day (n = 51; 71%). A concentration of 1 mg/10 mL was used in most patients (n = 68; 94%). The lower-dose group received a median dose of 2 mg (IQR, 2–2 mg), whereas the higher-dose group received a median dose of 4 mg (IQR, 4–4 mg). The majority received alteplase as initial therapy (69%), defined as treatment given within

Table 1. Baseline Characteristics

Characteristic*	All Patients (*N* = 72)	Alteplase Dose ≤2 mg (n = 45)	Alteplase Dose >2 mg† (n = 27)
Sex, male	36 (50%)	21 (47%)	15 (56%)
Age, yr	5 (1–8)	2.2 (0.7–6)	8 (5–14)
Race/ethnicity			
White	37 (51%)	24 (53%)	13 (48%)
African American	27 (38%)	17 (38%)	10 (37%)
Hispanic	4 (6%)	2 (4%)	2 (7%)
Asian	1 (1%)	1 (2%)	0 (0%)
Others	3 (4%)	1 (2%)	2 (7%)
Previous health issues			
Asthma	8 (11%)	4 (9%)	4 (15%)
Obesity	18 (25%)	8 (18%)	10 (37%)
Hospital LOS before chest tube insertion, days	2 (1–4)	2 (1–5)	1 (0–3)
PICU LOS before chest tube insertion, days	0 (0–2)	1 (0–2)	0 (0–1)
Chest tube output before alteplase			
mL/24 h	55 (16–178)	36 (10–94)	175.2 (67–269)
mL/kg/24 h	3 (1–7)	3 (1–6)	3 (1–7)
Supplemental oxygen requirement	46 (64%)	29 (40%)	17 (63%)
Indication for chest tube			
Parapneumonic effusion	70 (97%)	43 (96%)	27 (100%)
Pneumonia	54 (75%)	33 (73%)	21 (77%)
Chylothorax	6 (8%)	5 (11%)	1 (4%)
Retropharyngeal abscess	2 (3%)	1 (2%)	1 (4%)
Post–thoracic/abdominal surgery	2 (3%)	1 (2%)	1 (4%)
Malignancy/mass	2 (3%)	1 (2%)	1 (4%)
Trauma	2 (3%)	1 (2%)	1 (4%)
Splenic abscess	1 (1%)	0 (0%)	1 (4%)
Pancreatitis	1 (1%)	1 (2%)	0 (0%)
Pericardial effusion	2 (3%)	2 (4%)	0 (0%)

LOS, length of stay; PICU, pediatric intensive care unit

* All values expressed as median (IQR) or count (frequency).
† Patients who received at least one alteplase dose > 2 mg.

Table 2. Infectious Diseases Characteristics

Characteristic	All Patients (*N* = 72)
Positive culture results, n (%)*	37 (51)
Pathogen identification, n (%)†	
Methicillin–resistant *Staphylococcus aureus*	10 (21)
Streptococcus pneumoniae	8 (17)
Methicillin–susceptible *Staphylococcus aureus*	6 (13)
Streptococcus pyogenes	4 (8)
Streptococcus anginosus/constellatus/intermedius	4 (8)
Escherichia coli	2 (4)
Enterobacter cloacae	2 (4)
Other	12 (25)
Antibiotics administered before admission, n (%)	33 (46)
Antibiotics administered during admission, n (%)	68 (94)
Antibiotics administered after discharge, n (%)	50 (69)
Duration of antibiotics, median (IQR), days	
Inpatient antibiotics	10 (8–16)
Discharge antibiotics	13 (10–14)
Total	22 (18–26)

* Number of patients with any culture results identified during hospitalization.
† Pathogen identified from the results of blood, pleural, endotracheal, and pericardial cultures during hospitalization.

the first 2 days after chest tube insertion. Seventeen patients received alteplase with primary VATS, and 2 received intrapleural dornase alfa therapy. The treatment-failure group (n = 10) received a higher median alteplase dose (4 vs 2 mg) compared with the treatment-success group (n = 62). The characteristics of alteplase therapy are outlined in Table 3. Alteplase dose per age and dose per weight per age of alteplase are illustrated in Figure 1.

Treatment Outcomes. Treatment failure occurred in 10 (14%) patients; 7 required VATS and 3 had recurrent PPE. There was no significant difference in treatment failure rate between patients who received an alteplase dose of 2 mg or less compared with those who received a higher dose of more than 2 mg (9% vs 22%; p = 0.161). The median time to rescue VATS was 4 days (IQR, 4–8 days) after chest tube insertion and 3 days (IQR, 3–7 days) after alteplase initiation. The median chest tube output following alteplase instillation was 279 mL/24h (IQR, 120–432 mL/24h). The median duration of chest tube placement was 5 days (IQR, 4–9 days) (Table 4). A higher chest tube output (346 vs 175 mL/24h; p = 0.002) and a longer duration of chest tube placement (8 vs 5 days; p = 0.004) were observed in the higher dose group. However, after adjusting for weight, both groups showed a similar chest tube output (12 mL/kg/24h). There were no significant differences in hospital LOS, PICU LOS, or mortality rate.

Four patients died during the 6-month interval from the first alteplase dose. The causes of death were reported as cardiac arrest secondary to COVID-19 respiratory failure, cor pulmonale, right atrial perforation, and septic shock.

Figure 2 illustrates the differences between the median chest tube output 24 hours before and after the first alteplase dose. There was a higher rate of increment after the first alteplase dose in the lower dose group compared with the higher dose group (378% vs 118%). After adjusting for weight, both groups showed a comparable increment rate (333% vs 329%). Supplemental Table S1 shows treatment outcomes between treatment success and failure groups. Supplemental Table S2 shows laboratory values before and after alteplase therapy.

Post-hoc Analyses. In patients receiving alteplase with primary VATS, a chest tube was inserted immediately following the VATS, and alteplase was initiated in a median of 2 days (IQR, 1–2 days) after the VATS. Patients who received this combined therapy (n = 17) had a lower treatment failure rate (6% vs 17%; p = 0.434) compared with those who received alteplase alone (n = 54); however, this difference was not statistically significant (Table 5). Patients who received alteplase alone had a higher chest tube output (322 vs 166 mL/24h; p = 0.005). This was consistent after adjusting for weight (14 vs 10 mL/kg/24h; p = 0.046). Additionally, combination therapy was associated with a shorter duration of chest tube placement (4 vs 6 days; p = 0.001), hospital LOS (7 vs 13 days; p = 0.001), and PICU LOS (2 vs 11 days; p = 0.01).

In patients with pneumonia (n = 54), there were similar outcomes compared with the total study population (n = 72): treatment failure rate (13% vs 14%); median chest tube output (12 mL/kg/24h both groups); median duration of chest tube placement (5 days both groups); median hospital LOS (9 vs 10 days); and median PICU LOS (6 vs 7 days). Similarly, a higher dose was not associated with better outcomes (Supplemental Table S3).

Eight children younger than 3 months of age (median age, 23 days; range, 10–83 days) were included in a separate analysis (Supplemental Table S4). The indication for chest tube placement in these patients was PPE associated with pneumonia (n = 3), chylothorax (n = 3), pericardial effusion (n = 1), and intra-abdominal surgery (n = 1). All patients were treated with the lower dose strategy and achieved a 100% treatment success rate. The median duration of chest tube placement was 6 days (IQR, 4–11 days); the median hospital LOS was 57 days (IQR, 36–85 days); and the median PICU LOS was 57 days (IQR, 34–85 days).

Table 3. Alteplase Treatment Characteristics

Variable	All Patients (*N* = 72)	Treatment Success (n = 62)	Treatment Failure (n = 10)
Dose, mg			
Median (IQR)	2 (2–4)	2 (2–4)	4 (2–4)
Mean ± SD	2.8 ± 2.0	2.7 ± 2.1	3 ± 1.2
Dose, mg/kg			
Median (IQR)	0.13 (0.08–0.19)	0.12 (0.09–0.18)	0.14 (0.07–0.20)
Mean ± SD	0.15 ± 0.11	0.15 ± 0.12	0.16 ± 0.11
Volume, mL			
Median (IQR)	20 (20–40)	20 (20–40)	40 (20–40)
Mean ± SD	25.3 ± 11.7	24.4 ± 11.5	30.6 ± 11.6
Number of doses, n (%)			
1	18 (25)	16 (26)	2 (20)
2	9 (13)	8 (13)	1 (10)
3	19 (26)	15 (24)	4 (40)
4	12 (17)	12 (19)	0 (0)
> 4	14 (19)	11 (18)	3 (30)
Type of therapy, n (%)			
Initial therapy*	50 (69)	43 (69)	7 (70)
Rescue therapy†	22 (31)	19 (31)	3 (30)
Time to alteplase administration, median (IQR), days	1 (1–3)	2 (1–3)	1 (1–3)
Adjunctive dornase alfa, n (%)	2 (3)	2 (3)	0 (0)
Alteplase with primary VATS, n (%)	17 (24)	16 (22)	1 (10)

VATS, video-assisted thoracoscopic surgery

* Alteplase given within the first 2 days of chest tube placement.

† Alteplase given after 2 days of chest tube placement due to inadequate chest tube output.

Discussion

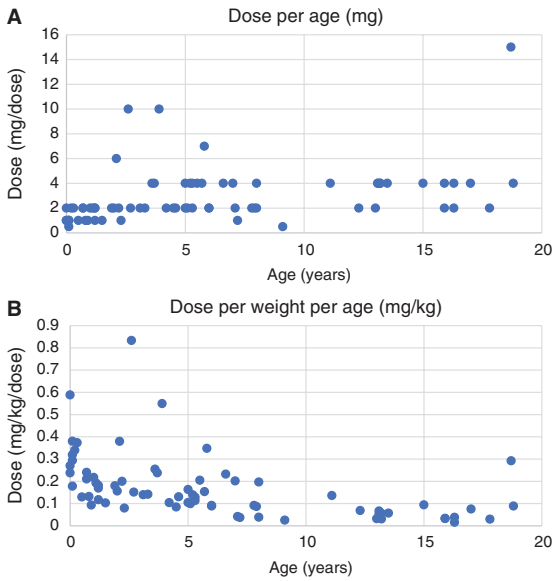
In this retrospective analysis, we report a 10-year experience with intrapleural alteplase for the management of PPE in children (*N* = 72). There was an overall treatment failure rate of 14%, which is comparable to results from previous studies that have reported various rates, including <10%,[17,23,28,29] 10–16.6%,[16,19,26,32,33] and >20%.[22] These studies used various fibrinolytic agents with different dosing strategies, and treatment failure was defined differently across studies. The median hospital LOS after chest tube placement was 10 days, slightly higher than LOS reported in both prospective (median, 6–6.9 days;[19,33] mean, 7.7–9 days[34,35]) and retrospective (median, 6.2–9 days[21,32,36]) studies.

There are 3 key findings from our study. First, lower intrapleural alteplase doses (≤2 mg) were associated with comparable clinical outcomes compared with higher alteplase doses (>2 mg). Our findings may have been influenced by disease severity, which we were unable to assess, and the number of patients who received primary VATS, which was higher in the ≤2 mg group (26.6% vs 18.5%). However, other studies using similar lower doses (1–2 mg) have reported positive overall outcomes.[21,28,29] In a retrospective study of 32 children (mean age, 6.8 years) treated for PPE with intrapleural alteplase, 81% received 1 mg doses, and 19% received 2 mg doses. Treatment success was achieved in 97% of patients.[28]

Our analysis showed that younger children (≤6 years) received a higher weight-based dose (≥0.1 mg/kg) compared with older children (>6 years) (Figure 2B). However, this difference is less likely to affect the outcomes because patients with treatment failure of all ages received a comparable median weight-based dose compared with the treatment-success group (n = 10; 0.14 mg/kg vs n = 62; 0.12 mg/kg).

In this study, most patients (64%) received only 1 to 3 alteplase doses, a finding consistent across both the treatment success (63%) and failure (70%) groups. While 2011 guidelines recommend 3 and 9 doses for the 4 mg fixed and the weight-based dosing regimens, respectively,[11] fewer doses might be sufficient for most patients. Thus, the decision to give repeated alteplase doses should be individualized based on patient response rather than an arbitrary number of doses. Our findings are consistent with those of Baram and colleagues,[23] who reported a 10-year prospective study evaluating outcomes associated with intrapleural

Figure 1. Alteplase dose per weight and age.



(A) The majority of patients aged ≤5 years received alteplase doses ≤2 mg.
(B) Patients aged <6 years received higher milligram per kilogram doses (≥0.1 mg/kg) compared with those aged >6 years (<0.1 mg/kg).

alteplase (0.1 mg/kg) in children with PPE; the mean number of alteplase doses administered was 2.1 doses (range, 1–3 doses). In the 95 patients assessed, the treatment success rate was approximately 98%.[23]

Although administration of fewer total alteplase doses appears to be effective, the optimal frequency of alteplase instillation remains unclear. Published studies have reported frequencies of daily,[19] twice daily,[29] three times daily,[20] and four times daily.[26] A randomized trial demonstrated higher than expected chest tube output the day following twice-daily dosing, suggesting potential benefit compared with once-daily dosing.[27] Another study that evaluated twice-daily dosing showed a significant reduction in the mean days of alteplase therapy from 4.1 to 2.8 days while eliminating the need for surgical intervention, leading to an insignificant reduction in the mean LOS.[29] In our analysis, we did not evaluate the frequency of alteplase instillation due to the lack of a standardized protocol, but most patients received once-daily dosing.

A second important finding is that alteplase therapy following primary VATS as combination therapy for children with PPE might be associated with better outcomes compared with alteplase therapy alone. While previous studies showed similar outcomes between VATS and fibrinolytic therapy when used alone,[14–17] little evidence is available for the combination. Gates and colleagues[21] reported that surgery (with or without fibrinolytic therapy) in children with PPE was associated with a significant increase in hospital and PICU LOS. In contrast, we found that the combination of primary VATS and alteplase was associated with a clinically and statistically significant reduction in the duration of chest tube placement, as well as hospital and PICU LOS, which could result in a reduction in overall cost. Variation between the 2 studies could be related to the fact that we only included primary VATS with alteplase, whereas Gates et al[21] included patients who received VATS at all stages of therapy with or without fibrinolytic therapy. Furthermore, owing to the lack of a control group of patients treated with VATS alone, it is possible that the positive impact was primarily driven by the VATS procedure. However, previous studies suggest that primary VATS and

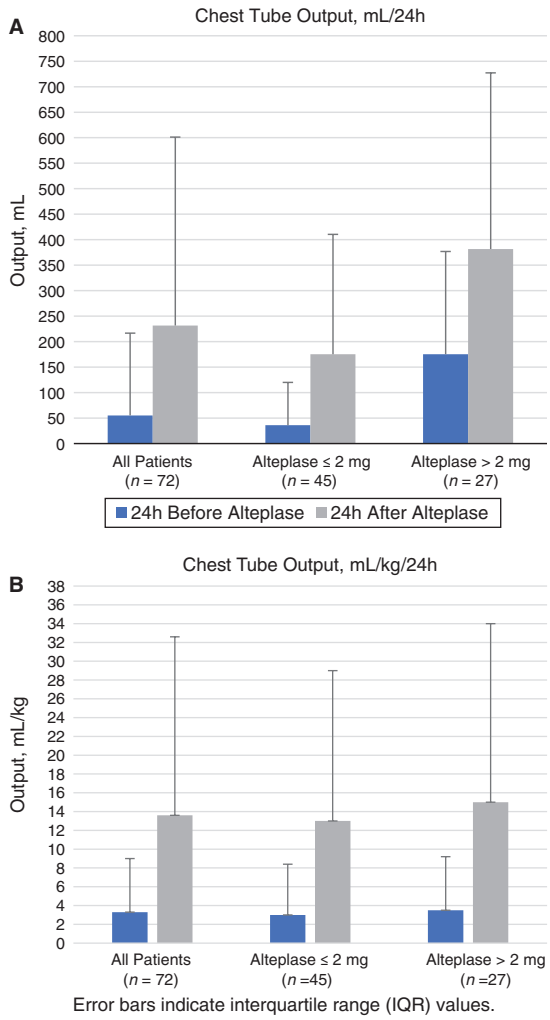
Table 4. Treatment Outcomes According to Alteplase Dose

Outcome*	All Patients (*N* = 72)	Alteplase dose ≤2 mg (n = 45)	Alteplase dose >2 mg† (n = 27)	p value
Primary outcomes				
Treatment failure	10 (14%)	4 (9%)	6 (22%)	0.161
Surgery	7 (10%)	2 (4%)	5 (19%)	–
Recurrence	3 (4%)	2 (4%)	1 (3%)	–
Secondary outcomes				
Chest tube output				
mL/24 h	279 (120–432)	175 (70–358)	346 (256–466)	0.002
mL/kg/24 h	12 (6–23)	12 (6–19)	12 (5–23)	0.949
Duration of chest tube placement, days‡	5 (4–9)	5 (3–7)	8 (4–12)	0.004
Hospital LOS, days	10 (8–26)	9 (7–21)	13 (8–30)	0.321
PICU LOS, days	7 (3–26)	6 (3–21)	14 (6–29)	0.191
6-month all–cause mortality§	4 (6%)	2 (4%)	2 (7%)	–

LOS, length of stay; PICU, pediatric intensive care unit

* All values expressed as median (IQR) or count (frequency).
† Patients who received at least one dose of >2 mg.
‡ Calculated from the first alteplase dose.
§ All patients died before treatment failure could be assessed.

Figure 2. Median chest tube output 24 hours before and after the first alteplase dose by treatment group.



Error bars indicate interquartile range (IQR) values.
(A) For patients in the alteplase dose ≤2 mg group, the median chest tube output increased by 387% from 36 mL per 24 hours before alteplase administration to 175.2 mL per 24 hours after alteplase administration. For the patients in the alteplase dose >2 mg group, the median chest tube output increased by 118% from 175.2 mL per 24 hours before alteplase administration to 381.6 mL per 24 hours after alteplase administration.
(B) For patients in the alteplase dose ≤2 mg group, the median chest tube output increased by 333% from 3 mL/kg/24h before alteplase administration to 13 mL/kg/24h after alteplase administration. For the patients in the alteplase dose >2 mg group, the median chest tube output increased by 329% from 3.5 mL/kg/24h before alteplase administration to 15 mL/kg/24h after alteplase administration.

fibrinolytic therapy alone are associated with similar outcomes.[14–17]

A total of 24 patients underwent VATS at various intervals in our analysis: 17 underwent primary VATS, and 7 underwent rescue VATS after initial alteplase (treatment failure). The timing of therapies and how they differ between the 2 groups might raise a concern. The difference in days between VATS and alteplase initiation was 2 days (IQR, 1–2 days) for the combination group (primary VATS) and 3 days (IQR, 3–7 days) for the treatment failure group (rescue VATS). While this could affect the validity of treatment failure as an outcome, secondary outcomes were better in the combination therapy (Table 5) compared with the treatment failure group (Supplementary Table S1). One possible explanation is that VATS early in the disease course might be associated with better outcomes than VATS performed as rescue therapy. A recent retrospective study conducted by Di Mitri et al[37] found that early VATS performed within 5 days from admission was associated with a shorter duration of PICU and hospital LOS compared with VATS performed later in the hospital admission. The PICU and hospital LOS were numerically lower in our patients who received combination therapy compared with the early VATS therapy reported by Di Mitri et al[37] (2 vs 7 days for PICU LOS; 7 vs 22 days for hospital LOS). Additional studies are needed to confirm whether the improved outcomes in our study were related to the timing of VATS or the use of combination therapy.

Table 5. Treatment Outcomes According to Initial Therapy

Outcome*	Alteplase (n = 55)	Alteplase + Primary VATS (n = 17)	p value
Primary outcomes			
Treatment failure	9 (17)	1 (6)	0.434
Secondary outcomes			
Chest tube output			
mL/24h	322 (167–450)	166 (67–250)	0.005
mL/kg/24h	14 (6–24)	10 (5–13)	0.046
Duration of chest tube placement, days†	6 (4–11)	4 (3–4)	<0.001
Hospital LOS, days	13 (8–34)	7 (7–8)	<0.001
PICU LOS, days	11 (4–30)	2 (1–7)	0.01
6-month all-cause mortality‡	4 (7)	0 (0)	–

LOS, length of stay; PICU, pediatric intensive care unit; VATS, video-assisted thoracoscopic surgery

* All values are expressed as median (IQR) or count (frequency).
† Calculated from the first alteplase dose.
‡ All patients died before treatment failure could be assessed.

A third key finding is that intrapleural alteplase appears to be effective among children younger than 3 months of age with various thoracic effusions. A recent review suggested that the youngest patient reported in the literature to receive intrapleural alteplase was 3 months.[38] Our study included 8 children younger than 3 months of age (median age, 23 days; range, 10–83 days) who were treated with alteplase doses ranging from 0.5 to 2 mg, achieving a 100% treatment success rate. The median duration of chest tube placement was similar to that of the total population (6 vs 5 days), but the hospital and PICU LOS were higher in this group, likely due to their underlying conditions.

Chest tube output is one of the parameters used to evaluate the effectiveness of alteplase therapy in children with PPE.[12,13] Despite the lack of evidence to guide therapy based on drainage volume in children and its uncertainty as a surrogate marker for treatment success,[12] it has generally been used as the sole primary outcome.[26,27] In our analysis, chest tube output did not correlate with clinical outcomes. Similarly, in a retrospective study evaluating alteplase compared with urokinase in children with PPE, the significantly higher chest tube output seen after alteplase instillation did not translate to superior clinical outcomes compared with the urokinase group.[36] In another prospective study, a significantly shorter hospital LOS was achieved in the fibrinolysis group despite a lower total drainage volume compared with patients who did not receive fibrinolytic therapy.[35]

Limitations of Study

This study has several limitations. First, given the retrospective design, we were unable to assess several crucial factors, including disease severity, all adverse events, and the need for additional procedures (e.g., thoracentesis, additional chest tube insertions). Second, our study included a relatively small sample size, which led to considerable baseline differences between the dosing groups that may have affected the findings. Third, our analysis included patients with thoracic effusions caused by various etiologies, whereas most previous studies included only pneumonia-related etiologies. However, most patients had pneumonia as their primary etiology for PPE, and post-hoc analysis showed similar outcomes when the analysis was restricted to patients with pneumonia. This is one of the few studies describing the use of intrapleural alteplase in children with PPE secondary to the other noninfectious etiologies. Finally, owing to the lack of a standardized protocol, the optimal timing of alteplase instillation following primary VATS (n = 17) cannot be determined; however, most patients received alteplase on postoperative day 1 or 2. Similarly, because treatment failure was defined differently among providers, defining a specific time to treatment failure was challenging (rescue VATS; n = 7). Different practice guidelines recommend different timing for surgical evaluation (2–3 vs 7 days after initial therapy). Therefore, in all our patients who were initially treated with chest tube placement and alteplase, the need for VATS at any time was considered a treatment failure.

There are several opportunities for future research to improve outcomes in children with PPE. Additional prospective studies are needed to determine the optimal alteplase dosing strategy and to evaluate the cost-effectiveness of various treatment approaches. Although, randomized trials may not be feasible for various reasons, the design and implementation of institutional protocols and pathways can significantly contribute to the literature.[29] Although predictors of treatment failure have been evaluated previously in children with PPE,[22,35] additional studies are needed to identify populations at risk that could potentially benefit from primary VATS with alteplase to improve clinical and economic outcomes. While several studies have reported the effectiveness of alteplase therapy at various doses, future research should focus on safety parameters. Even with the use of relatively low alteplase doses, bleeding has been reported.[39] Additionally, weight-based dosing should be further investigated in various age groups. Only 2 weight-based alteplase doses have been evaluated in children with PPE. The current standard dose of 0.1 mg/kg has been evaluated in several studies;[20,25,27] however, studies use different maximum alteplase doses. A larger alteplase dose of 0.4 mg/kg extrapolated from adult data was evaluated in 1 study.[26] Of note, none of the aforementioned studies evaluated weight-based dosing across different age groups. Prolonged dwell time after alteplase instillation has been reported to reduce the required dose in adults,[40,41] but this has not been evaluated in children. Last, in clinical practice, many providers use fibrinolytic therapy only when there is inadequate chest tube output. In our study, only 31% of patients received alteplase as a rescue therapy. Currently, it is unclear whether the timing of alteplase administration affects outcomes, as previous studies have shown conflicting results.[21,27,42]

Conclusions

Lower alteplase doses (≤2 mg) resulted in successful treatment of PPE in most patients, including patients younger than 3 months. Higher alteplase doses were not associated with better clinical outcomes. While intrapleural fibrinolytic therapy alone appears to be effective in resolving PPE, alteplase combined with primary VATS may be associated with better clinical and economic outcomes in some patients. Larger studies are required to confirm these results and estimate the cost-effectiveness of various treatment strategies.

Article Information

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JPPT | Compounding and Stability

Chemical Stability of Diphenhydramine in "Magic Mouthwash" Stored at Room and Refrigerated Temperatures for 90-Days

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OBJECTIVE This study aimed to investigate the chemical stability of diphenhydramine in a pediatric "Magic Mouthwash" preparation, specifically a 1:1 mixture of aluminum hydroxide/magnesium hydroxide/simethicone (Mylanta comparable product) and liquid diphenhydramine over 90 days under different storage conditions.

METHODS A high-performance liquid chromatography-ultraviolet method was developed for quantifying diphenhydramine in the mouthwash. A total of 10 bottles of mouthwash were prepared, with half stored in the refrigerator and half kept at room temperature. The method was applied to analyze the stability of diphenhydramine in the mouthwash preparations, with 5-mL aliquots removed from each bottle at 0, 1, 7, 14, 30, 60, and 90 days. Stability was defined as maintaining 90–110% of the initial concentration.

RESULTS Both storage conditions (room temperature: 19.3 ± 0.8°C; refrigeration: 3.01 ± 0.3°C) maintained stable temperatures. The pH remained stable (room temperature: 8.34 ± 0.4; refrigeration: 8.38 ± 0.4). Diphenhydramine concentrations stayed within the 90–110% range for the entire study duration under both conditions. No statistically significant differences in diphenhydramine concentration were observed between storage conditions or over time.

CONCLUSION The pediatric "Magic Mouthwash" demonstrated stable pH and diphenhydramine potency over 90 days, regardless of whether it was stored at room temperature or refrigerated. This supports the feasibility of bulk preparation and extended storage of this formulation, providing a safe and effective alternative to lidocaine-containing mouthwash for pediatric patients.

ABBREVIATIONS HPLC, high-performance liquid chromatography; UV, ultraviolet

KEYWORDS oral mucositis; "Magic Mouthwash"; diphenhydramine; stability; pediatrics

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Introduction

"Magic Mouthwash" is a mixture of medications routinely prepared by pharmacists in hospitals and community settings to treat oral mucositis. The product has various recipes, with the most common formulation containing equal parts of Mylanta (or a comparable product with aluminum hydroxide, magnesium hydroxide, and simethicone), diphenhydramine, and viscous lidocaine. This combination is commonly referred to as BMX.[1,2] Additionally, a kit is available to compound this product. The FIRST - Mouthwash BLM kit contains 0.1 grams diphenhydramine, 0.8 grams lidocaine, 1.58 grams aluminum hydroxide, 1.58 grams magnesium hydroxide, and 0.158 grams simethicone per 4 ounces.[3] Viscous lidocaine should not be used in "Magic Mouthwash" preparations for young children due to the risk of cardiovascular and other systemic side effects.[4] Furthermore, viscous lidocaine carries a Boxed Warning from the Food and Drug Administration regarding its use in infants and children, which lists potential side effects such as seizures, cardiopulmonary arrest, and death in patients under the age of 3 years.[5,6] Owing to these risks, an alternative preparation is recommended for pediatric patients, which excludes lidocaine. This alternative to the BMX preparation for "Magic Mouthwash" is a 1:1 mixture of Mylanta and diphenhydramine. Diphenhydramine exerts an anti-inflammatory effect, while the components of Mylanta help restore oral pH and coat the oral surfaces.[2] Furthermore, pediatric oncology patients tend to have lower salivary pH, making them vulnerable to dental caries.[7] The relatively higher pH of "Magic Mouthwash" helps correct the oral pH in these patients and combats flare-ups of oral mucositis, which are more common in pediatric oncology patients than in adults.[8] Commercially available compounding kits with extended beyond-use dates contain the

lidocaine. Thus, pediatric-suitable "Magic Mouthwash" preparations must be compounded.[9] The stability of lidocaine in "Magic Mouthwash" preparations has been established,[1] and the stability of diphenhydramine has been investigated in various aqueous media.[11–13] However, data supporting the stability of diphenhydramine when mixed with aluminum hydroxide (200 mg), magnesium hydroxide (200 mg), and simethicone (20 mg) per every 5 mL (eg, Mylanta) or a comparable product for pediatric "Magic Mouthwash" is lacking. As such, we investigated the chemical stability of diphenhydramine in a "Magic Mouthwash" preparation suited for children.

Methods

A high-performance liquid chromatography method with ultraviolet detection (HPLC-UV) was developed for the quantification of diphenhydramine in a high-pH "Magic Mouthwash" preparation. In brief, the chromatographic conditions included an isocratic separation with 10 mM of triethylammonium acetate in water (A) and acetonitrile (B). The mobile phase was delivered in a 55%A/45%B ratio at a flow rate of 0.400 mL/min on an Agilent Eclipse XDB-C18 column (150 x 4.6 mm; 3.5-µm particle size). The column was maintained at 50°C, and the UV detector set at 227 nm. For the stability investigation, 10 bottles of 60-mL "Magic Mouthwash" using the 1:1 vol/vol ratio of components were prepared. The products used were Leader Children's Allergy Relief (Lot 14191, Exp 04/26) and GERICARE Geri-Lanta (Lot AAR015, Exp 03/25). The GERICARE Geri-Lanta contains aluminum hydroxide (200 mg), magnesium hydroxide (200 mg), and simethicone (20 mg) per every 5 mL. Thirty-milliliter syringes were used to separately measure the 2 components of the mouthwash, which were pale pink and opaque after vigorous mixing. The bottles used were 4-oz polypropylene amber child-resistant syrup bottles. The bottles were randomly assigned to room temperature or refrigerated storage, and the temperature in each storage condition was recorded on each sampling day.

Additionally, the pH of the prepared mouthwashes was recorded at study initiation and on each sampling day using a benchtop pH meter. Baseline quantification of diphenhydramine in each bottle was conducted at the initiation of the study and was defined as the benchmark for 100% recovery. Five samples from each condition (refrigerated and room temperature) were evaluated in triplicate for diphenhydramine recovery on study initiation and days 1, 7, 14, 30, 60, and 90. Five-milliliter aliquots were removed from each bottle after 30 seconds of vortex mixing on each sampling day. Each aliquot was further partitioned into three 1-mL samples to allow for replicates from each bottle. Each sample was filtered using a 0.22-µm nylon filter and injected into the HPLC without further dilution. As such, the target diphenhydramine concentration in each sample was 1.25 mg/mL due to the initial concentration on the product label of 12.5 mg/5mL. A fresh calibration curve was prepared daily to facilitate the quantification of diphenhydramine in the samples, and the pH from each individual bottle was measured on each sampling day. The calibration curve concentrations were 0.3125, 0.6250, 0.9375, 1.250, and 1.5625 mg/mL, representing 25%, 50%, 75%, 100%, and 125% of the target concentration, respectively. Percent error and percent relative standard deviation were assessed across 4 days (n = 3 each day) at each calibration concentration. Percent diphenhydramine recovery was calculated for all samples of each condition to stay within 90–110% of the initial concentration.[14] Statistical analyses of the data were conducted using GraphPad Prism (version 9.5.1) to assess the stability of diphenhydramine across conditions. A Welch's *t*-test was used to investigate pH differences between the 2 study groups. Diphenhydramine concentrations in samples between groups and across the 90-day study duration were compared using a 2-way analysis of variance with a threshold of $p = 0.05$. Additionally, a Dunnett's multicomparison post-hoc test was applied to examine statistically significant differences between time 0 and subsequent time points in each treatment group.

Results

The HPLC-UV assay demonstrated reproducible and accurate quantification of diphenhydramine at all concentrations. These data are summarized in Table 1.

Room temperature (19.3 ± 0.8°C) and refrigerator temperature (3.01 ± 0.3°C) remained stable and within acceptable ranges for the 90-day duration of the study. No statistically significant difference in pH was found between room temperature mouthwash (8.34 ± 0.4) and refrigerated mouthwash (8.38 ± 0.4), as determined by a Welch's *t*-test ($p = 0.6267$).

There was no statistically significant difference in the initial diphenhydramine concentrations between the bottles assigned to the 2 storage conditions (*t*-test, $p = 0.6788$). For room temperature preparations, diphenhydramine concentration was measured to be 1.276 ± 0.080 mg/mL initially, which was assigned to the "100% recovery" benchmark. Likewise, refrigerated preparations showed an initial diphenhydramine concentration of 1.264 ± 0.076 mg/mL. As the study progressed, the 2-way analysis of variance yielded no statistically significant differences in diphenhydramine concentration between the 2 conditions or throughout the study sample days. The 90-day diphenhydramine concentrations were 1.219 ± 0.062 and 1.239 ± 0.077 mg/mL for room temperature and refrigerated samples, respectively. The concentration of diphenhydramine in all preparations stayed within the desired 90–110% recovery range for the entire study.[14] These data are shown in Figure 1. After 90 days of storage, recovery of diphenhydramine was 95.5% in room temperature samples

Table 1. Precision and accuracy for the quantification of diphenhydramine using HPLC-UV

	Intraday Validation (n = 3 per day)		Interday Validation (n = 12)	
Diphenhydramine Concentration, mg/mL (% Assay Level)	% RSD Range	% Error Range	% RSD	% Error
0.3125 (25%)	1.36–2.92	0.93–4.51	2.05	2.90
0.6250 (50%)	1.15–4.83	2.58–3.19	2.69	2.83
0.9375 (75%)	0.14–3.13	0.81–4.39	1.78	1.93
1.250 (100%)	2.28–3.32	0.86–3.46	2.77	2.29
1.5625 (125%)	0.99–2.61	0.65–2.91	1.84	1.40

RSD, relative standard deviation; HPLC-UV, high-performance liquid chromatography-ultraviolet

Precision (represented by %RSD) and accuracy (represented by % error)

Figure 1. Mean diphenhydramine concentration found in samples for duration of stability study.

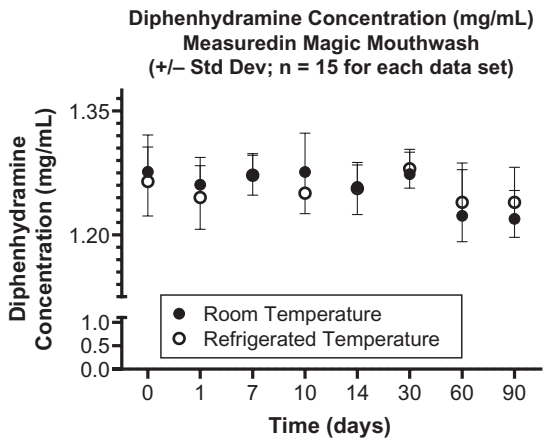

Table 2. Measured diphenhydramine concentrations (mg/mL) and percentage recovery relative to initial concentration for the 90-day stability investigation

Timepoint, days	Room Temperature	Refrigerated Temperature
0	1.276 ± 0.080 (100)	1.264 ± 0.076 (100)
1	1.261 ± 0.059 (98.8)	1.245 ± 0.070 (98.4)
7	1.273 ± 0.046 (99.1)	1.272 ± 0.044 (100.6)
10	1.276 ± 0.085 (99.9)	1.250 ± 0.045 (98.9)
14	1.258 ± 0.048 (98.6)	1.256 ± 0.057 (99.3)
30	1.273 ± 0.048 (99.8)	1.280 ± 0.042 (101.2)
60	1.223 ± 0.101 (95.8)	1.239 ± 0.086 (98.0)
90	1.219 ± 0.062 (95.5)	1.239 ± 0.077 (98.0)

Percentage recovery in parenthesis, n = 15 for each data point

and 98.0% in refrigerated samples compared with the initial concentration. Calculated concentrations and recovery data for the entire study are shown in

Figure 2. Comparison of diphenhydramine recovery across the 90-day storage.

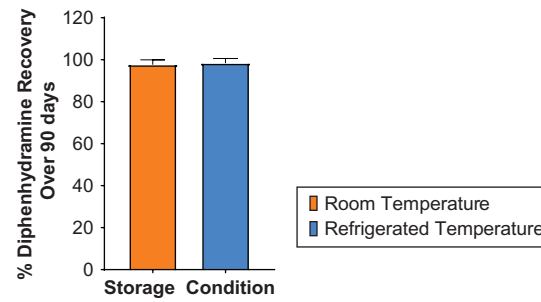

Table 2. The average recovery over 90 days is shown in Figure 2 for the mouthwash preparations at room and refrigerated temperatures. Finally, no change in the physical characteristics was detected between refrigerated and room temperature samples for the duration of the study.

Discussion

The stability of the mouthwash pH under both room and refrigerated conditions confirmed that the pH maintenance provided by the Geri-Lanta components was not affected by temperature. The relatively high pH maintained by the aluminum hydroxide and magnesium hydroxide in Geri-Lanta likely helped preserve the stability of the diphenhydramine component. Previous research has shown that diphenhydramine degrades less in basic pH conditions compared with acidic pH environments.[13]

One limitation of this study was the low room temperature conditions relative to the USP metric (20–25°C).[15] Despite this, there is no evidence that diphenhydramine stability would be negatively impacted at USP-defined room temperature, given that the difference between our refrigerated and room conditions did not initiate degradation. Furthermore, the stability of the preparation's pH provides additional confidence that the

mixture would sustain at a slightly higher room temperature. While the USP allows excursions of 15–30°C to still be considered controlled room temperature, other pharmacopeias define room temperature as 15–25°C.[15–17] Finally, other investigators have demonstrated the thermal stability of diphenhydramine in basic solutions.[12]

Conclusions

These data support the preparation of bulk "Magic Mouthwash" using Mylanta (or a comparable product) and diphenhydramine (1:1 vol/vol) for pediatric patients. Mouthwash pH and diphenhydramine potency remained stable for 90 days, regardless of storage condition. Additionally, multiple withdrawals from the bulk container did not affect product stability.

Article Information

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JPPT | Single Center Survey Study

A Pilot Assessment of Caregivers' and Patients' Perception of Naloxone Coprescribing in a Pediatric Sickle Cell Population

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OBJECTIVE The purpose of this survey was to evaluate knowledge and perception of naloxone among patients with sickle cell disease and their caregivers.

METHODS A 13-question survey about naloxone and the subject's perception of naloxone was developed by the research team and reviewed by 5 advocates for pediatric patients with sickle cell disease. The survey was offered to patient-caregivers and patients ≥12 years old with sickle cell disease and a prescription for home opioid medication. The survey was conducted during a clinic visit or inpatient admission with a convenience sampling strategy.

RESULTS A total of 23 surveys were completed (9 patients and 14 caregivers). Nine of 23 subjects (40%) said they had heard of naloxone. Three subjects had naloxone at home. Only 3 caregivers said having naloxone at home would change their opioid use behavior.

CONCLUSION There is a lack of awareness about naloxone in the pediatric sickle cell disease population. Those who were aware of naloxone did feel it was an important medication and appeared to have a positive view of it.

ABBREVIATIONS ASH, American Society of Hematology; CDC, Centers for Disease Control and Prevention; MME, morphine milligram equivalents

KEYWORDS coprescription; naloxone; opioids; pediatrics; sickle cell disease

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Introduction

As of 2016, the Centers for Disease Control and Prevention (CDC) recommends dispensing naloxone alongside any opioid prescription for patients at an increased risk of overdose. The CDC defines "increased risk" as an opioid prescription of ≥50 morphine milligram equivalents (MME) per day, in patients taking additional sedating medications like benzodiazepines, or patients with abuse history.[1] This was in response to the 351,630 deaths caused by an opioid overdose from 1999 to 2016.[2] Studies in the adult population have shown that naloxone coprescribing and increasing access to naloxone in the community decreased opioid-related emergency department visits and opioid-related deaths.[3,4] There is currently no definition of "high-risk" in the pediatric population and the CDC recommendations do not include children.

Opioids, in addition to nonsteroidal anti-inflammatory drugs, are standard of care for treating acute and chronic pain in sickle cell disease as recommended by the guidelines such as the 2020 guidelines of the American Society of Hematology (ASH).[5,6] With repeated opioid exposures, patients can build a tolerance and require higher opioid doses for the same pain efficacy.[7] This commonly occurs in patients with sickle cell disease because they have continued opioid exposure throughout their life.[8] Owing to high doses and frequency of opioid use, patients with sickle cell disease are highly stigmatized in the community and in health care.[9] In the community, patients with sickle cell disease have been labeled as "weak, lazy, or pretending to be ill."[9] Patients are often treated as if they have a physical or cognitive impairment and are unable to achieve similar goals to their peers.[9] In 2013 there were 16,225 opioid-related deaths in the United States but only 10 (<0.001%) involved patients with sickle cell disease, suggesting that this population is less affected by opioid overdoses than the general population.[10] However, in 2016, 23% of hematologists incorrectly believed more than 20% of patients with sickle cell disease were addicted to opioids.[10] In the pediatric population, this stigmatization may translate to increased concerns of caregivers and

a more conservative opioid approach. Interviews were published of patients with sickle cell disease who had experienced at least 3 pain episodes that required opioids in the past year.[11] Ten caregivers and 10 patients ranging in age from 5 to 18 years participated.[11] Caregivers of all ages expressed concern for opioid tolerance, dependence, and misuse. The caregivers also reported giving opioids as a "last resort" and trying other non-opioid methods first.[11] The ASH 2020 Guidelines for Sickle Cell Disease: Management of Acute and Chronic Pain state that administration of adequate pain medication should happen within the first hour of arrival at the hospital.[6] This is supported by data showing quicker administration of adequate pain medications results in fewer hospitalizations and shorter lengths of stay.[6] These data prove the importance of starting adequate treatment early in the pain crisis and the harmful effects of delaying opioids when indicated.

The ASH 2020 Guidelines for Sickle Cell Disease have a good practice statement saying providers should strongly consider coprescribing of naloxone. However, this is not a recommendation, and there are no studies looking at the benefit of coprescribing to the pediatric sickle cell disease population.[6] Additionally, there is no literature on whether pediatric patients or caregivers are receptive to naloxone coprescribing. This study was developed to evaluate the current knowledge and attitudes of patients and caregivers regarding naloxone.

Materials and Methods

This was a single center, prospective survey study. The survey was conducted for 6 months from January to June 2024. Patients were included if they were managed in The University of Illinois Hospital & Health Sciences System Pediatric Hematology clinic or were admitted to the inpatient pediatric hematology/oncology service. All patient-caregivers and patients ≥12 years old with a diagnosis of sickle cell disease and a previous prescription for a home opioid medication were invited to participate. Subjects were excluded if they were unable to consent, prisoners, or non-English speaking. Written informed consent and/or assent was obtained from all subjects. Patients were identified through chart review of the clinic schedule and inpatient list. During the survey period, this pediatric sickle cell disease center had no standard practice of educating patients and families about naloxone. It should be noted that our electronic medical record has a best practice advisory that fires for any patient being prescribed greater than 50 MME per day, suggesting that the provider coprescribe naloxone.

Survey Tool. A brief 13-question survey was developed by the research team. Five adults living with sickle cell disease provided feedback on the wording of questions and suggested additional questions. All feedback was implemented into the final survey. The survey asked about patients'/caregivers' awareness and perception of naloxone. It was composed of multiple-choice and free-response answers. The survey was designed for fifth-grade health literacy level and took approximately 5 minutes to complete.

Data Collection. The survey was conducted during a clinic visit or inpatient admission. Patients and caregivers were asked to complete a 5-minute survey to help the hematology team learn what patients know about naloxone. After consent was obtained, the survey was administered via Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN), on a laptop provided to the patient by one of the study investigators. The survey questions were filled out by the patients or caregivers on the laptop provided. Patient demographics and the most recent opioid doses were collected by the study team from the medical record.

Results

After a chart review of the hematology/oncology clinic schedule and inpatient list, a sample of 30 subjects was eligible for the survey. A total of 23 surveys were completed (9 patients and 14 caregivers), for a response rate of 76%. Nine declined the survey, either because they were unfamiliar with naloxone or because they lacked time for a survey during the clinical encounter. The 23 surveys included 18 different households (Table 1). Nine of 23 participants (40%) responded "yes" when asked if they had heard of naloxone. Three of 18 households (17%) reported having naloxone at home (Table 2).

Patient Completed Surveys. Five (55%) of the responding patients were 12 to 17.9 years old, and 4 patients (44%) were 18 years of age or older. The most recent opioid dosage prescribed ranged from 20 MME per day to 70 MME per day (Table 1). Patients most frequently responded that they were comfortable with opioids. Three of 9 patients (33%) had heard of naloxone. All

Table 1. Demographics

	Patients (n = 9)	Caregivers (n = 14)
Age of child, yr, n (%)		
0–2.9	—	3 (21)
3–5.9	—	2 (14)
6–11.9	—	2 (14)
12–17.9	5 (55)	7 (50)
≥18	4 (44)	—
Race of child Black/African American, n (%)	9 (100)	14 (100)
MME per day, median (range)	30 (20–70)	20 (4–60)

MME, morphine milligram equivalents

Table 2. Survey Responses

Question		Patients, n (%)	Caregivers, n (%)
		n = 9	n = 14
How often do you/does your child take opioids for their pain?	Daily	2 (22)	2 (14)
	Weekly	2 (22)	0 (0)
	Every other week	0 (0)	1 (7)
	Monthly	0 (0)	3
	6–8 times per yr	2 (22)	1 (7)
	2–3 times per yr	1 (11)	2 (14)
	Yearly	1 (11)	1 (7)
	Never	1 (11)	4 (29)
How comfortable are you with taking opioids as a part of a SCD pain management strategy/ giving opioid to your child as part of a SCD pain management strategy?	Very comfortable	1 (11)	4 (29)
	Comfortable	5 (55)	4 (29)
	Slight uncomfortable	0 (0)	1 (7)
	Extremely uncomfortable	1 (11)	2 (14)
	Unsure	2 (22)	3 (21)
Number of Subjects Who Replied "Yes" to the Following		n = 9	n = 14
Have you ever heard of Narcan (naloxone)?		3 (33)	6 (42)
Have you ever been offered Narcan at the pharmacy or talked about it with a pharmacist?		3 (33)	2 (14)
Has your sickle cell doctor ever talked with you about Narcan?		3 (33)	2 (14)
Do you currently have Narcan in your home?		2 (22)	1 (7)
Would/does having Narcan in your home change how/when you take/give opioids to your child?		0 (0)	3 (21)
Subjects Who Had Heard of Naloxone Were Asked an Additional 3 Questions		n = 3	n = 6
How have you heard of Narcan?	Social media	1	1
	News	2	0
	Friends/family	1	2
	Doctor or health care professional	3	5
Are you familiar with what Narcan does and why it is administered? Yes (n, %)		3 (100)	5 (83)
Do you believe that Narcan helps others and is an important medication? Yes (n, %)		3 (100)	6 (100)

SCD, sickle cell disease

3 patients said they were familiar with how to administer naloxone and believed it was an important medication that helped others. Of all 9 patients, 2 had naloxone at home. The most recent opioid prescriptions for those 2 patients were for 60 and 70 MME per day. Zero patients felt having naloxone at home would change their opioid use behavior (Table 2).

Caregiver Completed Surveys. Seven (50%) of the responding caregivers' children were younger than 12 years, and 7 (50%) were 12 to 17.9 years old. The most recent MME prescribed ranged from 4 MME per day to 60 MME per day (Table 1). Six of 14 caregivers (43%) said they had heard of naloxone. Five of those caregivers said they were familiar with how to administer naloxone, and all 6 caregivers believed it was an important medication that helped others. Only 1 caregiver said they had naloxone at home and their child was most recently prescribed 40 MME per day. Three caregivers felt having naloxone at home would change their opioid use behavior. As for how comfortable caregivers were with opioids, caregiver 1 had a 16-year-old child who was prescribed 40 MME per day and used opioids daily. This caregiver was aware of naloxone and very comfortable with opioid use. Caregiver 2 had a 4-year-old child who was prescribed 6 MME per day and used opioids yearly.

This caregiver was unaware of naloxone and slightly uncomfortable with opioid use. Caregiver 3 had a 13-year-old child who was prescribed 20 MME per day and used opioids 2 to 3 times per year. This caregiver was unaware of naloxone and comfortable with opioid use (Table 2). Additionally, 2 caregivers asked for and were provided with naloxone prescriptions after completing the survey.

Free Response. For the question "Do you believe that Narcan (naloxone) helps others and is an important medication?" subjects were asked to elaborate on their response in a free-response box. Please see Table 3 for detailed responses.

Discussion

This survey showed there is a lack of awareness and availability of naloxone among pediatric patients and caregivers in the sickle cell disease population. This study showed 40% of subjects had heard of naloxone and only 13% of households had naloxone at home. Those who were aware of naloxone did feel it was an important medication and appeared to have a positive view of it, based on the free responses. These findings are consistent with adult literature. There are 2 similar adult naloxone surveys conducted in a clinic setting. The surveys reported naloxone awareness rates of 42% (n = 36) and 40% (n = 52).[12,13] The survey by Ko and colleagues[12] reported that 27 patients (90%) accepted the naloxone prescription, and 25 patients (71%) would recommend it to someone they know.[12] In the study of Behar and colleagues,[13] 56 patients (93%) attempted to fill their naloxone prescriptions. This literature suggests that recommendations, education, and discussions with a health care professional may alleviate some of the misconceptions and concerns surrounding the coprescribing of naloxone.

Although there are many positive views on naloxone coprescribing there is also stigma and concern identified in the literature.[14,15] When conducting this study, we found misconceptions about naloxone as well. Parents were surprised we were talking about naloxone at "such a young age" or when asked about naloxone, they replied, "Is that the drug for drug abusers?" These data show there is a significant opportunity for enhanced naloxone education in this population.

Table 3. Free Responses

Question: Do you believe that Narcan helps others and is an important medication? Please elaborate on your response.	
Caregiver 1 "Because if they are experiencing respiratory depression, this medicine will reverse their symptoms. So, it's very necessary."	**Patient 1** "Narcan is often used to help reverse an overdose, which could lead to death if not taken care of in a timely fashion."
Patient 2 "It's administered because of pain and helps people."	**Patient 3** "I believe it's an important medicine because it can help when you have too much medicine."

Patients older than 18 years and adult caregivers in our survey seemed to have a greater awareness of naloxone than teenaged patients, although the numbers were too small for statistical comparison. The difference between adults and teens might reflect exposure to news and information. Furthermore, it should be noted that our electronic medical record has a best practice advisory that fires for any patient being prescribed greater than 50 MME per day, suggesting that the provider coprescribe naloxone. Older patients are more likely to be prescribed greater than 50 MME per day, so the best practice advisory may have prompted some providers to educate patients on naloxone.

Limitations of this research include a single center design, small sample size, and limited population, as the survey was only offered to patients with sickle cell disease. These results may not be generalizable to pediatric patients with other indications for opioids, or persons living outside the geographic area of the study. The survey had sampling bias, as some patients and caregivers declined participation because they were unfamiliar with naloxone. A future survey could ask for information about who provided the patient with naloxone (primary care physician or subspecialty doctor specializing in sickle cell disease). The survey could also be structured to have follow-up questions, such as following up an answer stating that opioid dosing might change if they had naloxone in the household, then asking what the dosing changes might be. There may be trends in responses related to MME per day, age, or other factors that could not be determined owing to the small sample size.

A limitation to the pediatric literature is the lack of data to support that increased naloxone in the community results in decreased opioid overdose deaths. In the adult population, there are data to support this benefit. For example, Wilkes County in North Carolina started an opioid prevention program that included provider education, naloxone coprescribing, and distribution of naloxone to high-risk groups. Overdose death rates went from 46.6 per 100,000 in 2009 to 29.0 per 100,000 in 2010.[3] CDC-published data from 2021 reported that up to 66.9% of fatal overdoses had 1 or more bystanders present and 60% of overdoses occurred at home, showing that having naloxone in homes has the potential to save lives.[16] While these data related to increased community access and do not include pediatric patients prescribed opioids, it follows that increasing naloxone access in the community in any capacity could have a positive impact.

Based on the supporting data, governments continue to assist in increasing naloxone access. One method that has been implemented in 18 states is legislation. As of May 2024, seven states have laws that require naloxone to be offered to a patient, and 11 states have coprescribing laws. Many of the coprescribing laws include mandatory coprescribing with any prescription between ≥50 MME per day and ≥120 MME per day.[17] Notably, the pediatric population was not mentioned in the coprescribing laws, so it remains unclear which pediatric population and which MME per day should be targeted for coprescribing in children. In addition to new coprescribing laws, all 50 states have made it easier for pharmacists to distribute naloxone without a prescription through a law, standing order, or collaborative practice agreement.[18] In March 2023, the US Food and Drug Administration approved the first over-the-counter 4-mg naloxone spray to continue to increase access to naloxone.[19] As naloxone access grows, patients have a greater chance of learning about naloxone from other health care professionals, such as retail pharmacists.

Conclusion

Our study demonstrated a current lack of knowledge about naloxone in a sample of pediatric patients with sickle cell disease, but those who heard of it had a positive view of the medication.

The impact of this survey at our institution is that providers are now more aware of naloxone and are assured that families will accept it if offered. Patient responses and reactions helped develop appropriate counseling strategies for providers and pharmacists to use when approaching families. There are currently plans to complete a quality improvement initiative to increase naloxone prescribing in the pediatric population.

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JPPT | Case Series

Use of Granulocyte-Colony Stimulating Factor for Beta-Lactam Induced Neutropenia in Children With Bacterial Meningitis

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Drug induced neutropenia is an uncommon but potentially serious side effect in children receiving prolonged β-lactam antibiotic therapy. Management of β-lactam induced neutropenia in children remains challenging and often requires antibiotic therapy interruption or modification. There are limited data in pediatric patients about use of granulocyte-colony stimulating factor (G-CSF) for the treatment of drug induced neutropenia. We report the use of G-CSF for β-lactam induced neutropenia in four pediatric patients between the ages of 3 months and 18 years with bacterial meningitis in this case series.

ABBREVIATIONS ANC, absolute neutrophil count; CSF, cerebrospinal fluid; G-CSF, granulocyte-colony stimulating factor; IV, intravenous; LP, lumbar puncture; VP, ventriculoperitoneal; WBC, white blood cell

KEYWORDS β-lactam; bacterial meningitis; granulocyte-colony stimulating factor; neutropenia

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Introduction

Beta-lactam antibiotics are commonly prescribed for the treatment of bacterial meningitis in children. However, prolonged courses of β-lactam antibiotics (>14 days) increase the risk of drug-induced neutropenia.[1–3] Although β-lactam induced neutropenia is a relatively uncommon side effect, early identification of the etiology of the neutropenia and management can be challenging. Delayed management can lead to the development of complications including life-threatening infections.[4] Multiple case reports in adults describe use of granulocyte-colony stimulating factor (G-CSF) for decreasing the duration of β-lactam-induced neutropenia and improving clinical outcomes.[3,5–7] Discontinuation of the offending agent or changing antibiotic therapy to another agent (β-lactam or non-β-lactam) remains the primary management of β-lactam induced neutropenia in children given the lack of data describing use of G-CSF in pediatric patients for this indication.[1,3] We report our experience using G-CSF for β-lactam induced neutropenia in children with bacterial meningitis in this case series.

Methods

We included patients that were admitted to Texas Children's Hospital between 2012 and 2023 with a diagnosis of bacterial meningitis using ICD-10 codes[8], who received a β-lactam antibiotic and at least one dose of G-CSF. Neutropenia was defined as absolute neutrophil count (ANC) <1500 cells/mm^3 as institutional preference. Patients with neutropenia from other sources were excluded.

Results

Fifty-three patients with bacterial meningitis were identified through ICD-10 codes and medical record chart review. Of those 53 patients, 48 patients were excluded for not receiving G-CSF during the treatment course for meningitis and 1 patient was excluded due to underlying hematologic condition (congenital neutropenia). Of note, no adverse events related to G-CSF administration were noted during chart review.

Case 1

In 2012, a 2-year-old 12.2 kg girl with history of extreme prematurity, necrotizing enterocolitis, and hydrocephalus requiring a ventriculoperitoneal (VP) shunt was admitted with fever, lethargy, clumsiness, and abnormal eye movements. Cerebrospinal fluid (CSF) was obtained from lumbar puncture (LP) and shunt fluid; the VP shunt was removed and an external ventricular drain was placed. Cerebrospinal fluid revealed a white blood cell (WBC) count of 361 cells/mm^3 (87% neutrophils, 11% lymphocytes) and elevated protein of 2928 mg/dL. She received intravenous (IV) vancomycin 15 mg/kg per dose every 6 hours and cefotaxime 75 mg/kg per dose every 6 hours as empiric antibiotic therapy for meningitis. Cerebrospinal fluid cultures from all sampled sites grew *Streptococcus pneumoniae* susceptible to penicillin and cefotaxime. She continued

therapy with cefotaxime alone. Despite negative repeat cultures from the ventricles, she continued to experience seizure episodes and intermittent fever. Cefotaxime was discontinued on day 9 of treatment and the patient received IV penicillin 100,000 units/kg per dose every 6 hours with gentamicin 2.5 mg/kg per dose every 8 hours from days 9 to 13. Since day 13, antibiotic therapy was narrowed to IV penicillin alone and the patient remained clinically stable and afebrile with slowly down-trending WBC and ANC values.

On day 28 of antibiotic treatment, the peripheral blood ANC was 190 cells/mm^3. She was given a one-time dose of filgrastim 5 mcg/kg subcutaneously (SQ). On day 29, the patient's ANC improved to 730 cells/mm^3 and antibiotic therapy was changed to cefotaxime and vancomycin from penicillin due to hemodynamic changes concerning for new hospital-acquired infection including infection of the VP shunt. Vancomycin was discontinued on day 30 of therapy after repeat CSF cultures were sterile from a newly placed VP shunt. The ANC from day of therapy 30 also increased to 1900 cells/mm^3. She completed cefotaxime on day 42 of therapy, and the ANC continued to increase and remained above 1500 cells/mm^3.

Case 2

A 4-month-old 8.5 kg boy with history of Erb palsy was admitted for fever, increased fussiness, and seizure in 2012. A lumber puncture showed CSF with 2399 cells/mm^3 WBC (92% neutrophils, 5% lymphocytes) and elevated protein of 108 mg/dL. He received IV cefotaxime 75 mg/kg per dose every 6 hours, vancomycin 15 mg/kg per dose every 6 hours, acyclovir 15 mg/kg per dose every 8 hours, and gentamicin 2.5 mg/kg per dose every 8 hours as empiric antibiotic therapy. Acyclovir was discontinued on day 3 of treatment after confirmation of negative herpes simplex virus polymerase chain reaction test result from CSF fluid. Cerebrospinal fluid culture grew *Escherichia coli* (*E coli*) susceptible to third generation cephalosporins. The antibiotic regimen was narrowed to cefotaxime monotherapy on day 8 of treatment. He continued to have persistently elevated inflammatory markers, C-reactive protein of 13.1 mg/dL and erythrocyte sedimentation rate of 108 mm/hr, on day 9 of treatment without resolution of subdural empyema on the subsequent magnetic resonance imaging findings also on day 9 of treatment.

Between days 21 and 24 of cefotaxime monotherapy, his ANC decreased from 2840 to 760 cells/mm^3 and further decreased to 380 cells/mm^3 on day 28. He received 2 doses of filgrastim 10 mcg/kg SQ daily on days 29 and 30, and the ANC was 8250 cells/mm^3 on day 31; however, on day 36 of treatment, the ANC decreased to 340 cells/mm^3 and a one-time dose of filgrastim 5 mcg/kg was given SQ. The ANC rebounded to 9840 cells/mm^3 the next day and remained above 1500 cells/mm^3 while continuing cefotaxime. He received 42 days of IV antibiotics and was discharged home.

Case 3

An 18-year-old, 65.5 kg previously healthy male was transferred from an outside hospital for surgical management of CSF infection again in 2012. He initially presented for evaluation after 5 days of frontal headache with neck stiffness and 2 days of fever. Cerebrospinal fluid from LP showed 926 cells/mm^3 WBC (63% neutrophils, 3% lymphocytes). Severe pansinusitis and epidural abscess fluid collections were noted from head imaging. He underwent craniectomy/craniotomy for empyema drainage and received IV cefotaxime 2000 mg every 4 hours, metronidazole 500 mg every 6 hours, and vancomycin 1000 mg every 6 hours. Cultures obtained during the surgery, and CSF cultures from both institutions did not grow any pathogens. Vancomycin was initially discontinued on day 6 of treatment, and the patient remained on cefotaxime and metronidazole. The patient continued to experience frontal headaches, intermittent fever, and seizure episodes on cefotaxime and metronidazole resulting in resuming vancomycin on day 9 of treatment. Antibiotic therapy was narrowed again to cefotaxime and metronidazole on day 13 of treatment.

The patient's ANC decreased from 6030 to 560 cells/mm^3 between days 19 and 26 with a nadir of 30 cells/mm^3 on day 29. He received filgrastim 5 mcg/kg SQ daily on days 32 and 33, and the ANC increased to 7510 cells/mm^3 on day 34. He remained clinically stable and was discharged home after completing 42 days of IV antibiotics.

Case 4

A 3-month-old, 13.2 kg previously healthy female was admitted in 2023 for fussiness and low-grade fever. No antibiotics were initiated at that time. On hospital day 2, she had increased irritability, and a LP was performed with CSF results as follows: WBC 1615 cells/mm^3 (57% neutrophils, 21% lymphocytes), Gram-negative rods on Gram stain, and bacteria present. She empirically received IV ceftriaxone 50 mg/kg per dose every 12 hours and gentamicin 2.5 mg/kg per dose every 8 hours. Later that day, the patient had seizure episodes and developed fever. On day 4 of hospitalization, ceftriaxone was changed to IV ceftazidime 50 mg/kg per dose every 8 hours and gentamicin was continued pending susceptibilities. Cerebrospinal fluid cultures grew *E coli,* and brain magnetic resonance imaging demonstrated ventriculitis and bilateral subdural empyemas. On hospital day 5, repeat CSF was obtained and showed 140 WBC/mm^3 (67% neutrophils, 22% lymphocytes). The CSF culture grew *E coli* susceptible to ceftriaxone, ceftazidime, and meropenem but resistant to gentamicin. Ceftazidime and gentamicin were discontinued and ceftriaxone was resumed. She developed fever

Table. Summary of Cases

Case	Age, Sex	Infection (etiology)	Definitive Therapy	Baseline WBC ($\times 10^3/\mu L$)	Baseline ANC cells/ mm^3	Total Treatment Duration (days)	Time to Neutropenia (<1000 cells/ mm^3) (days)	G-CSF Therapy	Day of treatment and ANC at time of G-CSF	Time to ANC Improvement
1	2 yr, F	Bacterial meningitis (*S pneumoniae*)	Penicillin IV 100,000 units/kg/ dose Q6H	24.09	16,480	42	19	5 mcg/kg SQ once	Day 28: 190	2
2	4 mo, M	Bacterial meningitis (*E coli*)	Cefotaxime IV 75 mg/ kg/dose IV Q6H	13.2	9320	42	1st occurrence: 19	10 mcg/ kg SQ daily for 2 days	Days 29 and 30: 380	1
							2nd occurrence: 36	5 mcg/kg SQ once	Day 26: 340	1
3	18 yr, M	Pansinusitis and subdural empyema (unknown)	Cefotaxime 2000 mg Q4H	20.02	18,680	68	26	5 mcg/kg SQ daily for 2 days	Day 29: 30	2
4	3 mo, F	Ventriculitis and bilateral subdural empyema (*E coli*)	Ceftriaxone IV 50 mg/ kg/dose IV Q12H	8.01	2120	68	32	5 mcg/kg SQ once	Day 47: 100	1

F, female; M, male; SQ, subcutaneously

and new seizure episodes on day 10 of hospitalization, and cultures were obtained with drainage of one of the subdural empyemas. The culture grew *E coli*. The patient continued to receive ceftriaxone monotherapy. Ceftriaxone was changed to IV meropenem 40 mg/kg per dose every 8 hours on day 28 of hospitalization after the patient developed hypotension requiring vasoactive agents and increased episodes of seizures.

Neutropenia developed on hospital day 31, and the ANC continued to drop and remained <500 cells/mm^3 between day 32 to 41 with a nadir of 100 cells/mm^3 on day 47. Filgrastim 5 mcg/kg SQ was administered on day 47. The patient's ANC improved to 3160 cells/mm^3 the following day. She remained clinically stable without further seizure episodes, and her ANC remained above 1500 cells/mm^3 until day 66 (1008 cells/mm^3). No G-CSF was given, as therapy was stopped on day 68 of antibiotics with no ANC between days 66 and 68. She was discharged home after completing 68 days of treatment.

Discussion

The majority of the β-lactam induced neutropenia episodes in adult patients are associated with prolonged exposure to IV β-lactam antibiotic courses, especially in those receiving more than 2 weeks of treatment. Certain β-lactam antibiotics such as penicillin G, nafcillin, oxacillin, piperacillin-tazobactam, ceftriaxone, and ceftaroline have been reported to cause more neutropenia episodes compared with other agents.[3,4,7] The incidence of β-lactam induced neutropenia in pediatric patients varies significantly among published studies. A systematic review by Battini et al[1] identified 2602 pediatric patients who received antibiotic courses and 228 patients who developed neutropenia episodes during therapy. The most commonly administered antibiotics were penicillin, amoxicillin, ampicillin, β-lactam/β-lactamase inhibitors, and cephalosporins. Our pediatric patients that developed neutropenic episodes received cefotaxime, ceftriaxone, cefepime, and penicillin G, among other agents (Table).

The mean onset of β-lactam induced neutropenia in our patients was 26 days, which was similar to the timing reported in adults but was longer when compared with case studies in other pediatric patients (range of median values 10–23 days).[1–3,9]

In pediatric patients, the current primary management of β-lactam induced neutropenia includes discontinuing the offending antibiotic agent, reducing the dose, withholding the antibiotic for 24 to 48 hours or changing therapy in addition to close monitoring. Some clinicians recommend interruption of the offending antibiotic therapy when the ANC is <1000 cells/mm^3 due to the potential for serious complications associated

with severe neutropenia (ANC <500 cells/mm).[3,10,11] It is crucial to monitor patients' ANC closely and determine the appropriate time to interrupt the antibiotic therapy in the setting of other confounding comorbidities and/or medications. Battini et al[1] noted that among 228 patients all less than 18 years old with β-lactam induced neutropenia, 77 had therapy discontinued while others achieved normalization of the ANC without any interventions.[1] Data regarding the use of G-CSF to decrease the duration of neutropenia is mainly from critically ill adult patients.[3,5–7] Our cohort of patients received G-CSF at doses between 5 and 10 mcg/kg SQ daily and their ANCs rebounded to >1000 cells/mm^3 within the following 2 days. None of the patients had any adverse effects reported from G-CSF use. Since G-CSF directly stimulates the creation and maturation of neutrophil precursors, the response seen in our cohort matches the reported onset of action in the package insert.[12]

However, use of G-CSF may increase patient costs and risk of adverse events that also may require treatment (e.g., nausea, pain, fever, etc), and there are no current data evaluating the benefits of using G-CSF in children with meningitis and β-lactam-induced neutropenia compared with the previously mentioned risks. Given this lack of data, we suggest to consider giving G-CSF in this population when other treatment options do not exist due to patient contraindications and/or resistance patterns of the pathogens.

We cannot draw significant conclusions from our small number of patients at a single institution. However, our case series provides a basis for considering G-CSF administration in pediatric patients who develop β-lactam-associated neutropenia during prolonged antibiotic treatment for bacterial meningitis, especially when other treatment options are limited or unavailable. A larger study is needed to evaluate the role of G-CSF in β-lactam induced neutropenia in children with meningitis and other severe infections requiring long courses of β-lactam antibiotics.

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant international guidelines on human experimentation and have been approved by the appropriate committees at our institution. However, given the nature of this study, informed consent was not required by our institution.

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JPPT | Case Reports

Intravenous Ceftaroline in Extremely Premature Neonates With Coagulase-Negative Staphylococci Septicemia: A Report of 2 Cases

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Sepsis is one of the primary causes of newborn morbidity and mortality, particularly in preterm infants, and coagulase-negative staphylococci (CoNS) is a major cause of bacterial infections in the neonatal intensive care unit (NICU). The treatment of late-onset neonatal staphylococcal sepsis is challenging owing to increased minimum inhibitory concentrations and the potential side effects of vancomycin. Herein, we describe 2 cases of extremely preterm newborns treated with intravenous (IV) ceftaroline (6 mg/kg/dose every 8 hours) for late-onset neonatal staphylococcal sepsis. Both cases were diagnosed with bacteremia and treated with ceftaroline. However, one of the patients died, most likely from sepsis or other factors, including chronic lung illness and prematurity, despite sterile blood cultures after starting the ceftaroline treatment. Large-scale randomized studies are required to examine the optimal dosing, safety, and effectiveness of IV ceftaroline for sepsis caused by CoNS in neonates.

ABBREVIATIONS ABSSSIs, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; CBC, complete blood count; CoNS, coagulase-negative staphylococci; CRP, C-reactive protein; DOL, day of life; ESBL, extended-spectrum beta-lactamase; FDA, US Food and Drug Administration; IV, intravenous; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; PLT, platelet; UVC, umbilical venous catheter; WBC, white blood cell

KEYWORDS bacteremia; coagulase-negative staphylococci; ceftaroline; neonatal intensive care unit; premature neonates; sepsis

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Introduction

Neonatal sepsis remains a leading cause of neonatal morbidity and mortality.[1–3] Coagulase-negative staphylococci (CoNS), a common cause of bacterial infection encountered in the neonatal intensive care unit (NICU), are the second most common etiology of late-onset sepsis in very low birth weight infants admitted to the NICUs in the United States and United Kingdom.[1,2] Antimicrobial resistance is of increasing concern among neonatologists and a primary focus of clinical and microbiologic research among pediatric infectious disease specialists.[1,2] Ceftaroline, a newer cephalosporin with broad-spectrum bactericidal activity, is US Food and Drug Administration (FDA) approved for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and community-acquired bacterial pneumonia (CABP) caused by *Streptococcus pneumoniae* and other susceptible bacteria in children aged 2 months or older.[3]

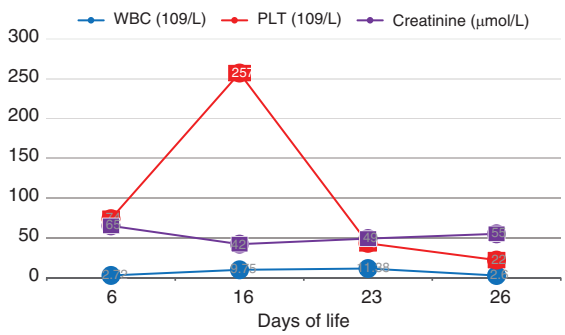
Studies on the safety and efficacy of ceftaroline in neonates and infants are lacking, and the use of ceftaroline in extremely premature neonates with sepsis due to CoNS has not been reported so far. Moreover, few published cases reported the use of ceftaroline in treating MRSA septicemia in neonates.[4] We usually prescribe vancomycin, linezolid, or daptomycin in treating CoNS infections. Herein, we report 2 unique cases of premature neonates who received ceftaroline for persistent CoNS infections.

Case 1

A 900-g 27-week-old female was born to a 31-year-old female by spontaneous delivery. The Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. The infant experienced respiratory distress and was transported to a Level III NICU, where surfactant was administered via the endotracheal route, and the infant was placed on a mechanical ventilator. An umbilical venous catheter (UVC) was placed, blood cultures and complete blood counts (CBCs) were obtained, and ampicillin (50 mg/kg/dose intravenous [IV] every 12 hours) and gentamicin (5 mg/kg/dose IV every 48 hours) were started empirically. A brain ultrasonography performed on day of life (DOL) 3 showed

a grade II intraventricular hemorrhage. On DOL 4, the baby was shifted to a high-frequency ventilator for 6 days, and ampicillin and gentamicin were replaced with linezolid (10 mg/kg/dose IV every 8 hours) and meropenem (40 mg/kg/dose IV every 8 hours) following an endotracheal culture positive for an extended-spectrum beta-lactamase (ESBL)–producing *Klebsiella pneumoniae*. On DOL 6, the UVC was removed and a peripherally inserted central catheter line was inserted. Additionally, linezolid was discontinued, whereas meropenem was continued for an additional 8 days. On DOL 10 the patient was shifted from a high-frequency ventilator to a conventional ventilator. On DOL 14, linezolid (10 mg/kg/dose IV every 8 hours) was reinitiated because the repeated blood culture was positive for *Staphylococcus epidermidis*. Moreover, the peripherally inserted central catheter line was removed. CBC showed a white blood cell (WBC) count of 10.8 × 10^9/L and a platelet (PLT) count of 27 × 10^9/L. A C-reactive protein (CRP) measurement was not obtained. On DOL 15, the neonate was extubated from the conventional ventilator; however, she developed episodes of apnea and was re-intubated and subjected to a complete septic workup on DOL 21. Treatment with meropenem (40 mg/kg/dose IV every 8 hours) was reinitiated, and linezolid was switched to vancomycin (15 mg/kg/dose every 12 hours) owing to persistent positive CoNS blood cultures that were unresponsive to linezolid. The laboratory results of the patient were as follows: WBC count, 3.68 × 10^9/L; neutrophils, 1.77%; lymphocytes, 1.25%; PLT count, 34 × 10^9/L; and vancomycin serum trough concentration, 12 mcg/mL (therapeutic goal: 10–20 mcg/mL). The tracheal culture was positive for *Klebsiella pneumoniae*, and the isolate was sensitive to meropenem, imipenem, amikacin, and gentamicin. In addition, the blood culture demonstrated persistent CoNS. Treatment with concurrent vancomycin and meropenem was continued for 16 days. However, the patient remained clinically ill with persistent positive CoNS results. On DOL 37, meropenem was discontinued, and vancomycin was replaced with daptomycin (10 mg/kg/dose IV every 24 hours) and linezolid (10 mg/kg/dose IV every 8 hours). CBC showed a WBC count of 3.88 × 10^9/L and a PLT count of 10 × 10^9/L with persistent staphylococci infection in the blood culture. Consequently, rifampicin (10 mg/kg/dose IV every 12 hours) was added to linezolid and daptomycin on DOL 40, and the CBC and blood cultures were repeated. The laboratory results were as follows: WBC, 4.54 × 10^9/L; CRP, 66.7 mg/L; neutrophils, 2.46%; lymphocytes, 0.93%; and PLT count, 33 × 10^9/L. The patient remained clinically ill with persistent staphylococci in the blood culture. On DOL 46, ceftaroline (6 mg/kg/dose IV every 8 hours) was added to linezolid, whereas daptomycin and rifampicin were discontinued. The repeated blood culture was sterile on DOL 48; however, the patient died on DOL 49. No adverse renal effects were observed during the entire therapy. Figure 1 shows the trend of WBC, PLT, and creatinine from admission until death. The results of cultures, organisms, and antimicrobial sensitivity are shown in Table 1.

Figure 1. Trends of WBC, PLT, and creatinine from admission until death.



PLT, platelet; WBC, white blood cell.

Case 2

An 890-g 26-week-old female was born to a 27-year-old female by cesarean delivery. The Apgar scores were 5 and 7 at 1 and 5 minutes, respectively. The neonate experienced respiratory distress and was transported to a Level III NICU, where surfactant was administered via the endotracheal route, and the infant was placed on a mechanical ventilator. An UVC was placed, a blood culture was performed, CBC was performed, and ampicillin (50 mg/kg/dose IV every 12 hours) plus gentamicin (5 mg/kg/dose IV every 48 hours) therapies were empirically initiated. The antibiotics were discontinued on the third DOL after a negative blood culture result. The patient was extubated to continuous positive airway pressure on DOL 5. A brain ultrasonography showed a grade III intraventricular hemorrhage. On DOL 6, the baby developed apnea and lethargy; treatment with cloxacillin (50 mg/kg/dose IV every 12 hours) and amikacin (15 mg/kg/dose IV every 36 hours) was initiated for suspected sepsis. The WBC and PLT counts were 2.72 × 10^9/L and 74 × 10^9/L, respectively, while the proportions of neutrophils and lymphocytes were 28.3% and 52.6%, respectively. A CRP measurement was not obtained. On DOL 8, the blood culture was positive for *S epidermidis* with a vancomycin minimum inhibitory concentration (MIC) of 2 mg/L. The culture was sensitive to vancomycin, linezolid, rifampicin, and daptomycin and resistant to oxacillin. Thus, the UVC was removed, and the antibiotics were switched to linezolid (10 mg/kg/dose IV every 8 hours) and piperacillin-tazobactam (100 mg/kg/dose IV every 12 hours). Repeated blood cultures on DOL 10 and 14 continued to be positive for *S epidermidis*. However, the clinical picture of the patient was unstable. Therefore, the infectious disease team suggested to continue piperacillin-tazobactam therapy for 6 days, which was then discontinued, followed by linezolid for 8 days. On DOL 16, linezolid

Table 1. Clinical Course of Neonate Described in Case 1

Day of Life	Culture	Organism	Vancomycin MIC, mg/L	Antimicrobial Sensitivity	Antimicrobial Resistance	Antibiotic
1	Blood (central) Tracheal	No growth *Klebsiella pneumoniae* ESBL				Ampicillin and gentamicin for 3 days
4	Blood (central)	No growth				Linezolid and meropenem for 2 days
6	Blood (central)	No growth				Meropenem for 8 days
8	Blood (central, peripheral)	*Staphylococcus hominis*	2	Vancomycin, linezolid, daptomycin	Cloxacillin, rifampicin, gentamicin	No change
14	Blood (central, peripheral)	*Staphylococcus epidermidis*	2	Vancomycin, linezolid, daptomycin, rifampicin	Cloxacillin, gentamicin	Linezolid for 7 days
16	Blood (peripheral)	*S epidermidis*	1	Vancomycin, linezolid, daptomycin	Cloxacillin, rifampicin, gentamicin	No change
21	Blood (peripheral) Tracheal Urine CSF	*Staphylococcus capris* *S epidermidis* *K pneumoniae* ESBL No growth No growth	1 1	Vancomycin, linezolid, daptomycin, rifampicin	Cloxacillin, gentamicin	Vancomycin and meropenem for 16 days
23	Blood (peripheral)	*S hominis*	1	Vancomycin, linezolid, daptomycin, rifampicin	Cloxacillin, gentamicin	No change
25	Blood (peripheral)	*Staphylococcus simulans*	1	Vancomycin, linezolid, daptomycin, rifampicin	Cloxacillin, gentamicin	No change
27	Blood (peripheral)	*S simulans*	1	Vancomycin, linezolid, daptomycin, rifampicin	Cloxacillin, gentamicin	No change
29	Blood (peripheral)	*S epidermidis*	1	Vancomycin, linezolid, daptomycin, rifampicin	Cloxacillin, gentamicin	No change
31	Blood (peripheral)	*S capris*	2	Vancomycin, linezolid, daptomycin, rifampicin	Cloxacillin, gentamicin	No change
34	Blood (peripheral)	*S epidermidis*	1	Vancomycin, daptomycin, rifampicin	Cloxacillin, gentamicin, linezolid	No change

(*Table cont. on page 511*)

Table 1. Clinical Course of Neonate Described in Case 1 *(cont.)*

Day of Life	Culture	Organism	Vancomycin MIC, mg/L	Antimicrobial Sensitivity	Antimicrobial Resistance	Antibiotic
37	Blood (peripheral)	*S epidermidis*	1	Vancomycin, linezolid, daptomycin, rifampicin	Cloxacillin, gentamicin	Daptomycin and linezolid for 3 days
40	Blood (peripheral)	*S epidermidis* *Staphylococcus lentus*	1	Vancomycin, linezolid, daptomycin, rifampicin	Cloxacillin, gentamicin	Daptomycin and linezolid and rifampicin for 6 days
44	Blood (peripheral)	*S lentus*	1	Vancomycin, linezolid, daptomycin, rifampicin	Cloxacillin, gentamicin	No change
46	Blood (peripheral)	No growth				Ceftaroline and linezolid for 2 days

CSF, cerebrospinal fluid; ESBL, extended-spectrum beta-lactamase; MIC, minimum inhibitory concentration

was switched to daptomycin (10 mg/kg/dose IV every 24 hours) owing to persistent *S epidermidis* infection. The laboratory results were as follows: WBC and PLT counts, 9.75 × 10^9/L and 257 × 10^9/L, respectively; neutrophils, 72.6%; and lymphocytes, 17.1%. On DOL 20, rifampicin was started (10 mg/kg/dose IV every 12 hours) owing to a high antimicrobial MIC (*S epidemidis* MIC of 2) and a persistent positive blood culture result. Daptomycin and rifampicin were continued for an additional 3 days. However, vancomycin (15 mg/kg/dose IV every 6 hours) was started with rifampicin on DOL 23 owing to the unavailability of daptomycin. The serum vancomycin trough concentration was 16 mcg/mL (therapeutic goal: 10–20 mcg/mL). In spite of this, the repeated culture was positive for *S epidermidis*; the CBC showed WBC and PLT counts of 11.38 × 10^9/L and 43 × 10^9/L, respectively; 65.4% neutrophils; and 20.4% lymphocytes. On DOL 26 and after 3 days of vancomycin initiation, ceftaroline (6 mg/kg/dose IV every 8 hours) was added to the treatment regimen. The CBC showed a WBC count of 2.6 × 10^9/L and a PLT count of 22 × 10^9/L. Repeated cultures on DOL 28 and 31 remained positive for *S epidermidis*. On DOL 36, the baby was shifted to nasal cannula. Repeated blood culture tests showed no bacterial growth, and the WBC and PLT counts were 7.48 × 10^9/L and 72 × 10^9/L, respectively. Table 2 shows the responsible organisms with susceptibilities and concurrent antibiotic regimens. No impairment in renal or liver functions were noticed during therapy. Figure 2 presents the trend of WBC, PLT, and creatinine from admission until discharge. On DOL 48, the nasal cannula was removed. The infant was discharged at the corrected age of 39 weeks, weighing 1790 g.

Discussion

This report describes 2 unique cases of infants who were treated with ceftaroline (6 mg/kg/dose IV every 8 hours) for persistent CoNS infections in extremely premature neonates.

Gram-positive organisms, including CoNS, remain the leading causative organisms of late-onset sepsis in premature infants.[5] The incidence of CoNS in the NICU is around 30% to 45%, and *S epidermidis* is reported as the most common causative organism.[6,7] Increasing antibiotic resistance during the treatment of invasive Gram-positive bacteria will accelerate the chances of antibiotic treatment failures.[8–10] Thus the management of these infections, especially in extremely premature infants, may be challenging for health care providers owing to the limited therapeutic options. While vancomycin remains the drug of choice for the treatment of severe CoNS infections, its use in neonates remains limited owing to fluctuations in the pharmacokinetics, the need for therapeutic drug monitoring, and reported treatment failures.[11] Hence, identifying alternative medications for the treatment of CoNS is critical. Linezolid and daptomycin are the currently available options.[9,10,12] The safety and efficacy of daptomycin in neonates and infants are limited, and linezolid is not recommended for endocarditis infections because of its bacteriostatic effects.[9,10,12,13] Therefore, ceftaroline may be a promising option owing to its bactericidal effects. Ceftaroline is the

Table 2. Clinical Course of Neonate Described in Case 2

Day of Life	Culture	Organism	Vancomycin MIC, mg/L	Antimicrobial Sensitivity	Antimicrobial Resistance	Antibiotic
1	Blood (central)	No growth				Ampicillin and gentamicin for 3 days
6	Blood (central)	*Staphylococcus epidermidis*	2	Vancomycin, linezolid, daptomycin	Gentamicin, cloxacillin	Amikacin and cloxacillin for 2 days
8	Blood (central)	*S epidermidis*	1	Vancomycin, linezolid, daptomycin, rifampicin	Gentamicin, cloxacillin	Linezolid and piperacillin-tazobactam for 6 days
10	Blood (peripheral)	*S epidermidis*	1	Vancomycin, linezolid, daptomycin, rifampicin, gentamicin	Cloxacillin	No change
14	Blood (peripheral)	*S epidermidis*	2	Vancomycin, linezolid, daptomycin, rifampicin, gentamicin	Cloxacillin, clindamycin	Linezolid for 2 days
16	Blood (peripheral)	*S epidermidis*	2	Vancomycin, linezolid, daptomycin, rifampicin, gentamicin	Cloxacillin, clindamycin	Daptomycin for 4 days
18	Blood (peripheral)	No growth				No change
20	Blood (peripheral)	*S epidermidis*	1	Vancomycin, linezolid, daptomycin, rifampicin, gentamicin	Cloxacillin, clindamycin	Daptomycin and rifampicin for 3 days
23	Blood (peripheral)	*S epidermidis*	1	Vancomycin, linezolid, daptomycin, rifampicin, gentamicin	Cloxacillin, clindamycin	Vancomycin and rifampicin for 3 days
26	Blood (peripheral)	*Staphylococcus hominis*	1	Vancomycin, linezolid, daptomycin, rifampicin, gentamicin	Cloxacillin, clindamycin	Vancomycin and ceftaroline for 28 days
28	Blood (peripheral)	*S epidermidis*	1	Vancomycin, linezolid, daptomycin, rifampicin, gentamicin	Cloxacillin,	No change

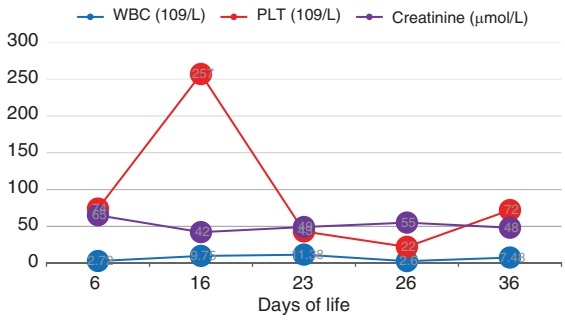
(*Table cont. on page 513*)

Table 2. Clinical Course of Neonate Described in Case 2 *(cont.)*

Day of Life	Culture	Organism	Vancomycin MIC, mg/L	Antimicrobial Sensitivity	Antimicrobial Resistance	Antibiotic
31	Blood (peripheral)	*S epidermidis*	1	Vancomycin, linezolid, daptomycin, rifampicin, gentamicin	Cloxacillin,	No change
36	Blood (peripheral)	No growth				No change
38	Blood (peripheral)	No growth				No change

MIC, minimum inhibitory concentration

Figure 2. Trends of WBC, PLT, and creatinine from admission until discharge.



PLT, platelet; WBC, white blood cell.

active form of ceftaroline fosamil, a parenteral cephalosporin that exhibits time-dependent bactericidal effects. Initially, ceftaroline fosamil was approved by the FDA and the European Medicines Agency for treating CABP and ABSSSIs, including ABSSSIs caused by MRSA, in adults.[10,11] Since 2016, ceftaroline has been approved for treating ABSSSIs and CABP caused by MRSA in infants aged 2 months and older, as well as infections caused by penicillin-resistant and other cephalosporin-resistant *S pneumoniae* isolates, *Haemophilus influenzae*, and non–ESBL-producing Enterobacteriaceae species.[3] The safety, efficacy, and pharmacokinetics of multiple-dose ceftaroline in neonates and very young infants (7 to <60 days of age) with late-onset sepsis were recently reported by reported by Yim et al[14] Bradley et al[15] The authors found that ceftaroline (6 mg/kg every 8 hours) was well tolerated among this population with no safety concerns.[14,15] However, limited data are available on the safety, efficacy, and optimal dosage of ceftaroline in extremely premature (<28 weeks' gestational age) infants. Salerno et al[16] reported the pharmacokinetics of ceftaroline in the treatment of MRSA pneumonia in a premature infant born at <28 weeks' gestational age.[16] A dose of 8.5 mg/kg IV every 8 hours was adequate for achieving the pharmacodynamics endpoint associated with efficacy for MRSA. Recently, Heger and Al-Sayyad[4] reported the successful treatment of invasive MRSA, using a combination of daptomycin (6 mg/kg/dose IV every 12 hours) and ceftaroline (8 mg/kg/dose IV every 8 hours) in a premature neonate with a liver abscess.

In our NICU, the selection of optimal antibiotics for the treatment of empirical and proven sepsis (initiation, duration, and discontinuation) depends on an interprofessional team approach involving infectious disease experts, senior clinical pharmacists, and neonatologists. Several factors, such as the source of infection, antibiotics used, antimicrobial sensitivity results, bacterial outbreak, presence of persistent infections, hemodynamic stability of the patient, status of the laboratory tests before treatment, pharmacokinetic properties of the medication, and availability of the medication, are taken into consideration. According to our NICU guideline, ampicillin and gentamicin are provided as the first-line treatment for early-onset sepsis, whereas amikacin and cloxacillin are used for late-onset sepsis. The patient may develop new symptoms of sepsis even if the preliminary blood culture results are negative. Therefore, the physician initiates broad-spectrum antibiotics, such as cefotaxime, meropenem, and vancomycin. In addition, a stewardship program team reviews the patient's medications frequently and adjusts the treatment course according to the culture results, clinical conditions, and other laboratory results.

This report highlights 2 cases with brief follow-up periods until discharge or death, in which ceftaroline was administered alongside other antibiotics to enhance its effectiveness. It suggests that ceftaroline may show increased efficacy when used in combination with other antibiotics, although further studies are needed to investigate this potential. The level of the medication in the serum was not measured, so the need for dose adjustments based on the serum concentration remains unknown. To the best of our knowledge, this is the first

report describing the use of ceftaroline in premature neonates with persistent bloodstream infections.

Conclusion

Based on our findings, ceftaroline (6 mg/kg/dose IV every 8 hours) appears to be a potential treatment option for persistent CoNS infection with high antimicrobial MIC in the extremely premature neonatal population. However, large, well-designed, and prospective studies investigating the safety, efficacy, and pharmacokinetic characteristics of ceftaroline in premature infants are warranted.

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JPPT | Case Report

Myalgia and Rigidity as Adverse Effects of Trametinib Therapy

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Mitogen-activated extracellular kinase inhibitors, including trametinib and selumetinib, are increasingly used to treat pediatric low-grade gliomas. Trametinib, while administered orally and with minimal myelosuppression, is reported to cause rash, diarrhea, and fatigue. Selumetinib has been associated with skin irritation, diarrhea, and musculoskeletal pain. This case report describes an 8-month-old male with a low-grade glioma (LGG) that progressed 6 months post-chemotherapy and was started on trametinib due to its liquid formulation and minimal side effect profile. However, the patient developed severe diarrhea, abdominal pain, neck pain, rigidity, and decreased stamina. These symptoms necessitated discontinuation of trametinib, after which all symptoms resolved within a week. This case highlights the first reported instance of trametinib-induced myalgia and rigidity in a pediatric patient receiving trametinib therapy for a LGG. Clinicians should consider these rare but significant adverse effects when choosing an antineoplastic therapy for the treatment of progressive LGG.

ABBREVIATIONS MEK, mitogen-activated extracellular kinase; MRI, magnetic resonance imaging; LGG, low-grade glioma

KEYWORDS Gliomas; MEK inhibitor; myalgia; trametinib; case reports; side effects of drugs

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Information Box

What specific question does this report address?

Can trametinib have a side effect profile similar to other drugs in its class?

What does this report add to our current knowledge?

Trametinib therapy may cause myalgia and rigidity, which were previously only reported for salumetinib.

Introduction

Mitogen-activated extracellular kinase (MEK) inhibitors, such as trametinib and selumetinib, are being used with increasing frequency for the treatment of pediatric low-grade glioma (LGG).[1–4] MEK inhibitors stabilize the helical conformation of the MEK 1/2 activation segment, rendering it resistant to phosphorylation by rapidly accelerated fibrosarcoma (Raf), which arrests mitogen-activated protein kinase signaling.[5–7] Inhibition of this pathway causes cellular proliferation and cell cycle arrest.[8] The known benefits of MEK-inhibitor therapy include oral administration and minimal myelosuppression.[9–12]

Trametinib is associated with side effects, including rash, asthenia, diarrhea, fatigue, elevated creatine phosphokinase, and vomiting.[9,10] Selumetinib is reported to cause skin irritation, diarrhea, increased liver function tests, fatigue, increased creatine phosphokinase, arthralgia, and myalgias.[12–15] Indeed, up to 58% of patients on selumetinib experienced musculoskeletal pain, and 78% of patients exhibited elevated creatine phosphokinase levels. However, trametinib therapy in combination with dabrafenib has been reported to cause muscle pain.[16] Despite this, monotherapy of trametinib is not reported to have side effects, such as muscle pain or rigidity; however, the trial comparing trametinib monotherapy to trametinib and dabrafenib combination therapy only appeared to include adverse effects with an incidence of 30% or more.[2,16]

Case Report

In February 2022, a magnetic resonance imaging (MRI) of the brain was performed on an 8-month-old male weighing 6.6 Kgs (Figure 1) for evaluation of oral aversion, failure to thrive, and new-onset nystagmus. The MRI revealed a large, multilobulated, heterogeneously enhancing solid sellar/suprasellar mass with a significant mass effect on the midbrain, upper pons, and third ventricle. Subtotal tumor resection was performed, with pathology confirming the diagnosis of pilomyxoid astrocytoma with KIAA1549-BRAF fusion.

Figure 1. A photo of a patient before trametinib therapy.

After recovering from surgery, the patient was started on a 12-week induction course of carboplatin and vincristine. A follow-up MRI demonstrated a reduction in tumor size and enhancement, and he went on to complete a total of 8 maintenance chemotherapy cycles over the next 12 months. Treatment was well tolerated overall.

However, approximately 6 months after the completion of chemotherapy, a routine follow-up MRI demonstrated evidence of tumor progression. Based on this finding, the decision was made to start an oral MEK inhibitor. Specifically, trametinib was chosen because of its availability as a liquid formulation, and standard weight-based dosing was applied. Parents were counseled on common side effects, including skin rash, abdominal pain, diarrhea, fatigue, and cardiac dysfunction.

Clinical signs, laboratory values, and dosing of trametinib are presented in the Table. Five days after initiating therapy, the patient began having diarrhea and abdominal pain that necessitated a dose reduction. By week 2 of daily trametinib, the patient began experiencing neck pain, rigidity (Figure 2), postural changes, and decreased stamina. Laboratory evaluations at that time demonstrated normal blood calcium, liver enzymes,

Table. Clinical Signs, Lab Values, and Dosing of Trametinib

	Days After Initiation of Trametinib						
	0	**5**	**7**	**15**	**18**	**29**	**34**
Abdominal pain		†	†				
Diarrhea		†	†				
Fatigue				†			
Shoulder pain					†	†	
Neck pain/stiffness					†	†	
Trametinib dose (mg/day)	0.7	0.55	0.55	0.55	0.55	0*	
CK (U/L)					263	148	
Urine myoglobin					Negative		
Cr (mg/dL)			<0.20	0.22	0.24	0.34	
Na (mEq/L)			144	151	147	153	163
K (mEq/L)			4.3	3.9	3.7	4.4	
Cl (mEq/L)			113	117	113	116	
Ca (mg/dL)			9	9.3	9.4	9.5	
Mg (mg/dL)					1.8		
AST (U/L)					30		
ALT (U/L)					12		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ca, serum calcium; Cl, serum chloride; CK, creatine kinase; Cr, serum creatinine; K, serum potassium; Mg, serum magnesium; Na, serum sodium

* Cessation of trametinib
† Presence of symptoms listed in first column

Figure 2. A photo of the painful, sustained neck rigidity on day 26 of trametinib therapy.

creatinine, and magnesium levels, as well as mild elevation of creatine kinase, and a negative urine myoglobin result. Supportive care measures, including massage, magnesium supplementation, and treatment with nonsteroidal anti-inflammatory drugs, did not help manage symptoms. Pain and rigidity worsened in intensity over the following week; he was unable to participate in play and physical/occupational therapy. Ultimately, his parents decided to discontinue trametinib on day 29 due to impaired quality of life. All musculoskeletal symptoms resolved within 1 week after discontinuation. The only additional medications the patient was receiving during this period were levothyroxine and desmopressin for hypothyroidism and diabetes insipidus, respectively. He had been on both medications without adverse effects for 2 years each before starting trametinib.

After discontinuing trametinib, the patient was restarted on a reduced dose of 0.175 mg of trametinib 2 months later. He is tolerating the lower dose, and dose escalation is being considered. If side effects recur, future treatment options include tovorafenib or monthly intravenous carboplatin.

Discussion

Gliomas are neuroepithelial tumors that originate from the supporting glial cells and are classified based on the type of cell involved, such as astrocytoma, ependymoma, or oligodendroglioma.[17] Cytological atypia, mitotic activity, anaplasia, microvascular proliferation, and necrosis are high-grade histological features, which are absent in LGG.[18] LGGs are typically slow-growing tumors.[17] However, more than 70% of LGGs gain higher-grade features or aggressive behavior within 10 years.[19] *IDH1*, *FUBP1*, *CIC*, BRAF, and *P53* gene mutations are all clinically associated with LGGs,[20–25] but radiation to the head is the only known environmental predisposing factor.[26]

Treatment of LGGs typically begins with a gross total resection, provided that more than 90% of the tumor can be resected, as this has been shown to have a significant impact on overall survival.[27,28] However, many tumors are not amenable to upfront resection, and medical therapies are therefore indicated. Carboplatin and vincristine are accepted as the standard of care for children with newly diagnosed LGG that are not amenable to surgical resection.[29,30] However, there is no standard of care for disease progression or recurrence. For this purpose, MEK inhibitors are being used; however, their superiority or inferiority to other treatments remains unclear.

Patients with LGGs have limited treatment options, and although the KIAA1549-BRAF fusion is of uncertain significance, those with BRAF V600 mutations tend to have a poor response to standard chemotherapy.[31,32] In this case, a MEK inhibitor was used to target possible increased mitogen-activated protein kinase signaling in the relapsed tumor, as well as for its formulation as a liquid. Selumetinib was considered but not chosen because it is only available as an oral capsule, which the child would have difficulty consuming. His parents were not advised as to possible muscle pain or rigidity with trametinib therapy, as these side effects had only been previously associated with selumetinib therapy.

Trametinib is a reversible, highly selective, allosteric inhibitor of MEK1 and MEK2.[2,5] All MEK inhibitors insert an aromatic group into a lipophilic site behind the inhibitor-binding pocket of MEK[5] to stabilize the helical conformation of the activation segment.[6,7] However, selumetinib contains a polar arm that forms hydrogen bonds with a bound nucleotide in MEK, while trametinib makes additional hydrophobic interactions along the activation segment helix and van der Waals contact with BRAF instead.[5] Although their interactions are different, similar mechanisms and structures likely contribute to the shared adverse effects of this class.

This case is the first that reports myalgia and rigidity as a clear time and dose related, unexpected adverse reaction attributed to trametinib monotherapy.[33] The Naranjo score is a method to assess whether there is a causal relationship between an identified untoward clinical event and a drug.[34] The Naranjo score in this clinical case was 6 (see Supplemental Table), corresponding to a probable association, as the adverse reaction followed drug administration, was a recognized response to the drug, was resolved by withdrawal from the drug, and could not be reasonably explained by other characteristics of the patient's clinical state.[35,36] This case report aimed to educate clinicians on these

potential side effects, so they can be considered when choosing between targeted therapies for LGGs. The authors recommend that trametinib be held when muscle pain and rigidity interfere with a child's activities of daily living and that the medication be resumed at a low dose when toxicities resolve. It is common for patients with unresectable LGG to require several second-line therapies, and trametinib should not be rejected as a treatment option if a lower dose proves to be efficacious and well tolerated.

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. However, given the nature of this study, informed consent was not required by our institution. All authors attest to meeting the four criteria recommended by the ICMJE for authorship of this manuscript.

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JPPT | A Pediatric Pharmacy Association Position Paper

Pediatric Pharmacists' Participation in Cardiopulmonary Resuscitation Events

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The Pediatric Pharmacy Association (PPA) understands the dilemma and varying factors that many institutions face concerning the routine participation of pharmacists in emergency resuscitation. Acknowledging these challenges, the PPA encourages all institutions to strongly consider creating, adopting, and upholding policies to address pharmacists' participation in cardiopulmonary resuscitation (CPR) events. The PPA advocates that pharmacists be actively involved in the institution's medical emergency team committees and the preparation of emergency drug kits and resuscitation trays. The PPA advocates that all institutions requiring a pharmacist's participation in CPR events consider adopting preparatory training programs. The PPA recommends that pharmacists obtain emergency response credentialling with basic life support and pediatric advanced life support and may consider advanced cardiac life support and neonatal resuscitation program certification dependent on practice area. Additionally, the PPA recommends that pharmacists are educated on the pharmacotherapy of drugs used in the CPR process, including, but not limited to, medication preparation and administration guidelines, medication compatibility, recommended dosing for emergency medications, and familiarity with the institutional emergency cart.

ABBREVIATIONS CPR, cardiopulmonary resuscitation; PALS, pediatric advanced life support; PPA, Pediatric Pharmacy Association

KEYWORDS cardiopulmonary resuscitation; pediatric advanced life support; pediatrics; pharmacist

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Introduction

Over the past 30 years, there has been a notable increase in the overall survival of cardiac arrest in children.[1,2] Approximately 15,000 hospitalized children receive cardiopulmonary resuscitation (CPR) for cardiac arrest each year in the United States. Several interventions have been recommended to improve CPR outcomes, such as optimizing the depth and quality of compressions, forming rapid response teams, and establishing postarrest monitoring parameters. Despite these interventions, the portion of cardiac arrests caused by nonshockable rhythms more than doubled between 2000 and 2009.[3] Therefore, for patients experiencing nonshockable rhythms, medications remain a crucial element of CPR interventions.

The role of pharmacists in providing drug information and preparing medications during CPR events in a hospital setting has been documented over the past 50 years; however, most of these data have been gathered from surveys conducted within health care systems.[4,5] The first report of pharmacist participation in CPR events was in the 1970s,[6] and by 1992, Bond et al[7] reported pharmacist participation at rates up to 30%. In 1991 and 1995, surveys conducted by Raehl et al[4] and Shimp et al,[8] respectively, concluded that pharmacist attendance at CPR events occurred in approximately 30% to 35% of represented hospitals but did not differentiate between adult and pediatric CPR events.

While there are limited studies evaluating the impact of pediatric pharmacists in CPR events, the systematic review by Currey et al[9] reported the beneficial effect of pharmacist involvement and intervention during emergency responses and resuscitations. Pharmacist involvement improved the time to initiation of time-critical medications, medication appropriateness, and guideline compliance in various patient conditions such as cardiac arrest and sepsis. This position statement aimed to discuss CPR events in children, renew the position of the Pediatric Pharmacy Association (PPA) in endorsing pediatric pharmacists' participation in all CPR events involving children, and offer recommendations for effective implementation.

Controversy

Only 1 study has documented the frequency of pediatric pharmacists responding to pediatric emergencies. Hahn et al[10] surveyed children's hospitals and found that only 63% of institutions had pharmacists who responded

to CPR events. There is literature demonstrating that pharmacists in the pediatric intensive care unit positively impact patient care and outcomes, including reducing and preventing medication errors.[11,12] However, there are no studies evaluating the impact of pharmacist response to pediatric code events and there are multiple studies that show improvement in teamwork, medication turnaround time, medication error rates, and post-code feedback implementation when pharmacists participate in adult code response and oversight committees.[13–16] Given that pharmacists have such a significant impact on the care of patients in the pediatric intensive care unit and with beneficial outcomes from pharmacist participation in adult code response, one can reasonably presume the expertise of pediatric pharmacists would similarly enhance the ordering, preparation, and administration of medications during CPR events for pediatric patients. Despite the possible benefits, several challenges persist in expanding pharmacy services to resuscitation teams. These challenges include insufficient staffing within pharmacy departments, a lack of advanced formal training in resuscitation, a perceived lack of available resources, and apprehension and limited understanding of the pharmacist's role during resuscitation events. Overall, CPR is a highly complex process with significant variability in pharmacists' involvement, training, and baseline expertise.

Recommendations

Training of Pediatric Pharmacists. The PPA recommends that pediatric pharmacists participating in CPR and rapid response events maintain appropriate certifications such as basic life support and pediatric advanced life support (PALS). Additional certifications can be considered, such as neonatal resuscitation program (NRP) certification for any pharmacists that practice in areas where neonatal patients may be admitted or in maternal-fetal care units. Advanced cardiac life support may be considered for any pharmacists who practice in areas where adult patients may be admitted, such as cardiac care units or emergency departments. Recommendations for credentialling pediatric pharmacists for CPR events are listed in Table 1. While these certifications can provide pharmacists with baseline knowledge, they alone may not adequately prepare pharmacists for routine participation in hospital CPR events, as they lack information related to specific aspects of pharmacotherapy, including medication dosing, manipulating multiple drug concentrations and dosing formulations, intravenous medication compatibility considerations, and bedside dose preparation. To fill in these gaps and improve the comfort of pharmacists responding to CPR events, the PPA recommends that pharmacy leadership support the creation of training competency programs for all pharmacist staff involved in CPR events. This training should include education sessions with pediatric case examples, hands-on mock codes using simulation labs for CPR events and common pediatric medical emergency scenarios, and continuing education programs. Several published articles support additional pharmacist training beyond the aforementioned certifications. Machado et al[17] found that pharmacists had a more favorable attitude toward participating in CPR events if they felt they had adequate training. Roddy et al[18] demonstrated that combined didactic education and pediatric simulation-based training increased pharmacist knowledge and confidence in pediatric emergency response.

Table 1. Recommendations for Credentialing for Pediatric Pharmacists for Cardiopulmonary Resuscitation Events

Basic Life Support	Require for all pharmacy staff
Pediatric Advanced Life Support	Require for all pharmacy staff
Neonatal Resuscitation Program	Consider requiring for pharmacists who may care for neonates, such as those who work in the neonatal ICU, cardiac ICU, or maternal-fetal unit
Advanced Cardiac Life Support	Consider requiring for all pharmacists who may respond to adult codes

ICU, intensive care unit

Many institutional training programs have been published that focus on various aspects of pharmacotherapy during emergency response.[18–22] These training programs dedicated time for hands-on experience to help participants become familiar with code trays and intravenous admixtures. Many sessions emphasized identifying common medication errors, reviewing code dosing sheets and common algorithms, calculating patient-specific doses, preparing medications, and practicing closed-loop communication to enhance teamwork skills. These studies illustrate how training programs for pharmacists involved in CPR events can improve comfort levels and competency through education interventions, written assessments, certification, and practical training.

Pharmacist training sessions for pediatric emergencies within simulation laboratories and regular multidisciplinary mock codes provide valuable opportunities for pharmacists and pharmacy residents to identify different patterns of medication use, enhance communication skills in critical situations, and engage in postsimulation debriefing to discuss errors and successes.[23,24] Thompson Bastin et al[24] evaluated simulation exercises designed to prepare pharmacy residents for a 24-hour, in-house, on-call program. The investigators found that self-perceived preparedness

increased following sepsis (p = 0.001) and stroke and status epilepticus (p = 0.042) exercises. These results highlight that simulation training incorporated into pharmacy residency programs can increase resident readiness for medical emergencies.

Before implementing an institution-specific training program, hospital pharmacy leadership should assess data and review patient safety guidelines to identify the specific training needs of their pharmacists. Pharmacists should be involved in institutional patient safety committees and quality assurance programs. Table 2 lists recommendations for education and training to prepare pharmacists for pediatric CPR events. Institutions should engage pharmacists in developing and implementing appropriate resources, such as standardized pediatric and neonatal medication code algorithms and weight-based reference cards for emergency medications to aid in medication preparation.

Participation in CPR Oversight Committees. The PPA advocates for pediatric pharmacists to participate in CPR and rapid response committees. Pharmacist participation is crucial as these committees review CPR events for individual patients to identify areas for quality improvement and develop policies and procedures for such events. The findings from a retrospective multidisciplinary code review committee that included a pharmacist demonstrated that approximately 60% of reviewed code events resulted in education initiatives, and 47% resulted in a new policy or modification of an existing policy.[15] A study by Anderson et al[14] demonstrated the need for synchronous, multidisciplinary code review to provide rapid feedback and further identified that top-performing hospitals in emergency events had responsive, multidisciplinary leadership teams who listened and modified programs to align with the needs of their staff.[14] Pharmacist participation in multidisciplinary code review committees can help identify departmental or hospital-wide deficiencies and lead to educational patient care improvement initiatives.

Additionally, pharmacists can be vital in overseeing emergency carts and kits for CPR, rapid-response

Table 2. Recommendations for Education and Training for Pediatric Pharmacists for Cardiopulmonary Resuscitation Events

	Pharmacists	Pharmacy Residents
Didactic education	• For new pharmacists or pharmacists who do not frequently respond to codes, consider PALS review and overview of medications used in CPR events • For all pharmacists, provide sessions that focus on non-PALS emergency situations, such as hyperkalemia and status epilepticus	• For pharmacy residents, consider PALS review and overview of medications used in CPR events • Provide additional sessions that focus on non-PALS emergency situations, such as hyperkalemia and status epilepticus
Mock codes and simulations	• Minimum 1 mock code per year	• Minimum 1 mock code per quarter
	Recommended Activities: • Calculate medication doses • Draw up medications • Identify potential medication incompatibilities and admixture concerns • Familiarization with the code cart • Practice closed-loop communication with other health care professionals • Learn how to administer medications (depending on pharmacy practice laws) • Become familiar with treatment algorithms and guidelines	
Mentorship activities	• New or inexperienced pharmacists must respond to codes accompanied by other experienced pharmacists	• Pharmacy residents must respond to codes accompanied by other experienced pharmacists
Additional education activities	• Code sheet review with hands-on activities and patient case examples • All pharmacists must demonstrate an understanding of general emergency drug processes so they can respond to requests for more medications during a code, correctly refill emergency carts, etc.	
Ongoing continuous quality improvement and evaluation	• Participate in debrief sessions for mock codes and real-life codes • Means of documentation of training on annual review • Develop a communication tool for drug shortage documentation and recommended therapeutic interchanges	

CPR, cardiopulmonary resuscitation; PALS, pediatric advanced life support

situations, rapid-sequence intubations, and trauma responses. A lack of standardization and organization of emergency carts, particularly regarding medications, can adversely affect outcomes. Disorganization can lead to significant delays because response time is crucial for patient survival.[25,26] Pharmacists play a vital role in this process, as emphasized by the American Society of Health-System Pharmacists[27] and The Joint Commission,[28] to ensure that medications in emergency carts and kits are properly organized and stored, especially in drug shortages.

In addition to these responsibilities, pharmacists can contribute to developing institution-specific protocols and dosing tools for CPR events. Pediatric pharmacist expertise is particularly beneficial for creating protocols for emergencies, such as hyperkalemia and status epilepticus, which are not specifically covered in the 2020 PALS guidelines.[29] These protocols can help clinicians anticipate potential medication therapies tailored to the institution's formulary. Furthermore, pharmacist involvement in developing dosing tools for emergency medications is crucial for preventing medication errors during CPR events, especially because children require weight-based dosing.

Participation in Individual Patient CPR and Rapid Response Events. The PPA recommends that all hospitals have pediatric pharmacists respond to all neonatal and pediatric CPR events. The rarity of pediatric CPR events highlights the need for immediate access to a drug therapy expert for clinical pharmacotherapy recommendations. Additionally, the PPA suggests that institutions consider including a pediatric pharmacist on rapid response teams to offer therapy recommendations in line with the PALS guidelines and help ensure medication safety. Draper and Eppert[30] conducted a retrospective study that evaluated 74 CPR events in adults to determine compliance with American Heart Association advanced cardiac life support guidelines and found that compliance was more likely when a pharmacist was present (59.3% v 31.9%, p = 0.03). While this study did not specifically target pediatric patients, it seems reasonable to suggest that pediatric pharmacists could also ensure that medication regimens adhere to PALS recommendations.

Pharmacists attending emergency responses may bring additional medications that are not typically stored in emergency carts due to storage or regulatory requirements. In a retrospective cohort study conducted by Bembea et al,[13] pediatric medical emergency teams showed that only 40% of medications ordered during an emergency response were readily available. Additional medications supplied by the responding pharmacist provided an additional 35% of dosages, increasing bedside availability of requested medications from 40% to 75%. By their involvement in developing and maintaining an emergency response team, pharmacists can understand their role and help identify additional medications or supplies that may be useful when responding to an emergency.

Pharmacists can also help reduce medication errors during CPR events, which are more common in pediatrics. Pediatric medication error rates are reported to be more than 70%, which is 3 times the error rate compared with adult institutions.[31] However, the collaboration of clinical pharmacists with nursing staff has been shown to prevent 58% of medication errors and 72% of high-risk errors.[23] While these pediatric error rates are higher than reported adult rates, these error rates are not specific to medical emergencies. Medication error event rates would likely be higher during pediatric medical emergencies due to the high-stress environment, limited access to immediate resources, and involvement of mathematical calculations and drug manipulation. A systematic review and meta-analysis by Marufu et al[31] reviewed pediatric and neonatal studies published from 2000 to 2020 that implemented interventions to reduce medication errors. Most studies used clinical pharmacist involvement as part of a multi-intervention approach that included education programs, independent double checks, and reduced interruptions while calculating and preparing weight-based doses. This meta-analysis surmised that the presence of a clinical pharmacist may help nurses make informed clinical decisions, provide updated reconstitution and dilution instructions at the bedside, and improve therapeutic interchange choices in light of intravenous incompatibilities or medication shortages. In addition to nursing support, pharmacists can also provide support for providers. A review of simulated CPR events found that the presence of a pediatric pharmacist significantly reduced medication errors made by pediatric resident physician trainees.[32] Pharmacist involvement in the emergency response team can help mitigate medication errors and reduce medication turnaround time for safer delivery of medications to pediatric patients.[13,16]

Owing to unforeseen medication shortages, emergency carts may be stocked with alternatives to the expected medications. Whether these stocked medications are alternative formulations or require the use of pharmacy-generated kits, the likelihood of medication errors increases when unfamiliar medications need to be prepared. Pediatric pharmacists assist clinicians in anticipating these changes and ensure that the most appropriate medication is selected, prepared, and administered accurately.

Conclusion

The PPA encourages all institutions to create, adopt, and uphold policies to address pediatric pharmacists' training requirements, participation in CPR events, and emergency cart preparedness. The PPA further advocates that all institutions require pharmacists to participate in emergencies and consider adopting

preparatory training and competency programs for resuscitation using nationally accepted guidelines. Although the PPA does not advocate for any particular program, pharmacists should obtain emergency response credentialling with basic life support and PALS. They may consider additional certification, such as advanced cardiac life support and neonatal resuscitation programs, dependent on the practice area. Additionally, the PPA recommends that pharmacists are educated on the pharmacotherapy of drugs used in the CPR process, medication procurement, medication preparation and administration guidelines, medication compatibility, recommended dosing for emergency medications, and familiarity with the institutional emergency cart and available resources.

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JPPT | Invited Commentary

Do Not Throw Away Your Patient's Shot at Complete Vomiting Control

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ABBREVIATIONS CIV, chemotherapy-induced vomiting; CINV, chemotherapy-induced nausea and vomiting

KEYWORDS chemotherapy-induced vomiting; chemotherapy-induced nausea; antiemetics; clinical practice guidelines

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Introduction

During the early days of chemotherapy, chemotherapy-induced nausea and vomiting (CINV) was considered manageable when chemotherapy could continue with receipt of intravenous hydration. Not surprisingly, CINV was the treatment-related adverse effect most dreaded by patients. Today, nausea and vomiting are repeatedly identified by pediatric cancer patients as among the top 5 most bothersome symptoms they experience.[1–3] However, recent pediatric trials report rates of complete chemotherapy-induced vomiting control of 79% to 92%[4–7] and clinical practice guidelines make strong recommendations that pediatric patients receive specific antiemetic prophylaxis known to be safe and effective.[8–10] Why the disconnect?

Four key steps to optimize a pediatric patient's chance at experiencing complete CINV control are as follows: (1) providing evidence-based CINV prophylaxis; (2) including dexamethasone and (fos)aprepitant in antiemetic regimens thoughtfully; (3) responding in timely and effective ways to treat breakthrough CINV; and (4) deprescribing medications given for antiemetic purposes for which there is little or no evidence of efficacy. These steps are discussed below.

Evidence-Based CINV Prophylaxis

We now have evidence-based recommendations from pediatric clinical practice guidelines to guide the selection of CINV prophylaxis[8,11] and the management of anticipatory,[9] breakthrough, and refractory[10] CINV. These recommendations have been endorsed by the Children's Oncology Group and the Multinational Association of Supportive Care of Cancer and have been adapted for use by many institutions internationally. They represent the international standard for chemotherapy-induced vomiting (CIV) prophylaxis for pediatric patients. Yet, implementation of these clinical practice guidelines is challenging and guideline-consistent prophylaxis is often not provided.[12]

In some instances, guideline-inconsistent prophylaxis may be reasonable. For example, a recommended antiemetic may not be licensed in a jurisdiction or, even when available, its off-label use as an antiemetic (eg, olanzapine) may not be permissible. A recommended antiemetic may be inappropriate for an individual patient because of allergy, history of adverse reaction, or concurrent conditions. However, when recommended agents are obtainable, their pediatric use is permissible and when there is no patient-specific contraindication for their use, pharmacists must advocate strongly for the implementation of guideline-consistent care. Advocacy may include arguments regarding the cost-efficiency of guideline-recommended antiemetics and the false economy of not including effective antiemetics, such as palonosetron, on the formulary. Incorporation of guideline-consistent antiemetic regimens into chemotherapy order sets is a commonly employed implementation tactic. However, tools such as care pathways, algorithms, educational modules, and posters will likely be required to change local practice and facilitate the delivery of evidence-based CINV prophylaxis. Pharmacists are often best placed to lead guideline-consistent CINV management implementation.

Dexamethasone and (Fos)Aprepitant Restrictions

Both dexamethasone and (fos)aprepitant are extremely effective antiemetics. Dexamethasone, when added to a first-generation 5-hydroxytryptamine-3 receptor antagonist, such as ondansetron or granisetron, increases the complete acute phase CINV control rate among patients receiving highly emetogenic chemotherapy substantially (RR 1.36, 95% CI, 1.23–1.50).[13] Similarly, neurokinin-I inhibitors such as (fos)aprepitant, when added to a 5-hydroxytryptamine-3 receptor antagonist and dexamethasone, significantly increase the complete acute phase CINV control rate among patients receiving highly emetogenic chemotherapy

(RR 1.07, 95% CI, 1.01–1.13).[13] However, dexamethasone is frequently withheld from chemotherapy-naïve pediatric patients for reasons that are not grounded in evidence, including concerns of wound healing and neutrophil recovery impairment. Conversely, although (fos)aprepitant can increase the dose intensity (area under the concentration vs time curve) of chemotherapy agents that are CYP3A4 substrates by 2- to 5-fold or reduce the CYP3A4-mediated activation of chemotherapy agents to their active form,[14] it is often given without regard to the potential resultant toxicities or reduced treatment efficacy. Ideally, the circumstances for the use of each agent would be based on a thoughtful evaluation of their risks and benefits and include the perspectives of patients or their representatives. Institutional standardization would permit iterative quality improvement.

Responsiveness to Breakthrough CINV

Without assessment, it is impossible to realize when a patient is experiencing breakthrough CINV and, thus, impossible to initiate a timely response. As a minimum practice standard, nurses should record the time hospitalized patients vomit or retch in the health record. Ideally, nausea severity would be assessed by inpatients and outpatients during the acute and delayed phases of each chemotherapy block using a validated pediatric patient-reported measure.[15,16] This information should also be recorded in the health record. Symptom screening measures such as SSPedi may also be used to flag patients with bothersome nausea or vomiting who may benefit from more focused evaluation.[1]

The availability of patient outcome data in the health record enables the creation of dashboards that inform clinicians of their patients' situation in real time and makes quality-improvement projects more manageable because data extraction from the electronic health record can be automated. For example, Walsh et al[17] have created a dashboard that displays each inpatient's chemotherapy and antiemetic regimen, the congruence of the antiemetic regimen with institutional CINV management policy, and the vomiting rate.

Modern adult and pediatric trials evaluating interventions to manage breakthrough CIV initiate the intervention when participating patients vomit once.[10] To repeat, the first vomit triggers an intervention. Pediatric clinicians, on the whole, are relaxed about vomiting and often seem to expect their patients to vomit: "It is bone marrow transplant conditioning, after all!" Because a history of vomiting is an important risk factor for future vomiting, it is important to intervene quickly and effectively when a patient vomits. Each patient should have a breakthrough CINV management plan that can be initiated when a patient vomits or experiences bothersome nausea despite prophylaxis. This management plan should include revisiting decisions to withhold dexamethasone or (fos)aprepitant because the risk:benefit equation will have shifted once the patient has experienced breakthrough CINV. The patient's experience with breakthrough CINV should be incorporated into the antiemetic selection for the next chemotherapy block so that refractory CINV can be prevented. This requires clear and accessible charting of antiemetic treatment plans in the health record.

Deprescribing Antiemetics

Before the availability of 5-HT3RA, metoclopramide, phenothiazines, diphenhydramine, and dimenhydrinate were commonly used to prevent CINV. Complete CIV control rates were dismally low. While metoclopramide continues to be recommended for specific pediatric patients with refractory CINV,[10] agents other than those recommended in current clinical practice guidelines may offer patients only potential toxicity with little or no efficacy. They may also introduce an opportunity cost because the initiation of effective antiemetics may be delayed, and the risk of future vomiting may therefore increase.

Institutional antiemetic practices may be deeply entrenched and difficult to shift. Pharmacists may undertake retrospective or prospective quality-improvement projects to understand how historical practices contribute to CIV control. Pharmacists undertaking such projects should publish their findings to benefit the larger community. An audit of CINV prophylaxis provided and feedback on patient outcomes to clinicians may be effective ways to improve complete CIV control rates.

In many institutions and jurisdictions, pharmacists prescribe antiemetic prophylaxis either independently or following a standardized rubric. Rather than following historical practices, pharmacists must advocate for evidence-based and experience-informed antiemetic practices, particularly when writing these orders.

In conclusion, it is our vision that all patients receiving cancer treatment will be free of vomiting, retching, and nausea and will maintain their usual appetite throughout therapy. To realize this vision, pharmacists must ensure that each of their patients enjoys the highest probability of complete CINV control starting with their very first chemotherapy block—that they do not throw away their patient's shot. This can be accomplished by delivering guideline-consistent care, responding quickly to breakthrough CINV, and avoiding ineffective and potentially unsafe interventions. However, gaps in our knowledge of CINV remain (eg, uncertainties regarding emetogenicity classification, antiemetic dosing, individual risk factors), and even with careful attention, some patients will not achieve complete CINV control. However, we can do better for our patients, even with the tools currently available.

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JPPT | Invited Commentary

Microbial Biofilms: Where Are We and Where Are We Going?

Sudi Shatha Harbool and Mahmoud Ghannoum, PhD

ABBREVIATIONS IBC, intracellular bacterial community; IMD, implantable medical device; LE, lipid emulsion; QS, quorum sensing; ROS, reactive oxygen species; YFP, Yellow Fluorescent Protein

KEYWORDS bacteria; biofilm; definition and challenges; fungi

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Historical Perspective

The discovery of biofilms is attributed to the father of microbiology, Antonie van Leeuwenhoek (1632–1723), when he was examining his own dental plaque and noticed the presence of "animalcules."[2] However, it was not until the 1970s that it became widely accepted that bacteria in all-natural ecosystems lived in the biofilm state. This timeframe coincided with research focusing on the biodeterioration of "Dhows," a lateen-rigged ship with 1 or 2 masts, used in the Indian Ocean in the 70s, in the Arabian Gulf, where upon examination of the hull of these ancient boats, researchers focused on the slime layer or microfouling, which turned out to be biofilms.[3] The association of biofilms with indwelling medical devices (IMDs) as they relate to infections was recognized in the early 90s when microscopic examinations revealed the presence of many microbes, mainly bacteria, enveloped by extracellular matrix. This realization, however, was not acknowledged as an important cause of IMD infections until the early 1990s when electron microscopic examination of explanted IMDs, believed to be the foci of infection, revealed large numbers of bacteria encased in a thick extracellular matrix.[4] This discovery led to a rapid increase in the number of researchers investigating biofilm-related IMD infection.

Recent studies brought to the forefront that gut resident bacteria and fungi residing in the gastrointestinal tract interact to form biofilms.[5] Biofilms formed by beneficial microbes are helpful to our gut lining. In contrast, biofilms formed by microbial pathogens are detrimental and could potentially exacerbate inflammatory symptoms, becoming resistant to antimicrobial drugs and immune cells. Similar interkingdom interactions have been observed in sites other than the gastrointestinal tract. In this regard, studies investigating chronic wounds observed that mixed-species bacterial (e.g., *Citrobacter freundii*) and fungal (*Candida albicans*) biofilms form rapidly with *Candida* forming the biofilm core, while bacteria are associated with the biofilm boundary. These findings propelled researchers to investigate approaches to manage biofilms.

What Are Biofilms?

The formation of microbial communities on natural surfaces, in chronic wound infections, in medical device buildup, and in dental plaque all share a common denominator: biofilms. Biofilms are an aggregation of bacteria and/or fungi surrounded by a self-produced extracellular matrix. This matrix gives rise to the main impediment in treating biofilms, because it makes the microorganisms inside highly resistant to antimicrobials and host defense mechanisms. The unique features and appearance of the biofilm are highlighted in Figure 1.

Biofilms in intravascular catheter-associated infections as well as diseases such as periodontitis, cystic fibrosis, and otitis media[5] are linked to several pathogenic fungi; however, the most prevalent fungi found within these conditions are the *Candida* species.[6]

There are several reasons why *Candida*, and especially *C albicans*, are the main contributors to fungal biofilms. Their ability to adhere to various surfaces as well as each other is facilitated by a unique class of proteins called adhesins, which have repeatedly shown significantly higher adhesion and cohesion abilities.[7,8] They also possess the trait of dimorphism, which is a key component in biofilm production because it allows them to effectively maneuver the change between yeast and hyphal growth.[9] Within a biofilm, *C albicans* also has an intense resistance mechanism, making it extremely resistant to antifungal treatments, and finally it has a complex system for metabolic adaptation that allows it to thrive in diverse environments.[10]

When looking at IMDs in particular, several characteristics define a traditional biofilm-induced IMD infection. These characteristics have multiple similarities with what has been observed in biofilm-related infections, including delayed onset of symptoms, inability of the

Figure 1. Visualization of a biofilm, using scanning electron microscopy. (A) The image displays the dense layers of co-aggregating yeast as well as hyphal forms. (B) Fungi embedded in the extracellular polymeric material; the image highlights the amorphous granular appearance of the extracellular material.

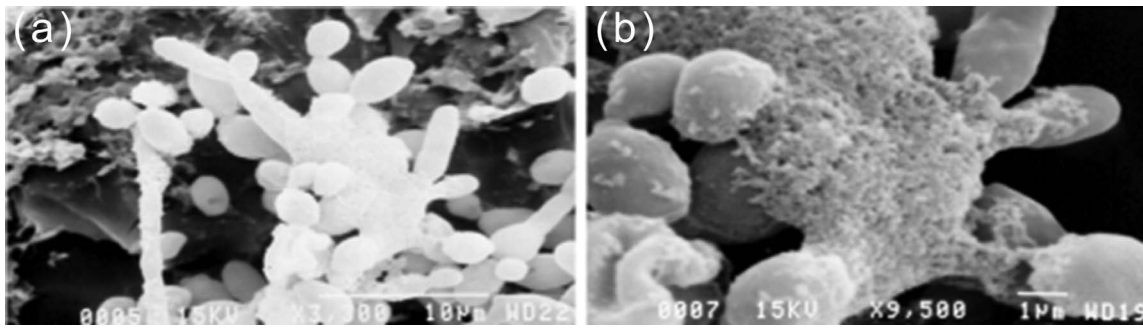


Table 1. Summary of Biofilm Components

No.	Components	Percentage (%)
1	Microbial Cells	2–5
2	Water	Up to 97
3	Polysaccharides	1–2
4	Proteins	<1–2 (including enzymes)
5	DNA and RNA	<1–2

host defense mechanisms to inhibit them, programmed detachment acting as a nidus for infection,[11] and inability of antimicrobials to significantly affect the biofilm. Biofilms are a proven major contributor to IMD-related infections, with the main route of treatment being the removal of the device. This method, however, is risky for the patient and is often not recommended because IMD removal requires surgery, which can damage the tissue surrounding the device. In addition, there is also a psychological component to be considered, as a surgery to remove a device used to control a critical and chronic condition usually has drawbacks. Moreover, IMD removal is also expensive, costing an average of 5 to 7 times more than IMD insertion.

The good news is that current research on biofilms has come a long way. With an increase in IMD insertions and removals has come a greater need for understanding the underlying mechanisms behind biofilms, how biofilms can be diagnosed, how they can cause other diseases, and how they are prevented and treated. While a vast amount of research has been conducted in several of these areas, there is still a great need for more dialogue on the topic, as well as more research on the treatment methods for patients in general.

An Overview of Biofilm Composition

Biofilms are microbially diverse structures composed of a mixture of bacteria and/or fungi. Current literature suggests that up to 80% of bacteria and archaeal life can be found within biofilms.[12] Biofilms develop an extracellular matrix of polysaccharides, protein, and extracellular DNA to protect the microorganisms within the matrix from a host of problems. This matrix gives the microorganism the ability to survive at lower oxygen and nutrient availability, osmotic shock, and gives a layer of protection against antimicrobials.[13] The top layer contains the bulk of oxygen and nutrients, which decreases gradually toward the center of the biofilm, sometimes allowing for certain anaerobic bacteria to survive at the center.[13] A summary of the composition of biofilms is listed in Table 1.

Most of the biofilms contents are suspended in water, while components of the extracellular matrix average about 1% to 2% each.[14]

The composition and formation of biofilms can also be better understood when looking at the complete biofilm life cycle, as described in Figures 2 and 3.

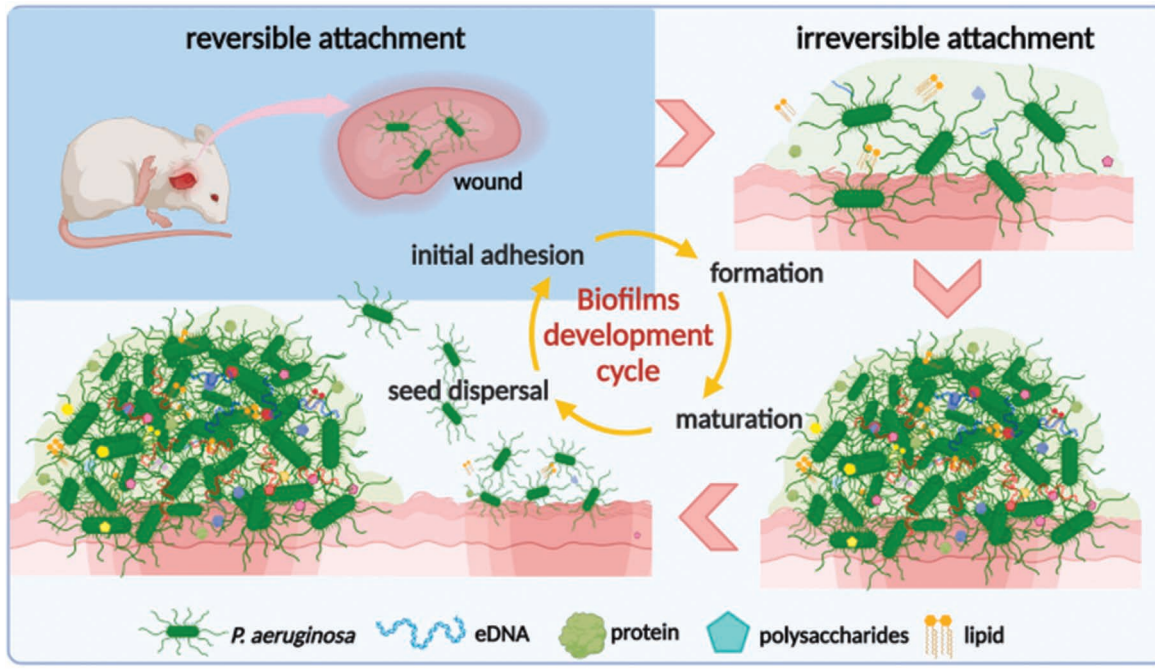
To test whether biofilms can act as a nidus of infection, biofilms were formed on catheters, using YFP (Yellow Fluorescent Protein)-tagged *Candida*. After 3 days, kidneys were aseptically harvested and examined microscopically. Immunofluorescence microscopy showed that YFP-tagged *Candida* was colonizing the kidneys in a fashion similar to the catheter. This suggests that eliminating the biofilm is critical to treat the catheter as well as biofilms formed internally (i.e., systemically).

The 3-dimensional structure of biofilms can vary depending on the bacterial species involved. For example, *Streptococcus pneumoniae* biofilms form in a linear pattern, while *Pseudomonas aeruginosa* biofilms adopt a mushroom shape.[13] In fact, the environment is a significant contributor to the overall biofilm 3-dimensional shape, because the local conditions allow the biofilm to adapt.[17]

Biofilms in Human Disease

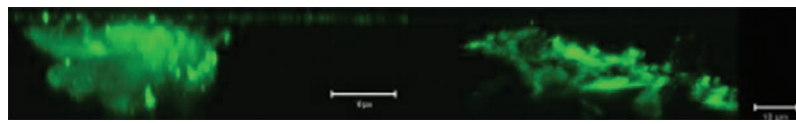
Around 75% of the infectious diseases found in humans can be attributed to biofilms.[18] Owing to the structure of biofilms, especially the matrix, the microorganisms within are much more resistant to

Figure 2. Stages of biofilm formation. Biofilm formation proceeds in 4 different steps: 1) Reversible attachment is where the microbes can attach onto a surface and is in a dynamic state where it is possible for it to return to its plankton form. 2) Irreversible attachment is when the microbial community gains more structure, and the matrix that allows the microorganism to thrive is formed. 3) Maturation phase is where the biofilm develops its 3-dimensional form to best fit the environment. 4) Microbial cell dispersal occurs when the biofilm has accumulated enough volume to cause nutrient deficiencies in the inner layer, which eventually results in a central cavity, allowing microbial cells to disperse.[15]



eDNA, Extracellular DNA.

Figure 3A. The displayed imaging shows YFP-tagged *Candida* as present on the catheter (A) and the kidney.



YFP, Yellow Fluorescent Protein.

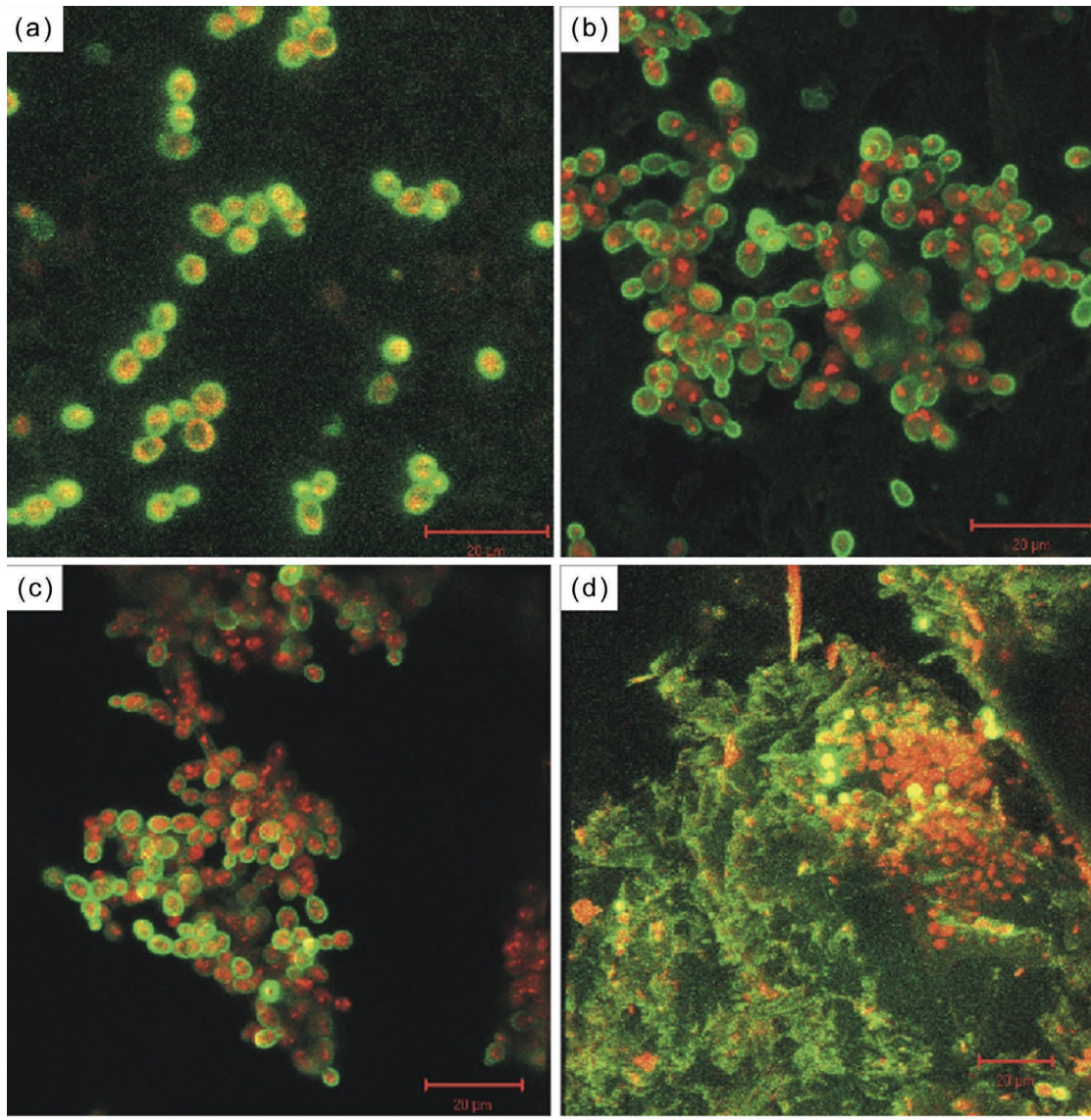
antimicrobial medications as well as attacks by the host immune armamentarium, manifesting in various physiologic problems for humans, as summarized in Table 2.

These biofilm-associated diseases are largely due to the extensive use of IMDs including catheters, prosthetic heart valves, pacemakers, implants, cerebrospinal fluid shunts, among others.[5,19]

While there are several human diseases associated with biofilm production, there are certain conditions that specifically concern the pediatric population. The development of otitis media and acute otitis media caused by biofilms has been extensively studied in the pediatric population, where biofilm formation is naturally more likely to occur owing to the Eustachian tube being shorter and wider in children than in adults, allowing for bacteria such as *S pneumoniae* and *Haemophilus influenzae* to spread rapidly.[20,21] Tympanostomy tube insertion is also a common procedure for children and is used to treat this condition with effusion. Here otorrhea is a common complication that can lead to biofilm growth, and several studies have demonstrated that failure to control the biofilm growth can lead to tube removal.[19,22]

Pertussis (also commonly referred to as whooping cough), is associated with *Bordetella pertussis* as well as *B parapertussis*. This disease—although easily avoided by vaccination—has been on the rise in children.[19] Biofilm growth in relation to pertussis has been studied in mouse models, where growth

Figure 3B. Confocal scanning electron microscopy examination showed that *Candida* biofilms pass through (a) adhesion phase (2 hours), (b) proliferation phase (8 hours), (c) microcolony formation (8 hours), and (d) maturation phase (24–48 hours).[16]



on the ciliated epithelium was observed, and a link between increased biofilm production and infection was observed. It has also been suggested that biofilm growth itself can be a contributing factor to pertussis. Thus, it was suggested that one way to control biofilm formed in pertussis is to include biofilm protein antigens in pertussis vaccines.[19]

Urinary tract infections can be a chronic condition, and a growing amount of evidence points to the intracellular bacterial community (IBC) as the root cause of its persistence. In mouse models, it was found that IBC growth is facilitated by the formation of biofilms, which allows the bacteria to grow with minimal disruptions. In the pediatric context, IBC/biofilm growth was found in around 36.8% of children with cystitis,[23] indicating a significant occurrence of biofilm-related problems within the pediatric population as well.

Another risk factor for developing biofilm-associated infections in the pediatric population is the extensive use of parenteral lipid emulsion (LE).[24] Our team studied the effect of LE on the ability of *Candida* to germinate and form biofilms on medical catheter material.[25] Our testing showed that adding LE to standard fungal growth medium increased the ability of *C albicans* to form biofilms and led to changes in biofilm architecture and morphology. Moreover, incorporation of LE

Table 2. Biofilm-Associated Diseases and Targeted Organs

Body System	Affected Organs	Disease
Auditory	Middle ear	Otitis media
Cardiovascular	Cardiac valves Arteries	Infective endocarditis Atherosclerosis
Digestive	Salivary glands	Sialolithiasis
	Gallbladder	Recalcitrant typhoid fever and predisposition to hepatobiliary cancers
	GI tract (especially the small and large intestine)	Inflammatory bowel disease and colorectal cancer
Integumentary	Skin and underlying tissue	Wound infections
Reproductive	Vagina Uterus and fallopian tubes Mammary glands	Bacterial vaginosis Chronic endometriosis Mastitis
Respiratory	Nasal cavity and paranasal sinuses Throat (pharynx with tonsils and adenoids, and larynx with vocal cords) Upper and lower airways Upper and lower airways	Chronic rhinosinusitis Pharyngitis and laryngitis Pertussis and other Bordertella infections Cystic fibrosis
Urinary	Prostate gland Urethra, bladder, ureters, kidney	Chronic bacterial prostatitis Urinary tract infection

GI, Gastrointestinal

to the growth media induced candidal germination (a critical virulence factor for *C albicans*). Our results provided insight into the underlying mechanism for the increased risk of candidemia in pediatric patients receiving LE via medical catheters.

Overall, biofilms play a crucial role in the production and persistence of several diseases, especially within the pediatric population. This highlights the ongoing need to test and develop novel approaches to manage and control biofilm-related human diseases in this population.

Challenges and Treatment Strategies

Biofilm Management. There are 2 main management strategies when it comes to combating the health effects of biofilms: prevention or treatment (a responsive measure, taken after the biofilm has matured). Both routes have several challenges, as highlighted in Table 3.

Preventative Measures and Challenges. Preventative measures focus on interrupting biofilm growth and production well before the patient manifests symptoms of biofilm-related diseases. A perfect time to block the development of biofilms is interrupting the adhesion phase, thereby interfering with matrix formation. Inhibiting the ability of the microorganism to adhere *in vivo* or to inanimate surfaces offers a potential solution to the problem. This can be achieved by using a special surface coating (which is created by growing nano-daggers) to further prevent the adhesion of the microbial cells and decrease the chance of biofilm creation.[15] A key challenge in such strategies, however, is the resulting dead cell mass and debris; however, the nano-dagger method effectively controls for this by also inhibiting the ability for these masses to coagulate. Several additional options for decreasing bacterial adhesion are available (such as gold nanoparticle layer–phase transition lysozyme film coating, zwitterionic hydrogel coating, among others), however these techniques are increasingly complicated and may not be practical in many settings. These coating types (because they are created as a mixture of 2 coatings) may also be unable to retain their capabilities in the long run.[26] In the medical context, it is important to understand the complexity behind implanting different coatings in certain patients, as there is always a chance of immunologic rejection of the coating. Hence, more research also needs to be done prior to bringing novel coatings to clinical practice, as well as making them adaptable to a variety of environments (e.g., varying temperatures and pressures).

Another approach to inhibiting biofilms recognizes that the biofilm matrix depends on specific proteins for its structure and drug resistance. The Csg A and B proteins are crucial for forming the biofilm, while Lec A and B contribute to its resistance against drugs.[26] By disrupting the function of these proteins, it is possible to significantly delay the development of the biofilm. This is possible by using small-molecule inhibitors to block binding sites of Csg A and B in order to prevent

Table 3. Summary of the Challenges in Both the Prevention and Treatment Methods of Biofilms

Preventative	Treatment
Dead cell mass and debris coagulation can be caused by the methods used to destroy the biofilm	Antimicrobials have very limited efficacy in terms of curing biofilm-related infections due to resistance to treatment
Complexity of coating techniques may not make all treatments feasible for the general population	Antibiotic resistance further complicates the ability to cure matured biofilms
Long-term efficacy needs to be established for several methods	Photothermal therapy can risk other healthy cells owing to the high heat required
Immunologic rejection is a risk as coatings may be rejected by the patient's body	As with preventative measures, treatments also have immunologic risks
Interfering with bacterial metabolism is relatively novel and needs further development	Nanometers as a treatment is still in its infancy and needs further research

polymerization and assembly of biofilms. RNA interference can also be used effectively to reduce the expression levels of Lec A and B, thus diminishing their role in drug resistance.

Another route that can be taken to prevent biofilm formation is by interfering with the signaling between bacteria that is primarily implemented through the use of molecules termed *autoinducers*. Autoinducers allow for cell-density–dependent regulation of expression,[26] and the quorum sensing (QS) systems that facilitate bacterial communication hold the key to inhibiting bacterial communication, and therefore biofilm production. The QS system of bacteria, however, is complex to characterize, rendering this method of prevention less realistic to implement in patients in a timely fashion.

The final preventative measure to inhibit biofilm formation is through metabolic interference. Bacteria, in their basic form, are migratory organisms. Through altering the metabolism of bacteria, it is possible to make them lose this migratory capacity, and greatly reduce the chance of biofilm growth. It is currently hypothesized that the alteration of purine biosynthesis and wound-healing metabolic pathways[9] are leading to the growth of biofilms. However, similar to the aforementioned bacterial-signaling method, this method is also novel, and more research is needed to completely harness this approach.

Treatment Measures and Challenges. Treatment measures focus on tackling the biofilm after it has matured. The first strategy often used in response to biofilm production is the use of antimicrobials, although these often have minimal efficacy on decreasing biofilm-related diseases and infections because most biofilms are diagnosed at a late stage, when they are more developed and less likely to be affected by antibiotics. This has caused a rise in the study of antimicrobial peptides, which have been found to help curb the impact caused by antibiotic resistance. Bacteriophages (phages) are another alternative to antibiotics, because they are less disruptive to the patient's system, are more cost-effective, and more targeted. The invasion technique of phages allows for the structure of the biofilm to rapidly deteriorate, therefore allowing faster relief for the patient. This technique, however, is one of the latest efforts to combat biofilms and needs several additional clinical trials as well as a greater understanding of how the human immune system can react to phages (to avoid situations such as allergic reactions or other negative immunologic responses). Reactive oxygen species (ROS) are yet another strategy, as they cause peroxidation reactions that damage the nucleic acids, proteins, and structures that give the biofilm its properties.[15] Delivery methods for ROS include photodynamic therapy, where a photosensitizer generates ROS upon laser activation. Additionally, nano-enzymes like CoPt@graphene (G) @glucose oxidase (GOx) (CoPt@G@GOx) can produce ROS from glucose, targeting infections without relying on oxygen. These systems enable controlled release of ROS at the infection site, enhancing their antibacterial efficacy against biofilms.[15]

Photothermal therapy is another possible choice for biofilm treatment, where light irradiation is used to induce local hyperthermia. The purpose of doing so is to disrupt the nucleic acids and proteins of the biofilm to deactivate them, and ultimately sterilize them. The use of this method poses a challenge, as temperatures above 70°C are used, which can have a detrimental impact on other, healthy cells in the body. Another method by which the biofilm matrix can be destroyed is by using nanomotors, because they possess more motion and greater permeability. Thus, nanomotors can permeate the matrix and effectively allow for secondary drugs to penetrate the biofilm and attack the microbe within. While promising, this technique is still in need of more research to ensure safety.[27]

The final option for treatment is one of the most simple and easy to implement: probiotics. *Enterococcus faecium* and *Pediococcus pentosaceus* are examples of beneficial bacteria with properties that can affect biofilm production.[28] The incorporation of probiotics into a diet can be an effective, low-cost, and straightforward method to avoid the complications of biofilm accumulation. A study focusing on treating biofilms demonstrated that a combination of probiotics and amylase effectively disrupts biofilm structure. Specifically, the probiotic formulation, which includes

Bifidobacterium breve, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Saccharomyces boulardii*, and amylase significantly decreased *Candida* growth within 4 weeks of daily consumption. This suggests that such probiotic-enzyme combinations can be effective in managing gastrointestinal biofilms and improving overall gut health.[29] These methods of destroying the mature biofilm are summarized in Figure 4.

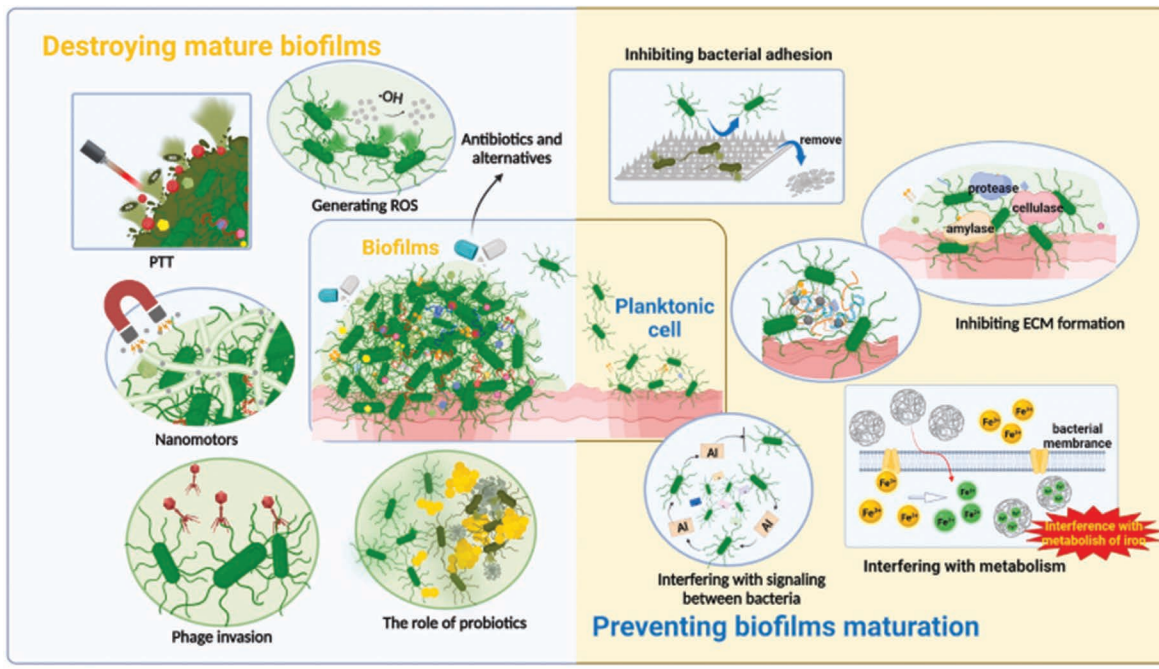
Diagnosis and Treatment Strategies for the Future

It currently remains very challenging to diagnose biofilm-related diseases and infections because they manifest as nonspecific symptoms in patients and there is currently no specific clinical protocol in practice to diagnose such conditions.[30] An example of a clinical case that highlights the complexities of dealing with the condition is presented in Figure 5. In general, a typical biofilm-related infection in a clinical setting presents as a chronic infection that worsens in intervals and that slightly alleviates after antibiotic therapy but does not completely resolve. Traditionally, biofilm growth can be detected through collecting a sample from the patient, performing microbial cultivation, and identifying antibiotic susceptibilities. The device suspected to cause the infection (such as a catheter) can also be removed and taken for further microbial testing.[31]

There are several published techniques detailing how biofilm-related diseases can be diagnosed; however, these methods are often laborious and not practical in the clinical setting. One of the more reliable techniques currently being studied is the use of biopsy to detect biofilm-related disease. This involves obtaining a sample from the patient and staining the sample to visualize the matrix along with other characteristics of the biofilm and immune response.[30] Biopsies are not always indicated in the clinical setting; in these situations, sonication is another promising technique that separates the biofilm (aggregated microbes) from the patient's surface implant and is analyzed.

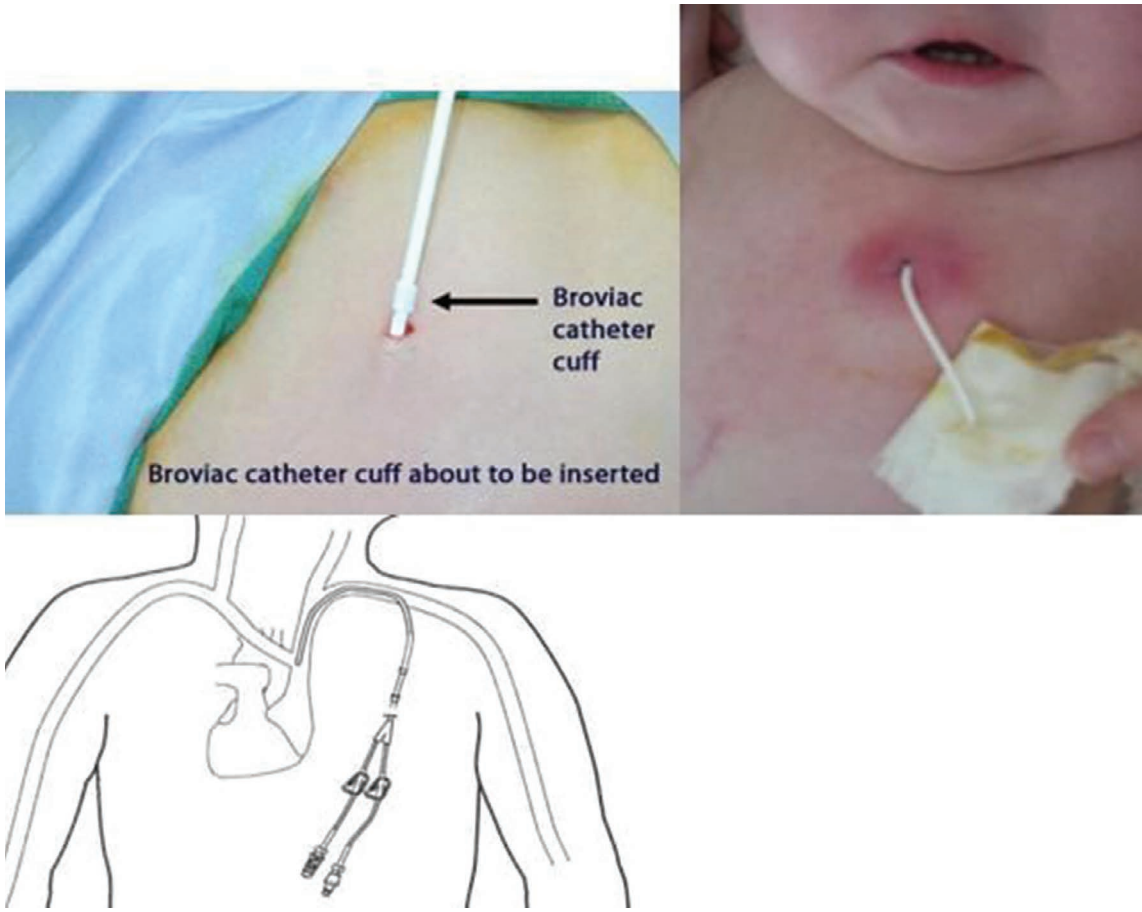
Several novel diagnostic strategies are also being developed, with crystal violet and *Drosophila melanogaster* being among the most promising because of their several advantages. Crystal violet is a low-cost, simple technique, with high reproducibility. It involves staining the entire structure of the biofilm and allows for a total assessment of its biomass. Because the entire structure is stained there is a loss of specificity; the need to also wash the biofilm after being deposited into the plate results in a loss of important biofilm

Figure 4. Schematic representation of reactive and preventative approaches to combating biofilm maturation. The preventative approach strategy focuses on stopping the development of biofilm at different stages of its growth. The reactive approach involves options such as antibiotics, nanomotors, phage invasion, probiotics, and ROS generation.[15]



ECM, extracellular matrix; PTT, photothermal therapy; ROS, reactive oxygen species.

Figure 5. The above is a clinical case published in 2005 in *Pediatric Infectious Diseases*[1]. This serves as a good example of the complexity of handling biofilm production, as it is not always feasible to remove the catheter. After 2 days of treatment, the patient became afebrile, and blood cultures at the end of the antifungal lock period were negative. Antifungal lock therapy with liposomal amphotericin B was initiated and continued for 2 weeks, along with systemic treatment for an additional week, resulting in sterile blood cultures and no signs of deep-seated mycosis. The findings suggest that when central venous catheter removal is not feasible, 8-hour daily antifungal lock therapy combined with systemic administration may be an effective treatment option for managing catheter-related infections[1].



components, highlighting the areas of improvement. *D melanogaster* offers *in vivo* biofilm detection, with high homologies between the *drosophila* and human genomes, is easy to work with, and is inexpensive to operate.[30] Overall, *D melanogaster* is used in biofilm detection by serving as a model organism for studying infections *in vivo*. Researchers have used this approach owing to challenges in mammalian studies, such as ethical approval. Studies have shown that *D melanogaster* can be orally infected with *Vibrio cholerae* to explore biofilm-related behaviors and host interactions. Techniques involve monitoring the effects of QS on the host's metabolic pathways during these infections, which have allowed researchers to gain deeper insights into the role of biofilms in disease progression.[30]

Treatment of a biofilm-associated infection or disease is mainly dependent on whether the biofilm growth is caused by an endogenous or exogenous factor. If a non-foreign body is the cause of infection or disease, high-dose antibiotics given over a long period can significantly reduce the problem. For exogenous causes, removal of the device causing the biofilm buildup will be the fastest and most effective solution.[31]

Conclusion

Looking ahead, it is important to understand that the complexity of treating biofilm-associated diseases can be significantly decreased by detecting the biofilm growth in its early stage. Today's medical technology in the context of biofilms works as a treatment rather

than preventive measure, and with further medical advances, biofilms can be tackled with a preventative focus. The ability to control biofilm growth at an early stage will increase the efficacy of medications (such as antibiotic treatment), will decrease the need to administer various treatments, and will invariably improve the patient's quality of life.

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JPPT | Invited Commentary

The New Wave of Blocking Taste

Hassan Almoazen, PhD

ABBREVIATIONS GPCRs, G protein-coupled receptors; P1, Adenosine receptors; P2, adenine nucleotide receptors

KEYWORDS bitter taste; purinergic taste signaling; taste inhibition; taste masking; taste receptors; taste suppression

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Taste is divided into 5 categories: sweet, bitter, sour, salty, and umami. The sweet taste usually detects carbohydrates such as sugars, the bitter taste is linked to a variety of compounds that have different properties and structures and many of them are toxic. The therapeutic compounds can be listed under this group. The sour taste is related to weak acids such as citric or acetic acids and other organic acids. The salty taste resembles the taste of sodium chloride, and the umami taste or (the savory taste) is linked to amino acids such as glutamate and aspartate which are available in meat, fish, cheese, and many vegetables.[1]

Taste sensation is evaluated by taste buds which are specific organs designed to distinguish taste, they are located within the tongue epithelium; it contains specialized cells which act as sensory receptors for different tastes. These cells are divided into types I, II and III. Type I cells are about half of the total number of cells in the taste buds, they have narrow and irregular shape nuclei, they contain enzymes and transporters that remove neurotransmitters and work on redistribution of the potassium ions associated with ion transport channels. Type II cells have a larger diameter than type I, have spherical nuclei, and act as a receptor for sweet (sugars), umami (amino acids) and bitter tastes. Type II cells are about one third of the total number of cells in the taste buds. These taste cells express taste receptors which are categorized as G protein-coupled receptors (GPCRs) which are named taste receptor type 1 or 2 (T1R1, T1R2, T1R3, T2Rs). T1R2 and T1R3 are receptors which respond to sweet and umami tastes. T2Rs belong to the GPCRs family and are receptors for bitter taste. Type III cells represent 2% to 20% of total cells in the taste buds. They respond to sour taste (weak acids, i.e., citric acid). Salty taste is detected by undefined taste buds.[2–7]

Purinergic signaling includes purine and pyrimidine receptors which were identified and cloned in the 1990s. There were 2 types identified: Adenosine receptors (P1) and adenine nucleotide receptors (P2). The adenosine receptors (P1) were classified into 4 subtypes (A_1, A_{2A}, A_{2B}, A_3). The P2 receptors were classified into 8 subtypes of G-coupled protein receptors ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$), and seven subtypes of cation ion channel receptors ($P2X_1$-$P2X_7$). P1 and P2 purinergic receptors are distributed in brain, kidney, heart, lung, and gut. They are implicated in epilepsy, vascular diseases, immune responses, gout and tumors. P2X2 and P2X3 are expressed in taste cells on the tongue. They are considered heteromultimer receptors and ATP major transmitters in the taste cells. In a study published in 2015, knockout mice of P2X2 and P2X3 lacked response to all taste stimuli. This was a direct implication to their involvement in taste stimulation (see figure 1).[8–15]

AF-353 (see Figure 2) is a novel P2X3 and P2X2/3 antagonist. Studies in rats reveled an oral bioavailability of 32.9% elimination half-life of 1.63 hours and 98.2%

Figure 1. Classification of purinergic receptors.

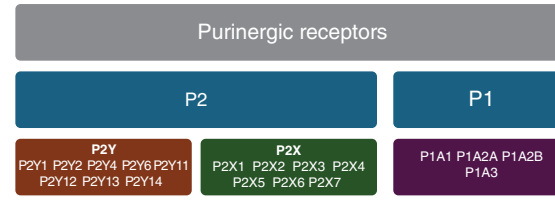
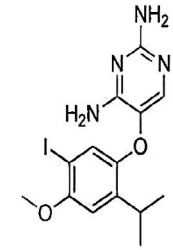


Figure 2. Chemical structure of AF-353.



5-(5-iodo-4-methoxy-2-propan-2-ylphenoxy)pyrimidine-2-4-diamine

plasma protein binding. The inhibitory potency estimate pIC50 for inhibiting human and rat P2X3 was 8.0 and human P2X2/3 was 7.3.[16,17]

Flammer et al[18] utilized AF-353 to evaluate its ability to inhibit all types of taste stimulants in mice and humans. For this purpose, the authors used 3 different concentrations of AF-353 (125, 250, and 500 μM) to block the taste of bitterness stimulant represented individually in quinine hydrochloride, 0.169 mM, sucrose octaacetate, 0.0632 mM, urea, 750 mM, praziquantel, 0.487 mM, and tenofovir alafenamide, 0.844 mM; sweetness taste stimulant represented in sodium saccharin, 2.1 mM, and sucrose, 450 mM; sourness taste stimulant represented in citric acid, 4.8 mM, and monopotassium glutamate, 600 mM); saltiness taste stimulant represented in sodium chloride, 150 mM, and astringency taste stimulant represented in citric acid in humans. The long-term objective as stated by Flammer et al[18] was "to develop a bitter blocker that suppresses bitterness as completely and rapidly as possible for a duration that would allow drug ingestion, but no longer than this." The experimental design was initiated by subjects rinsing their mouth with filtered water 4 times to remove any residues in their mouths. Thereafter, each subject placed 10 mL of individual taste stimulant solution in his/her mouth for 5 seconds then immediately expectorant. After that they recorded the intensity of each taste stimulant (sweet, sour, salty, bitter, and astringent) on a scale of 1 to 33. After 5 minutes from the stimulant study (time 0), subjects tried 10 mL of AF-353 solution or 10 mL vehicle as a control and swished for 30 seconds. They also repeated this for another 30 seconds. After 5 minutes, they tried the previous taste stimulant again and repeated the stimulant at 10, 15, 30, 60, and 90 minutes after the initial AF-353 treatment. Separately for the bitterness experimental design, they asked the human subjects to rinse with variable concentrations of AF-353 (125, 250, and 500 μm) for two 15 seconds, two 30 seconds rinses and two 60 seconds rinses over 60, 90, and 120 minutes to evaluate the degree of taste blocking. Results indicated that 15- and 30-second rinses of 125, 250, and 500 μm of AF-353 suppresses the taste of 0.169 mM of quinine hydrochloride QHCl and up to 50% recovery takes up to 90 minutes. The bitterness recovery was much slower for 30 seconds rinse with 500 μm of AF-353. Overall, they noticed a block of bitter, sweet, sour, salty, and astringency tastes and the recovery took about 90 to 120 minutes for full recovery. Flammer et al[18] provided a novel approach to block the taste of bitter drugs.

There are several challenges to the experimental design of Flammer et al.[18] Typically, when you block the taste of any drug, you provide the drug and taste suppressant in the same vehicle as it is not feasible to ask the patient to take the taste suppressant 5 minutes before taking the medication, plus if you use a taste suppressant that has the affinity to interact with specific receptors that can influence a pharmacological and physiological response in the body, you will have to make sure there is very limited absorption from the taste buds and the gastrointestinal tract which opens the door to multiple questions about the affinity of the taste suppressant and the actual drug with bitter taste toward the taste receptors. Which entity has stronger affinity to the taste receptors and for how long this affinity can last. The amount of the taste suppressant used and its bioavailability? In the Flammer et al[18] study, AF-353 has an efficacy that has lasted up to 90 and 120 minutes which is a very long time. It will not be acceptable to patients not being able to taste food nor drinks for up to 2 hours after taking the medication.

A good taste suppressant is the one that blocks the taste during taking the medication but does not last more than few minutes from the time of consuming the medication. This issue can be resolved by designing novel taste suppressants that have limited absorption from the oral cavity and gastrointestinal tract, strong or medium affinity toward binding to the taste receptors relatively to the drug itself and has quick removal from taste buds by saliva. Currently, taste masking is limited to either adding natural or artificial sweeting agents to overwhelm the taste receptors or by encapsulating the drug within a biodegradable polymer to prevent contact with the taste buds. The Flammer et al[18] study opens a new door toward the discovery of novel molecules for the purpose of taste masking by competitive inhibition of taste signaling.

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JPPT | Letter to the Editor

Do Postnatal Corticosteroids Negatively Impact the Neurodevelopmental Outcomes of Extremely Preterm Infants?

To the Editor—The study by David et al[1] assessed the impact of postnatal corticosteroids (PNC), used to treat hypotension or respiratory conditions, on neurodevelopmental outcomes at 20 months corrected age. The study concluded that prolonged, repeated exposure to dexamethasone (DEX) with or without hydrocortisone (HC) was associated with adverse cognitive, language, and motor outcomes at 20 months corrected age.[1]

The diagnosis and grading of bronchopulmonary dysplasia (BPD) are not defined. The authors state that the use of PNC was based on individual physician preferences. Did these factors lead to practice variation in the use of PNC? Why was HC used as the first-line drug to prevent BPD as it is not effective in significantly decreasing the risk of BPD.[2]

The infants who received PNC, compared with those who did not, were significantly more immature, with lower birthweight, and with more morbidities (BPD, retinopathy of prematurity, necrotizing enterocolitis, and home oxygen (see Table 1 in David et al.[1]). Why did the authors not match the subjects based on gestational age, birthweight, and severity of respiratory disease?

The initiation of DEX was at an average of 51.8 ± 28.7 days of life. Is this not beyond the postnatal window when PNC is useful to prevent BPD?[2] Infants who were treated with PNC had significantly higher rates of BPD compared with infants who were not treated with PNC (HC 83%, DEX ± HC 92% vs no PNC 43%; see Table 1 in David et al.[1]). Thus, in this study, PNC did not decrease BPD, and infants with BPD are at increased risk of neurodevelopmental impairment (NDI),[3] especially those who require protracted ventilatory support.[4] Thus, is it not likely that the DEX ± HC group consisted of infants with severe BPD, inherently placing them at higher baseline risk for adverse neurodevelopmental outcomes? Without adjusting for BPD severity or incorporating it as a mediator or moderator variable, the attribution of poorer outcomes solely to PNC exposure may be misleading.

Should the authors not follow the TRIPOD guidelines outlined by the EQUATOR Network,[5] which are the standard for transparent reporting of prediction model development and validation? For example, the multivariable model in their published Table 4[1] lacks model performance measures, which are essential for evaluating the validity of predictive models. The stability of the model estimate is uncertain given the small sample size and the number of covariates that were included. Furthermore, unmeasured confounders, such as genetic predispositions,[6] socioeconomic status,[7] and intraventricular hemorrhage Grades 1 to 2,[8] may also influence neurodevelopmental outcomes but are not accounted for in the analysis. In addition, is it not better to evaluate infants for diagnosing significant developmental delay using Bayley III at 21 to 24 months instead of at 18 to 20 months?[9]

The study by Melan et al[10] is a retrospective, single-center cohort study like the study by David et al,[1] but used betamethasone or HC to prevent BPD and found that there was an increased risk of NDI in the PNC-treated infants compared with those who were not (62.7% vs 38.1%, p = 0.0020). However, when the investigators did a multivariable analysis, the results showed that the risk factors for NDI were male sex (p = 0.027) and severe neonatal morbidity (p = 0.007) and not PNC.[10] Onland et al[11] found that higher cumulative doses of DEX administered after the first week of life decreased the risk of BPD without increased risk of NDI and that DEX started between 7 and 14 days decreased the risk of adverse Mental Development Index. Raghuveer et al[2] found that a medium cumulative dose (2–3 mg/kg) of DEX, administered for 14 days or more, significantly reduced BPD without increasing the risk of NDI. These studies contradict the conclusions of the David et al study.[1]

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AUTHOR RESPONSE: Thank you to Franco, Zackula, and Raghuveer for their thoughtful response to our article entitled, "Neurodevelopmental outcome at 20 months corrected age in extremely preterm infants after exposure to dexamethasone and hydrocortisone in the NICU."[1] We agree that the group subjected to dexamethasone was a "sicker" cohort, with lower gestational age, lower birthweight, and higher neonatal morbidities. As stated in our discussion, it is possible that the negative neurodevelopmental outcomes observed relate to these potential neonatal confounders or exposures. Regarding the timing of Bayley developmental testing, earlier testing may under-identify developmental delays; thus, it remains concerning that poorer outcomes were observed in this earlier follow-up period.[2] Similar to studies suggesting an increased risk of cerebral palsy with dexamethasone therapy,[3–5] providers during our study years were using higher doses of dexamethasone and longer durations of treatment as was historically traditional. More recently, there is growing evidence to suggest that a shorter course and lower doses of dexamethasone may lead to more favorable outcomes.[6] Since this time, our unit has similarly adopted the initial corticosteroid selection of dexamethasone with shorter courses and lower doses in treating early evolving bronchopulmonary dysplasia (BPD) (>7 days of age, <28 days of age).

With regard to the timing of treatment initiation, the subjects receiving dexamethasone were often treated for late-evolving BPD (>1-month postnatal age, <36-weeks postmenstrual age), contributing to the later age at initiation. Later courses of postnatal corticosteroids (PNC) are used to treat late-evolving BPD,[7] but current literature is limited with regard to guidance on treatment for this age group. Data from the National Institutes of Health's Prematurity and Respiratory Outcomes Program demonstrate that dexamethasone is primarily used in this population.[8] A single-center, retrospective study comparing dexamethasone, hydrocortisone, and methylprednisolone administration with the initial mean postnatal age of PNC administration of 27 days suggested that dexamethasone most effectively facilitates extubation[9]; however, lower doses and the duration of dexamethasone were again used in this study population. Data in treating late-evolving BPD remain limited, and we believe more studies are needed to appreciate the appropriate corticosteroid course for these infants. Given that dexamethasone, particularly at high doses and prolonged durations, may be harmful to the developing brain, we caution clinicians to weigh its benefits versus risks and use judicious management with regard to its dose, duration, and timing, especially in higher-risk patients with contracted or repeat courses of PNC.

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ANALYZING PEDIATRIC AND NEONATAL VANCOMYCIN DOSING AND MONITORING FOR INSTITUTIONAL GUIDELINE UPDATES. Marta Galagoza, Suzannah Kokotajlo, Christine Robinson. Atlantic Health System.

Introduction: Vancomycin dosing and monitoring in pediatrics and neonates have limitations, including therapeutic failures and lack of clinical data demonstrating vancomycin pharmacokinetic goals. Recent studies have shown that vancomycin dosing regimens for infants vary worldwide and that target antibiotic concentrations occur in only 25-41% of infants. The purpose of this study is to update the current institutional pediatric intravenous vancomycin guidelines and guide appropriate interval dosing for neonatal and adolescent populations.

Methods: This study was a retrospective chart review of patients admitted to the general pediatric floor, neonatal intensive care unit, and pediatric intensive care unit from January 1, 2023 to December 31, 2023, receiving intravenous vancomycin. The primary objective includes assessing the current empiric intravenous vancomycin ordering practice with respect to age ranges and to update the current institutional pediatric intravenous vancomycin guidelines.

Results: 150 patients were analyzed with 56% males, mean age of 7.4 years and weight of 29.8 kg. All patients had stable baseline serum creatinine with 50.7% admitted to the general pediatric floor, 40.7% in the pediatric intensive care unit, 6.7% in the neonatal intensive care unit and 2% from the pediatric emergency department. Vancomycin was indicated for the following infections: respiratory (27%), bloodstream (22%), meningitis/CNS (17%), fever/source unknown (16%) and skin/soft tissue (10%). Other indications include (history of MRSA, orbital cellulitis). The average days on vancomycin was 3.5 and 4.8 overall for those with susceptibilities favoring vancomycin, respectively 51% of cultures had growth but only 22% favored vancomycin use. On average, 1.5 troughs were drawn per patient with an average level of 14 mg/L. In patients greater than or equal to 13 years of age, 7 patients had supratherapeutic troughs (greater than 20 mg/L) with 71.4% of these troughs occurring while on every 6-hour dosing interval. A subgroup analysis conducted on the neonatal intensive care population determined that all patients received a 15 mg/kg dose with one incidence of a supratherapeutic trough. All dosing was correct as per NeoFax vancomycin dosing recommendations. No episodes of acute kidney injury while on intravenous vancomycin were found.

Conclusion: Vancomycin was commonly prescribed as 15 mg/kg weight-based dose every 6 hours on the pediatric unit. Based on patients greater than or equal to 13 years of age, a majority of supratherapeutic troughs occurred on a every 6 hours interval which may support initiating every 8-hour interval dosing regimens specifically in this population. All neonatal vancomycin dosing followed NeoFax recommendation. The future directions include presenting these results to the pediatric hospitalists, intensivists and infectious disease team to develop an age-appropriate vancomycin dosing guideline.

BRIDGING THE GAP: A NEEDS ASSESSMENT TO ENHANCE PEDIATRIC PRECEPTOR DEVELOPMENT. Pooja Shah, Danielle Alm. Ernest Mario School of Pharmacy at Rutgers, The State University of New Jersey.

Introduction: Recommendations for developing pediatric pharmacy competency within pharmacy schools are dispersed across various literature sources. Most recently, a joint statement on pediatric education at schools of pharmacy strongly recommends that each PharmD student complete at least one pediatric-focused advanced pharmacy preceptor experience (APPE). Previous studies have indicated that while 97% of pharmacy schools have offered APPE experiential, only one-fifth of students have completed them and only 61% of schools have a pediatric elective offered. Preceptor development topics specific to improve pediatric pharmacy education can strengthen the didactic or experiential learning experience and potentially enable preceptors to host and teach learners more effectively. To address the needs of pediatric pharmacists, the Pediatric Pharmacy Association (PPA)' academia Special Interest Group (SIG) conducted a needs assessment to inform the development of preceptor development opportunities. This survey was conducted to gain a better understanding of the needs of our pediatric pharmacist preceptors with regard to preceptor development opportunities.

Methods: In December 2024, an 8-question survey was distributed by email to all the PPA members.

Results: Fifty-six members responded to the needs assessment. Demographic data revealed that clinical preceptors comprised the largest group (64%, n=35), followed by full-time faculty (n=15). A significant majority (76%) had been in practice forever six years. A strong interest (75%) in attending professional development activities was expressed. Regarding learner types, 87% precept students, 85% precept PGY1 learners, and 58% precept PGY2 learners. The number of learners precepted varied considerably, with student learners ranging from 1-3 per rotation and 1-20 per year. Only two preceptors reported taking more than one PGY1 resident per year, and none took more than one PGY2 learner per rotation. Among the topics offered, the four most popular (selected by >50% of respondents) were "Innovations in teaching strategies," "Integration of technology in teaching,"

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"Pediatric research and publication guidance," and "Effective mentorship and student engagement."
Conclusions: Pediatric pharmacists are involved in educating learners experientially and are interested in preceptor development opportunities. The Academia Sig will use these results to host a series of topics for the PPA membership.

CHARACTERIZATION OF ANTITHROMBIN III USE IN INFANTS ON ECMO. Belyin Gutierrez Euceda, Caitlin Murtagh, Densley Perez. NewYork-Presbyterian Hospital.
Introduction: Extracorporeal membrane oxygenation (ECMO) is used to support infants with cardiac or respiratory failure. Heparin, an anticoagulant that potentiates the endogenous anticoagulant antithrombin III, is the anticoagulant of choice for ECMO due to low cost, short half-life, and reversibility. However, antithrombin III levels in infants are normally reduced due to an underdeveloped coagulation system leading to a diminished effect of heparin to provide adequate anticoagulation. Antithrombin III supplementation can increase the likelihood of attaining a therapeutic anti-Xa level. The current literature offers mixed results regarding the effect of antithrombin III on rates of thrombosis, bleeding, heparin dose, and therapeutic anti-Xa level attainment. The purpose of this study is to characterize the use of antithrombin III supplementation and determine its impact on heparin in infants on ECMO.
Methods: This was a single center retrospective cohort study evaluating the current prescribing practices of antithrombin III in infants (less than 1 year old) on ECMO between February 2020 and September 2024. Exclusion criteria included discontinuation of ECMO within24 hours of cannulation or dose of antithrombin III, heparin indication not anticoagulation, and antithrombin III given greater than 7 days after initial ECMO cannulation. The main outcomes were to evaluate incidence of antithrombin III usage, antithrombin III regimen used, change in heparin infusion rate (units/kg/hour) and antithrombin III level pre- and post-antithrombin III dose, and therapeutic anti-Xa level attainment. Other outcomes included survival and complications such as stroke, hemorrhage, and thrombosis.
Results: A total of 77 subjects were included in this study. Most subjects were less than 6months old with median weight of 3kg. Antithrombin III was given in 23 of the 77 subjects. Median baseline antithrombin III level in the non-antithrombin III and antithrombin III groups were 35% and 25%, respectively (p=0.06) with an increase in level seen in all patients who received antithrombin III. The median dose of antithrombin III was 200 units. The median heparin infusion rate pre- antithrombin III was 28 units/kg/hour and the maximum rate was 40units/kg/hour post-antithrombin III. A therapeutic anti-Xa level was achieved in 100% and 83.8% (p=0.051) in the antithrombin III and non-antithrombin III subjects, respectively. The most common complication was hemorrhagic in both groups with no significant differences in survival.
Conclusions: This study demonstrated that subjects that received antithrombin III had a lower baseline antithrombin III level. All subjects who received antithrombin III attained therapeutic anti-Xa levels while there was a portion of those who did not achieve therapeutic levels without antithrombin III. Regardless, subjects on antithrombin III required almost double the initial heparin rate to become therapeutic reflecting the difficulty in attaining therapeutic anti-Xa levels in this patient population.

EVALUATION OF DEXMEDETOMIDINE USE IN A TINY BABY UNIT (TBU) WITHIN A LEVEL IV NEONATAL INTENSIVE CARE UNIT (NICU). Jillian Garrett, Britany Walls, Madeline O'Bryan. Norton Children's Hospital
Introduction: Dexmedetomidine (DEX) use for pain and sedation has increased in the neonatal population over the past decade (1). Increased use is attributed to its preferable side effect profile and potential to decrease opioid and benzodiazepine requirements (2, 3). Benzodiazepine (BZD) use in neonates may be a risk factor for poor neurodevelopmental outcomes with neuronal apoptosis during brain development, which has not been shown with DEX use (4). Consequences of inadequate sedation and analgesia in this population include metabolic stress, altered pain response over time, and increased morbidity and mortality (5). However, few studies have described sedation requirements of very-low birthweight (VLBW) neonates with DEX (6). The aim of this study is to characterize the use of DEX in preterm infants with birth weight (BW) less than 1250 grams in a tiny baby unit (TBU).
Methods: This is a retrospective study of DEX use in a newly formed TBU within our Level IV NICU from April 1, 2024 to August 4, 2024. Patients were included if they were admitted to the TBU, initiated on DEX, and had a BW of less than 1250 grams. Variables of interest included NICU length of stay (censored at 9/30/24), duration of mechanical ventilation, unplanned extubation occurrences, length of DEX therapy, DEX dosing range, and concurrent use of opioids, benzodiazepines, inotropes, and/or need for clonidine. Descriptive statistics were used to characterize DEX use among included patients.
Results: During the study period, 25 patients of 43 total admissions to the TBU received DEX. The study group had a median (IQR) BW of 700 (549 to 795) grams and a median (IQR) gestational age of 25 (23.5 to 26.5) weeks. The median (IQR) NICU length of stay was 119 (75 to 160.5) days. All 25 patients required mechanical ventilation. Mortality occurred in four patients (16%). DEX was started on median (IQR) day of life seven (2 to 11) and the median (IQR) duration of therapy was 30 (8 to 48) days. Clonidine was required to aid weaning of DEX in 40% of the study group.
Conclusion: Over half of all patients admitted to our TBU received DEX therapy for sedation. Our median duration of DEX therapy is 30 days, which is longer than previous reports from other institutions (6). This increase in duration may contribute to the high rate of clonidine utilization for weaning DEX seen in our study population. All patients included in this study required mechanical ventilation. This is not believed to be directly related to the use of DEX, but rather an expected complication of early GA and ELBW infants.

EVALUATION OF INTRAVENOUS SODIUM FERRIC GLUCONATE ADMINISTRATION IN PEDIATRIC PATIENTS WITH IRONDEFICIENCY ANEMIA. Patricia Rodriguez, Michelle Perez, Rosemary Sampedro. Holtz Children's Hospital.
Introduction: Iron deficiency is one of the most common causes of anemia worldwide, frequently affecting hospitalized pediatric patients. Risk factors include decreased iron intake, malabsorption, and acute or chronic inflammatory states. Intravenous (IV) iron administration is recommended when oral supplementation has proven ineffective, suboptimal response is expected, or rapid hematologic response is required. There

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are several IV iron formulations available, however, limited pediatric experience and shortages affect product selection. Sodium ferric gluconate (SFGC) is approved for use in pediatric patients 6 years and older on hemodialysis. Data remains limited in younger and non-hemodialysis patients. The purpose of this evaluation was to assess the safety and efficacy of SFGC in pediatric patients with iron deficiency anemia (IDA) at Holtz Children's Hospital (HCH).

Methods: This study was a single-center, retrospective, chart review conducted from July 1, 2022 to September 30, 2024. Pediatric patients with IDA who received SFGC at HCH were included. Data was collected via electronic medical records and included patient demographics, iron studies, complete blood count, and dosing.

Results: Forty patients and 139 orders were included in this analysis. Patient's age ranged from 1 to 18 years (mean, 9 years) at the time of administration; thirteen were younger than 6 years (32.5%). Of the patients included, five were on hemodialysis (12.5%). The most common indication for SFGC administration was intestinal transplant (39.5%) and the most common prescribing service was gastrointestinal solid organ transplant (48.9%). Average dose was 1.5 mg/kg (range, 1 to 3 mg/kg); total cumulative dose average was 5 mg/kg (range, 1 to 22 mg/kg). Patients received an average of five doses. Pre and post infusion hemoglobin and mean corpuscular volume (MCV) was collected for 61 patients (44%) with an average change of 0.1 g/dL and 1.5 fL, respectively. Pre and post infusion change in serum iron and ferritin was collected for nine patients (6.4%) with an average change of 12.3 mcg/dL and 6 ng/mL, respectively. One anaphylactic event was documented in a 13-year-old, while no other adverse effects were observed throughout the study period.

Conclusion: Our results showed that administration of SFGC was well tolerated in pediatric patients with IDA. Additionally, our analysis revealed that the most frequent dosing strategy was weekly doses of 1.5 mg/kg. There was no significant change in hemoglobin or MCV after SFGC administration. Future studies are needed to determine optimal dosing and efficacy in non-hemodialysis pediatric patients with IDA.

EVALUATION OF NIRSEVIMAB ADMINISTRATION IN A CHILDREN'S HOSPITAL. Lauren Deck. SUNY Upstate Golisano Children's Hospital.

Introduction: Nirsevimab (Beyfortus) was released onto the US market in 2023 for the prevention of respiratory syncytial virus (RSV) in infants and children less than 24 months old. With the second season of RSV after nirsevimab introduction starting fall 2024 we wanted to characterize how frequently we will or could be immunizing infants less than 8 months old with nirsevimab while they are admitted at Upstate Golisano Children's Hospital.

Methods: Pediatric patients less than 8 months old admitted to Upstate Golisano Children's Hospital were reviewed and a chart note was placed if they qualified to receive nirsevimab administration during their hospital admission. As part of their normal clinical workflow, a pharmacist reviewed if nirsevimab was already administered previously or whether the infant's mother was appropriately administered Abrysvo during pregnancy by accessing the New York State Immunization Information System database and using Epic data. This study was a retrospective review of pharmacist interventions. All data was collected via REDCap without patient identifiers. Collected data included patient age, patient gestational age at birth, month of admission, reason for admission, respiratory panel results, previous nirsevimab administration, previous maternal Abrysvo administration, whether nirsevimab administration was recommended during hospital admission, and whether nirsevimab was administered during hospital admission. The primary outcome was the frequency of infants less than 8 months old whom it was recommended to receive nirsevimab during hospital admission. Secondary outcomes included percentage of those patients whom received nirsevimab during admission, trends by month of admission, frequency of previous nirsevimab administration prior to admission, frequency of maternal Abrysvo administration during pregnancy.

Results: Thus far 102 infants age less than 8 months were reviewed. Of those 102 infants, 54 infants (52.9%) qualified to receive nirsevimab during admission. Seventeen (31.5%) of those 54 infants received nirsevimab during admission. Trends by month of admission cannot be assessed at this time. Thirty-seven (36.3%) infants had already received nirsevimab prior to admission and 12 (11.8%) of infant mothers reported receiving the Abrysvo vaccine during pregnancy with 1 receiving Abrysvo too close to delivery to preclude the infant from receiving nirsevimab.

Conclusion: Thus far over 50% of infants less than 8 months old admitted to our hospital were eligible to receive nirsevimab during admission and over 30%of those patients went on to actually receive it prior to discharge. These outcomes support the continued need to keep nirsevimab on hand at our institution and additionally support pediatric pharmacist involvement in vaccinating children while admitted.

IVABRADINE USE FOR ARRYTHMIAS IN CHILDREN. Katy Stephens, Jamie Miller, Monica Le, David Foote, David Foote, Peter Johnson. Oklahoma Children's Hospital at OU Health

Introduction: Ivabradine is an inhibitor of hyperpolarization-activated cyclic nucleotide-gated channels (f-channels) in the sinoatrial node. It has a labeled indication for dilated cardiomyopathy in adults and children but has been used off-label for refractory arrhythmias. The purpose of this study is to identify the line of therapy that ivabradine is added for pediatric arrhythmias and evaluate dosing for this indication.

Methods: This descriptive, retrospective cohort study included patients aged 0-17 years admitted to a tertiary care academic children's hospital who received at least twenty-four hours of ivabradine between January 1, 2021 and November 30, 2023. Patients were excluded if they received ivabradine prior to admission or for any indication other than arrhythmia. Data collection included demographics, ivabradine dosing regimens, concomitant antiarrhythmic medications in the seven days prior to ivabradine initiation, concomitant medications with drug-drug interactions, and adverse events. The primary objective was identification of the line of therapy and type of arrythmia for which ivabradine was initiated. Secondary objectives included initial and peak median dose of ivabradine and concomitant drug interactions with a class C, D, or X, as well as evaluation of adverse events. Adverse events included bradycardia (defined as less than 100 beats/min in neonates and less than 50 beats/min in infants and children), prolonged QTc (defined as greater than 480 ms), significant QTc prolongation (defined as greater than 550ms), and incidence of emesis attributed to ivabradine as documented in the medical record. Descriptive statistics were performed for data analyses.

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Results: Seventeen patients were included. Most patients (64.7 percent) were less than one year of age. The types of arrythmias were atrial tachycardia(n=8), junctional ectopic tachycardia (n=4), ventricular tachycardia (n=4), and accelerated idioventricular rhythm (n=1). The majority (70.5 percent) were initiated on ivabradine as a third-, fourth- or, fifth-line anti-arrhythmic. Amiodarone was the most common concomitant antiarrhythmic (n=13). Ivabradine was initiated at a median dose of 0.051 mg/kg/dose, with a median peak dose of 0.07 mg/kg/dose; doses were most frequently administered every 12 hours (n=11; 64.7 percent). For adverse events, three patients (18.8 percent) experienced bradycardia, three (18.8 percent) experienced QTc prolongation, one (6.3 percent) experienced significant QTc prolongation, and two (11.8percent) had reported emesis. Only one patient required a dose decrease for their adverse event of bradycardia. For drug-drug interactions, almost all patients (n=16) had a Class C interaction, and three had a Class X interaction.
Conclusions: Ivabradine was initiated as a third-, fourth-, or fifth-line anti-arrhythmic. Ivabradine dosing was comparable to other published data for treatment of pediatric arrythmia. Most patients had at least one drug-drug interaction, while eight had reported adverse events with ivabradine. Overall, larger studies of ivabradine use in pediatric arrhythmias is needed.

MANAGEMENT OF PERSISTENT STAPHYLOCOCCUS AUREUS BACTEREMIA. Lauren Bull, Eva Wagner, Alisha Chesser, Avani Patel, Jessica Tansmore. Nationwide Children's Hospital
Introduction: Ideal management of Staphylococcus aureus bacteremia includes a regimen with the least number of narrow-spectrum antimicrobials for the shortest effective duration to help minimize adverse effects and resistance. Persistent S. aureus bacteremia definitions range from two to seven days of positive cultures. There are currently no formal national guidelines on the management of persistent S. aureus bacteremia. There is no standardized protocol for the management of persistent S. aureus bacteremia at our institution. The purpose of this medication use evaluation was to review antibiotic regimens for persistent S. aureus bacteremia and determine which regimen(s) allowed for quickest clearance after source control while minimizing adverse effects.
Methods: This was a retrospective chart review of patients admitted to our institution from06/01/2019 through 06/01/2024 with at least two positive S. aureus blood cultures on different calendar days during the same encounter. The date of first positive S. aureus blood culture, source of infection, date of source control, date of last positive blood culture, and total number of positive blood cultures were used to determine the time to clearance. The antibiotic regimens, including dose, route, frequency, and duration, were collected and compared to evaluate the regimen with fastest clearance. Safety of antimicrobial therapies was assessed through reported side effects, including acute kidney injury, myopathy, Clostridium difficile infection, peripheral neuropathy, white blood cell count, platelet count, and absolute neutrophil count.
Results: There were 20 unique patients with 21 incidences of bacteremia. The most common source was osteomyelitis. There were 16 incidences of methicillin-susceptible S. aureus bacteremia, and the average time to clearance was 5 days. There were 5 incidences of methicillin-resistant S. aureus bacteremia, and the average time to clearance was 6.6 days. The most common initial agent for methicillin-susceptible S. aureus was nafcillin, followed by cefazolin. Nine patients received an adjunct agent with daptomycin being the most common. Nine patients were transitioned to oral cephalexin. Vancomycin was the initial agent for methicillin-resistant S. aureus for all patients. Daptomycin was used as an adjunct agent in all 5 patients, and cefazoline was also used in 2 patients. Acute kidney injury occurred in 57% of bacteremia cases. The majority of patients receiving vancomycin developed an acute kidney injury. No patients were diagnosed with C. difficile infection.
Conclusions: There is variation in prescribing practices for persistent S. aureus bacteremia at our institution, including agent of choice, dose, frequency, second-line agents, and duration. A broader time-frame with more patients should be analyzed to determine which regimen is superior.

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PEDIATRIC HYPERHIDROSIS: DEMOGRAPHICS AND PRIMARY VS. SECONDARY TREATMENT CHARACTERIZATION. Chad Knoderer, David Cao, Shannon Ruiz, Joree Ruiz., Yvonne Chiu. Butler University College of Pharmacy and Health Sciences.
Introduction: Data on pediatric hyperhidrosis (HH) remain limited. This condition, marked by excessive sweating in one or more areas of the body, can lead to significant psychosocial challenges and social stigma. In severe cases, HH may profoundly disrupt daily life and activities. Oraland topical anticholinergics, aluminum chloride hexahydrate, and botulinum toxin are often used as treatment, but their optimal place in HH management remains unclear due to limited data. This study examines the demographics, initial treatment recommendations, and subsequent treatment adjustments at follow-up visits for pediatric patients with HH presenting to a dermatology clinic.
Methods: A retrospective chart review was performed of consecutive new patients </= 18 years with primary HH presenting to a HH clinic within a single tertiary care academic institution. Data extracted from the electronic medical records included age, sex, race/ethnicity, body mass index (BMI), family history, HH site, and HH disease severity scale (HDSS) score. Initial treatment recommendations, secondary treatment adjustments, and reasons for treatment change were also collected.
Results: Data from 264 patients, having a mean ± standard deviation of 13.8 ± 3.4 years (range: 6 months – 18 years), were included. Female (72.0%) and white patients (75.0%) predominated. Most common locations of HH were concurrent palmoplantar and axillary sweating (29.9%), palmoplantar only (21.6%), and focal axillary (19.7%). Generalized HH was noted in 56 patients (21.2%). Aluminum chloride hexahydrate solution (31.1%) and oral oxybutynin (35.6%) were the most common treatments at initial visit. Most common initial treatments for generalized were oxybutynin (57.1%) and glycopyrrolate (23.2%), while focal axillary sweating was initially treated with aluminum chloride solution (51.9%) and topical glycopyrronium (26.9%). Follow-up data were available in 158 (60%) patients. About half (n=80) continued their original therapy. Of the 91 patients who initially received oral medications, 61.5% (n=56) continued with oral treatment. Seventeen

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of the 57 (29.8%) patients initially started on topical therapies continued with topicals. In the 78 patients with a treatment change, the common reasons were due to side effects alone (42.9%), lack of improvement (31.2%), a combination of the two (13%), or patient preference/cost (11.7%). Changing between oral medications (n=20) was most often due to anticholinergic side effects (80%), followed by lack of improvement (20%).

Conclusion: Our retrospective study longitudinally characterizes a pediatric HH clinic and provides valuable information on common initial treatments and follow-up data, offering insights into primary pediatric HH management. Additional research, including the development of treatment algorithms, would be valuable.

REVIEW OF CORTICOSTEROID-INDUCED ADRENAL INSUFFICIENCY IN THE NEONATAL INTENSIVE CARE UNIT (NICU). Jennifer Barnes, Marissa Marks. Atrium Health Levine Children's Hospital

Introduction: Patients in the Neonatal Intensive Care Unit (NICU) receive corticosteroids for a variety of reasons. Prolonged exposure to corticosteroids may cause adrenal suppression, adrenocorticotropic hormone (ACTH) stimulation testing is the diagnostic gold standard. A guideline was recently developed in the NICU at Atrium Health Levine Children's Hospital (AH LCH) to identify patients at the highest risk of corticosteroid-induced adrenal insufficiency and to standardize its diagnosis and management. The purpose is to assess guideline adherence and describe the patients who received ACTH stimulation testing as a part of the corticosteroid-induced adrenal insufficiency guideline.

Methods: This a retrospective, observational, single-center evaluation. The study included infants who had received corticosteroids in the AH LCH NICU from December 1, 2022 to July 31, 2023.The primary objective is to assess the percentage of patients who received corticosteroids that qualified for an ACTH stimulation test based on the guideline. Further analysis was completed on those infants who received ACTH testing. Data collection includes cortisol levels at baseline and 30 and 60 minutes after the ACTH test and the percentage of patients that "pass" according to guideline. Secondary objectives include the duration of corticosteroids, inhaled corticosteroid use at the time of the ACTH test, time from the last corticosteroids to the ACTH test, percentage of cortisol levels timed correctly, route of administration of the ACTH test, hospital length of stay and percentage of patients who receive an endocrine consult/discharged on systemic corticosteroids with a "failed" ACTH test.

Results: During the study, 122 patients were on corticosteroids and 24% of patients received an ACTH stimulation test. Overall, 38 ACTH stimulation tests were administered to 29 patients. Adherence to the corticosteroid-induced adrenal insufficiency guideline for who should receive testing was very high at 94%. The average patient who received an ACTH stimulation test was gestation age 26 weeks and received approximately 27 days of corticosteroids. Only 66% of ACTH stimulation tests were passed at 30, 60 minutes, or both with approximately 80% of the levels timed correctly. Of the 9 patients who received a second and/or third ACTH stimulation test, approximately half of the patients subsequently passed. A lower percentage of patients who failed the ACTH stimulation test received an endocrine consult (~54%) and were discharged appropriately on corticosteroids (~31%).

Conclusion: Approximately a quarter of patients in the NICU that receive steroids qualify for ACTH stimulation test and many of those patients will demonstrate adrenal insufficiency. A guideline approach to adrenal insufficiency monitoring is needed for identifying, testing and providing follow-up for those high-risk patients. Our results showed opportunities for improvement within our NICU such as preference of IV over IM administration and closer collaboration with endocrinology upon discharge.

RETROSPECTIVE REVIEW OF TIME TO REACH THERAPEUTIC TACROLIMUS LEVELS IN HEART TRANSPLANT PATIENTS. Kayleigh Cress, Megan Lewis. Nationwide Children's Hospital.

Introduction: Tacrolimus is a key component in maintenance immunosuppression (IST) regimens following heart transplantation (HT). Typical starting doses range from 0.1 to 0.3 mg/kg/day divided twice daily. Blood concentrations are followed to ensure adequate dosing for the prevention of acute cellular rejection, to ensure graft survival and to avoid toxicities. Goal tacrolimus levels are typically between 10-15 ng/mL for the first year after HT. Tacrolimus blood concentrations are affected by age, renal function, enteral feed tolerance, and hepatic function. This purpose of this study is to evaluate the time it takes to reach therapeutic tacrolimus levels in the immediate post-operative period following HT as well as the average dose (mg/kg/day) that is required to reach therapeutic levels.

Methods: This study is a single-center, retrospective chart review including patients of all ages who received enteral tacrolimus after HT from January 1st, 2014 to July 31st, 2024. Patients were excluded if their tacrolimus goal differed from 10-15 ng/mL, they experienced death prior to initial HT discharge, did not receive tacrolimus as part of their IST regimen, or if tacrolimus was discontinued for adverse effects or inability to effectively administer. Tacrolimus doses and levels were collected for each post-operative day, and therapeutic levels were defined as two consecutive levels within goal range. Additional data collection included patient demographics, estimated renal function, and route of administration. This study received expedited IRB approval.

Results: 67 patients were evaluated, and 58 patients were included for data analysis. The mean age was 10.4 years (range 0.17 to 45 years) including 37 males (63.8%) and 40 white (69%) patients. The mean time to initiation was 6.1 days, and the mean initiation dose was 0.09mg/kg/day. The mean time to therapeutic levels was 28.1 days, and the mean therapeutic dose was 0.21 mg/kg/day. Demographic differences associated with higher dose requirements to achieve therapeutic levels included age less than 1 year (mean therapeutic dose 0.34 mg/kg/day), Black/African American (mean therapeutic dose 0.35 mg/kg/day), and patients receiving tacrolimus through a feeding tube (mean therapeutic dose 0.33 mg/kg/day).

Conclusions: Initial dosing of tacrolimus at our institution is on the lower end of the recommended dosing range which may contribute to longer time to therapeutic levels and increased risk of rejection. The majority of patients required 0.21 mg/kg/day to reach therapeutic goal levels, with higher dosing requirements in certain patient populations.

Scientific Research (Con't)

Scientific Research Awardee

ROMIPLOSTIM DOSING AND EFFECTIVENESS IN CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA. Julianne Fava. Kristen Curry, Cassandra Rush, Mara Crabtree. Nationwide Children's Hospital.

Introduction: Chemotherapy-induced thrombocytopenia (CIT) is a common toxicity secondary to pediatric cancer treatment. CIT can result in negative impacts on patients' overall treatment leading to chemotherapy delays, bleeding complications, increased platelet transfusions, and risk of relapse. To mitigate these risks, romiplostim is frequently prescribed to increase platelet production; however, optimal dosing strategies in pediatric oncology patients are not well-established. This single-center medication use evaluation aimed to describe the dosing strategy, efficacy, and safety of current prescribing practices of romiplostim for CIT.

Methods: This study was a medication use evaluation exempt from institutional review board review at Nationwide Children's Hospital (NCH). A retrospective electronic medical record review was conducted of patients under the age of 25 years if they received romiplostim from August 1, 2019 to July 31, 2024 for CIT. Patients who underwent bone marrow transplant prior to romiplostim, were prescribed an alternative thrombopoietin receptor agonist or rituximab during the study period, received oncologic treatment outside of NCH, or received romiplostim for a different indication were excluded. Collected outcomes include dose (initial, effective, and time between dose escalations), time to response (defined as platelets above treatment threshold), and reported adverse events. Data analysis was performed using descriptive statistics.

Results: There were 18 unique patients included with a total of 21 romiplostim courses. The majority of patients had Ewing's sarcoma, followed by rhabdomyosarcoma. The mean initial dose was 3.7 mcg/kg, and the mean effective dose was 5.7 mcg/kg. Patients had a mean of 2.3 dose escalations per course, with an average increase of 1.4 mcg/kg for each dose escalation. The mean time to response was 26.7 days. There was one adverse drug reaction reported of thrombocytosis that occurred at a dose of 3.2 mcg/kg.

Conclusion: Romiplostim appears safe and effective for CIT. With the time-critical nature of avoiding chemotherapy delays, romiplostim should be started at higher doses than is recommended for other indications. Providers can consider starting romiplostim at 5 mcg/kg and increasing weekly by 1-2 mcg/kg for pediatric CIT.

SOTALOL CONTINUOUS INFUSIONS IN CRITICALLY ILL NEONATES AND CHILDREN. Katy Stephens, Jamie Miller, Avery Parman, Ashley Benedict, Shashank Behere, Peter Johnson. Oklahoma Children's Hospital at OU Health

Introduction: Sotalol, a class III antiarrhythmic, works by non-selectively blocking beta-adrenergic receptors and potassium channels. In hemodynamically unstable patients, a continuous infusion may be preferred over intermittent intravenous (IV) sotalol to decrease the risk of hypotension and bradycardia. However, there is a paucity of literature regarding continuous infusion sotalol. The purpose of this study was to describe the use of intravenous sotalol continuous infusions in critically ill neonates and children.

Methods: This was a retrospective cohort study of patients less than 18 years admitted to a tertiary care academic medical center from January 1, 2018 to November 30, 2023 and received a sotalol continuous infusion for at least twelve hours. Data collection included demographics, type of arrhythmia, presence of congenital heart disease, sotalol dosing and duration, concomitant antiarrhythmics, concomitant drug interactions with class C, D, or X agents, and adverse events. The primary objective was to identify the median dose and duration of sotalol continuous infusions. Secondary objectives included identifying class C, D, or X drug interactions with sotalol and identifying any adverse effects associated with sotalol administration. For this study, adverse events included bradycardia (defined as less than 100 beats/min in neonates and less than 50 beats/min in infants and children), prolonged QTc (defined as greater than 480 ms), and significant QTc prolongation (defined as greater than 550 ms). Descriptive statistics were performed for data analyses.

Results: Seven patients were included. The age range for these patients was 0.33-192 months. Three patients had supraventricular tachycardia, and four patients had atrial tachycardia. Four patients had congenital heart disease. Sotalol was initiated as a second or third-line agent and five patients received a sotalol loading dose prior to the continuous infusion. The median initial dose was 71 mg/m^2/day and ranged from 22.8-85.2 mg/m^2/day. The median infusion duration was 135.9 hours and ranged from 25.3-2129.2 hours. Four patients had adverse events. Two patients required a dose reduction, one for bradycardia and prolonged QTc and the other for hypotension. One patient required the addition of vasopressors. All patients were on concomitant antiarrhythmics while on sotalol continuous infusions. All patients had at least two drug interactions, with a median of six interactions per patient.

Conclusions: Sotalol was initiated as a second- or third-line anti-arrhythmic. There was variability between patients for the dosing and duration of the sotalol continuous infusions. Adverse events and drug interactions were notable, with three patients requiring dose adjustments or other interventions for the adverse event, and all patients having documented drug interactions. Overall, larger studies evaluating intravenous continuous infusion sotalol in children and neonates is needed.

Category: Best Practice

CONTINUING PROFESSIONAL DEVELOPMENT SELF-REPORTING BY BOARD-CERTIFIED PEDIATRIC PHARMACY SPECIALISTS. Ellie LaNou, Kenja Hanniford, Brian Lawson. Board of Pharmacy Specialties.

Introduction: Board certified pediatric pharmacy specialists (BCPPS) meet eligibility criteria including education, licensure, and practice experience requirements. Through achieving a passing score on the certification examination, BCPPSs demonstrate advanced knowledge, skills, and experience necessary to optimize safety and outcomes for the pediatric patient population. BCPPSs design, implement, monitor, and modify pharmacotherapeutic treatments for pediatric patients. Maintaining competency through continuing professional development (CPD) is critical to BCPPS providing high quality patient care.

CPD can be defined as a commitment to life-long learning through a process of intentional reflection, planning, learning,

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evaluation, and application while recording and reviewing throughout the process. Among pharmacists outside of the United States and other healthcare professionals globally, CPD is employed for maintaining and/or enhancing professional competencies. The integration of CPD into the BPS recertification framework was announced in January 2023. In January 2024, the Board of Pharmacy Specialties (BPS) began integration of CPD into the recertification framework for board-certified pharmacists. This project aims to monitor the uptake of CPD by comparing the number of self-reported entries for BCPPS certifications to the number of self-reported entries for all eligible specialty certifications at the end of Q3 2024.

Methods: Through the MyBPS platform, board-certified pharmacists with certifications eligible for the CPD-recertification framework self-reported annual reflections/plan entries and CPD activities from various categories including: continuing pharmacy education (CPE) and CPD portfolios; academic, professional and interprofessional study; teaching and precepting learners; scholarly activities; workplace activities; and leadership and professional service. At the end of Q3 2024, activities within the BPS database were queried to quantify CPD uptake by specialty.

Results: At the end of Q3 2024, 8592 certifications across the 14 BPS specialty certification programs were eligible for the CPD-recertification framework, 415 of which were BCPPS certifications. Across all specialties, 4613 entries were self-reported at the end of Q3 2024, including 3153 CPD activities and 1460 annual reflection/plan entries. 211 total entries were self-reported for BCPPS certifications at the end of Q3 2024, including 140 CPD activities and 71 annual reflection/plan entries. 0.51 self-reported entries were made per eligible BCPPS certification at the end of Q3 2024 compared to 0.54 self-reported entries per eligible certification across all specialty certifications.

Conclusion: At the end of Q3 2024, the proportion of self-reported entries for BCPPS credentials was similar to the proportion of entries among all eligible specialty certifications. This finding indicates that BCPPSs are well positioned to make recertification progress within the updated CPD-recertification framework. BCPPSs may benefit from additional outreach and education on CPD for BPS recertification. BPS will continue monitoring the uptake of CPD.

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COMPARING THE SAFETY OF INTRAVENOUS KETOROLAC BEFORE AND AFTER THE IMPLEMENTATION OF ORDER OPTIMIZATION ON A GENERAL MEDICINE PEDIATRIC UNIT. Molly Brong, Christina Schwarz, Melanie Pena. Driscoll Health System - Rio Grande Valley

Introduction: Ketorolac is a nonsteroidal anti-inflammatory medication indicated for the short term (maximum 5 days) management of acute, moderately severe pain in adults. Ketorolac use has been associated with significant adverse reactions and carries boxed warnings including acute kidney injury (AKI), cardiovascular thrombotic events, and bleeding. Studies have demonstrated an analgesic ceiling effect associated with intravenous ketorolac. Doses higher than 15 mg have proven no significant difference in analgesia and a higher risk of adverse events. While not currently indicated for pediatric use, ketorolac is commonly utilized for pain management with a maximum recommended treatment duration of 72 hours.

Methods: This is a single center, retrospective chart review of the electronic medical record for patients admitted to the

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general pediatric unit who received intravenous ketorolac as part of their analgesia regimen. Changes were implemented within Driscoll Children's Hospital's computerized order entry system that included removal of a 30mg dose button and modification of the preset duration from 5 days to 48 hours. Patients were randomly selected from pre and post intervention cohorts. Data points were collected on patient demographics, number of administered doses greater than 15 mg, and incidence of AKI during or after treatment. AKI was defined per the KDIGO guidelines. This medication use evaluation was not determined to require institutional review board approval.

Results: A total of 77 patients that met inclusion criteria were followed. Thirty-eight patients from the pre-intervention group, and thirty-nine patients from the post-intervention group were randomly selected. Both groups had similar distribution for race and ethnicity. The mean age for both groups was 10.5 years and 9 years respectively. There was an even distribution of males to females in the pre-intervention group, and the post-intervention group was predominantly male (62%). In the pre-intervention group, 127 doses of ketorolac were administered with 37% of doses greater than 15 mg. This resulted in 42% of patients developing an AKI during treatment. In the post-intervention group, 120 doses were administered with 25% of doses greater than 15 mg. This change reduced the incidence of AKI to 21%. A chi-square test of independence was performed which revealed a statistically significant difference between both groups with number of doses greater than 15 mg, as well the incidence of AKI.

Conclusion: Implementation of order optimization in the CPOE system resulted in a 12% decrease in doses greater than 15 mg and a 21% decrease in AKI events. These results indicate that small optimizations made to order panels produce significant impacts on practices and patient safety. Prescribers should be educated on the risks associated with ketorolac and limitations placed on dosing. Further optimizations, such as a dose and duration hard stop may further improve patient safety.

ELEVATING PATIENT SAFETY BY IMPLEMENTING NEONATAL ELECTRONIC HEALTH RECORD (EHR) PHARMACY TOOLS AT SIX ADULT HOSPITALS. Colleen Djordjevich, R. Zachary Thompson, Jennifer Park, Rebecca Patton. Nationwide Children's Hospital

Introduction: Nationwide Children's Hospital (NCH) is a free standing pediatric academic medical center that manages seven neonatal intensive care units (NICU) across six delivery (host) hospitals. Each host leases NCH EHR to ensure consistency across the organization. Host pharmacy staff dispense first doses, intravenous fluids, and re-dispensed medications for NCH neonatal patients, but historically did not have access to NCH EHR. Neonatal doses require multiple manipulations to make measurable and administrable doses, creating high risk practices. Host staff utilized paper and manual manipulation to prepare doses for the NICU patients, which differed from host and NCH institutional standards for compounding. Leadership teams and front-line staff suspected events were going unrecognized due to the lack of standard safety precautions, primarily barcode scanning. The objective of the project sought to increase patient safety by implementing an EHR with pharmacy dispensing tools at the six host hospitals.

Methods: An evidenced based practice project was performed utilizing NCH's Project Management Office methodology (Image 1) and the interprofessional team was assembled. Using the model for improvement framework, this project followed the concepts of plan, do, study, and act (PDSA) when implementing the neonatal EHR in host pharmacies. Significant EHR build was completed and modified to meet the needs of host staff.

Previous information was not available to determine the number of medication events that occurred within the pharmacy. However, near miss data was followed longitudinally throughout the project to complete necessary quality improvement.

Each site required individualized planning due to institutional needs and the sites crossed three different health-systems (Table 1). This included assessing current state, integrating new workflows and technology into existing, training planning, and being available to support host staff. Training occurred via multiple modalities to meet the needs of host staff and ensure competency. The following flowchart was created to describe the project process and outputs (Image 2).

Results: Each site successfully implemented EHR safety tools to dispense neonatal doses. A total of 567 users were added to the system to ensure appropriate dispensing, all of which were non-NCH employees requiring customized build within identity software. Near miss information showed mis-scanned medications, compounding errors, and dispensing errors. This confirmed the core team's hypothesis of misses that could have previously reached patients with the previous paper workflows. Near misses decreased through the duration of the implementation across sites (Graph 1). Lesson's learned strategies were utilized and implemented before engaging the next site (Table 2).

Conclusion: Implementation of EHR safety tools lead to identification of near miss dispenses and resolution before reaching patients. Unique hospital and pharmacy models can be utilized to improve neonatal and pediatric care in adult hospitals. Future directions include EHR compliancy, annual training, and assessment of near misses.

IMPLEMENTATION AND MONITORING OF A PEDIATRIC PHARMACIST-LED AMINOGLYCOSIDE DOSING PROTOCOL. Leigh Ann Witherspoon, Lulu Jin, Steve Grapentine. UCSF Benioff Children's Hospital

Introduction: Aminoglycosides are narrow therapeutic index medications. When dosed and monitored suboptimally it increases the risk of clinical treatment failure and serious side effects such as ototoxicity and nephrotoxicity. Clinical pharmacists are best suited to manage aminoglycoside dosing and monitoring due to their extensive training and knowledge in pharmacotherapy. The goal of this quality improvement project was to implement aminoglycoside dosing prescribing authority and protocol in pediatric patients at Benioff Children's Hospital – San Francisco (BCH-SF). As part of this prescribing authority, for any pediatric patient elected to be in the protocol by the provider, the pharmacist can modify the initial aminoglycoside dose, order aminoglycoside levels, and adjust subsequent aminoglycoside dose based on levels and renal function. There are several outcome metrics measured as part of this project to ensure quality and safety of this pharmacist-led aminoglycoside dosing protocol.

Methods: In preparation for the implementation of aminoglycoside dosing prescribing authority and protocol in pediatric patients at BCH-SF, all inpatient pharmacists at BCH-SF were

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required to complete an online competency course. Upon completion of this course, all pharmacists had to pass a course exam with 100% accuracy. In addition, multiple in-services were provided to pharmacists at BCH-SF to review the protocol and example patient cases as well as addressing clinical questions and concerns. The metrics that have been continuously measured post-implementation include overall utilization rate of aminoglycoside per pharmacy protocol in pediatric patients at BCH-SF as providers may elect to opt out of the protocol and the overall aminoglycoside-associated acute kidney injury (AKI) events post-implementation compared to pre-implementation baseline. The latter metric is to ensure and maintain patient safety in utilization of this pharmacist-led dosing protocol.
Results: Following education, our pharmacist-led protocol was implemented in October 2024. Following implementation, our goal has been to maintain at least 50% protocol utilization. In October 2024 it was 100% and in November 2024 it was 95%. Our safety metric of acute kidney injury events was defined as a serum creatinine absolute value greater than 0.3 mg/dL or a 50% increase in serum creatinine from baseline in patients not on hemodialysis. In both October and November 2024 there were no AKI events documented. Further results will be submitted with the final poster.
Conclusions: With the preliminary results available, our organization has seen greater than 90% utilization of our pharmacist-led protocol without a change in AKI events in our patients. Additional conclusions will be submitted with final poster after further evaluation.

IMPLEMENTATION OF IV PRODUCT IMAGE CAPTURE IN A PEDIATRIC HOSPITAL. Sarah Scarpace, Vinnie Ortiz, Felicia Lee, Jennifer Ou. UCSF Benioff Children's Hospital
Introduction: Image capture implementation for sterile compounding has been associated with improved medication safety and decreased medication errors. We sought to implement this technology in a pediatric hospital to further improve medication safety. Our pediatric main inpatient pharmacy prepares and dispenses an average of 226 IV products daily and our chemotherapy satellite dispenses 28 IV products daily based on a 3-month average.
Methods: Prior to implementation we estimated the additional time added per day for both the main pharmacy (~5 hours) and chemotherapy satellite (0.5 hours) based on internal time studies of 1.1 minute/medication as well as reviewed the IV compounding workload by hour and added in an additional IV compounding technician resource during the busiest 4 hours of the day. Initial implementation included a training competency along with hands-on training for Hovercam in July 2024 for all technicians along with deployment of a superuser available on-site for the pharmacists along with additional ad hoc training as needed for enhanced comfort. On-site supervisory pharmacist and technician staff were also trained as additional superusers to be able to further support staff and provide basic troubleshooting after initial on-site trainers left. Initial challenges that were identified that were different and needed additional staff guidance and modifications included hood/computer placement, ergonomic screen arms, dilutions, standard mid-prep checks, and smaller syringe sizes necessitating different picture resolutions.
Results: We set the overall departmental goals initially at 50% image capture rate by 6-month of utilization and >95% to match the system goals by the end of the FY. We set initial goals in a phased approach with requesting technician staff to utilize the camera initially for 10 IV products compounded per month in July 2024 and increasing by 5 products monthly to an ultimate goal to utilize image capture for as many products as possible during a particular shift. We provided monthly feedback to the staff on progress of each of the work areas including our OR satellite, chemotherapy infusion satellite and main pharmacy. Starting in September 2024, we implemented limited mid-prep checks that were successful and saved time for technicians and pharmacists. We met our overall initial goals for 50% image capture rate within 4 months of initiation and are continuing to make monthly progress on track. Our OR satellite and chemotherapy satellite adopted image capture early on and have continued to have high compliance reaching 87.5% and 94.5% for November 2024 respectively. Our main pharmacy reached >50% image capture rate by November 2024.
Conclusions: Overall, our innovative approach including appropriate resources, training and support, phased implementation, limited mid-prechecks along with monthly process feedback along allowed us to successfully implement image capture of pediatric IV preparations.

IMPROVING PEDIATRIC OPIOID SAFETY THROUGH ENHANCED PATIENT EDUCATION. Alina Forin, Caitlin Aberle, Lydia Hart, Jael Kemp-Powell, Kristina Melchert, Mary Tomlinson. Maria Fareri Children's Hospital, Westchester Medical Center Health Network
Introduction: Pediatric patients discharged from the hospital postoperatively often receive prescriptions for oral liquid opioids for pain management. Caregivers are responsible for administering the correct dosage using syringes, but without proper education, dosing errors can result in serious adverse effects including opioid overdose. The primary goal of this initiative was to develop standardized best practices for prescribing, dispensing, documenting and educating caregivers on liquid opioid administration to ensure safer discharge practices and prevent opioid overdose in pediatric patients. The project also aimed to improve EHR documentation of opioid-related education and ensure consistent counseling through a collaboration with outpatient pharmacy. Furthermore, the project sought to evaluate the effectiveness of incorporating a teaching method that uses return demonstration to verify caregiver comprehension and adherence.
Methods: The project began in July 2022 and concluded in December 2023. A multidisciplinary team created a comprehensive, standardized process for pediatric opioid discharge, focusing on caregiver education regarding safe liquid opioid administration, storage, overdose recognition, and disposal. Nursing staff were trained to educate caregivers on the critical aspects of opioid safety. Caregivers were asked to verbalize and demonstrate their understanding, which was then documented by nurses in the EHR. Retrospective chart audits were conducted to assess compliance with opioid discharge education, counseling, and documentation. Key metrics included: Opioid Discharge Education Enhancement, Discharge Counseling Provided by outpatient pharmacy, and Enhanced Documentation of Opioid Discharge Counseling in the EHR. Any nonconformities were addressed through collaboration with clinical leadership.
Results: At the start of the project, compliance rates were 10% for Opioid Discharge Education Enhancement, 10% for

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Discharge Counseling Provided by outpatient pharmacy, and 0% for Enhanced Documentation of Opioid Discharge Counseling in the EHR. By December 2022, 100% compliance was achieved for both Opioid Discharge Education Enhancement and Discharge Counseling Provided by outpatient pharmacy. Compliance for Enhanced Documentation of Opioid Discharge Counseling in the EHR increased to 90% by the end of December 2023. There were no opioid overdose events reported after project implementation which supports that return demonstration significantly improved caregiver understanding and adherence.

Conclusion: Standardizing discharge practices for opioid prescribing, caregiver education, and EHR documentation led to improved compliance and caregiver comprehension. The success of this initiative highlights the importance of continuous training for clinical staff and caregivers to sustain best practices in pediatric opioid stewardship. Replication of this approach in other institutions is feasible, offering a model for improving safety and reducing opioid-related risks in pediatric patients.

INNOVATIVE APPROACH TO IMPLEMENTATION OF AUTOMATED MEDICATION TRACKING MECHANISMS TO IMPROVE LOCATING MEDICATIONS IN A PEDIATRIC HOSPITAL. Sarah Scarpace Lucas, Jennifer Ou, Leigh Ann Witherspoon, Lulu Jin, Vinnie Ortiz, Felicia Lee. UCSF Benioff Children's Hospital.

Introduction: We sought to decrease the number of missing medications requiring redispensing through the implementation of automated dispense tracking and dispense receiving on the inpatient units. Prior to implementation of automated tracking, we identified a baseline percentage of 11.53% (15.3K redispenses annually) from the previous 2 years of missing medication requests from the inpatient pharmacy. The overall goal of an automated tracking and receiving system was to further identify and assist nursing to identify the correct location of medications and ultimately to improve the patient experience through a greater number of medications being available for administration.

Methods: We implemented an electronic dispense tracking process in October 2023 to assist in improving the tracking of medications when they physically left the inpatient pharmacy. We implemented a dispense receiving process in the medication rooms by pharmacy personnel in January2024 and further refinement to location tracking in June 2024 to further identify where medications leaving the pharmacy were placed upon delivery. We set goals for overall dispense tracking and dispense receiving at >95% to match our system goals. Initially dispense receiving location tracking was not standardized leading to suboptimal receiving results. Starting in June 2024, we developed and implemented barcodes for all areas where medications could be delivered including Refrigerator, Cassette, Fluid Bin, Hazardous Bin and Oversized Bin. These codes were further refined with the addition of Refrigerated Chemo Bin based on staff feedback. To identify scanning compliance challenges, we completed weekly data review and developed additional filters for discontinued products as well as if medications were sent in a different manner due to patient transfers.

Results: We provided monthly feedback on scanning compliance of medications that are scanned to the correct locations, entered manually, scanned to the medication room only and not scanned. In addition, we specifically provided feedback to delivery technicians demonstrating the importance of utilizing the location barcodes for tracking for further nursing location clarity and to avoid manual entries with a goal of <3% that was achieved by mid-August 2024. Dispense tracking and receiving allowed for a reduction in the number of medications being redispensed by 2.04% to 9.49% (12K redispenses annually) demonstrating utility of the automated tracking mechanism.

Conclusions: Overall, our innovative approach including barcoding, continued data analysis and monthly and individual staff feedback allowed our dispense tracking and receiving implementation to be successful. This automated tracking mechanisms decreased the number of pediatric medications that were requested by nursing to be remade decreased overall pharmacy workload and improving the number of medications available for patient administration.

PEDIATRIC MEDICATION SAFETY IMPROVEMENTS THROUGH PHARMACY TRACKING MECHANISMS. Kimery Leong, Sarah Scarpace Lucas. Terrie Abel, Donna Pang. UCSF Benioff Children's Hospital Oakland

Introduction: The implementation of automated pharmacy scanning tools has been demonstrated to assist in decreasing medication errors in an inpatient pharmacy setting. Our inpatient pharmacy services approximately 200 pediatric beds, dispensing about 750 medication doses daily, where 15% are filled through ADC, 25% through robotics and 60% through traditional manual fills. We wanted to further augment the automated dispense preparation and checking mechanisms initiated earlier through improvements in these functions, as well as adding in both dispense tracking in the pharmacy and on the patient, care floors to improve medication safety. A secondary benefit would be a decrease of redispenses through fewer missing medication requests.

Methods: We set goals for Dispense Prep, Check, and Tracking at 95% or greater, based on our overall pharmacy system goals. We reviewed initial baseline data from January to July 2024 and identified we were at target for Dispense Prep (97.1%), below target for Dispense Check (92.8%) and hadn't started any Dispense Tracking elements. The baseline redispense rate was 15.53% (21K redispenses). Tactics used included staff in-services on process change, educational flyers, staff meeting communications on goals and progress, regular staff updates on progress at morning and afternoon huddles and feedback sessions. Pharmacy Tracking elements were initiated in multiple phases over a 4-month period. Phase 1: Inpatient Dispense Tracking started in August 2024 with first and missing doses, achieving roughly 35% compliance in the first month. Phase 2: Addition of tracking of non-IV manual pull batches and IV batches in October 2024. The Dispense Tracking rate increased to about 70%. Phase 3: Added Dispense Tracking of robotic fills for cassettes in November 2024. One barrier to Dispense Tracking doses from the robot was that no EMR associated barcode printed with each dose. Successful tracking of the cassette medications required the development of a report including order barcodes. Also, equipment was purchased to facilitate barcode scanning.

Results: Dispense tracking rates continued to increase with each implementation phase with dispense tracking occurring for 90% of dispensed inpatient doses four months after implementation. The Dispense Prep, Check, and Track processes are the first 3 steps in the 4-step process of tracking where

Best Practice (Con't)

a dose is in the filling process. Dispense Track allows for visibility as to when and how a dose left the pharmacy. The fourth and final step will be to use a mobile device application to track where a dose is located after leaving the pharmacy.
Conclusion: Overall, our phased approach for implementation of the Dispense Tracking process was successful for utilizing a pharmacy tracking mechanism in a pediatric inpatient pharmacy. We will be assessing rates of redispenses, as well.

Best Practice Awardee

PHARMACIST INTEGRATION INTO PRIMARY CARE CLINIC FOR CHILDREN WITH MEDICAL COMPLEXITY. Billie Mitchell, Erica Shepperd-Debnam, Samuel Anti, Nicola Brodie, Kathryn Detwiler. Children's National Medical Center
Introduction: Children with medical complexity (CMC) comprise a vulnerable patient population. CMC are defined as children with multiple chronic health conditions which affect multiple organ systems and result in extremely high health care utilization, as well as a reliance on medical technology. These children comprise about one percent of the pediatric population, but account for about one third of all pediatric health care spending, and this number is projected to increase over time. CMC rely on medications to treat a variety of disease states and maintain quality of life. This puts this population at risk of polypharmacy and adverse drug events. Existing healthcare models do not easily meet the needs of CMC. Studies have found that pharmacy involvement in caring for CMC has identified drug therapy problems and discrepancies in medication reconciliations. To reduce these risks, The Transitions of Care pharmacy team at Children's National Hospital has worked to integrate into the Complex Care Program (CCP), a primary care medical home for CMC within our health system.
Methods: In January 2024, pharmacists on the Transitions of Care team at Children's National Hospital began integration into the Complex Care Clinic. A standard operating procedure was developed at the initiation of pharmacy involvement and is continuously reviewed and updated. Pharmacists are present in the clinic 2 days per week to meet with families. They perform medication histories and reconciliation, create daily medication schedules, and intervene on drug therapy problems as identified. Interventions were documented in Sentri 7 (r) Clinical Surveillance platform, and data was obtained from the same platform.
Results: From April 22, 2024 to October 18, 2024, the team was present in the CCP clinic 2days per week. In this time, we completed 272 medication histories, created 117 Medication Action Plans, and documented 166 additional interventions. 49% of medication histories required changes. Of the 166 additional interventions, the most common were: outpatient medication coordination (39%); medication counseling sessions (20%); providing drug information (19%); and optimizing medication regimens (10%). Soft costs saved over the 6months totaled to $111,894.
Conclusion: Pharmacists cared for 242 unique patients during the study period and their presence has been well received by the interdisciplinary team. Pharmacist interventions such as resolving medication access problems and optimizing medication regimens also led to cost savings Limitations to our services include an inability to follow up with patients after appointments, a presence in clinic < 50% of the time, and not having current involvement in Telehealth visits. We also are not able to compare our metrics to data from prior to pharmacist integration. Moving forward, our team hopes to start integrating into Telehealth services to reach a larger patient population and allow for follow-up between visits.

Category: Scholarship in Teaching

EVALUATION OF STUDENT COMFORT WITH GENDER-AFFIRMING THERAPY IN A PEDIATRIC PHARMACOTHERAPY ELECTIVE. Caroline Sierra. Marina Garner, Jessa Koch. Loma Linda University School of Pharmacy
Introduction: Gender-affirming therapy (GAT) is an emerging topic in pharmacy education and particularly in pediatric patients, who present unique social, legal, and ethical challenges. The purpose of this study is to evaluate student pharmacists' comfort in communicating with and counseling patients who identify as transgender or are receiving GAT before and after a course session focused on GAT in the pediatric population.
Methods: Faculty from Loma Linda University's Schools of Pharmacy and Religion collaborated to design a class session on GAT in pediatric patients within an Advanced Pediatric Pharmacotherapy elective. Topics discussed included gender affirmation, moral distress, gender-affirming hormone therapy, and pubertal blockers. Patient cases addressed ethical issues in dispensing medications for GAT to pediatric patients, potential challenges communicating with caregivers, and benefits of and challenges with different therapeutic options for a given patient. Student pharmacists were surveyed regarding their experiences with patients who identify as transgender or are receiving GAT before and after the class session.
Results: Seventeen students participated in the class session. Out of 9 students who stated they had cared for a patient who identified as transgender, seven (41%) cared for a patient who identified as transgender at work and two (12%) on an Introductory Pharmacy Practice Experience. Most students somewhat or strongly agreed it is their responsibility as a pharmacist to dispense GAT to adult patients (n=16, 94%) and pediatric patients (n=14, 76%). There was no significant difference in students' comfort approaching and speaking to patients who identify as transgender (p=0.40) or counseling on GAT in adult (p=0.12) or pediatric (p=0.30) patients after the class session, though more students strongly agreed they were comfortable in each of these areas after the class session (38% vs 18%, 38% vs 18%, and 31% vs 18%, respectively). Most students agreed or strongly agreed that discussing GAT in pediatric patients was valuable (n=15, 94%) and supported including education on GAT for all student pharmacists (n=14, 88%).
Conclusions: A dedicated class session improved student pharmacists' comfort with counseling patients on GAT and was valuable to the students. Education on GAT should be considered for all student pharmacists.

PRE-POST QUALITATIVE/QUANTITATIVE ASSESSMENT OF A PEDIATRIC COMMUNICATION ASSIGNMENT WITH LIVE CHILDREN. Madison Zelan, Jacob Kelley, Allison Chung. Auburn University Harrison College of Pharmacy
Introduction: Pharmacy students need effective communication skills not only for interacting with adult patients but also with pediatric patients. Children have unique healthcare needs, and their ability to understand medical concepts can be limited by age and developmental stage. Pharmacists must

Scholarship in Teaching (Con't)

learn to communicate in a way that is simple, empathetic, and appropriate for a child's level of understanding. While pharmacy schools focus extensively on communication with adults, the emphasis on pediatric communication is often limited, leaving students less prepared in pediatric settings. This study explores whether a role-play assignment with live children can help increase pharmacy students' confidence in interacting with pediatric patients.

Methods: This qualitative and quantitative analysis assessed a pre/post-survey on a pediatric communication assignment in the Introduction to Pediatrics elective course at the Harrison College of Pharmacy over three years. P2 students counseled pediatric "patients" on their medications, using four case scenarios for different age groups: 3-5, 6-10, 10-14, and 14-18 years. Students had at least two weeks to prepare and were required to find their own pediatric patients, with faculty assistance available. The pre-survey assessed students' comfort and experience communicating with children, and the post-survey allowed reflection on their experiences after completing the assignment. Surveys, administered via Qualtrics, collected both quantitative data (confidence and comfort levels) and qualitative data (expectations, challenges, feedback). Both surveys were anonymous. Inductive thematic analysis was used to analyze open-ended survey responses.

Results: Seventy P2 students (80% aged 20-25) participated in the assignment, most of whom reported baseline comfort as "somewhat comfortable" (51.45%). The pre-survey revealed that 58.57% were only "somewhat confident" in communicating with children, with 4.29% "not confident." The primary concern was explaining medical topics in ways children could understand. The post-survey showed increased confidence, with confidence rising with patient age: 14.49% for 3-5-year-olds, 31.88% for 6-10-year-olds, 55.22% for 10-14-year-olds, and 71.64% for 14-18-year-olds. Ninety-three percent of students found the assignment useful, and 67.7% and 16.9% somewhat or strongly agreed that the activity helped them address challenges in pediatric communication. Four themes emerged from the open-ended responses: 1) commitment to caring for children, 2) developmentally appropriate language, 3) building relationships based on trust, and 4) moments of tension and growth.

Conclusions: Providing pharmacy students with role-play assignments involving live children increases their comfort with pediatric communication and helps them overcome challenges like explaining medical concepts to children. These experiences build their skills and confidence, better preparing them to engage with pediatric patients in clinical settings.

Category: Case Reports

CASE SERIES: MANAGING SEVERE ASTHMA WITH INCREASED FREQUENCY OF BENRALIZUMAB ADMINISTRATION IN THREE ADOLESCENT PATIENTS. Stephanie Duehlmeyer, Celtina Reinert. Children's Mercy Kansas City

Introduction: Benralizumab (BEN) is an interleukin-5 receptor monoclonal antibody indicated for the add-on maintenance treatment of individuals with severe asthma (IwSA) with an eosinophilic phenotype. The dosing for people 12 years and older is 30mg subcutaneously (SC) every 4 weeks for 3 doses then 30mg SC every 8 weeks thereafter. This case series describes the clinical journey of three patients who required more frequent dosing to maintain asthma control.

Methods: A retrospective chart review of IwSA prescribed BEN within the pulmonary clinic at Children's Mercy Kansas City was completed. Individuals whose BEN dosing interval was changed to a maintenance frequency less than every 8 weeks were included. Hospitalization frequency, emergency department (ED) visits, oral corticosteroid (OCS) prescriptions, and relevant laboratory values were examined before and after BEN dose frequency changes.

Results: Three IwSA were included, of whom 67% were female, 100% African American, and the mean age was 14.5 years. All individuals changed BEN dosing frequency, after an average of 5.3 months, due to inadequate control of asthma symptoms and were transitioned to every 7-week dosing as an initial step in maintaining asthma control. When asthma control remained inadequate, two individuals shifted to an every 6-week frequency. One IwSA switched to tezepelumab (TEZ) after 34 months on every 6-week BEN and remains on TEZ presently. The other individual remained on every 6-week BEN for 38 months and continues on this regimen presently. The third individual switched to a 4-week dosing regimen for 32months, briefly trialed a single dose of dupilumab but developed urticaria, and subsequently returned to BEN, continuing this therapy presently. IwSA had an average of 7.4 OCS courses, 3.1 ED visits, and 1.6 hospitalizations between dosing frequency changes. The average baseline blood eosinophil count (BEC) was 910 cells/μL. No one had repeat BEC prior to a dosing frequency change. Following the initiation of BEN, all individuals had a repeat BEC of 0 cells/μL, measured at an average of 37 months after starting treatment. No increase of adverse reactions was noted with increased dosing frequency of BEN during the study period.

Conclusions: While 8-week maintenance dosing of BEN proved effective in clinical trials, real-world experience indicates that some IwSA need more frequent dosing to maintain asthma control. For IwSA who remain inadequately controlled with standard dosing of BEN, shortening the dosing interval maybe a beneficial option, particularly for those unable to switch biologics due to intolerance of other agents or insurance barriers.

HIGH DOSE INSULIN EUGLYCEMIC THERAPY FOR MANAGEMENT OF CALCIUM CHANNEL BLOCKER TOXICITY IN CRITICALLY ILL PEDIATRIC PATIENTS: A CASE SERIES. Lauren Steil, Jessica Anderson, Meredith Jenkins. Monroe Carell Jr. Children's Hospital at Vanderbilt.

Introduction: Calcium channel blockers (CCBs) have a high affinity for plasma proteins, high hepatic first pass metabolism, and a large volume of distribution and therefore are not effectively removed by hemodialysis or hemofiltration. CCBs block calcium channels not only in myocytes, but also within beta cells of the pancreas, and in overdose cause insulin resistance, profound hyperglycemia, and transition of cardiac energy source from glucose to free fatty acids. Therefore, current treatment recommendations include high dose insulin euglycemic therapy (HIET). Data on the use of HIET for pediatric CCB overdose is limited to case reports, but the Pediatric Expert Consensus group recommends a dosing range of 1 to 10units per kilogram per hour continued until hemodynamic stability is achieved. The purpose of this case series is to describe utilization of HIET within a single pediatric intensive care unit, identify areas for standardization and assess clinical outcomes associated with HIET therapy.

Case Reports (Con't)

Methods: This is an IRB approved, single center, observational, retrospective case series of patients less than 18 years old admitted to the pediatric intensive care unit from January 1, 2020 to December 31, 2023 for the treatment of CCB toxicity managed with HIET. Data collected includes patient demographics, insulin titration regimens, insulin doses and infusion duration, dextrose dosing, and adverse effects.
Results: Four patients with calcium channel blocker toxicity were treated with HIET. The average age was 14.5 years (range 14-15). All ingestions were intentional with amlodipine involved in 3 cases. Three patients were receiving vasopressors at the initiation of HIET and none of the patients were titrated off vasopressors while on insulin therapy. Overall decrease in Vasoactive-Inotropic Score while on insulin therapy was not observed. Median fluid balance on day 1 of treatment was positive 6.2 liters. Three patients required extracorporeal membrane oxygenation (ECMO) and 2 required continuous renal replacement therapy (CRRT). The median insulin dose was 3.46 units/kg/hour (range 0.71-8.53) and the median maximum dose was 4.56 units/kg/hour (range 1.5-10). The median maximum glucose infusion rate of dextrose containing fluids was 8.2 mg/kg/minute (0.49 g/kg/hour). The median duration of insulin infusion was 42.4 hours (range 12.2-65.2). Three patients survived to hospitals discharge. Only two patients experienced hypoglycemia (defined as <70 mg/dL) requiring treatment and all patients experienced hypokalemia (defined as <3.0 mEq/L) that required treatment during insulin therapy.
Conclusions: In 4 patients with CCB treated with HIET, 1 patient did not make a recovery and survive to discharge. There was a wide range of insulin infusion doses utilized across patients, emphasizing the need for standardization. The most common adverse event experienced was hypokalemia, followed by hypoglycemia.

PTSD MASKING NEUROCYSTICERCOSIS IN 14-YEAR-OLD REFUGEE WITH EPILEPSY. Evan Horton, Hailey Friedrich, Maura Brennan, Cecilia Di Pentima. MCPHS University - Worcester/Manchester
Introduction: Neurocysticercosis is the most common nervous system helminthic infection and a leading cause of epilepsy worldwide. Humans contract the disease through the ingestion of eggs from the tapeworm Taenia solium, typically from fecal matter of an asymptomatic Taenia carrier. When Taenia larvae migrate to tissues within the nervous system (brain parenchyma, subarachnoid space, ventricular system and/or spinal cord), they form cysts leading to pathological changes resulting in clinical symptoms. Seizures and headaches are most common but patients may also develop focal and cognitive deficits. Diagnosis should be obtained through an extensive history, CNS imaging, and serological testing. Treatment consists of the anthelmintics medications albendazole and praziquantel, and potentially corticosteroids. Proper identification and treatment can significantly improve the prognosis of most patients with neurocysticercosis.
Case Report: 14-year-old female Congolese refugee by way of Ugandan camp for several years, who suffered numerous physical and psychological traumas prior to emigrating, presented to neurology clinic due to suspicion of psychogenic non-epileptic seizures, treated with carbamazepine for 5 years. Patient was seen 6 weeks later in the emergency department for potential concussion following unrelated head injury and found to have scattered peripheral calcifications with irregular parenchymal hypodensities on CT. Follow-up MRI two months later found at least 11 cystic lesions of varying age, consistent with neurocysticercosis. Infectious disease admitted patient to begin albendazole, praziquantel, and dexamethasone. Upon review, pharmacy recommended a cross taper of carbamazepine and levetiracetam to avoid a CYP3A4 interaction that would reduce praziquantel concentrations. Patient completed 14 days of anthelmintics and 28 days of corticosteroids followed by a two-week taper. Recommended SSRI therapy was deferred until acute treatment was completed. Six-week follow up imaging showed improvement and patient reported no clinical symptoms.
Observations: Patients emigrating from areas considered highly-endemic for neurocysticercosis (Latin America, sub-Saharan Africa, South and Southeast Asia) who carry additional risk factors (poor sanitation, access to pigs) should have the condition considered and ruled out if displaying more common symptoms like seizures and headache, regardless of other potential causes. In this case, neuroimaging was only performed due to an unrelated head trauma. When treating patients with praziquantel and albendazole, anti-epileptic and analgesic medications should be reviewed for potential drug-drug interactions, specifically cytochrome P450 interactions. Medications should be adjusted in conjunction with neurology providers to insure appropriate anti-infective and symptomatic treatment.
Conclusions: This case highlights the need to explore various diagnoses when encountered with a medically complex patient with an extensive social history. The patient had several risk factors for parasitic infection but symptoms could be easily explained through other more prominent aspects of their history. This case also highlights the need for a pharmacist review of medications prior to initiation of therapy to avoid poor clinical outcomes.

USE OF INTRAVENTRICULAR POLYMYXIN B FOR THE TREATMENT OF RESISTANT VENTRICULITIS IN A PEDIATRIC PATIENT. Richard Haftmann, Selena Warminski. UC Davis Children's Hospital
Introduction: According to IDSA guidelines, select antibiotics may be administered via the intrathecal (IT) or intraventricular routes (IVT) for persistent and difficult to treat ventriculitis and meningitis. There is presently limited data for the use of IVT polymyxin B in pediatric patients. IDSA guidelines provide general guidance on monitoring intrathecal antibiotics, but do not have specific recommendations on the use of polymyxin B since only case reports exist currently.
Case Report: This case report describes a previously healthy five-year-old girl presenting with a history of headaches and subsequent pilocytic astrocytoma who developed Klebsiella pneumoniae meningitis after tumor resection and external ventricular drain (EVD) placement. Prior to polymyxin B, she had received cefepime, ceftriaxone, levofloxacin, and intraventricular gentamicin. The decision to administer polymyxin B intrathecally was based on surgical visualization of ongoing purulence and organized fluid collection in the ventricle despite 4 weeks of appropriate antibiotic coverage. In addition, the klebsiella

Isolate developed resistance to gentamicin so IVT gentamicin was no longer beneficial. Polymyxin B was administered by neurosurgery via the intraventricular route at 10,000 units on

Case Reports (Con't)

day one, 20,000 units on day two, followed by the goal dose of 50,000 units every24 hours for four days. Doses were then spaced to every 48 hours to complete a total of 14 days of therapy. The EVD was kept clamped for one hour after each dose administration.

Observations: The patient tolerated each IVT administration of polymyxin B. A brain MRI near the end of the polymyxin B course demonstrated decreasing size in lesion and normalized ventricle size. Hypomagnesemia and hypokalemia were not observed. The patient did not experience any systemic effects or toxicities associated with polymyxin B, including neurotoxicity and nephrotoxicity. Serum polymyxin B concentrations were not evaluated. Although unclear if related to polymyxin B, there was ongoing and profound sodium supplementation requirement despite the EVD being clamped with limited cerebrospinal fluid losses. The patient demonstrated complete resolution after an additional 2 weeks of appropriate systemic antibiotic therapy after IVT polymyxin B was given with eventual discharge home after rehabilitation.

Conclusions: As part of a complex treatment regimen, IVT polymyxin B was safely administered to a pediatric patient with persistent ventriculitis despite 4weeks of appropriate antibiotic therapy. Additional research is needed to confirm the safety and effectiveness of IVT polymyxin B in the pediatric population.

Category: Student Research

COMPARATIVE EFFICACY OF RSV PROPHYLAXIS IN HIGH-RISK INFANTS AND CHILDREN. Jessica Helwig, Jennifer Pham, Mya Nguyen, Leslie Briars. University of Illinois Retzky College of Pharmacy

Introduction: Respiratory syncytial virus (RSV) is the leading cause of hospitalization among infants in the U.S. Historically, RSV prevention relied on monthly intramuscular palivizumab injections for up to five doses for high-risk infants (e.g., those born less than 29 weeks' gestation or 29 – 31+6 weeks with chronic lung disease. The limited half-life of palivizumab requires frequent dosing and adherence to monthly injections. Additionally, infants who were not categorized as high risk would not qualify for palivizumab. Currently, the CDC's Advisory Committee on Immunization Practices recommends nirsevimab, a long-acting monoclonal antibody, as a single-dose regimen, for all infants less than eight months old entering their first RSV season and for high-risk infants aged 8–19 months entering their second season. There is lack of clinical data regarding efficacy of nirsevimab in the highest-risk populations, infants born before 29 weeks 'gestation. This study evaluates the effectiveness of palivizumab and nirsevimab in preventing RSV-associated hospitalizations and medically attended lower respiratory tract infections (LRTIs) in high-risk infants.

Methods: This retrospective, single-center, IRB-approved study compared two cohorts of infants receiving RSV prophylaxis at the University of Illinois Hospital. Cohort 1 (2021- 2023 RSV seasons) received palivizumab, while Cohort 2 (2023-2024 RSV season) received nirsevimab during their first or second RSV season. The primary outcome was RSV-related hospitalizations and medically attended LRTIs in infants born before 29 weeks' gestation and those born 29 – 31+6 weeks with qualifying conditions. Secondary outcomes include mortality, costs, and compliance with RSV prophylaxis. Chi-square tests, t-tests, and regression analyses assessed differences between groups.

Results: Forty-five patients less than 29 weeks' gestation were included: 25 qualified for palivizumab, and 20 for nirsevimab. In the palivizumab group, 18received prophylaxis during the first season, 7 during the second season, and 6 in both seasons. In the nirsevimab group, 5 received nirsevimab during the first season and 3 during the second season. Mean gestational age and birth weight were similar between groups (25.9 ± 1.5 vs 26.4 ± 1.4 weeks, p=0.23; 806 ± 215 vs 884 ± 230grams, p=0.25, respectively). RSV-positive cases were minimal, with 1 case in each cohort and no significant difference in RSV-associated hospitalizations (3.2% vs 0%). The median cost of RSV was significantly lower with nirsevimab ($7129 vs $500, p = 0.006). About 65% of qualified infants received RSV prophylaxis in both groups, and no deaths occurred in either group.

Conclusion: Preliminary results suggest nirsevimab is a more cost-effective option for preventing RSV infections in high-risk infants born less than 29 weeks' gestation. Nirsevimab demonstrated similar efficacy to palivizumab in reducing RSV hospitalizations and LRTIs. These findings support CDC recommendations for nirsevimab as a viable alternative to palivizumab for RSV prevention in high-risk infants.

Student Research Awardee

DEVELOPMENT AND EVALUATION OF A MUCOLYTIC STEP-DOWN ALGORITHM AT A PEDIATRIC CYSTIC FIBROSIS CENTER. Katherine Vitou, Nour Kadouh, Samya Nasr, Hanna Phan. University of Michigan College of Pharmacy

Introduction: Discontinuation of nebulized hypertonic saline (HS) or dornase alfa (DA) for 6 weeks in people with cystic fibrosis (pwCF) age 12 years and older taking elexacaftor/tezacaftor/ivacaftor (ETI) was not associated with diminished lung function per the SIMPLIFY trial and subsequent cohort studies. As a result, our pediatric CF center developed and implemented a mucolytic step-down algorithm (MSDA) for pwCFprescribed ETI. The objective of this study was to evaluate the adoption and outcomes of our MSDA.

Methods: This was a retrospective cohort study evaluating the adoption and outcomes of a MDSA developed and implemented in a large, accredited pediatric CF center between 11/01/2022 and 02/29/2024. MDSA criteria were based on the SIMPLIFY trial and care center team input. PwCF followed by our pediatric CF care center who met algorithm criteria were included. Patients diagnosed with CF transmembrane conductance regulator-related metabolic syndrome and lung transplant recipients were excluded. Data collection included demographics, algorithm processes, and clinical outcomes including lung function (forced expiratory volume in 1 second (FEV1)) and pulmonary exacerbations. Baseline outcomes were defined as the highest value in the previous 12 months at the time of step-down. Data was analyzed with descriptive statistics using Microsoft Excel and SPSS with alpha priori of 0.05.

Results: Of the 265 patients screened, 73 (27.5%) met the MSDA criteria and 47 stepped down therapy. Some reasons for not stepping down therapy included concern regarding lung function trend (11.8%), concern for poor adherence to ETI (7%), family declining step down (5.9%), and exacerbation at time of eligibility (1.2%). Of those in which the MDSA was applied, 26 (55.3%) were initiated by a pharmacist, 10 (21.3%) by a physician, and 11 (23.4%) self-initiated due to nonadherence.

Student Research (Con't)

Among MSDA patients, 36 (76.6%) discontinued HS alone, 4 (8.5%) discontinued alone, and 7 (14.9%) stopped both. The median time from MSDA initiation to post FEV1 measurement was 51 weeks (IQR 21.4). Pre- and post-MSDA change in median FEV1 (p=0.043, baseline 104, IQR 13; post 100, IQR 17.3) was statistically significant; however, not clinically significant. There was no significant change in the number of systemic antibiotic courses prescribed, nor admissions due to pulmonary exacerbations. Among the 47 patients who stepped down in therapy, 5 (10.6%) re-started mucolytic therapy due to factors including decreased lung function (28.6%), pulmonary exacerbation(s) requiring systemic antibiotics and admission (14.3%), and family electing to re-start (28.3%).
Conclusion: In a real-world setting, a majority of pediatric pwCF on ETI, stepping down mucolytic therapy for over 6 months did not result insignificant change of clinical outcomes such as lung function and frequency of pulmonary exacerbations.

DRUG INDUCED LIVER INJURY (DILI) IN NEONATES AND INFANTS: REAL WORLD ELECTRONIC HEALTH RECORDS REVEAL ELEVATED INCIDENCE OF ADVERSE DRUG REACTIONS AND INCREASED MORTALITY RISK. Nicole Kayrala, Martin Yi, Ruud Verstegen, Tamorah Lewis, Cindy Hoi Ting Yeung. The Hospital for Sick Children.
Introduction: Drug-induced liver injury (DILI) ranges from mild liver enzyme elevations to severe liver failure. The global incidence is 14-19 per100,000 persons, with 7-15% of acute liver failures in U.S. adults due to non-acetaminophen causes. Limited data exist for infants and newborns. This study aims to characterize DILI in neonates and infants using electronic health records from a large pediatric teaching hospital in Canada.
Methods: A retrospective cohort study was conducted using de-identified data from the Hospital for Sick Children in Toronto, Canada. Subjects ages range from 0 days to 6 months of age. Outcomes include 1) DILI prevalence, 2) common medication exposures, and 3) comparisons of mortality and hospital stay between DILI and non-DILI patients. Study drugs included meropenem, acetaminophen, ampicillin, morphine, fluconazole, and intralipids. DILI diagnosis required specific liver enzyme criteria between the start of exposure and up to 14 days following the end of exposure.
Results: The study identified 15,634 exposures from 6,710 patients, with 1,228 (7.9%) related to DILI. Among first exposures, 656 (7.5%) were associated with DILI. The most common medications associated with DILI were morphine, ampicillin, and intralipids. Patients with DILI had higher mortality rates and longer hospital stays compared to non-DILI patients. Analyses confirmed significant differences in hospital stay and mortality between DILI and non-DILI groups.
Conclusion: The study highlights the need for improved monitoring and prevention strategies for DILI in neonates and infants, given the significant prevalence among drugs of interest and the associated increased mortality and hospital stay.

TREATMENT OF MILD TO MODERATE PEDIATRIC ANEMIA IN THE AFRICAN REGION: A SYSTEMATIC REVIEW. Kate-Lynn Garst, Mary Sweeney, Emily K. Flores. Bill Gatton College of Pharmacy, East Tennessee State University.
Introduction: According to the World Health Organization (WHO), the African Region has the largest prevalence of pediatric anemia in the world at 60.2% in 2019. Pediatric anemia can lead to poor nutrition, delayed development, and stunted growth; however, singular, clear guidance does not exist for outpatient management in the African Region. We seek to describe current approaches for safe and effective outpatient management of mild to moderate pediatric anemia in the African region.
Methods: Systematic review followed PRISMA guidance and was registered through PROSPERO. PubMed, CINHAL, WHO African Index Medicus, Web of Science, and Cochrane CENTRAL were searched. Search terms of "Anemia," "Africa," "Anemia, Iron Deficiency" were utilized with results limited to the English language, the African Region, pediatric populations, outpatient setting, mild to moderate anemia, and published after 2000.Articles were excluded if conducted outside of the African region (as defined by the WHO), included pregnant population, lacked discussion of treatment intervention, or focused on inpatient treatment of severe anemia. Literature search yielded 624 articles, and after primary and secondary review 32 articles were included for analysis. Each article was screened for bias with either the Newcastle-Ottawa scale for case controls or Modified Downs Black for randomized and non-randomized studies. During primary review, data points such as objectives, inclusion and exclusion criteria, interventions and comparators, patient setting, baseline, and endpoint hemoglobin were extracted. Secondary review was utilized to confirm the data extracted and establish consensus on bias scoring.
Findings: Multiple themes for the treatment of mild to moderate iron deficiency anemia have emerged. Themes include utilization of different iron formulations, inclusion of additional vitamins, use of multiple micronutrient powders, school-based programs, deworming protocols, and evaluation of comorbid infections such as malaria. Presented findings will expand upon these themes.
Conclusion: Systematic review results will be utilized to develop an implementable protocol that can be distributed to healthcare providers in the African region for safe and effective care of children with anemia.

TRENDS IN DOSAGE FORMS FOR PEDIATRIC APPLICATIONS. Stephanie Ekufu, Joslin Bawek, Ochain Okey. University of Iowa College of Pharmacy
Introduction: Pediatric patients require medications tailored to their unique needs based on their physiological and developmental characteristics. To meet specific needs, a variety of dosage forms have emerged for pediatric medical use. Each of these forms comes with its own set of advantages and disadvantages, addressing the practical challenges of ensuring accurate dosing and enhancing adherence in pediatric patients. Despite liquid oral dosage formulations being commonly used within this population, oral solid dosage formulations are preferred for pediatric drug delivery. The purpose of this project is to examine the types of oral dosage formulations used in pediatric clinical trials and those ultimately newly approved for pediatric drug delivery to assess if there are age-appropriate oral solid dosage formulations for the pediatric population.
Methods: Data in this study includes drugs that were FDA-approved for pediatric use between 2019-2023. Clinical trials obtained for specific medications were assessed whether they had an oral solid dosage form as one of the drug formulations. Clinical trials evaluated includes a study protocol that ensures information on dosing and other inclusion criteria for subjects were available. Data collected includes age group

Student Research (Con't)

studied, size of the dosage form studied, as well as manufacturer, indication, dosage form approved for use, and weight requirement for dose, if applicable.

Results: There were a total of 60 clinical trials for FDA-approved drugs for pediatric use. Tablets (41%) and suspensions (21%) were the most common dosage form studied in clinical trials, with tablets greater than 3 millimeters in size being the most common solid oral dosage form. Granules (7%), chewable tablets (2%), and pellets (2%) were the least common solid oral dosage form studied in these clinical trials. The number of suspensions studied stopped growing after age group of 3 years and older, with the number of tablets studied growing significantly at age group of 3 years and older. Out of the studied oral dosage forms, only 12.5% of drug products were classified as sprinkles (pellets and granules), less than 3 millimeters in size.

Conclusions: Majority of pediatric drugs studied and approved within the 5-year time period are tablets greater than 3 millimeters, which may not be appropriate due to swallowability issues. Sprinkles offer advantages including ease of swallowing, effective taste-masking, and flexibility in dose adjustments. Utilizing specialized dosage forms, such as sprinkles and mini tablets, can provide safer and more effective therapy options, as well as contribute to the improved well-being of this unique population.