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JPPT | Review

The Current State of Unapproved Cannabidiol Product Use in Children

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Cannabidiol (CBD) is a naturally occurring cannabinoid isolated from *Cannabis sativa*. CBD has therapeutic benefit for the treatment of seizures associated with various epilepsy syndromes in children; however, data are lacking related to the use of CBD for other indications in pediatric patients. Despite this lack of clinical data, the use of CBD products as a complementary treatment for various conditions in children continues to increase. Thus, it is imperative that those involved in the care of children and adolescents are well informed with current information related to CBD use in pediatrics. This review will address the pharmacology of CBD, legal and regulatory factors, usage patterns, current efficacy data, and safety concerns related to the use of CBD in children and adolescents. Recommendations for clinicians, public health officials, and researchers are also provided to effectively manage the use of unapproved CBD products in the pediatric population.

ABBREVIATIONS ABC-CFXS, Aberrant Behavior Checklist–Community Edition – Fragile X Syndrome; ADHD, attention-deficit hyperactivity disorder; AEA, N-arachidonoylethanolamine; ASD, autism spectrum disorder; AUC, area under the curve; BDNF, brain-derived neurotrophic factor; CBD, cannabidiol; CGI-I, Clinical Global Impression–Improvement; cGMPs, current good manufacturing practices; CNS, central nervous system; DEA, Drug Enforcement Agency; FDA, US Food and Drug Administration; FXS, fragile X syndrome; GABA, gamma–aminobutyric acid; GAD, generalized anxiety disorder; GPR55, G protein–coupled receptor 55; PPARγ, peroxisome proliferator-activated receptor gamma; THC, tetrahydrocannabinol; T_{max}, time to maximal concentration; TRPV, transient receptor potential vanilloid; 5-HT, 5-hydroxytryptamine

KEYWORDS cannabidiol; cannabinoid; pediatrics

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Introduction

Cannabidiol (CBD) use has expanded rapidly in recent decades within the United States, including among children and adolescents.[1,2] It is important for pediatric health care professionals, including pharmacists, to understand key elements related to CBD products to guide conversations with parents and guardians who may be considering or already use such products for the care of their children. This includes the regulatory landscape, clinical science, and safety concerns related to these products.[3–9] Thus, the aims of this review are to provide a comprehensive review of unapproved CBD product use in children and to provide the clinician with practical considerations when communicating with families regarding these products, including the pharmacology, historical and current regulations, safety and efficacy, and health beliefs surrounding use of CBD products.

Pharmacology and Pharmacokinetics of CBD

There are 3 main classes of cannabinoids: endocannabinoids (naturally occurring within the body), phytocannabinoids (naturally occurring within the *Cannabis sativa* plant), and synthetic cannabinoids (synthesized for therapeutic use). Over 100 different phytocannabinoids have been discovered from the *C sativa* plant, with delta-9-tetrahydrocannabinol (THC) and CBD being most abundant.[10] While THC is well known for its psychotropic effects, CBD lacks these properties. In addition, CBD may exert anti-inflammatory, antiemetic, and neuroprotective effects.[11]

CBD is thought to exert its primary action on receptors within the endocannabinoid system. Within this system, 2 endocannabinoids, N-arachidonoylethanolamine (anandamide/AEA) and 2-arachidonoylglycerol, are transferred across the synaptic cleft where they bind to the cannabinoid receptors. The cannabinoid receptors, CB1 and CB2, are inhibitory G protein–coupled receptors. CB1 receptors are the most abundant, with expression on gamma–aminobutyric acid (GABA) and glutamatergic neurons, particularly in areas of the brain associated with motor control, learning, memory, cognition, and emotions. CB2 receptors are less prominent and primarily found in the peripheral tissues including

immune cells, the spleen, and cardiovascular tissues. CB2 is also expressed in neural cells involved in pain perception, located in postsynaptic locations throughout the central nervous system (CNS).[1,10,12,13] Binding of endocannabinoids to CB1 and CB2 receptors results in the release of neurotransmitters such as glutamate, GABA, dopamine, serotonin, and acetylcholine.[1,10,12,13] While human data are limited, the expression of cannabinoid receptors is believed to change throughout development. In rodents, CB1 receptor expression and levels of AEA and 2-arachidonoylglycerol in the CNS peak in adolescence. CB1 receptor expression is thought to peak around 5 years of age in human prefrontal cortex followed by a slow decrease into adulthood.[14] While a full review of these factors is beyond the scope of this review, clinicians should be aware that the clinical effects of cannabinoids may vary throughout development in humans owing to physiologic changes in the endocannabinoid system.

CBD acts as an indirect antagonist of CB1 and CB2 receptors. Compared with THC, which is a strong agonist at CB1 receptors, CBD has a much lower affinity for these receptors, acting as a negative allosteric modulator. Thus, CBD may reduce the clinical effects of THC.[8] CBD is also believed to work by blocking the metabolism and uptake of AEA,[10] allowing for more activation of CB1 and release of downstream neurotransmitters. Further, *in vitro* research suggests that CBD may have CB2 receptor inverse agonism.[15] The interaction of CBD with CB2 receptors expressed in brain circuits that are hyperactive in patients with schizophrenia is also noteworthy.[16] These CB2 receptor interactions likely explain the lack of certain psychotropic effects, such as hallucinations, with CBD compared with THC.

CBD exerts other important effects, such as agonism at glycine, transient receptor potential vanilloid (TRPV)-1, 5-hydroxytryptamine (5-HT) 1A, and 5-HT3A receptors; partial agonism at D2 and D3 receptors; inhibition at sodium and calcium channels; modulation of peroxisome proliferator-activated receptor gamma (PPARγ); and antagonism at G protein–coupled receptor 55 (GPR55).[8,10] The anticonvulsant properties of CBD are thought to be mediated by interaction with many of these receptors, including GABA, glycine, TRPV1, TRPV2, and GPR55 receptors.[8] Additionally, the administration of CBD increases brain-derived neurotrophic factor (BDNF) and 5-HT levels in animal models. Considering decreased BDNF levels in the CNS in patients with depression, the potential to modulate 5-HT1A and 5-HT3A receptors, and interactions with PPARγ and other PPARs, CBD may have antidepressant and anxiolytic effects.[8] This also points to the potential for CBD to be used in the treatment of substance use and dependence.

Most of what is known regarding the pharmacokinetics of CBD is derived from studies of oil-based oral formulations used for the treatment of seizures associated with epilepsy. The oral bioavailability of CBD is relatively low at 13% to 19% owing to variable absorption and extensive first-pass metabolism via CYP3A4.[17] Absorption after oral administration is greatly increased when CBD is given with a high-fat meal, demonstrated by a 5-fold increase in maximum concentration and a 4-fold increase in area under the curve (AUC). Additionally, the AUC of CBD after oral administration is dose-dependent.[18] Time to maximal concentration (T_{max}) after administration of oromucosal drops or sprays ranges from 1.64 to 4.2 hours, with similar T_{max} values reported with sublingual drops. The bioavailability of CBD after smoking or inhalation has been reported to be around 31%.[17] Absorption and systemic exposure of CBD after topical administration is highly variable because of lipophilic properties and a tendency to degrade when exposed to light, temperature, and air.[19]

CBD is highly protein bound (>94%), leading to a large volume of distribution (20,963 to 42,849 L in adults).[4] The major CYP450 enzymes responsible for the biotransformation of CBD to its active metabolites are CYP3A4 and CYP2C19.[20] CYP2C9, CYP2C19, UGT1A9, and UGT2B7 have also been implicated in the metabolism of CBD. The resultant half-life of CBD in children is highly variable, ranging from 1 to 2 days with chronic oral administration, and may be significantly shorter with other routes of administration.[17] Nearly 40 different metabolites of CBD have been identified, all with varying potency.[21,22] 7-Hydroxy CBD, the primary active metabolite of CBD, has reduced activity compared with CBD itself and exhibits unique pharmacokinetic properties.[20] For example, the AUC of 7-hydroxy CBD is 38% lower than CBD itself.[4] CBD is primarily excreted in the feces.[4] While a full review of the pharmacology and pharmacokinetics of CBD is beyond the scope of this review, clinicians should be aware of how these factors affect the clinical effects of CBD in children.[23]

Factors Affecting Unapproved CBD Product Use in the United States

In 2018, the first CBD (Epidiolex, Greenwich Biosciences, Carlsbad, CA) dosage form was approved by the US Food and Drug Administration (FDA).[3] Epidiolex is an oil-based oral solution containing 100 mg/mL of CBD and is indicated for the treatment of seizures associated with Dravet syndrome, Lennox-Gastaut syndrome, and tuberous sclerosis complex.[4] While the use of Epidiolex in children with various epilepsy diagnoses continues to grow, so does the use of unapproved CBD products for epilepsy and other indications. CBD products have reportedly been used in a variety of other disease states as both monotherapy and adjunctive therapy,[5–7] including the treatment of muscle spasticity, sleep disorders, loss of appetite, nausea and vomiting, and neuropsychiatric disorders including autism spectrum disorder (ASD).[8,9] Notably, all other CBD-containing

products are not approved by the FDA and are thus considered unapproved products.

The history of CBD use and approval within the United States is summarized in Figure 1.[2,24–29] Prior to 2018, legal access to CBD products was limited.[2,24–29] However, since the Farm Bill in 2018, there has been increasing legal access to a broad variety of CBD products.[24–28] Recent growth in CBD use is influenced by the changing public perceptions surrounding its utility for a wide range of indications and acceptability for use.[24]

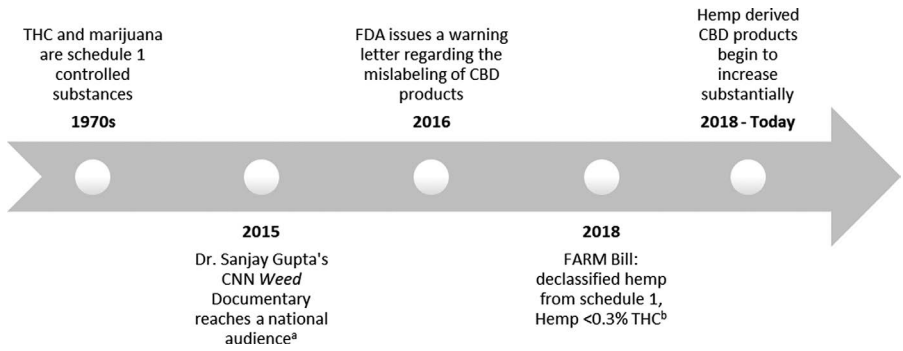
Analysts estimate that the CBD market could grow from an estimated $4.9 to $12.8 billion in 2021 to $47.2 to $56.2 billion by 2028.[24,30] Increased consumer interest and subsequent awareness in this market have spurred growth, and companies continue to expand research efforts to demonstrate the efficacy of CBD products in a broad variety of disease states and conditions.[31,32] Growth is also due to the broadening of available products in recent years, which now include oils, gummies, tinctures, infused food products, skincare products, sprays, patches, vape pens, and more.[24]

Changing attitudes toward CBD and prescription pharmaceuticals have also contributed to the increasing CBD market. Parents are often looking for alternative "natural" treatments for children. Because the general public is aware that CBD products are derived from a plant source, many parents may believe that these offer a natural and safer alternative to FDA-approved pharmaceuticals. This has driven research into public perceptions of CBD.[31,32] Perceptions of other drugs, such as opioids, have also changed parental attitudes toward CBD. For decades, opioids have been a therapeutic mainstay of pain management. However, there have been significant challenges with opioids involving misuse and addiction.[24] The visibility of the opioid epidemic and public media portrayal of its effects have resulted in many patients and families seeking alternative remedies for managing pain, including CBD products.[32]

Unapproved CBD products are purchased from both offline and online distributors. However, owing to a decrease in consumer confidence surrounding e-commerce with CBD products, the offline distribution is expected to make up an increasingly larger percentage of the market.[24] While dispensaries are responsible for most CBD sales today, predictions show a shift away from dispensaries toward retail stores, including some pharmacies in states that allow this practice.[24] With prices often ranging from $60 to $70 per unit (i.e., 1–fl oz bottle of oil, 30-day supply of gummies, 1.7–4 fl oz bottle or jar of topical cream/lotion), CBD products can have a substantial impact on community pharmacy profits owing to the margin on the products.[28] However, CBD products can also have a substantial negative impact on patient health care costs, as patients may purchase multiple products monthly, depending on the dose required to treat the condition. Health savings accounts and flexible spending accounts cannot be used to pay for CBD products, either. It is important to consider this impact, particularly for families that struggle with elements of the social determinants of health, such as financial stability or health insurance.

While the growth of the CBD market appears to be exponential, significant concerns remain related to mislabeling and illegal marketing. As noted by the FDA, "marketing unapproved products, with uncertain

Figure 1. Timeline of key events in CBD use and legality in the United States.



CBD, cannabidiol; CNN, Cable News Network; FARM Bill, Federal Agriculture Improvement Act of 2018; FDA, US Food and Drug Administration; THC, tetrahydrocannabinol.

[a] In 2015, Weed, the influential documentary highlighting Charlotte Figi's story was aired on CNN. This documentary showcased Charlotte's story of epilepsy and her positive experience with CBD products. It also elaborated on some of Colorado's biggest medical marijuana growers, the Stanley brothers, and their branding of Charlotte's Web hemp oils in 2012.

[b] This law, for the most part, leaves regulation regarding hemp production and marketing up to the states. The United States is thought to be one of the largest consumers of CBD-derived products. This is perceived to be largely due to the Farm Bill of 2018.

dosages and formulations can keep patients from accessing appropriate, recognized therapies to treat serious and even fatal diseases."[3] With expanding growth of the CBD market, it is important to monitor and address unreliable safety and efficacy data. Changing regulatory guidelines and expanded guidance may provide enhanced information regarding safety and efficacy, while preventing mislabeling and illegal marketing.[33]

Regulatory and Legal Landscape of Unapproved CBD Products

The regulatory and legal landscape of CBD products continues to change. Most updates to CBD regulations have occurred rather slowly, but the future of these standards is likely to change much more rapidly as states start to play a larger role in deciding how CBD and other hemp-derived products are managed.

Federal Regulations. Prior to 2018, all CBD-containing products were considered Schedule I controlled substances by the Drug Enforcement Agency (DEA). The 2018 Farm Bill created distinctions between cannabis (e.g., marijuana), which was illegal to cultivate, and hemp, which was distinguished as a legal crop if it contained less than 0.3% THC by weight.[34] Six months later, the FDA approved the first prescription form of cannabidiol, branded as Epidiolex.[3] According to the Food, Drug, and Cosmetic Act, supplements and foods cannot contain drugs, and any supplements or foods that do contain active drugs cannot be shipped across state lines.[35] These stipulations mean that any product other than Epidiolex does not meet FDA approval requirements as a drug or dietary supplement. Given the variety of both foods and supplements containing CBD, there are significant concerns whether CBD products fit within legal distribution regulations. Though many of these products are prohibited by the letter of the law, the current regulatory pathways through the FDA are insufficient to provide to fully manage the desire for CBD products and the corresponding risks associated with their use.[36] Owing to limited centralized regulation, as well as the Farm Bill's federal decriminalization of hemp cultivation, states typically determine the legality of CBD products, making the distribution and marketing of CBD products within states and across state lines increasingly complicated.

It is important to note that all manufacturers are still required to follow the current good manufacturing practices (cGMPs) for dietary supplements as specified in Title 21 of the Code of Federal Regulations.[37] Many dietary supplements and food additives containing CBD have remained on the market following this legislation, and there are concerns that they do not follow cGMPs. Further, citing the lack of data regarding long-term use and a lack of consistency with self-administered doses, the FDA has indicated that new regulations need to be established that will likely be stricter on current development of CBD supplements.[36] Additionally, the DEA has recently recommended that marijuana be reclassified as a Schedule III controlled substance following the recommendation of the Health and Human Services Department. Even if these regulatory changes are made, it is uncertain whether new rules and regulations will be enforced properly. As the FDA and the DEA work with lawmakers to develop clearer regulations, states will have to decide the processes and allowances for CBD sales, considering future federal regulations.

State Regulations. While several states have allowed expanded access to unapproved CBD products, a majority have instituted certain conditions that limit either how CBD can be supplied or from where it can be sourced. Specifically, most of the states that have restrictions regarding the supply of CBD either limit the THC content, require CBD to be derived from hemp, require medical cannabis licensures for products with higher THC content, or limit the dosage forms (e.g., edibles) that can be dispensed or sold. Further categorical information on state regulations can be found in Table 1.[38] For example, California has recently prohibited hemp-derived THC products and raised the minimum age to purchase hemp products to age 21 years. Both medicinal and recreational CBD

Table 1. State Regulations Regarding CBD Products as of July 2024

Fully Legal	Conditionally Legal	
Alaska	Alabama	New Mexico
Arizona	Arkansas	North Carolina
California	Delaware	North Dakota
Colorado	Florida	Ohio
Connecticut	Georgia	Oklahoma
District of Columbia	Hawaii	Pennsylvania
Illinois	Idaho	Rhode Island
Maine	Indiana	South Carolina
Massachusetts	Iowa	South Dakota
Michigan	Kansas	Tennessee
Montana	Kentucky	Texas
Nevada	Louisiana	Utah
New Jersey	Maryland	West Virginia
New York	Minnesota	Wisconsin
Oregon	Mississippi	Wyoming
Vermont	Missouri	
Virginia	Nebraska	
Washington	New Hampshire	

are allowed.[39] Georgia has banned the sale of all CBD products to persons younger than 21 years beginning October 1, 2024, but does not have the stricter prohibitions on hemp-derived products.[40]

Product Quality Assurance. As noted earlier, the FDA is considering new regulations related to CBD products,[36] while reaffirming their stance that unapproved CBD products do not meet the requirements necessary to be categorized as dietary supplements nor have any been evaluated for approval as a drug. Despite lacking an appropriate regulatory pathway for these products, CBD products are expected to be produced according to the good manufacturing requirements for both drugs and dietary supplements, including assessing purity, strength, and composition.[37] Yet, numerous reports suggest that CBD products continue to suffer from issues with label accuracy, including both incorrect concentrations and composition.

Spindle et al[41] reported that of the 105 products tested, only 24% were accurately labeled for their CBD content, while only 38% were correctly labeled for THC content. Similarly, the FDA conducted a sampling study of CBD and THC levels in 2020 to determine if the tested product ingredient concentrations were within 20% allowable deviation from the label.[42] They found that only 35% of products tested contained CBD levels within 20% of the label claim.[42] Suppliers of these CBD products are not required to report inactive ingredients, the CBD source, or whether pesticides or other chemicals were used in the growing or production process. This is an important area of consideration for health care professionals when counseling families on the safe use of CBD products.

Parental Health Beliefs and CBD Use Patterns Among Children

Despite limited information available on use patterns, there is a general understanding that parents have increasingly used unapproved CBD products for their children. A recent nationally representative US survey of parents found that nearly one-third (31.3%) reported that they had administered an unapproved CBD product to their child who was diagnosed with attention-deficit/hyperactivity disorder (ADHD), ASD, and/or generalized anxiety disorder (GAD).[43] Usage varied depending on geographic region, which could be due to state laws and regional societal views regarding CBD products. The highest prevalence was found in the western region at 43.4%, and the lowest was found in the northeastern region at 18.6% ($p < 0.05$).[43]

Many different formulations of unapproved CBD products are available, some of which mimic candies, which could increase the risk of accidental overdose in children. In one study, the most common CBD dosage form administered to children by parents was edible gummies. Oils, drops, tinctures, topical creams and lotions, lollipops, and other edibles were also reportedly administered to children.[43] Perceptions of CBD products overall vary. Most consumers desire well-known or trusted companies to produce CBD products, owing to a higher likelihood of safety controls in place, higher manufacturing standards, and more experience in producing high-quality products consistently.[44] Survey findings also indicate that over two-thirds of consumers who have never purchased CBD products are more likely to purchase them if they are regulated by a federal agency.[44] When asking parents, 83% prefer FDA regulation of CBD products, with 74% preferring it to be prescribed only.[45] While increased regulation may result in increased perceived safety and higher use of CBD products, it could raise the cost of manufacturing CBD products,[33] driving the consumer costs even higher. It may further increase use of unapproved products as well in an effort to reduce out-of-pocket costs.

Parents have used or contemplated the use of CBD products for a broad variety of indications. These include common uses in epilepsy[46] as well as emerging therapeutic areas such as neurologic and psychiatric disorders (GAD, ADHD, ASD),[43] juvenile rheumatoid arthritis,[47] and fragile X syndrome (FXS).[48] Expanding use indicates positive perceptions of CBD product efficacy and safety along with high interest for use. Interestingly, in a representative survey of parents who give their children CBD products for ASD, GAD, and/or ADHD, parents perceived stronger community support surrounding CBD use.[43] There is even less information on pediatric patients' perceptions of CBD products, but one study evaluated CBD oil use by adolescents in inflammatory bowel disease and found they had positive perceptions of efficacy.[49]

Effectiveness of CBD Products in the Pediatric Population

The efficacy of Epidiolex for the treatment of seizures in children associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex has been established through multiple prospective, placebo-controlled trials.[5,50] However, research efforts regarding the efficacy of Epidiolex in other forms of epilepsy remains ongoing. Further, data evaluating the use of unapproved products in children for indications other than epilepsy require additional scrutiny. Thus, we performed a rapid review of CBD studies in the pediatric population for indications other than epilepsy, published through 2022, using MeSH terms in PubMed with the aid of a research librarian. The articles were then screened in Covidence with the following inclusion criteria: research study (controlled study, case report, case series); uses purified, unapproved CBD products (contains <0.3% THC); and contains data on patients 0 to 21 years of age. Articles were excluded if they included Epidiolex, medical marijuana, or treated epilepsy. Two researchers independently reviewed each article for inclusion and exclusion, with a third

researcher resolving conflicts. The first phase of review focused on titles and abstracts, and the second phase of review focused on full text. A total of 576 studies were imported into Covidence, with 203 duplicates removed. After the review phases, a total of 14 studies were included. Table 2 summarizes these publications evaluating the efficacy and safety of CBD in children and adolescents.

Briefly, our review generated 14 studies that included 5 randomized controlled trials, 4 case reports/series, and 3 open-label studies (typically linked to a drug study phase [I, II, or III]). The most common condition was ASD (n = 5), followed by FXS (n = 2). Two studies were broad and included multiple diseases or conditions. Efficacy and safety results varied among the studies. Data from the studies are discussed further below.

Within the published literature, the use of CBD for the treatment of core deficits and maladaptive behaviors associated with ASD has received the most attention. To date, only aripiprazole and risperidone have been approved by the FDA for the treatment of irritability and aggression associated with ASD, and no medications lead to improvement in the core deficits associated with ASD.[51] These realities have been a primary driver of research to elucidate whether CBD might be efficacious for children with ASD. The largest of these trials was a prospective, double-blind, placebo-controlled crossover study published in 2021.[52] The investigators enrolled 150 participants 5 to 21 years of age with ASD. Participants were randomly assigned in a 1:1:1 fashion to receive either placebo, a whole-cannabis plant extract containing a 20:1 ratio of CBD to THC, or a purified CBD product containing the same 20:1 ratio of CBD to THC for 12 weeks. The whole-cannabis plant extract product retained all natural cannabinoids and plant terpenes, while the purified product did not. After a 4-week washout period, participants were switched from the placebo arm to a treatment arm or vice versa. Participants were started on 1 mg/kg/day of CBD and doses were increased by 1 mg/kg/day every other day to a maximum of 10 mg/kg/day for patients weighing between 20 and 40 kg or 7.5 mg/kg/day in patients >40 kg. No significant differences in Home Situation Questionnaire–ASD scores were observed when the CBD-rich products were compared with placebo. When comparing, Clinical Global Impression–Improvement (CGI-I) scale, 49% of patients receiving the whole plant extract, 38% receiving the purified CBD-rich product, and 21% receiving placebo reported improvement. Only the difference in CGI-I between the whole plant extract and placebo was statistically significant ($p = 0.005$). Median improvement in Social Responsiveness Scale-2 scores were 3.6 points for placebo, 14.9 points for whole plant extract ($p = 0.009$), and 8.2 for the purified product ($p = 0.80$). This secondary outcome is important to note because it may signal an improvement in social communication, one of the core deficits seen in patients with ASD. Over 20% of the participants reported somnolence and decreased appetite when taking either the whole plant extract or purified product. No serious adverse events were reported.[52]

Other studies have also evaluated the use of CBD in ASD. Barchel et al[53] evaluated 53 children between the ages of 4 and 22 years to receive a cannabis oil containing a 20:1 ratio of CBD to THC. The recommended dose of CBD was 16 mg/kg/day up to a maximum of 600 mg/day. Overall improvement in symptoms related to ASD was reported by 74.5% of parents. Looking at specific symptoms, 26 of 38 (68.4%) parents reported an improvement in hyperactivity, 23 of 34 (67.6%) reported an improvement in self-injury, 15 of 21 (71.4%) reported an improvement in sleep, and 8 of 17 (47.1%) reported an improvement in anxiety. However, none of these improvements were considered statistically significant when compared with conventional treatment responses published in the literature.[53] Somnolence and changes in appetite were the most reported adverse effects. However, this trial is limited by the small sample size, lack of blinding, lack of a true comparator group, and a requirement of only 30 days of follow-up.

Preliminary data on the use of CBD-rich products for the treatment of complex motor disorders with predominant spasticity or dystonia are promising. Libzon et al[54] conducted a pilot study in which pediatric participants between the ages of 1 and 17 years were given 5% CBD-enriched oil with either 0.25% or 0.83% THC for a duration of 5 months. These products had CBD to THC ratios of 20:1 and 6:1, respectively. The study was conducted in Israel, where fewer regulatory constraints allowed for the higher concentration of THC to be used. Patients were administered 1 drop 3 times daily of the allocated oil, with the dose titrated up until the drug was unable to be tolerated, serious side effects were noted, or a maximum of 15 mg/day of THC was reached. Twenty participants completed the study. The mean CBD doses at the final study visit were 3.73 mg/kg/day in the 6:1 group and 5.53 mg/kg/day in the 20:1 group ($p = 0.42$). Statistically significant improvements for the total cohort were seen in numerical rating of dystonia, spasticity, mood, stool function, sleep, pain, and appetite. Additionally, improvements were seen in both the Gross Motor Function Measure and the Cerebral Palsy Child questionnaire for quality of life. Statistically significant differences in clinical effects between the 2 products were not observed owing to the small sample size of the study. Worsening of seizures was reported in 2 patients, including one that experienced new onset gelastic seizures. One patient experienced excitation with rapid dose titration, and one reported mood fluctuations with concurrent methylphenidate use.[54]

Interest in using CBD in children with intellectual disability is also growing. Efron et al[55] published a

Table 2. Efficacy and Safety of CBD Products in Children and Adolescents for Treatment of Conditions Other than Epilepsy

Author (Year) | Study Design	CBD Product(s)	Condition(s) and Population	Outcomes
Aran[52] (2021) | RCT	167 mg/mL CBD and 8.35 mg/mL THC CBD:THC ratio 20:1	ASD 150 participants 5–21 years of age	**Efficacy:** *No difference between groups (CBD vs placebo):* • Home Situation Questionnaire–ASD • Autism Parenting Stress Index *Significant improvement for CBD vs placebo in:* • CGI-I scale with disruptive behavior anchor points (p = 0.005) • Social Responsiveness Scale (p = 0.009) **Safety:** • Somnolence was more common in CBD vs placebo (p < 0.001) • No other significant differences or severe/serious adverse events
Barchel[53] (2018) | retrospective observational study	Concentration of 30% and a CBD:THC ratio 20:1 Dosed by weight: • CBD - 16 mg/kg, up to 600 mg daily • THC - 0.8 mg/kg, up to 40 mg daily	ASD 53 participants 4–22 years of age	**Efficacy:** Change in symptoms: • No change = 21.6% • Improvement = 74.5% • Worsening = 3.9% **Safety:** Most common adverse event – somnolence
Berry-Kravis[58] (2022) | RCT	Transdermal gel (4.2% w/w CBD concentration) dosed by weight: • ≤35 kg = 250 mg daily • >35 kg = 500 mg daily	Fragile X syndrome 212 participants 3–17 years of age	**Efficacy:** *Improvement but no significant difference:* • Social avoidance • Irritability • Unresponsiveness/lethargy *Patients with ≥90% methylation of FMR1:* • Significant improvements in unresponsiveness/lethargy (p = 0.020) • Significant improvements in Caregiver Global Impression: SA and isolation, irritable and disruptive behaviors, and social interactions (p = 0.038, p = 0.028, and p = 0.002, respectively) **Safety:** Most common adverse effect was upper respiratory tract infection (double occurrence vs placebo)
Chelliah[59] (2018) | case series	Various CBD dosage forms including spray, oil, and cream	Epidermolysis bullosa 3 cases 6 months, 3 years, and 10 years of age	**Efficacy:** Improvement of blistering and symptoms associated with epidermolysis bullosa

(Table cont. on page 571)

Table 2. Efficacy and Safety of CBD Products in Children and Adolescents for Treatment of Conditions Other than Epilepsy *(cont.)*

Author (Year) | Study Design	CBD Product(s)	Condition(s) and Population	Outcomes
Efron[55] (2021) | RCT	98% CBD in oil, dosed by weight: • 5 mg/kg/day, titrated up to a maintenance dose of 20 mg/kg/day	Intellectual disability and severe behavioral problems 8 participants 8–16 years of age	**Efficacy:** • Significant reduction in Aberrant Behavior Checklist-Irritability subscale symptoms in the CBD group. ($p < 0.05$) • No significant reduction in the placebo group. **Safety:** No dose reductions, well tolerated
Heussler[57] (2019) | phase 1/2 open-label	Transdermal CBD, up to 250 mg daily	Fragile X syndrome 20 participants 6–17 years of age	**Efficacy:** Statistically significant reduction: • Mean Anxiety, Depression, and Mood Scale score ($p < 0.001$) • Manic/hyperactive behavior ($p < 0.001$) • Social avoidance ($p < 0.001$) • Compulsive behaviors ($p = 0.03$) • Secondary outcomes: Aberrant Behavior Checklist–Community, pediatric anxiety rating scale, pediatric QOL inventory, visual analogue scale (hyperactivity/impulsivity, tantrum/mood, and anxiety) **Safety:** • No serious adverse events • >10% experienced gastroenteritis, vomiting, and upper respiratory tract infection
Koren[56] (2021) | case report	CBD oil, smoked, and flower	Disruptive symptoms related to FASD 2 cases 5 and 12 years of age	**Efficacy:** Improvement in disruptive symptoms • Significant decrease in disruptive behavior score ($p = 0.0002$) across all 5 cases **Safety:** No reports of serious adverse drug reactions
Libzon[54] (2018) | RCT	5% oil formulation • 0.25% δ-9-tetrahydrocannabinol (THC) 20:1 • 0.83% THC 6:1 group	Complex motor disorders 20 participants 1–17 years of age	**Efficacy:** Significant improvement across multiple efficacy assessments • Barry-Albright Dystonia: $p = 0.009$ • Numeric Rating Scale for spasticity and dystonia: $p = 0.002$ • Gross motor function: total and lay, $p = 0.001$; sit, $p = 0.009$ • Quality of life: $p = 0.036$ • Visual Analog Scale: $p = 0.022$
Madden[81] (2020) | case study	CBD oil, up to 50 mg, 6 times per day	Neuroendocrine tumor with metastatic disease 13 years of age	**Safety:** Potential drug interaction between methadone and CBD, leading to fatigue and sleeplessness

(Table cont. on page 572)

Table 2. Efficacy and Safety of CBD Products in Children and Adolescents for Treatment of Conditions Other than Epilepsy *(cont.)*

Author (Year) | Study Design	CBD Product(s)	Condition(s) and Population	Outcomes
Palumbo[82] (2022) | phase 2 open-label	Transdermal CBD, 250 or 500 mg/day	ASD 37 participants 3–17 years of age	**Efficacy:** Statistically significant improvement: $p < 0.05$ • All Aberrant Behavior Checklist–Community subscales • Parent-Rated Anxiety Scale–ASD score • Autism Parenting Stress Index • Each Autism Impact Measure domain • Irritability **Safety:** • No serious adverse effects • One discontinuation due to local site reaction • No changes in laboratory parameters or ECG
Perez-Vilar[60] (2023) | case series	CBD (unspecified)	6496 cases All ages	**Safety:** Derived from American Association of Poison Control Centers reports • Cases most common in children 2–12 years of age due to unintentional exposure • Most frequent clinical effects: CNS depression, tachycardia, vomiting, neurological, dizziness/vertigo, nausea, and agitation • Most outcomes were mild in nature, with only 1 death likely due to comorbid conditions
Silva[83] (2022) | RCT	0.5% (5 mg/mL) CBD:THC ratio 9:1	ASD 64 participants 5–11 years of age	**Efficacy:** *Significant improvements in CBD vs placebo:* • Psychomotor agitation ($p < 0.01$) • Number of meals per day ($p < 0.05$) • Social interaction ($p < 0.001$) • Anxiety ($p < 0.05$) *No improvements in:* • Aggression, concentration, sleep, speech, stereotypy • Autism Treatment Evaluation Checklist • Childhood Autism Rating Scale **Safety:** 10% with dizziness, insomnia, colic, and weight gain
Stolar[84] (2022) | prospective, single arm, ongoing, open-label phase III study	CBD oil CBD:THC ratio 20:1	ASD 59 participants 5–25 years of age	**Safety:** Significantly higher after therapy: • LDH ($p = 0.003$) • Free T4 ($p = 0.03$) • TSH ($p = 0.01$)

(Table cont. on page 573)

Table 2. Efficacy and Safety of CBD Products in Children and Adolescents for Treatment of Conditions Other than Epilepsy *(cont.)*

Author (Year) | Study Design	CBD Product(s)	Condition(s) and Population	Outcomes
Zürcher[85] (2022) | retrospective, observational	THC/CBD THC Pure CBD solutions with concentrations of 2.5%, 5%, and 10% contained 0.7 mg, 1.4 mg, and 2.8 mg per drop	Various 51 participants in CBD group 4–17 years of age	**Efficacy:** • 33 of 51 experienced treatment success with the CBD • Mostly used to treat pain, seizures, and sleep disorders • Largest treatment effects were reported for pain, spasticity, and frequency of seizure in participants treated with THC, and for those treated with CBD only, the frequency of seizures **Safety:** • Tiredness, sedation, and dry mouth

ASD, autism spectrum disorder; CBD, cannabidiol; CGI-I, Clinical Global Impression–Improvement; CNS, central nervous system; ECG, electrocardiogram; FASD, fetal alcohol spectrum disorder; LDH, lactate dehydrogenase; QOL, quality of life; RCT, randomized controlled trial; SA, Static Assessment; THC; tetrahydrocannabinol; TSH; thyroid-stimulating hormone; T4, thyroxine

problems in children 8 to 16 years of age, diagnosed with intellectual disability and severe behavioral problems. Eight participants were allocated to receive 98% CBD oil or placebo for a total of 8 weeks. An initial dose of 5 mg/kg/day in divided doses was then titrated by 5 mg/kg/day every 3 days to a maintenance dose of 20 mg/kg/day with a total daily maximum dose of 500 mg. While the authors reported favorable efficacy data related to behavioral concerns, conclusions regarding the utility of CBD in these children cannot be made owing to the trial design and the resulting small sample size.[55]

Several case reports have been published regarding the use of CBD in children with other congenital disorders. Koren et al[56] describe the use of cannabis in 2 children and 3 young adults diagnosed with fetal alcohol spectrum disorder. The first of these children was a 5-year-old male also diagnosed with ADHD, global cognitive delay, and conduct disorder. The patient received 2 drops of a 20% CBD oil that also contained 0.2% THC. An improvement in the frequency of tantrums and aggression was reported along with an improvement in social communication. The second child was a 12-year-old male with comorbid learning disability and conduct disorder. This patient received 3 drops of an oil containing 15% CBD and 1% THC. Improvements in aggression, restlessness, and impulsivity were reported. It is important to note the drastic reports of symptom improvement despite very small doses of CBD in these 2 children. The remaining reports in 3 young adults involved inhalation or ingestion of cannabis preparations from the whole plant instead of CBD-specific products. No patients experienced adverse effects.[56]

Fragile X syndrome has been associated with signaling changes in the endocannabinoid system. An early phase 1/2 open-label study found improvements in behavioral outcomes with no serious adverse events. However, >10% of patients did experience gastrointestinal issues as well as upper respiratory tract infections.[57] Thus, Berry-Kravis et al[58] conducted the CONNECT-FX trial, a phase 3, double-blind, placebo-controlled trial of ZYN002, a novel transdermal CBD 4.2% gel in patients 3 to 17 years of age with FXS. Participants were randomly assigned to receive ZYN002 or placebo for 12 weeks. The dose of CBD was 250 mg/day in divided doses for patients ≤35 kg in weight, and 500 mg/day for patients >35 kg. The mean age of the 212 patients enrolled was 9.7 years. No statistically significant differences were observed for the primary outcome of change in social avoidance as measured using the Aberrant Behavior Checklist–Community Edition FXS (ABC-C_{FXS}) social avoidance subscale when the total cohort was evaluated. However, in the patients with ≥90% methylation of *FMR1* gene, differences were observed in ABC-C_{FXS} social avoidance subscale, Caregiver Global Impression–Change in social avoidance and isolation, irritability, and disruptive behaviors. Patients with ≥90% methylation of *FMR1* gene accounted for 79.7% of patients enrolled. The most common adverse effect reported was pain at the application site. No serious adverse events were reported in this study.[58]

Case reports have been published on the use of other topical CBD preparations in children for the treatment of epidermolysis bullosa, a group of congenital dermatoses that lead to bullae, blisters, and scarring of the skin and mucous membranes.[59] A 6-month-old male with recessive dystrophic epidermolysis bullosa was initiated on a CBD spray by the parents. This was misted over the affected areas 2 or 3 times daily. The parents reported a reduction of blistering, faster healing

of chronic wounds, and discontinuation of morphine prior to dressing changes. The second case involved a 4-year-old female with epidermolysis bullosa and *KRT5* mutation who was administered a blend of emu and CBD oils twice daily. Per parent report, healing time of facial blisters was reduced by 50%, the number of blisters was reduced, and the patient experienced reduced pain with ambulation. Lastly, a 10-year-old boy with debilitating keratoderma requiring wheelchair assistance was initiated on a topical CBD oil and cream. The family reported a reduction in blistering, reduced wheelchair use, and improved ambulation. Notably, the patient was able to discontinue regular use of naproxen and gabapentin for pain management following the use of topical CBD. Additional details about the specific CBD products used were not reported.[59] While controlled clinical trials are necessary to determine whether CBD is truly efficacious for this indication, the potential anti-inflammatory and analgesic properties may explain these findings.

While literature regarding the efficacy of unapproved CBD products in the treatment of various conditions in children and adolescents continues to grow, many publications are fraught with concerns, including small sample sizes, lack of methodologic rigor, variance in products used, a wide range of dosing strategies, short duration of follow-up, and positive publication bias. Interestingly, there are no published reports on the efficacy of CBD in children and adolescents with ADHD or GAD despite recent reports of use for these indications.[43]

Safety Concerns Related to Unapproved CBD Products

Poison centers in the United States began to see an increase in calls related to CBD in 2014; between July 2014 and June 2021, the US National Poison Data System reported 6496 cases involving CBD products, with 85.2% involving exposure to unapproved CBD products.[60] Children and adolescents younger than 18 years accounted for 51.2% of all cases.[60] Exposure to other products was observed in 19.1% of cases, and 18 cases required admission to a critical care unit. The most common clinical effects were CNS depression, tachycardia, and vomiting. Other effects reported include ventricular arrhythmias, non–ST elevation myocardial infarction, myopericarditis, bradycardia with heart block, blood pressure changes, respiratory depression, dyspnea, hallucinations, and contact dermatitis. It should be noted that the purity of these products was unknown; thus, these effects may be attributed to other substances also contained in the CBD products or coadministered substances.[60]

Adverse effect reporting in studies evaluating unapproved CBD products is variable and difficult to evaluate based on the varying doses and product formulations, as well as often being coadministered with other drugs. Based on clinical trials involving Epidiolex, several adverse effects are specifically associated with systemic CBD exposure. The most common dose-related adverse effects include somnolence. Diarrhea is often observed with increasing doses, possibly related to the amount of oil administered as CBD dosages are increased. Cannabinoid hyperemesis syndrome has not been reported in patients taking purified CBD products.[4] However, this may occur with unapproved CBD products because these often contain varying mixtures of cannabinoids. Thus, clinicians should maintain a healthy suspicion for cannabinoid hyperemesis syndrome in patients who are receiving an unapproved CBD product and present with abdominal pain, early morning nausea, loss of appetite, intractable cyclic nausea and vomiting, or using hot showers to provide temporary symptom relief.[61] This syndrome typically does not respond to antiemetic therapy and resolves with cessation of the marijuana-derived product.[61]

Additional studies evaluating the clinical toxicity of CBD indicate that doses of 20 mg/kg/day or higher are sufficient to produce a variety of adverse effects, including somnolence, decreased appetite, diarrhea, and increases in serum transaminases.[62,63] Patients who are treated with CBD for long periods often experience weight loss and/or loss of appetite, leading to growth issues. In addition, many studies report moderate to severe increases in aspartate aminotransferase, alanine aminotransferase, and, to a lesser extent, gamma-glutamyl transferase. However, these results are confounded by the higher doses used and the coadministration of other antiseizure medications. The risk of transaminase elevations is most common in the first 2 months of therapy when used in children with epilepsy, and the risk increases significantly with concomitant administration of valproic acid, and to a lesser extent, clobazam.[4] It is noteworthy that nonclinical studies in rhesus monkeys have demonstrated increases in liver weight, which suggests that CBD may directly cause hepatotoxicity.[63,64]

Owing to metabolism via hepatic enzymes and other effects on drug metabolism, the risk of drug-drug interactions with CBD is high when used systemically. CYP3A4, CYP2C19, CYP2C9, CYP2C19, UGT1A9, and UGT2B7 are all important in the metabolism of CBD.[20] From a clinical perspective, CBD doses may need to be increased when administered with carbamazepine, oxcarbazepine, phenobarbital, or phenytoin owing to enzyme induction. CBD is also an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and UGT2B7.[65,66] Concomitant use of CBD with clobazam leads to the accumulation of N-desmethylclobazam, a potent active metabolite of the parent drug. Some clinicians recommend empirically reducing the clobazam dose by up to 50% when initiating concomitant CBD. Close monitoring and careful titration of clobazam doses is necessary with this combination. CBD is also

known to alter the metabolism of certain antipsychotics, selective serotonin reuptake inhibitors, tricyclic antidepressants, and opioids. CBD can inhibit the metabolism of certain proton pump inhibitors, such as omeprazole, which is commonly used in children.[65,66] Additionally, oral doses of CBD should be reduced in patients with hepatic impairment.[4]

Purified forms of CBD could be safer for patients instead of the unapproved CBD products that oftentimes yield unpredictable proportions of THC. For example, a *post hoc* analysis of a phase 3 safety study assessing the safety of diazepam nasal spray in patients who also received CBD treatment found that the lowest rates of treatment emergent adverse events attributed to diazepam were reported in patients who received highly purified CBD.[67] Outside of CYP-related drug interactions, clinicians should be careful of additive adverse effects when CBD is used concomitantly with certain medications, such as CNS and respiratory depression with depressant medications (e.g., benzodiazepines, barbiturates, morphine, and insomnia agents).[4] Thus, clinicians should carefully ask about prescribed medications, over-the-counter medications, nutritional supplements, and unapproved medication use, such as CBD, to avoid drug-drug interactions.

Monitoring is also a key element to promote patient safety with CBD use. Transaminase (aspartate aminotransferase, alanine aminotransferase) and bilirubin levels should be checked at baseline then at 1, 3, and 6 months after initiation and periodically thereafter to ensure early identification of any liver damage. Other monitoring parameters could include vital signs such as heart rate and blood pressure. Jadoon et al[68] conducted a randomized, double-blind, placebo-controlled, crossover study with the aim to assess CBD's impact on cardiovascular response. They found that with acute administration of 600 mg of CBD, patients had lower blood pressure (−5 mm Hg; $p < 0.05$), reduced stroke volume (−13 mL; $p < 0.01$), and an increased heart rate (+10 bpm; $p < 0.01$).[68] While this was a small single-dose study, the evidence suggests the need to monitor patients' blood pressure and heart rate at each visit throughout therapy with CBD, especially in patients with comorbid cardiovascular conditions and when increasing doses.

Further, the most common vehicle for CBD products are edible oils such as olive oil, grapeseed oil, and sesame oil.[4,69] Epidiolex, for example, is made with sesame seed oil. [4] With the increasing prevalence among children of severe allergies to foods, including peanut and sesame products,[70,71] clinicians must guide parents to select products with third-party testing to verify the inactive ingredients in these cases or recommend against use altogether.[72] Furthermore, administration of CBD in lipid formulations has been shown to increase absorption of CBD by as much as 300% compared with non–fat-containing formulations.[73] Thus, it is important for providers to carefully counsel caregivers on the risks of allergic reactions and excessive exposure when using oil formulations of CBD products.

Little is known about the safety of CBD in pregnancy, including effects on embryonic development, the risk of major congenital malformations, pregnancy outcomes, and postnatal outcomes including long-term neurocognitive effects. Preliminary data from rodent models suggest that CBD exposure *in utero* is associated with decreased problem-solving behaviors in exposed offspring.[74] Thus, the use of CBD during pregnancy should be avoided. The use of CBD during breastfeeding has also not been studied. However, owing to detection of CBD in breastmilk in women using marijuana, and the risk of product contamination with THC and other substances, discontinuation of CBD or avoidance of breastfeeding is recommended.[75,76]

Recommendations on Pediatric CBD Use for Clinicians and Public Health Organizations

With nearly one-third of parents (31.3%) reporting pediatric administration of an unapproved CBD product for ADHD, ASD, and/or GAD,[43] clinicians should specifically ask parents and patients about the use of CBD products, particularly in children with behavioral health diagnoses and neurodevelopmental disorders. Often parents may not think of CBD products when asked questions about medications during the medication reconciliation process. Parents may also not consider CBD as a dietary supplement. Thus, asking specific, nonjudgmental questions about CBD use can be helpful in soliciting this information from parents. In the authors' experience, asking open-ended questions about other products or services parents use to "enhance the health" of a child often opens dialog related to complementary and alternative treatments, including CBD.

When addressing unapproved CBD product use in children, the ARMED approach may provide a useful rubric for clinicians.[77] Originally developed as a tool for discussing complementary and alternative therapies with parents, this approach focuses on A-asking effective questions, R-respect family's perspectives, D-demonstrating respect for parents, M-monitoring therapy, E-providing proper education, and D-distributing information in a nonjudgmental, evidenced-based manner.[77] For example, if a parent comes to the pharmacy asking for CBD gummies to help her child with ADHD, using the ARMED approach may help the pharmacist ask questions about other therapies used for ADHD and listen respectfully to discern the parent's rationale and perceptions of CBD use. The pharmacist could also ensure that there is a connection to primary care for monitoring of therapy and could provide information on the efficacy and safety of CBD products, using evidence without passing judgment on choices.

Multiple studies indicate the importance of the clinician having a conversation surrounding CBD use with a nonjudgmental approach.[78] Other approaches that could be used when discussing CBD products include motivational interviewing, which is a patient-centered approach that follows similar principles to the ARMED approach. This could be a particularly beneficial approach when parental knowledge and health beliefs need to be explored in an encounter. Parents often perceive that clinicians lack significant knowledge regarding CBD products, so it is important for those working with pediatric patients to enhance their knowledge of potential uses, along with safety and efficacy data, surrounding CBD products.[78,79] Key educational messages for clinicians to share with parents are included in Figure 2. Public health officials should partner with local poison centers and local clinicians to understand regional usage patterns and concerns, as this may uncover opportunities for monitoring and education of the public. These parties should also be familiar with federal and state legislation and regulations regarding the use of CBD products. Clinicians, public health officials, and parents should be involved in reporting adverse reactions associated with CBD-containing products through the FDA's MedWatch reporting system. Local health departments, regulatory agencies, and clinicians should work together to disseminate up-to-date information on the risks and therapeutic potential of CBD. Lastly, resources aimed at providing evidence-based information on unapproved CBD products should be created and distributed to both parents and adolescents. Social media communication strategies may be helpful for public-facing communication.

Recommendations for Future CBD Research

To truly elucidate the role that CBD plays in the treatment of pediatric conditions, additional research is imperative. The true extent of unapproved CBD product use in the pediatric population is still unknown and warrants further study. Exploring the relationship between parent perceptions, knowledge, and health behaviors could help the medical community identify key areas for intervention. Research to establish evidence-based approaches to educating clinicians, parents, and children on the risks of unapproved CBD use should be prioritized.

In clinical research studies involving CBD, reliable, purified, pharmaceutical-grade CBD products should be used. While CBD products show promise for several conditions in children as previously discussed, placebo-controlled trials should be supported to establish efficacy and safety. Based on the current literature, GAD and neurodevelopmental conditions, including ASD and ADHD, should be a primary focus of this research. Trials evaluating the use of CBD products in children with various forms of epilepsy, ASD, behavioral concerns in patients with intellectual disability (NCT04821856), anxiety (NCT05324449), youth alcohol disorder (NCT05317546), and youth at risk for psychosis[80] are ongoing and may help to answer some of these questions. Additionally, long-term efficacy and safety must be established, including evaluation of the effects of CBD on the developing brain. Future research should also focus on pharmacogenomic factors that affect CBD pharmacokinetics and pharmacodynamics across the lifespan.

Conclusion

CBD is an effective antiseizure medication in pediatric patients diagnosed with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex. While data evaluating the use of CBD for indications other than seizure treatment continue to grow, the application of these data to clinical care is limited owing to variability in product composition, differing routes of administration, variance in dosing strategies, concerns for product integrity, and small sample sizes. The use of unapproved CBD products among children and adolescents continues to increase despite a lack of clinical data supporting use. These products seem to be used more commonly to treat behavioral concerns in pediatric patients, including ADHD, ASD, GAD, and sleep disorders in the pediatric population. Clinicians,

Figure 2. Key educational messages for parents about unapproved CBD products

- Only one CBD product (Epidiolex®) has been approved by the FDA and is used to treat seizures in children with certain types of epilepsy.
- CBD products sold in stores are not checked by the FDA and only 1 out of every 4 products contains the dose listed on the label.
- Store-bought CBD products may contain THC (the part of marijuana that makes you "high"), pesticides, or other substances that can hurt your child.
- To date, there is little scientific proof that CBD helps with conditions other than epilepsy in children.
- The safe and effective dose of CBD for children is unknown when using store-bought products.
- Common side effects of CBD include being sleepy, not wanting to eat, diarrhea, and changes in growth.
- CBD can damage the liver, especially when taken with seizure medicines.
- CBD can change how other medicines work in your child's body, which can cause serious problems.
- Always tell your child's providers and pharmacist about any CBD products your child is taking.
- CBD products made with oils like sesame, soybean, or sunflower oil can cause serious allergic reactions in children with food allergies.
- Using CBD during pregnancy may harm the baby's development, and CBD passes into breast milk during breastfeeding.
- CBD laws are different in each state and may not be fully legal.

public health officials, and health care leaders must be prepared to address the ramifications of increasing use of unapproved products in the pediatric population through ongoing evaluation of usage patterns, provision of evidence-based education, reporting of adverse effects to the FDA, and support of further research in the field.

Article Information

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References

1. Dharmapuri S, Miller K, Klein JD. Marijuana and the pediatric population. *Pediatrics*. 2020;146(2):e20192629.
2. Campbell CT, Phillips MS, Manasco K. Cannabinoids in pediatrics. *J Pediatr Pharmacol Ther*. 2017;22(3):176–185.
3. US Food and Drug Administration. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. Accessed March 7, 2024. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms
4. US Food and Drug Administration. Epidiolex: package insert. Accessed March 7, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
5. Lattanzi S, Brigo F, Trinka E, et al. Efficacy and safety of cannabidiol in epilepsy: a systematic review and meta-analysis. *Drugs*. 2018;78(17):1791–1804.
6. Szaflarski JP, Bebin EM, Comi AM, et al. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: expanded access program results. *Epilepsia*. 2018;59(8):1540–1548.
7. Bonaccorso S, Ricciardi A, Zangani C, et al. Cannabidiol (CBD) use in psychiatric disorders: a systematic review. *Neurotoxicology*. 2019;74:282–298.
8. Vitale RM, Iannotti FA, Amodeo P. The (poly)pharmacology of cannabidiol in neurological and neuropsychiatric disorders: molecular mechanisms and targets. *Int J Mol Sci*. 2021;22(9):4876.
9. Legare CA, Raup-Konsavage WM, Vrana KE. Therapeutic potential of cannabis, cannabidiol, and cannabinoid-based pharmaceuticals. *Pharmacology*. 2022;107(3–4):131–149.
10. Pedrazzi JFC, Ferreira FR, Silva-Amaral D, et al. Cannabidiol for the treatment of autism spectrum disorder: hope or hype? *Psychopharmacology*. 2022;239(9):2713–2734.
11. Baron EP. Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: what a long strange trip it's been. *Headache*. 2015;55(6):885–916.
12. Meyer HC, Lee FS, Gee DG. The role of the endocannabinoid system and genetic variation in adolescent brain development. *Neuropsychopharmacology*. 2018;43(1):21–33.
13. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008;153(2):199–215.
14. Long LE, Lind J, Webster M, Weickert CS. Developmental trajectory of the endocannabinoid system in human dorsolateral prefrontal cortex. *BMC Neurosci*. 2012;13:87.
15. Thomas A, Baillie GL, Phillips AM, et al. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol*. 2007;150(5):613–623.
16. Ferranti AS, Foster DJ. Cannabinoid type-2 receptors: an emerging target for regulating schizophrenia-relevant brain circuits. *Front Neurosci*. 2022;16:925792.
17. Millar SA, Stone NL, Yates AS, O'Sullivan SE. A systematic review on the pharmacokinetics of cannabidiol in humans. *Front Pharmacol*. 2018;9:1365.
18. Devinsky O, Patel AD, Thiele EA, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology*. 2018;90(14):e1204–e1211.
19. Mahmoudinoodezh H, Telukutla SR, Bhangu SK, et al. The transdermal delivery of therapeutic cannabinoids. *Pharmaceutics*. 2022;14(2):438.
20. Brown JD, Winterstein AG. Potential adverse drug events and drug-drug interactions with medical and consumer cannabidiol (CBD) use. *J Clin Med*. 2019;8(7):989.
21. Harvey DJ, Mechoulam R. Metabolites of cannabidiol identified in human urine. *Xenobiotica*. 1990;20(3):303–320.
22. Jiang R, Yamaori S, Takeda S, et al. Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes. *Life Sci*. 2011;89(5–6):165–170.
23. Welty TE, Luebke A, Gidal BE. Cannabidiol: promise and pitfalls. *Epilepsy Curr*. 2014;14(5):250–252.
24. Global Market Insights. Cannabidiol (CBD) market size. Accessed March 7, 2024. https://www.gminsights.com/industry-analysis/cannabidiol-cbd-market
25. MacDonald JV. CBD: a look at the legal landscape. *Drug Top J*. 2020;165(11).
26. Young S. Marijuana stops child's severe seizures. CNN. Accessed March 7, 2024. https://www.cnn.com/2013/08/07/health/charlotte-child-medical-marijuana/index.html

27. Healthy Hemp Oil. The Charlotte's Web story: how a 6-year-old revolutionized the cannabis industry. Accessed March 7, 2024. https://healthyhempoil.com/charlottes-web/
28. Inman S. CBD making waves at community pharmacies. Pharmacy Times. Accessed March 7, 2024. https://www.pharmacytimes.com/view/cbd-making-waves-at-community-pharmacies
29. Centers for Disease Control and Prevention. Cannabis and public health. Accessed September 26, 2024. https://www.cdc.gov/cannabis/about/index.html
30. Vantage Market Research. CBD (Cannabidiol) market size to reach USD 47.22 billion by 2028: increased demand for CBD (Cannabidiol) for health and wellness purposes to drive market. Accessed March 7, 2024. https://www.vantagemarketresearch.com/industry-report/cannabidiol-cbd-market-1252
31. Villanueva MRB, Joshaghani N, Villa N, et al. Efficacy, safety, and regulation of cannabidiol on chronic pain: a systematic review. *Cureus*. 2022;14(7):e26913.
32. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health*. 2015;36:559–574.
33. Marcu J. The legalization of cannabinoid products and standardizing cannabis-drug development in the United States: a brief report. *Dialogues Clin Neurosci*. 2020;22(3):289–293.
34. Agriculture Improvement Act of 2018, Public Law 115–334, Congress, 115th Sess (2018). Accessed March 7, 2024. https://www.congress.gov/115/plaws/publ334/PLAW-115publ334.pdf
35. Federal Food, Drug, and Cosmetic Act, Congress, 75th Sess (1938). Accessed March 7, 2024. https://www.govinfo.gov/content/pkg/COMPS-973/pdf/COMPS-973.pdf
36. US Food and Drug Administration. FDA concludes that existing regulatory frameworks for foods and supplements are not appropriate for cannabidiol, will work with Congress on a new way forward. Updated January 26, 2023. Accessed March 7, 2024. https://www.fda.gov/news-events/press-announcements/fda-concludes-existing-regulatory-frameworks-foods-and-supplements-are-not-appropriate-cannabidiol
37. Code of Federal Regulations. Title 21. Part III . Current good manufacturing practice in manufacturing packaging, labeling, or holding operations for dietary supplements. Updated April 14, 2013. Accessed March 7, 2024. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-111
38. Laurence E. Your guide to CBD legalization by state. Updated September 7, 2023. Accessed July 9, 2024. https://www.forbes.com/health/body/cbd-legalization-by-state/
39. Governor Newsom issues regulations to protect kids from dangerous and intoxicating hemp products. Accessed September 26, 2024. https://www.gov.ca.gov/2024/09/06/governor-newsom-issues-regulations-to-protect-kids-from-dangerous-and-intoxicating-hemp-products/
40. Georgia Department of Agriculture. Hemp program. Accessed September 26, 2024. https://www.agr.georgia.gov/hemp-program
41. Spindle TR, Sholler DJ, Cone EJ, et al. Cannabinoid content and label accuracy of hemp-derived topical products available online and at national retail stores. *JAMA Netw Open*. 2022;5(7):e2223019–e2223019.
42. US Food and Drug Administration. *Report to the U.S. House Committee on Appropriations and the U.S. Senate Committee on Appropriations: Sampling Study of the Current Cannabidiol Marketplace to Determine the Extent That Products Are Mislabeled or Adulterated*. 2020.
43. Schwaller K, Krauss Z, Chen AMH, Cole JW. Parental perceptions and usage of unlicensed cannabidiol products in children with anxiety and neurodevelopmental disorders. *J Pediatr Pharmacol Ther*. 2023;28(4):323–328.
44. Consumer Brands Association. The urgent need for CBD clarity. Accessed March 7, 2024. https://consumerbrandsassociation.org/wp-content/uploads/2019/11/ConsumerBrands_CBD_Clarity.pdf
45. Mott Poll Report. Parent perspectives on CBD use in children. Accessed March 7, 2024. https://mottpoll.org/reports/parent-perspectives-cbd-use-children
46. Harte S, Singh Y, Malone S, et al. Cannabidiol and refractory epilepsy: parental and caregiver perspectives of participation in a compassionate access scheme. *BMC Health Serv Res*. 2022;22(1):173.
47. Failing CJ, Boehnke KF, Riebschleger M. Cannabidiol (CBD) use among children with juvenile idiopathic arthritis. *Pediatr Rheumatol*. 2021;19(1):171.
48. Maertens M, Silver H, Dixon Weber J, et al. Parent and caregiver perspectives towards cannabidiol as a treatment for fragile X syndrome. *Genes (Basel)*. 2022;13(9):1594.
49. Hoffenberg EJ, McWilliams S, Mikulich-Gilbertson S, et al. Cannabis oil use by adolescents and young adults with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2019;68(3):348–352.
50. Stockings E, Zagic D, Campbell G, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. *J Neurol Neurosurg Psychiatry*. 2018;89(7):741–753.
51. Fallah MS, Shaikh MR, Neupane B, et al. Atypical antipsychotics for irritability in pediatric autism: a systematic review and network meta-analysis. *J Child Adolesc Psychopharmacol*. 2019;29(3):168–180.
52. Aran A, Harel M, Cassuto H, et al. Cannabinoid treatment for autism: a proof-of-concept randomized trial. *Mol Autism*. 2021;12(1):6.
53. Barchel D, Stolar O, De-Haan T, et al. Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and co-morbidities. *Front Pharmacol*. 2019;9:1521.
54. Libzon S, Schleider LB-L, Saban N, et al. Medical cannabis for pediatric moderate to severe complex motor disorders. *J Child Neurol*. 2018;33(9):565–571.
55. Efron D, Freeman JL, Cranswick N, et al. A pilot randomised placebo-controlled trial of cannabidiol to reduce severe behavioural problems in children and adolescents with intellectual disability. *Br J Clin Pharmacol*. 2021;87(2):436–446.
56. Koren G, Cohen R, Sachs O. Use of cannabis in fetal alcohol spectrum disorder. *Cannabis Cannabinoid Res*. 2021;6(1):74–76.

57. Heussler H, Cohen J, Silove N, et al. A phase 1/2, open-label assessment of the safety, tolerability, and efficacy of transdermal cannabidiol (ZYN002) for the treatment of pediatric fragile X syndrome. *J Neurodev Disord*. 2019;11(1):16.
58. Berry-Kravis E, Hagerman R, Budimirovic D, et al. A randomized, controlled trial of ZYN002 cannabidiol transdermal gel in children and adolescents with fragile X syndrome (CONNECT-FX). *J Neurodev Disord*. 2022;14(1):56.
59. Chelliah MP, Zinn Z, Khuu P, Teng JMC. Self-initiated use of topical cannabidiol oil for epidermolysis bullosa. *Pediatr Dermatol*. 2018;35(4):e224–e227.
60. Perez-Vilar S, Karami S, Long K, Leishear K. Cannabidiol exposures in the United States, National Poison Data System, July 2014-June 2021. *Clin Toxicol (Phila)*. 2023;61(2):123–130.
61. Fleming JE, Lockwood S. Cannabinoid hyperemesis syndrome. *Fed Pract.* 2017;34(10):33–36.
62. Moreira GA, Moraes Neto R, Ribeiro RG, Crippa ACS. Cannabidiol for the treatment of refractory epilepsy in children: a critical review of the literature. *Rev Paul Pediatr*. 2022;41:e2021197.
63. Černe K. Toxicological properties of Δ9-tetrahydrocannabinol and cannabidiol. *Arch Ind Hyg Occup Med*. 2020;71(1):1.
64. Huestis MA, Solimini R, Pichini S, et al. Cannabidiol adverse effects and toxicity. *Curr Neuropharmacol*. 2019;17(10):974–989.
65. Balachandran P, Elsohly M, Hill KP. Cannabidiol interactions with medications, illicit substances, and alcohol: a comprehensive review. *J Gen Intern Med*. 2021;36(7):2074–2084.
66. Smith RT, Gruber SA. Contemplating cannabis: the complex relationship between cannabinoids and hepatic metabolism resulting in the potential for drug-drug interactions. *Front Psychiatry*. 2023;13:1055481.
67. Peters JM, Puri V, Segal E, et al. Concomitant cannabidiol does not impact safety and effectiveness of diazepam nasal spray for seizure clusters: post hoc analysis of a phase 3 safety study. *Epilepsy Behav*. 2023;144:109248.
68. Jadoon KA, Tan GD, O'Sullivan SE. A single dose of cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study. *JCI Insight*. 2017;2(12):e93760.
69. Feng W, Qin C, Abdelrazig S, et al. Vegetable oils composition affects the intestinal lymphatic transport and systemic bioavailability of co-administered lipophilic drug cannabidiol. *Int J Pharm*. 2022;624:121947.
70. Lange L, Klimek L, Beyer K, et al. White paper on peanut allergy—part 1: epidemiology, burden of disease, health economic aspects. *Allergo J Int*. 2021;30(8):261–269.
71. Sokol K, Rasooly M, Dempsey C, et al. Prevalence and diagnosis of sesame allergy in children with IgE-mediated food allergy. *Pediatr Allergy Immunol*. 2020;31(2):214–218.
72. Gupta RS, Warren CM, Smith BM, et al. The public health impact of parent-reported childhood food allergies in the United States. *Pediatrics*. 2018;142(6):e20181235.
73. Zgair A, Wong JC, Lee JB, et al. Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines. *Am J Transl Res*. 2016;8(8):3448–3459.
74. Swenson KS, Gomez Wulschner LE, Hoelscher VM, et al. Fetal cannabidiol (CBD) exposure alters thermal pain sensitivity, problem-solving, and prefrontal cortex excitability. *Mol Psychiatry*. 2023;28(8):3397–3413.
75. US Food and Drug Administration. What you should know about using cannabis, including CBD, when pregnant or breastfeeding. Accessed September 26, 2024. https://www.fda.gov/consumers/consumer-updates/what-you-should-know-about-using-cannabis-including-cbd-when-pregnant-or-breastfeeding
76. Yeung CHT, Bertrand KA, Best BM, et al. Cannabidiol exposure through maternal marijuana use: predictions in breastfed infants. *Clin Pharmacokinet*. 2023;62(11):1611–1619.
77. McClafferty H, Vohra S, Bailey M, et al. Pediatric integrative medicine. *Pediatrics*. 2017;140(3):e20171961.
78. Shelley BM, Sussman AL, Williams RL, et al; Rios Net Clinicians. 'They don't ask me so I don't tell them': patient-clinician communication about traditional, complementary, and alternative medicine. *Ann Fam Med*. 2009;7(2):139–147.
79. Sharma P, Holland A, Sheikh T, et al. Primary care provider attitudes, experiences and practices about cannabidiol (CBD) and barriers to patient-provider communication about CBD use: a qualitative study. *PEC Innov*. 2022;1:100044.
80. Amminger GP, Lin A, Kerr M, et al. Cannabidiol for at risk for psychosis youth: a randomized controlled trial. *Early Interv Psychiatry*. 2022;16(4):419–432.
81. Madden K, Tanco K, Bruera E. Clinically significant drug-drug interaction between methadone and cannabidiol. *Pediatrics*. 2020;145(6):e20193256.
82. Palumbo J, Heussler H, Duhig M, Hurst T, et al. Longer-term tolerability and efficacy of ZYN002 cannabidiol transdermal gel in children and adolescents with autism spectrum disorder: an open-label phase 2 study (BRIGHT [ZYN2-CL-030]). *J Am Acad Child Adolesc Psychiatry*. 2022;60(10):S258.
83. Silva EAd, Medeiros WMB, Santos JPMD, et al. Evaluation of the efficacy and safety of cannabidiol-rich cannabis extract in children with autism spectrum disorder: randomized, double-blind and controlled placebo clinical trial. *Trends Psychiatry Psychother*. 2024;46:e20210396.
84. Stolar O, Hazan A, Vissoker RE, et al. Medical cannabis for the treatment of comorbid symptoms in children with autism spectrum disorder: an interim analysis of biochemical safety. *Front Pharmacol*. 2022;13:977484.
85. Zürcher K, Dupont C, Weber P, et al. Use and caregiver-reported efficacy of medical cannabis in children and adolescents in Switzerland. *Eur J Pediatr*. 2022;181(1):335–347.

JPPT | Systematic Review

Clinical Uses of Nigella Sativa in Pediatrics: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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OBJECTIVE *Nigella sativa* (NS) has been widely used and investigated in several pediatric studies; however, its safety and efficacy in pediatrics are yet to be evaluated. This systematic review evaluates the clinical uses, safety, and efficacy of NS in pediatrics.

METHODS The search was conducted across 4 databases, including PubMed, Web of Science, Scopus, and Cochrane, up to September 6, 2023, and included clinical trials using NS in pediatrics. A methodological quality assessment was performed using the Cochrane risk of bias tool for randomized trials (Rob 2). A meta-analysis was conducted to evaluate safety. The systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

RESULTS Two hundred sixty-five studies were screened for eligibility, including 125 papers from Scopus, 31 from PubMed, 37 from Cochrane, and 72 from the Web of Science. Sixty-eight duplicate papers were eliminated, and 185 studies were excluded. Three studies were added from snowballing. Fifteen clinical trial studies were included in this review. Limited studies have been conducted on NS in pediatrics. Based on the meta-analysis, no statistically significant side effects have occurred. Different doses and forms of NS were used, and most studies have reported improvements in the outcomes.

CONCLUSION More high-quality studies are needed to establish the efficacy of using NS in different diseases, along with its effective dose and form. The studies in this review report no severe adverse effects and no statistically significant occurrence of side effects. However, further studies are needed to fully understand the safety of using NS in pediatrics.

ABBREVIATIONS NS, *Nigella sativa*; NSO, *Nigella sativa* oil; RCT, randomized control trial

KEYWORDS Nigella sativa; black seeds; children; pediatrics; systematic review; meta-analysis

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Introduction

The benefits of *Nigella sativa* (NS) have attracted considerable research attention due to its immunomodulatory, anti-inflammatory, and antioxidant properties. NS use has been widespread in traditional medicine throughout history, especially in Prophetic Medicine (Tibb-e-Nabwi), Unani, Siddha, and Ayurveda. The oil and seeds of this plant have been used in folklore as medicines and foods; it is considered one of the most effective healing methods in Islamic literature.[1] *Nigella sativa* is a medicinal herb belonging to the Ranunculaceae family and widely referred to as blackseed, also called black cumin or kalonji. The seeds and oils of NS contain various bioactive components, such as thymoquinone, thymohydroquinone, and carvacrol.[2] Thymoquinone is a major bioactive component of NS, identified as a potential antimicrobial, anti-inflammatory, and chemoprotective agent.[1]

Nigella sativa is native to several regions, including Southwest Asia, the Eastern Mediterranean, North Africa, and Asia, and has been used in numerous food cultures as a flavoring agent and adjuvant.[3] Nigella sativa comprises 38% to 45% lipids, 32% carbohydrate, and 21% protein; primary amino acids found in it are glutamic acid, aspartic acid, arginine, leucine, and glycine. It contains high levels of unsaturated fatty acids (57.71% linoleic acid and 24.46% oleic acid), mainly in *Nigella sativa* oil (NSO). The oil in NS seeds is rich in essential fatty acids, tocopherols, phytosterols, and polyphenols, making it a valuable ingredient in traditional medicine and the food industry.[4] The seeds of NS are rich in calcium, magnesium, sodium, potassium, phosphorus, manganese, iron, zinc, and copper.[5] Research has examined the plant's potential benefits for diabetes mellitus, skin cancer, acne vulgaris, and wound healing.[2] Furthermore, the plant has been shown to benefit the

reproductive, pulmonary, and immune system.[1] Gholamnezhad et al[6] reviewed numerous studies showing that NS and its main active compound, thymoquinone, have anti-inflammatory, antioxidant, antimicrobial, antitumor, antidiabetic, and antiepileptic properties that could benefit children. *Nigella sativa* and thymoquinone have glucose-lowering effects that could help manage diabetes in children and hepatoprotective effects that could prevent damage to liver tissue in children exposed to toxic substances.[7] In addition, NS and thymoquinone have been found to possess immunomodulatory effects that could strengthen the immune system. Additionally, it has a bronchodilator effect that could benefit children with asthma and allergies.[6,8] However, the safety of using NS in the pediatric population is unclear. Mashayekhi et al[9] investigated the toxicological profile of NS and reported that it is generally considered safe, but more detailed studies are needed to draw a definitive conclusion. The side effects of this medicinal herb did not cause serious adverse events, and it can be used in clinical trials because of its major effects that have been shown to be beneficial.[10] To our knowledge, no systematic review has been conducted to evaluate the efficacy, safety, and clinical uses of NS in pediatrics. Therefore, this systematic review aims to assess the safety, effectiveness, and clinical uses of NS in the pediatric population.

Materials and Methods

Search Strategies. This systematic review follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. It is registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42023475329).

A search was conducted across 4 databases for studies published until September 6, 2023. PubMed, Cochrane, Web of Science, and Scopus (Elsevier) databases were systematically searched for relevant English-language studies published in the literature. Search terms used were “Nigella Sativa” OR “black seed” OR “black cumin” OR “kalonji” AND “pediatric*” OR “child*” OR “adolescen*” (Table 1). No filter was used in the Web of Science and Scopus databases. The clinical trials filter was used in PubMed and Cochrane. The search was peer-reviewed by another independent reviewer. No date limits were applied. The criteria included clinical trials, studies on children/pediatric populations, and studies in the English language. Exclusion criteria included review papers, case studies, non-English language studies, studies on adults, irrelevant studies, studies that did not use NS, and studies published without full articles. Randomized control trials (RCTs) were considered eligible if they answered the following questions of the P-I-C-O-S model:

P: Participants: pediatric patients.

I: Intervention: using NS.

C: Comparator: compared with standard treatment or others.

O: Outcomes: outcomes measured by the study (no specific outcome).

S: Study design: RCT.

Data Collection and Data Extraction. Results were uploaded to the Rayyan website, and duplicates were removed based on title, date, author, and volume fields. After the duplicates were removed, titles and abstracts were screened for relevance. Two independent reviewers screened the studies based on the inclusion criteria and the PICOS model. The titles and abstracts of the studies were reviewed as the first step, followed by the complete articles of the relevant studies. Forward and backward citation (snowballing) searching was conducted for the included studies using Citationchaser.[11]

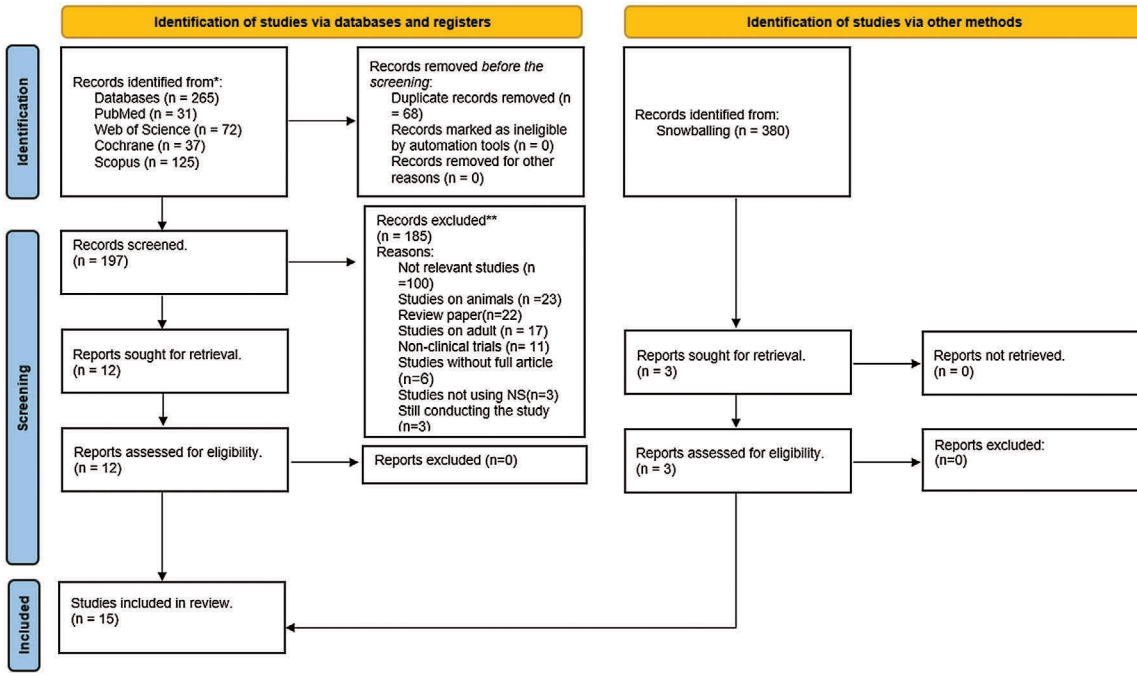
The RCTs were synthesized to describe the extracted data. Data were collected from studies by 2 independent reviewers. The data included the study author, year and country, population and sample size, study design, intervention, dose and duration of intervention, study outcome, reported side effects, and efficacy of using *Nigella*.

Data Synthesis and Statistical Analysis. A meta-analysis was conducted using the Meta-Mar online

Table 1. Search Strategy

Database	Searched Terms
PubMED	(“Nigella sativa”[MeSH Terms] OR (“nigella”[All Fields] AND “sativa”[All Fields]) OR “nigella sativa”[All Fields] OR (“black”[All Fields] AND “seed”[All Fields]) OR “black seed”[All Fields] OR (“black”[All Fields] AND “cumin”[All Fields]) OR “black cumin”[All Fields] OR “kalonji”[All Fields]) AND (“pediatrics”[MeSH Terms] OR “pediatrics” [All Fields] OR “pediatric”[All Fields] OR (“child”[MeSH Terms] OR “child”[All Fields]) OR (“adolescent”[MeSH Terms] OR “adolescent”[All Fields]))
Cochrane	(“Nigella Sativa” OR “black seed” OR “black cumin” OR “kalonji”) AND (“pediatric*” OR “child*” OR “adolescen*”)
Web of Science	(“Nigella Sativa” OR “black seed” OR “black cumin” OR “kalonji”) AND TS= (“pediatric*” OR “child*” OR “adolescen*”)
Scopus	TITLE-ABS-KEY (“Nigella Sativa” OR “black seed” OR “black cumin” OR “kalonji”) AND TITLE-ABS-KEY (“pediatric*” OR “child*” OR “adolescen*”)

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the search and study selection process.



software to assess the safety of using NS in pediatrics based on the presence of side effects among treated patients versus a placebo group. For the efficacy of using NS in pediatrics, it was only conducted in the treatment of epilepsy. Odds ratio and 95% CI were used. The p value threshold of 0.05 was used to determine statistical significance in both meta-analyses, as displayed in forest plots. Funnel graphs were used to detect the risk of publication bias in both meta-analyses.

Risk of Bias and Quality Assessment. To evaluate the evidence of quality included in this review, the Cochrane risk of bias tool for RCTs version 2 (Rob 2) was used to assess the risk of bias. Three independent reviewers conducted the assessment, and the review team only evaluated the published paper in the journal, aiming to adhere to the intervention (the per-protocol effect) based on the following 5 risks of bias domains: Domain 1: randomization process; domain 2: deviations from the intended interventions; domain 3: missing outcome data; domain 4: outcome measurement; and domain 5: selection of the reported result.

Results

Literature Search and Study Characteristics. Two hundred sixty-five studies were screened for eligibility; 125 papers from Scopus, 31 from PubMed, 37 from Cochrane, and 72 from the Web of Science. Sixty-eight duplicate papers were eliminated, and 185 studies were excluded. Reasons for excluding records were review papers (n = 22), studies on adults (n = 17), animal studies (n = 23), irrelevant studies (n = 100), nonclinical trials (n = 11), studies without full articles (n = 6), not using NS (n = 3), still conducting the study (n = 3). Studies that might meet the inclusion criteria but were excluded because of the study design.[10] Three studies were identified from 383 papers obtained through backward and forward (snowballing) citations. Fifteen clinical trial studies were included in this review, as depicted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram in Figure 1. The summary of the included studies is displayed in Table 2. All studies were published between 2008 and 2020. Four studies were conducted in Egypt, 4 in Iran, 2 in Iraq, 2 in Indonesia, 1 in India, 1 in Pakistan, and 1 in Bangladesh.

Diseases That Used Nigella Sativa. Three studies were conducted on children with epilepsy,[12–14] 3 on leukemia,[15–17] 1 on brain tumors,[18] 2 on asthma,[19] 1 on wheeze associated with lower respiratory tract illness,[20] 2 on children and adolescents with acne vulgaris,[21,22] 1 on allergic rhinitis,[23] 1 on neonates with staphylococcal skin infection,[24] and 1 on healthy adolescents.[25]

NS Forms, Doses, and Side Effects. Different forms of NS have been used to treat various diseases in children, such as natural seeds, aqueous extract, powdered form, oil, topical lotion, and nasal drops. Doses included oral powdered NS at a dose of 500 mg/day for 4 weeks up to 2 g/day for 3 months or based on

Table 2. Summary of Included Studies

Author, Publication Year, and Country of Origin	Objective of Study	Population and Sample Size	Study Design	Intervention	Study Findings
Akhondian, 2007, Iran[12]	To assess the efficacy of black cumin seed extract in reducing the frequency of seizures in children with refractory epilepsy	20 children, 13 mo to 13 yr old, with refractory epilepsy	RCT, double-blinded crossover clinical trial	Aqueous extract of black seed (40 mg/kg/8hr), placebo for 4 wk	The frequency of seizures significantly decreased, the water extract of NS has an antiepileptic effect, and may alter monoamine levels in the central nervous system in children with refractory seizures
Shawki, 2013, Egypt[14]	To evaluate the effects of black seed oil on oxidative stress markers, seizure frequency, and severity	22 children, aged 2–16 yr, with intractable seizures	Prospective, randomized, single-blinded, controlled, crossover pilot study	Black seed oil (40-80 mg/kg/day) for 4 wk	Black seed oil as an add-on therapy did not alter oxidative stress markers, seizure frequency, or severity in intractable epileptic patients
Ahmad, 2010, India[20]	To study the role of NSO in children with wheeze-associated lower respiratory tract illness	84 Children aged 6–15 yr with wheeze	RCT, prospective, open study	NSO in a dose of 0.1 mL/kg/day for 14 days, the control group received standard treatment	NSO has a beneficial effect in decreasing the pulmonary index and increasing the peak expiratory flow rate
Barlianto, 2017, Indonesia[26]	To investigate the potential antiasthmatic effect of NSO on Th1/Th2 cells, IFN g/IL-4 cytokines, and asthma control	82 children aged 6–15 years with asthma	RCT, single-blind	NSO 15–30 mg/kg/day with standard treatment guidelines for asthma for 8 wk	Supplementation with NSO improves children's IFN g/IL-4 balance and asthma control. There is no significant correlation between Th1/Th2 cells and ACT scores
Barlianto, 2018, Indonesia[19]	To investigate the effects of NSO on TH17/Treg and the improvement of asthma control in asthmatic children	28 children aged 4–14 yr with asthma	RCT, single-blind	NSO, 15–30 mg/kg/day for 8 weeks with standard treatment of asthma	NSO supplementation improves Th17/Treg balance and clinical symptoms in asthmatic children
Hagag, 2020, Egyp[16]	To evaluate the protective role of black seed oil against doxorubicin-induced cardiotoxicity in children with ALL	40 children aged 2–16 yr with ALL	RCT	Black seed oil 80 mg/kg/day, divided into three doses with doxorubicin therapy for 1 wk after each dose, placebo intervention in group 2	Black seed oil improves some cardiac side effects of doxorubicin, as shown by better systolic functions in children with acute lymphoblastic leukaemia

(Table cont. on page 584)

Table 2. Summary of Included Studies *(cont.)*

Author, Publication Year, and Country of Origin	Objective of Study	Population and Sample Size	Study Design	Intervention	Study Findings
Hagag, 2013, Egypt[17]	To evaluate the protective role of black seed oil against hepatotoxicity induced by methotrexate therapy in children with ALL	40 children with ALL, ages ranged from 4–13 yr	RCT	Oral NSO in capsule 450 mg (80 mg/kg/day) on 3 divided doses for 1 wk after each methotrexate dose	NSO can prevent hepatotoxicity from methotrexate therapy and improve overall survival in children with ALL
Dogar, 2009, Pakistan[15]	Assessing the efficacy of Nigella sativa seeds in children with ALL, and evaluating the efficacy of the 3 test treatments	48 children, ages between 2 and 18 yr with ALL	RCT	Powdered NS seeds (40 mg/kg orally in 2 equally divided doses) with conventional therapy for 3 mo	Nigella sativa seeds, in combination with cytotoxic drugs, could help treat children with ALL and improve treatment outcomes
Alsamarai, 2014, Iraq[23]	To evaluate the therapeutic efficacy of the NS extract as a treatment approach for allergic rhinitis	68 children, adolescents, and adults, aged 6–45 yr	RCT	Topical NSO (nasal drops) about 15 mL, 2 drops (one in each nostril) 3×/day for 6 wk	Topical NSO was influential in treating allergic rhinitis and improving symptoms
Mousa, 2017, Egypt[18]	To evaluate the effect of black seeds on the prevention of febrile neutropenia and length of hospital stay in children with brain tumors	80 children, aged 2–18 yr	RCT, randomized pretest-posttest control group study	Whole natural black seeds 5 g/day for 3–9 mo, the control group received no intervention (nothing)	Black seeds decrease febrile neutropenia and length of hospital stay in children with brain tumors
Momen, 2019, Iran[13]	To assess the efficacy of a mixture of NS and *Thymus vulgaris* extracts (Epistop) on seizure frequency and duration	22 children with refractory epilepsy aged between 2 and18 yr	RCT, double-masked placebo-controlled cross-over design	A mixture of NS and *Thymus vulgaris* extracts (Epistop) for 4 wk vs placebo group	No improvement was seen in the frequency and duration of seizures. Only a minority of highly selected children experienced a reduction in seizure frequency
Soleymani, 2020, Iran[21]	To assess the effect of topical Nigella sativa gel on acne vulgaris	60 patients, aged 15–35 yr	RCT, double-blind	Topical Nigella sativa hydrogel twice daily for 60 days, placebo hydrogel	NS hydrogel improved the symptoms of acne vulgaris and significantly decreased the count of acne lesions and reduced the mean number of pustules observed

(Table cont. on page 585)

Table 2. Summary of Included Studies *(cont.)*

Author, Publication Year, and Country of Origin	Objective of Study	Population and Sample Size	Study Design	Intervention	Study Findings
Bin Sayeed, 2014, Bangladesh[25]	To examine the effect of NS on anxiety, mood, and cognition in adolescents	48 healthy adolescents aged between 14 and 17 yr	RCT	500 mg/day of Nigella sativa once daily for 4 wk	Nigella sativa improves mood and cognition and decreases anxiety
Rafati, 2014, Iran[24]	To explore the antimicrobial effect of black seed extract on skin pustule infection	40 neonates with pustular infection aged between 6 and 11 days	Clinical trial	Black seed extract drops, were applied topically, 3×/day for 4 days, on the skin lesions	Black seeds extract is effective, like the standard drug (mupirocin), in treating localized infection and has antimicrobial activity. There was no significant difference in recovery time compared with traditional medicines
Nasir & Hadi, 2010, Iraq[22]	To evaluate the use of NSO lotion as a natural remedy for the treatment of acne vulgaris	81 adolescents and adults with acne vulgaris, ages ranging from 13–23 yr	RCT	10% of Nigella sativa oil lotion twice daily for 8 wk	Nigella sativa oil lotion was effective as a topical treatment for acne vulgaris, safe and well-tolerated topical treatment for moderate acne vulgaris

ACT, asthma control test; ALL, acute lymphoblastic leukemia; IFN, interferon; IL-4, interleukin-4; NS, Nigella sativa; NSO, Nigella sativa oil; RCT, randomized control trial; Th1, T-helper cell type 1; Th2, T-helper cell type 2; TH17, T-helper cell 17

body weight at a dose of 40 mg/kg in 2 equally divided doses for 3 months, with no side effects reported in those studies. One study used whole natural NS seeds at a dose of 5 g/day for 3 to 9 months with no side effects or adverse events reported.[18] Oil of NS was used at a dose of 15 to 30 mL/kg/day for 8 weeks, with no side effects reported, and at a dose up to 40 to 80 mg/kg/day for 4 weeks.[19,26] Nausea and vomiting were reported in 1 patient, and 2 patients had an exacerbation of seizures after receiving NS oil.[7] Topical NS in the form of skin lotion or hydrogel has been used to treat pustule infection and acne,[21–23] or as nasal drops at approximately 15 mL, 2 drops (1 in each nostril) administered 3 times/day for 6 weeks to treat allergic rhinitis.[23] A summary of the doses, forms, and side effects reported by each study has been described in Tables 3 and 4. None of the studies reported a severe adverse event, and a few reported mild side effects.

Quality Assessment and Risk of Bias. All included studies in the review were available in full text. The overall risk of bias across 15 studies was assessed; 4 had a low risk of bias, 1 had some concerns, and the remaining 10 RCTs had a high risk of bias, as shown in Figure 2. Despite this, we reported a low risk of bias concerning the randomization process (73% low risk). Some studies did not clearly describe the type of randomization process. The domain of deviations from the intended intervention had a 50% high risk of bias due to the lack of double blinding in most of the studies or blinding not being mentioned in the study.

Furthermore, almost none of the included studies have evaluated adherence to the intervention. Low risk of bias was judged regarding the domain of missing outcome data for all studies. However, most of the included studies reported a high risk of bias in the domain of measuring the outcome, with only 40% of studies having a low risk of bias. Finally, only 13% have a high risk of bias in the domain of selecting reported results, and most of the studies included showed a low risk of bias in this domain.

Statistical Analysis. Meta-analysis of the pooled data is shown in Figure 3. Of the 114 participants in the NS group, 12 reported side effects, compared

Table 3. Summary of the Reported Side Effects From Using Oral *Nigella Sativa*

Study	Dose, Type, and Duration	Total Number of Participants	Number of Patients With the Presence of Side Effects	Number of Patients With the Absence of Side Effects	Side Effects Reported
Akhondian[12]	Aqueous extract of black seed (40 mg/kg/8 h) for 4 wk	21	4	17	3 patients reported adverse events: 1 reported constipation in the NS group, 1 developed a maculopapular rash on the trunk, and 1 increased laughing at the time of seizure in the placebo group
Shawki[14]	Black seed oil (40–80 mg/kg/day) for 4 wk	22	3	19	1 patient developed nausea and vomiting, and 2 patients had an exacerbation of seizures after receiving black seed oil
Momen[13]	A mixture of NS and *Thymus vulgaris* extracts (Epistop) for 4 wk	22	2	19	Only 3 patients reported lethargy and diarrhea, 2 in the intervention group and 1 in the placebo group
Ahmad[20]	NSO 0.1 ml/kg/day for 14 days	84	1	83	1 patient developed diarrhea in the NSO group
Barlianto[19,26]	NSO 15–30 mg/kg/day for 8 wk	28	0	28	No side effects reported
Dogar[15]	Oral powdered nigella sativa (40 mg/kg) in 2 equally divided doses for 3 mo	48	0	48	No side effects reported, NS seeds improved the outcome of treatment
Mousa[18]	Whole natural black seeds 5 g/day for 3–9 mo	80	0	80	No side effects reported
Bin Sayeed[25]	500 mg/day of NS for 4 wk	48	0	48	No side effects reported

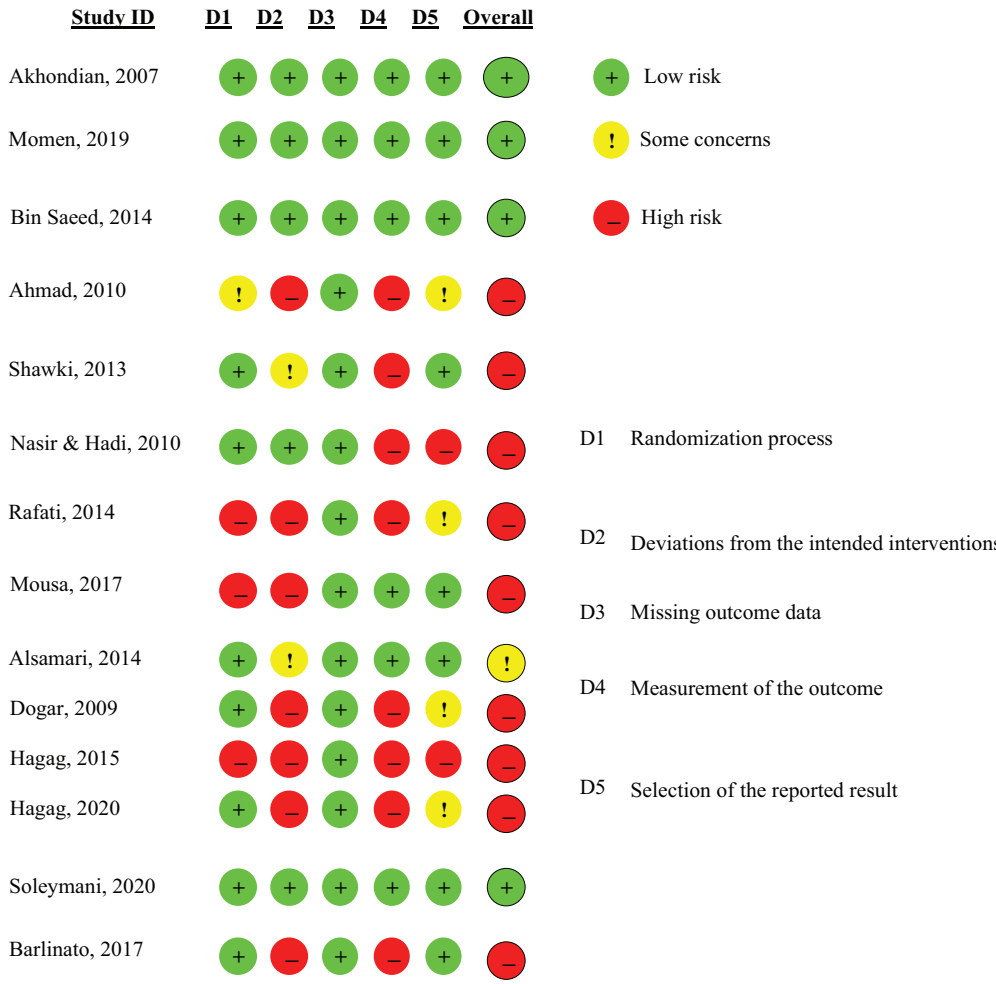
NS, Nigella sativa; NSO, Nigella sativa oil

with 102 participants in the placebo group, with only 3 experiencing side effects. Overall, the analysis shows that the reported side effects in the included studies are statistically not significant, as indicated by a p value > 0.05. No heterogeneity exists between studies (I^2 = 0%). For the efficacy of using NS in pediatrics, meta-analysis was applicable only to 3 studies conducted on children with epilepsy. The meta-analysis was pooled from 3 studies, which could generate the OR and CI to evaluate the efficacy of using NS in epilepsy (seizure frequency). As shown in Figure 4, the effect of NS on seizure frequency was not significant (p value > 0.05). No heterogeneity exists among the 3 studies, with an I^2 value of 0%. The risk of bias summary is presented in Figures 5 and 6. The symmetrical distribution of the points and their scatter suggests that there is a publication bias in both meta-analyses, due to the small number of studies included in the meta-analyses.

Table 4. Summary of the Reported Side Effects From Using Topical *Nigella Sativa*

Study	Dose, Type, and Duration	Total Number of Participants	Number of Patients With the Presence of Side Effects	Number of Patients With the Absence of Side Effects	Side Effects Reported
Nasir & Hadi[22]	10% of *Nigella sativa* oil lotion twice a day for 8 wk	81	0	81	No side effects reported
Alsamarai[23]	Topical *Nigella sativa* oil (nasal drops) about 15 mL, 2 drops (1 in each nostril) 3×/day for 6 wk	68	5	56	Nasal dryness was reported
Rafati[24]	Black seed extract drops were applied topically 3× daily for 4 days on the skin lesions	40	0	40	No side effects reported
Soleymani[21]	Topical Nigella sativa hydrogel twice daily for 60 days	60	0	60	No side effects were reported

Figure 2. Risk of bias in the included studies.



Discussion

Nigella sativa's immunomodulatory, anti-inflammatory, and antioxidant properties have been observed in many clinical trials. However, few studies have been conducted on the pediatric population. Three studies in this review have evaluated the efficacy of NS in children with epilepsy (Table 2).[13,14,27] Shawki et al[14] evaluated the efficacy of black seed oil at a dose of 40 to 80 mg/kg/day for 4 weeks. They reported that black seed oil did not significantly affect seizure frequency or severity. In addition, the study reported an exacerbation of seizures after receiving black seed oil in 2 patients. However, a greater than 50% reduction in seizure frequency was seen in 6 patients. A greater than 50% reduction in the severity of seizures was seen in 2 patients after the administration of black seed oil

Figure 3. Forest plot of the included studies to evaluate the safety of using *Nigella sativa* in pediatrics.

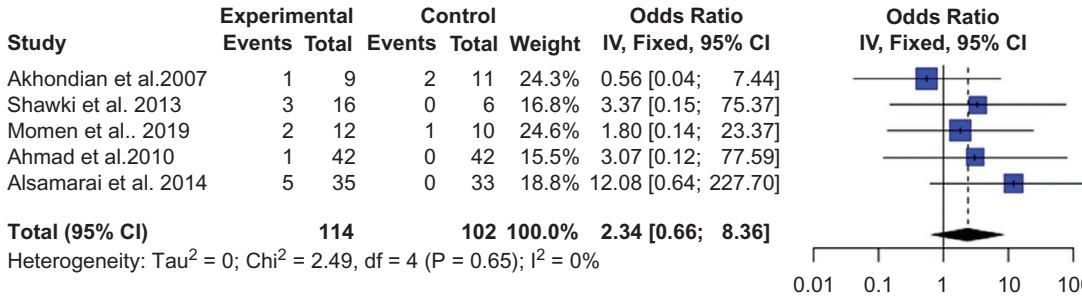


Figure 4. Forest plot to evaluate the efficacy of using *Nigella sativa* on epilepsy (seizure frequency) in 3 studies that used *N. sativa* with epilepsy.

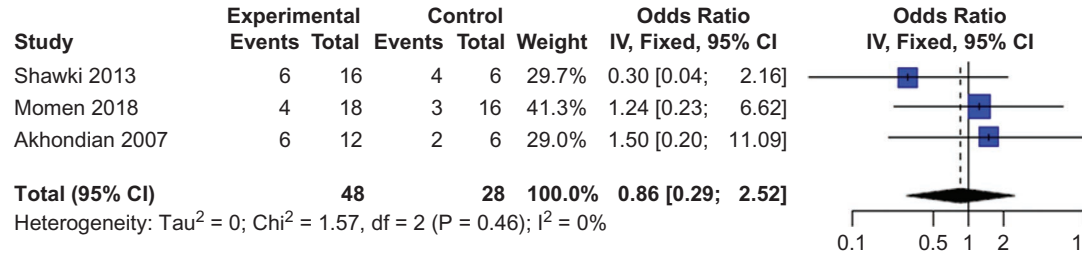


Figure 5. Funnel plot for publication bias in the included studies.

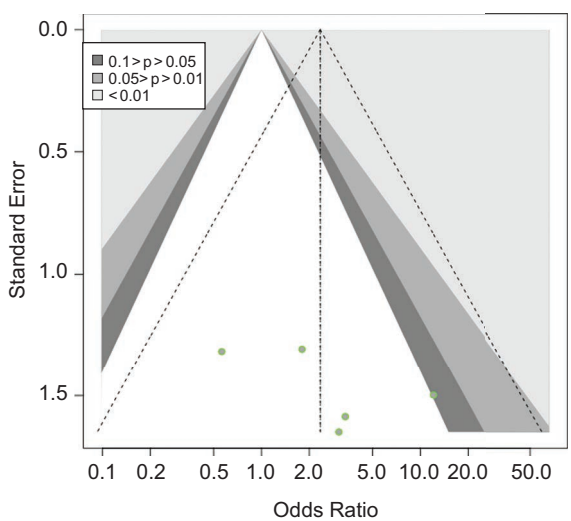


Figure 6. Funnel graph for publication bias in the included studies on *Nigella sativa* in epilepsy.

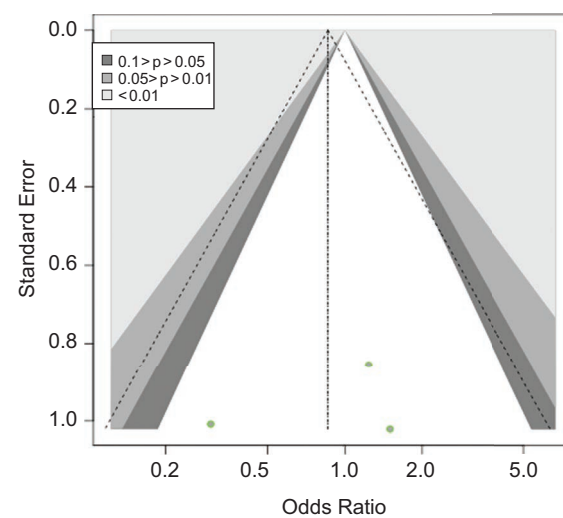


Table 5. *Nigella Sativa* and Children With Epilepsy

Study	Age & Sample Size	Sex	NS Group	Control Group	Seizure Frequency Before Treatment	Seizure Frequency After Treatment (NS)	p value
Shawky[14]	<18, 22	M = 10 F = 12	✓	✓	≥2 seizures/mo	6 patients showed >50% reductions in seizure frequency	0.552
Momen[13]	<18, 22	M = 8 F = 14	✓	✓	Seizure frequency ranged between 2 and 140 events/wk. Median seizure frequency = 35 events/wk	In 4 patients, seizure frequency was reduced by >60 %	0.0528
Akhondian[12]	<18, 20	M = 10 F = 10	✓	✓	≥1 seizure/mo	Improvement in seizure frequency was seen in 65 % of patients	≤0.001

F, female; M, male; NS, Nigella sativa

in the study by Noor et al.[28] Momen and colleagues[13] showed that using a mixture of NS and *Thymus vulgaris* extracts (Epistop) for 8 weeks does not affect the duration and frequency of seizures. However, 4 children with refractory epilepsy showed a significant reduction in seizure frequency after administration of Epistop. The author's opinion was that the administration of the Epistop might be beneficial in children with refractory seizures with typical development, normal magnetic resonance imaging and electroencephalogram, and low seizure frequency of less than 10 events per week. Using the aqueous extract of NS seeds in a dose of 40 mg/kg/8hr for 4 weeks was effective and had an antiepileptic effect in children with refractory epilepsy.[14] The benefits seen in epileptic patients included in those studies might be due to the thymoquinone presented in NS, which produces antinociceptive effects through indirect activation of the supraspinal mu (1)- and kappa-opioid receptor subtypes. Thymoquinone had anticonvulsant activity in rats, probably through an opioid receptor-mediated increase in GABAergic tone.[29] Almost all animal studies that have explored the effect of NS on seizure models have shown an anticonvulsive effect.[29–33]

In the current review, 2 studies have investigated the anti-asthmatic effect of NSO in asthmatic children,[19,26] and 1 study evaluates the role of NSO in wheeze-associated lower respiratory tract illness in children (Table 2).[20] Supplementation with NSO at a dose of 15 to 30 mg/kg/day with standard treatment for 8 weeks was compelling and improved interferon-g/interleukin-4 balance, T-helper cell 17/Treg balance, asthma control score, and symptoms in asthmatic children. The chemical composition of NS has been studied in detail. One of the main active components appears to be mainly attributed to thymoquinone. The mechanism of action of NS enables it to act as an immunomodulator and regulate T helper/Treg balance.[34] Boskabady and Farhadi[35] have reported a beneficial effect of using the aqueous extract of NS as a prophylactic measure to improve the asthma severity. Another study has shown that NSO helps decrease pulmonary index and increase peak expiratory flow rate in children with wheeze-associated lower respiratory tract illness.[20] *Nigella sativa* is therapeutically beneficial in controlling asthma symptoms and relieving airway inflammation.[36]

Three studies were conducted on children with leukemia and 1 on children with brain tumors. A review of NS and its anti-cancer properties *in vitro* and *in vivo* models found that this might be due to the high thymoquinone content in NS.[37] *Nigella sativa* has been shown to possess antineoplastic activity against tumors.[38] *Nigella sativa* exhibits an anti-cancer effect through different proposed mechanisms of action, including its effect on the activity of enzymes, usage of free radicals, intracellular glutathione changes, inhibiting cell proliferation, trapping the free radicals, and antioxidant activity.[39,40] All 3 studies in this review were focused on reducing treatment or disease-related side effects.

Dogar et al[15] reported that NS seeds, at a dose of 40 mg/kg/day in 2 equally divided doses for 3 months, in combination with a cytotoxic drug, could assist in the treatment of acute lymphoblastic leukemia. It significantly improved treatment outcomes and proved to be an excellent anticancer agent. The 2 studies from Hagag and colleagues[16,17] reported an improvement in some cardiac side effects of doxorubicin in children with ALL (n = 40), exhibiting better systolic function, as well as decreased methotrexate hepatotoxicity, and improved overall survival. Mousa et al[18] used whole natural black seeds at a dose of 5 g/day for 3 to 9 months to decrease the incidence of febrile neutropenia and length of hospital stay in children with brain tumors (n = 80).

The current review also included 2 studies on acne vulgaris patients[21,22] and 1 on newborns with a staphylococcal skin infection (Table 2).[24] A 10% NS oil lotion applied twice daily for 8 weeks was a safe and well-tolerated topical therapy for acne vulgaris.[22] Thymoquinone, the active component in NS, has been shown to suppress leukotrienes, prostaglandins, and 5-lipoxygenases in numerous inflammatory models and can also decrease the production of IL-1β, TNF-α, and monocyte chemoattractant protein.[34,41] Nitric oxide production in macrophages and mixed-glial cells is reduced by the NS extract and thymoquinone lipopolysaccharide-induced inflammation.[41,42] The aqueous extract of NS can suppress the expression of key inflammatory mediators, including nitric oxide, IL-6, and tumor necrosis factor.[37] *Nigella sativa* has anti-bacterial effects against many bacteria, and multidrug-resistant strains, such as *Staphylococcus aureus* and *Mycobacterium* tuberculosis. NS is active against several bacteria, including *Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli*. Alpha-pinene, one of the phytochemicals in NS, impacts *Propionibacterium acnes.*[43]

Additionally, Soleymani et al[21] showed that applying a topical NS hydrogel twice a day for 60 days reduced the symptoms of acne vulgaris when used topically 3 times a day for 4 days on skin lesions in newborns and infants aged 6 to 11 days.

Black seed extract drops were found to have antibacterial activity and to be as effective as the usual medication, mupirocin, in treating localized infections. *Nigella sativa* is thought to have potential as a medicinal plant for treating acne due to its immunomodulatory, anti-inflammatory, antioxidant, and antibacterial properties against *P. acne*. Other clinical uses of NS in pediatrics were used on children with beta-thalassemia major (n = 25); 2 g/day of powdered NS added to foods or drinks for 3 consecutive months was found to decrease iron overload-induced oxidative stress and hemolytic anemia. In addition, NS reduced the side effects of iron chelation therapy.[44] *Nigella sativa* was also used in patients suffering from allergic rhinitis as a topical oil (nasal drops) of approximately 15 mL, 2 drops (1 in each nostril) 3 times/day for 6 weeks; it improved the symptoms and was effective in the treatment of allergic rhinitis, and only nasal dryness was reported as a side effect.[23] *Nigella sativa* was used on healthy adolescents (n = 48) to examine the efficacy of NS on anxiety, mood, and cognition in adolescents. *Nigella sativa* administered at 500 mg/day once daily for 4 weeks was effective in stabilizing mood, modulating anxiety positively, and decreasing anxiety.[25] This is because NS increases the level of hydroxytryptamine-5 and thus decreases anxiety. Also, NS and thymoquinone decrease NO, decrease brain gamma-aminobutyric acid, and provide an anxiolytic effect.[33]

Regarding the safety of using NS in pediatrics, none of the included studies report a serious adverse event from using NS in pediatrics. Our analysis shows that the reported side effects in the included studies were not statistically significant. However, a few mild adverse events have been reported. Two patients experienced an exacerbation of seizures, which might raise concern when using NSO with epileptic children, and 1 patient developed nausea and vomiting after black seed oil administration.[14]

The gastrointestinal problems reported by Shawki et al[14] were similar to those of Kalus et al,[10] who reported a mild gastrointestinal problem after black seed oil administration on an empty stomach. In another study, 1 patient reported constipation with the use of black seed extract.[27] Momen et al[13] did not report an adverse event from using a mixture of NS and *Thymus vulgaris* extracts, and none of the children discontinued the treatment. A topical form of NS was used for acne, skin infections, and allergic rhinitis. None of the studies that used the topical form of NS reported any serious side effects. Some nasal dryness was reported in 1 study when NSO was used as nasal drops.[25] The meta-analysis in our study shows that the occurrence of side effects was not statistically significant. *Nigella sativa* seeds are approved by the United States Food and Drug Administration and recognized to be safe as a flavoring agent or an adjuvant in food (21 CFR§182.20).[45] An overview of NS safety concluded that studies assessing the toxicity of NS have reported it as a safe medicinal plant.[9] The extract of NS seeds, and its bioactive components, are considered chemicals with low toxicity[9,10,29] and a wide safety margin.[46,47] For thymoquinone and NS extracts, a high-quality clinical trial investigating the relationship of NS dose, form, and duration of use to clinical outcomes is needed.

Information about the bioavailability of NS constituents after human consumption is lacking, and additional information about the absorption, distribution, and disposition of NS bioactive constituents in humans is needed.[3]

For future studies, more detailed and high-quality studies are required to establish the safety and

efficacy of using NS in the pediatric population. None of the studies included in this review measures the participants' adherence to the intervention. Frequent supervision and follow-ups on compliance and adherence to the intervention are required in those studies conducted on pediatrics.

Limitations. The literature has some limitations. Limited studies have been conducted on NS use in pediatric diseases, and limited analyses were applicable. In addition, a high risk of bias was seen in the methodological quality assessment in most of the included studies in this review.

Conclusion. Limited studies have been conducted on NS in the pediatric population; more detailed studies are needed to establish the efficacy of using NS in different diseases, along with its effective dose and forms. Because there are limited studies on NS in pediatric populations, statistical analysis cannot be applied to a definitive conclusion on its efficacy. The studies in this review report no severe adverse effects, and the occurrence of side effects is statistically not significant. However, further high-quality studies are needed to fully understand uses, efficacy, and safety of NS in the pediatric population.

Article Information

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References

1. Begum S, Mannan A. A Review on Nigella sativa: A Marvel Herb. *J Drug Deliv Ther*. 2020;10(2):213-219.
2. Thakur S, Kaurav H, Chaudhary G. Nigella sativa (Kalonji): A Black Seed of Miracle. *Int J Res Rev*. 2021;8(4):342-357.
3. Singletary KW. Black Seeds: potential health benefits. *Nutr Today*. 2022;57(6):348-366.
4. Mazaheri Y, Torbati M, Azadmard-Damirchi S, Savage GP. A comprehensive review of the physicochemical, quality and nutritional properties of *Nigella sativa* oil. *Food Rev Int*. 2019;35(4):342-362.
5. Albakry Z, Karrar E, Ahmed IAM, et al. Nutritional Composition and Volatile Compounds of Black Cumin (Nigella sativa L.) Seed, Fatty Acid Composition and Tocopherols, Polyphenols, and Antioxidant Activity of Its Essential Oil. *Horticulturae*. 2022;8(7):575.
6. Gholamnezhad Z, Havakhah S, Boskabady MH. Preclinical and clinical effects of Nigella sativa and its constituent, thymoquinone: A review. *J Ethnopharmacol*. 2016;190:372-386.
7. Ragaa, Salama. Clinical and Therapeutic Trials of Nigella Sativa. *TAF Prev Med Bull*. 2010;9:513-522.
8. Hosseinzadeh H, Tavakkoli A, Mahdian V, Razavi BM. Review on Clinical Trials of Black Seed (Nigella sativa) and Its Active Constituent, Thymoquinone. *J Pharmacopuncture*. 2017;20(3):179-193.
9. Mashayekhi- Sardoo H, Rezaee R, Karimi G. Nigella sativa (black seed) safety: an overview. *Asian Biomed Res Rev News*. 2020;14(4):127-137.
10. Kalus U, Pruss A, Bystron J, et al. Effect of Nigella sativa (black seed) on subjective feeling in patients with allergic diseases. *Phytother Res*. 2003;17(10):1209-1214.
11. Haddaway NR, Grainger MJ, Gray CT. Citationchaser: A tool for transparent and efficient forward and backward citation chasing in systematic searching. *Res Synth Methods*. 2022;13:533-545.
12. Akhondian J, Parsa AD, Rakhshande H. The effect of Nigella sativa L. (black cumin seed) on intractable pediatric seizures. *Med Sci Monit Int Med J Exp Clin Res*. 2007;13 12:CR555-9.
13. Momen AA, Hemati AA, Houshmand G, Heydar Azadzadeh M, Azizi Malamiri R. The effect of a mixture of Nigella sativa and Thymus vulgaris extracts in children with refractory epilepsies: A randomized trial. *J Herb Med*. 2019;15:100242.
14. Shawki M, Wakeel LE, Shatla R, EL-Saeed G, Ibrahim S, Badary O. The clinical outcome of adjuvant therapy with black seed oil on intractable paediatric seizures: a pilot study. *Epileptic Disord*. 2013;15(3):295-301.
15. Dogar MZUH, Adi H, Akhtar MS, Sheikh MA. Preliminary assessment of efficacy of Nigella sativa seeds in acute lymphoblastic leukemia in local children. *Pharmacologyonline*. 2009;2:769-777.
16. Hagag AA, Badraia IM, El-Shehaby WA, Mabrouk MM. Protective role of black seed oil in doxorubicin-induced cardiac toxicity in children with acute lymphoblastic leukemia. *J Oncol Pharm Pract*. 2020;26(6):1397-1406.
17. Hagag A, AbdElaal A, Elfaragy M, Hassan S, Elzamarany E. Therapeutic Value of Black Seed Oil in Methotrexate Hepatotoxicity in Egyptian Children with Acute Lymphoblastic Leukemia. *Infect Disord - Drug Targets*. 2015;15(1):64-71.
18. Mousa HFM, Abd-El-Fatah NK, Darwish OAH, Shehata SF, Fadel SH. Effect of Nigella sativa seed administration on prevention of febrile neutropenia during chemotherapy

among children with brain tumors. *Childs Nerv Syst*. 2017;33(5):793-800.
19. Barlianto W, Wulandari D, Chusniyah M, Kusuma HC, Prawiro SR. Improvement of Th17/Treg balance and Asthma Control Test score by Nigella sativa supplementation in asthmatic children: a new approach to managing asthma. *Turk J Immunol*. 2018;6(1):1-7.
20. Ahmad J, Khan RA, Malik MA. A study of Nigella sativa oil in the management of wheeze associated lower respiratory tract illness in children. *Afr J Pharm Pharmacol*. 2009;3:248-251.
21. Soleymani S, Zargaran A, Farzaei MH, et al. The effect of a hydrogel made by Nigella sativa L. on acne vulgaris: A randomized double- blind clinical trial. *Phytother Res*. 2020;34:3052-3062.
22. Abdul-Ameer N, Al-Harchan H. *Treatment of Acne Vulgaris With Nigella Sativa Oil Lotion*. 2010;9:140-144.
23. Alsamarai AM, Abdulsatar M, Alobaidi AHA. Evaluation of topical black seed oil in the treatment of allergic rhinitis. *Anti-Inflamm Anti-Allergy Agents Med Chem*. 2014;13 1:75-82.
24. Rafati S, Niakan M, Naseri M. Anti-microbial effect of Nigella sativa seed extract against staphylococcal skin Infection. *Med J Islam Repub Iran*. 2014;28(1):42-42.
25. Bin Sayeed MS, Shams T, Fahim Hossain S, et al. Nigella sativa L. seeds modulate mood, anxiety and cognition in healthy adolescent males. *J Ethnopharmacol*. 2014;152(1):156-162.
26. Barlianto W, Rachmawati M, Irawan M, Wulandari D. Effects of Nigella sativa oil on Th1/Th2, cytokine balance, and improvement of asthma control in children. *Paediatr Indones*. 2018;57(5):223.
27. Akhondian J, Kianifar H, Raoofziaee M, Moayedpour A, Toosi MB, Khajedaluee M. The effect of thymoquinone on intractable pediatric seizures (pilot study). *Epilepsy Res*. 2011;93(1):39-43.
28. Noor NA, Ezz HSA, Faraag AR, Khadrawy YA. Evaluation of the antiepileptic effect of curcumin and Nigella sativa oil in the pilocarpine model of epilepsy in comparison with valproate. *Epilepsy Behav*. 2012;24:199-206.
29. Ali BH, Blunden G. Pharmacological and toxicological properties of Nigella sativa. *Phytother Res*. 2003;17(4):299-305.
30. Ilhan A, Gurel A, Armutcu F, Kamisli S, Iraz M. Antiepileptogenic and antioxidant effects of Nigella sativa oil against pentylenetetrazol-induced kindling in mice. *Neuropharmacology*. 2005;49:456-464.
31. Jaykare SC, Motghare VM, Padwal SL, et al. Evaluation of Anticonvulsant Activity of the Seed Oil Extract of Nigella sativa: an Experimental study. In: 2013. https://api.semanticscholar.org/CorpusID:4800165
32. Abdel-Rahman RM, Makki MST, Ali TE, Ibrahim MAM. 1,2,4-Triazine Chemistry Part III: Synthetic Strategies to Functionalized Bridgehead Nitrogen Heteroannulated 1,2,4-Triazine Systems and their Regiospecific and Pharmacological Properties. *Curr Org Synth*. 2013;10:136-160.
33. Gilhotra N, Dhingra D. Thymoquinone produced antianxiety-like effects in mice through modulation of GABA and NO levels. *Pharmacol Rep*. 2011;63(3):660-669.
34. Majdalawieh AF, Fayyad MW. Immunomodulatory and anti-inflammatory action of Nigella sativa and thymoquinone: A comprehensive review. *Int Immunopharmacol*. 2015;28(1):295-304.
35. Boskabady MH, Farhadi J. The Possible Prophylactic Effect of *Nigella sativa* Seed Aqueous Extract on Respiratory Symptoms and Pulmonary Function Tests on Chemical War Victims: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Altern Complement Med*. 2008;14(9):1137-1144.
36. Koshak A, Koshak E, Heinrich M. Medicinal benefits of Nigella sativa in bronchial asthma: A literature review. *Saudi Pharm J SPJ*. 2017;25(8):1130-1136.
37. Majdalawieh AF, Hmaidan R, Carr RI. Nigella sativa modulates splenocyte proliferation, Th1/Th2 cytokine profile, macrophage function and NK anti-tumor activity. *J Ethnopharmacol*. 2010;131(2):268-275.
38. Attoub S, Sperandio O, Raza H, et al. Thymoquinone as an anticancer agent: evidence from inhibition of cancer cells viability and invasion in vitro and tumor growth in vivo. *Fundam Clin Pharmacol*. 2013;27(5):557-569.
39. Musa D, Dilsiz N, Gumushan H, Ulakoglu G, Bitiren M. Antitumor activity of an ethanol extract of seeds. *Biologia (Bratisl)*. 2004;59(6):735-740.
40. Tayarani-Najaran Z, Sadeghnia HR, Asghari M, Mousavi SH. Neuroprotective effect of Nigella sativa hydro alcoholic extract on serum/glucose deprivation induced PC12 cells death. *Physiol Pharmacol*. 2009;13:263-270.
41. El-Mahmoudy A, Matsuyama H, Borgan M, et al. Thymoquinone suppresses expression of inducible nitric oxide synthase in rat macrophages. *Int Immunopharmacol*. 2002;2 11:1603-1611.
42. Salem M. Immunomodulatory and therapeutic properties of the Nigella sativa L. seed. *Int Immunopharmacol*. 2005;5 13-14(13-14):1749-1770.
43. Eltahir K, Bakeet DM. The Black Seed Nigella sativa Linnaeus - A Mine for Multi Cures: A Plea for Urgent Clinical Evaluation of its Volatile Oil. *J Taibah Univ Med Sci*. 2006;1(1):1-19.
44. El-Shanshory M, Hablas N, Aboonq M, et al. Nigella sativa improves anemia, enhances immunity and relieves iron overload-induced oxidative stress as a novel promising treatment in children having beta-thalassemia major. *J Herb Med*. 2019;16:100245.
45. 21 CFR 182.20 – Essential oils, oleoresins (solvent-free), and natural extractives (including distillates). Accessed September 17, 2025. https://www.ecfr.gov/current/title-21/part-182/section-182.20
46. Zaoui A, Cherrah Y, Mahassini N, Alaoui K, Amarouch H, Hassar M. Acute and chronic toxicity of Nigella sativa fixed oil. *Phytomedicine Int J Phytother Phytopharm*. 2002;9 1(1):69-74.
47. Zaghlol DA, Kamel E, Mohammed D, Abbas N. The possible toxic effect of different doses of Nigella sativa oil on the histological structure of the liver and renal cortex of adult male albino rats. *Egypt J Histol*. 2012;35: 127-136.

JPPT | Single Center Retrospective Study

Continuous Hemodynamic Response to Angiotensin II in Critically Ill Pediatric Patients: A Single Center Cohort Study

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OBJECTIVE To report efficacy, safety, and dosing of angiotensin II (AT-II) in pediatric patients with refractory vasodilatory shock.

METHODS This was a single center retrospective cohort study using automated, high-fidelity hemodynamic data in a large tertiary pediatric academic medical center. Pediatric patients who required multimodal vasopressor therapy for fluid refractory vasodilatory shock and received AT-II between June 2017 and November 2022 were included. High-fidelity hemodynamic data were captured via the Etiometry T3 platform. Vasoactive-inotropic score (VIS), AT-II dosing, demographics, clinical characteristics, and potential adverse effects were collected from the electronic medical record.

RESULTS Fourteen pediatric patients with a median age of 11.6 years (range, 13 days–16.8 years) received AT-II at a dose of 2.5 to 80 ng/kg/min for a median of 32 hours (range, 3.1–72.4). Ten of 14 patients (71%) responded favorably to AT-II therapy, experiencing a clinically significant decrease in VIS or increase in mean arterial blood pressure. The median age of responders was significantly higher than that of nonresponders (12.5 years vs 0.4 years; p = 0.002), and responders had a higher baseline VIS (56 vs 33; p = 0.008) than nonresponders. One patient (7%) experienced peripheral ischemia.

CONCLUSIONS Angiotensin II has a potential role in the management of pediatric patients with vasodilatory shock resistant to multimodal vasopressor therapy. Demographic and clinical characteristics predicting response in the pediatric population require careful, prospective evaluation.

ABBREVIATIONS AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AT-II, angiotensin II; ECMO, extracorporeal membrane oxygenation; EMR, electronic medical record; FDA, US Food and Drug Administration; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; LOESS, locally estimated scatterplot smoothing; MABP, mean arterial blood pressure; NED, norepinephrine equivalent dose; PELOD, pediatric logistic organ dysfunction; PICU, pediatric intensive care unit; PRISM, pediatric risk of mortality; RRT, renal replacement therapy; VIS, vasoactive-inotropic score; VTE, venous thromboembolism; ΔMABP, change in mean arterial blood pressure; ΔVIS, change in vasoactive-inotropic score

KEYWORDS angiotensin II; pediatrics; sepsis; shock; vasoconstrictor agents

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Introduction

Pediatric sepsis occurs worldwide in 1.2 million children annually. Mortality can be as high as 50% and is most often attributed to refractory shock and/or multiorgan dysfunction. Current pediatric guidelines recommend catecholamine agents as first-line treatment for fluid refractory shock.[1] Owing to receptor downregulation and endogenous catecholamine metabolism, patients often require increasing amounts of catecholamines to maintain hemodynamic stability and adequate end-organ perfusion.[2] High doses and extended durations of catecholamine agents can lead to serious adverse effects including peripheral ischemia, myocardial cellular apoptosis, and arrhythmia development.[3] The addition of vasopressin is suggested if patients require high doses or continued titration of catecholamines.[1] Additional non-catecholamine agents used in clinical practice, including stress-dose hydrocortisone and methylene blue, lack reliable efficacy data to be strongly recommended in pediatric guidelines and remain last-line agents.[4–6] Disadvantages of high-dose catecholamine and vasopressin use, combined with a paucity of literature regarding third-line agents, necessitate additional research for an efficacious vasopressor

with a mechanism of action that augments guideline recommendations.

Angiotensin II (AT-II) is a novel non-catecholamine vasopressor that binds to peripheral AT-II receptors resulting in vasoconstriction. In adults, AT-II increased mean arterial blood pressure (MABP) and reduced norepinephrine vasopressor equivalents at hour 3 compared with placebo leading to US Food and Drug Administration (FDA) approval in adults for use in septic or other distributive shock in 2017.[7] Angiotensin II similarly reduced vasopressor requirements while maintaining goal MABP in a small number of pediatric patients; however, data are limited to descriptive case reports and a single center case series that rely on intermittent blood pressure evaluation.[8–10] At St. Louis Children's Hospital, AT-II is used in pediatric patients with vasodilatory shock who require multimodal vasopressor therapy and who cannot meet or maintain their MABP goal. Our institution also uses data management software that captures continuously monitored vital sign data from patients admitted to an intensive care unit (ICU).

In this study, we aimed to use automated, high-fidelity hemodynamic data and vasopressor requirements to study the efficacy of AT-II in a pediatric population with vasodilatory shock requiring multimodal vasopressor therapy. Also, we aimed to identify patient and clinical characteristics of patients who responded or did not respond to AT-II therapy. Finally, we aimed to report AT-II dosing strategy and adverse events following AT-II initiation.

Materials and Methods

Patients admitted to the St. Louis Children's Hospital Pediatric Intensive Care Unit (PICU) who received AT-II between June 2017 and November 2022 were identified by using the hospital electronic medical record (EMR). The availability of corresponding hemodynamic data in the Etiometry T3 Quality Improvement System (Etiometry Platform, Etiometry Inc, Boston MA) during AT-II administration was evaluated. Etiometry T3 is an FDA-cleared data management software integrated into the EMR system that captures and archives prospective ICU clinical data from multiple sources in near real-time. Patients were included if they received AT-II for at least 3 hours and had hemodynamic data from arterial access archived in Etiometry T3 for the duration of the AT-II infusion. Patients were excluded if they received AT-II for less than 3 hours or did not have hemodynamic data available for the duration of the infusion. This study was approved by the Institutional Review Board at Washington University in St. Louis.

Baseline patient characteristics and clinical data were collected through retrospective chart review. Baseline demographics included patient age, sex, weight, severity of illness, and cause of vasodilatory shock. Race and ethnicity were not collected owing to the impact of potential socioeconomic, health care, and social constructs on the incidence and outcomes of pediatric septic shock and the inability to account for these confounders.[11] Severity of illness at PICU admission was quantified by calculating the Pediatric Risk of Mortality (PRISM-III) score.[12] The Pediatric Logistic Organ Dysfunction–2 (PELOD-2) score was calculated at PICU admission, prior to AT-II initiation, and at AT-II discontinuation.[13] Additional data collected prior to AT-II initiation included stress-dose hydrocortisone use, need for mechanical ventilation, need for renal replacement therapy (RRT), left ventricular fractional shortening percentage, and serum lactate concentration. The use of venous thromboembolism (VTE) prophylaxis or documented contraindications, the need for extracorporeal membrane oxygenation (ECMO) during the PICU admission, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), and mortality during AT-II infusion and at 30 days were captured. Acute kidney injury was assessed 48 hours prior to AT-II initiation through 24 hours post AT-II discontinuation and categorized by worst AKI stage using standard pediatric Kidney Disease: Improving Global Outcomes (KDIGO) definitions.[14] ARDS severity was calculated from data within 6 hours prior to AT-II initiation as outlined by the Pediatric Acute Lung Injury Consensus Conference Group.[15] Patients were assessed for adverse events including cardiac arrest, cardiac dysfunction, arrhythmia, thrombosis, and peripheral ischemia through review of daily progress notes during ICU admission. Imaging studies were reviewed for any patient with a documented thromboembolic complication to determine presence before or after AT-II administration.

Angiotensin II first became available at our institution for treatment of refractory shock in 2017, with use at the discretion of the attending intensivist. In 2020, an institutional protocol was implemented to guide AT-II use. Criteria included clinical features of vasodilatory shock in the setting of adequate volume resuscitation and cardiac output and the inability to obtain or maintain desired MABP despite high-dose multimodal vasopressor therapy (minimum criteria of ≥0.2 mcg/kg/min of epinephrine or norepinephrine and ≥0.5 milliunits/kg/min or 40 milliunits/min of vasopressin). The recommended starting dose for AT-II was 5 ng/kg/min with titrations every 5 minutes to a maximum dose of 80 ng/kg/min based on a blood pressure goal determined by the attending intensivist.

Information on AT-II and other vasopressor dosing and duration was collected via documentation in the electronic medication administration record and the nursing critical care flowsheets to create a single vasopressor titration timeline. Weaning of AT-II and other vasopressors was at the discretion of the attending intensivist. Non–AT-II vasopressor support was quantified into a single vasoactive-inotropic score (VIS).[16,17] The VIS was calculated as a continuous variable and data were imputed from the most recent documented dose for each vasopressor.

Baseline VIS reflects the median VIS in the 10 minutes immediately prior to AT-II initiation. High-fidelity hemodynamic data were accessed via the Etiometry T3 platform, which prospectively collected second-by-second blood pressure data via arterial line. All blood pressure data analyzed were obtained from an invasive hemodynamic monitoring device. Data for MABP were analyzed as the median values per minute. Baseline MABP was the median MABP during the 10 minutes immediately prior to the start of the AT-II infusion. To account for the variance in MABP goals based on patient age, the difference between an evaluated MABP and a patient's baseline MABP was calculated (ΔMABP).

The primary objective of our study was to assess acute hemodynamic response after initiation of AT-II. A response was defined as either an increase in ΔMABP by ≥10 mm Hg and/or 15% at 3 hours after AT-II initiation with a stable VIS (change of ≤10) or a reduction in VIS of >10 at 3 hours after AT-II initiation.[7] A change in VIS (ΔVIS) of >10 was used because it corresponds to a norepinephrine equivalent dose (NED) change of >0.1 mcg/kg/min. The 3-hour ΔMABP and VIS were calculated by using the median value over a 3-minute span at hour 3 of the AT-II infusion. Demographic and clinical characteristics were compared between AT-II responders and nonresponders. Secondary analyses included impact of AT-II infusions on PELOD-2 scores over time, description of AT-II dosing, use of VTE prophylaxis, and assessment for potential adverse effects.

Descriptive statistics were used to summarize demographic data, baseline clinical characteristics, vasopressor use, AT-II dosing, VTE prophylaxis, and adverse effects. Univariate comparisons of demographic and clinical characteristics between responders and nonresponders were performed by using the Mann-Whitney *U* test and Fisher's exact test for non-normally distributed continuous and categorical data, respectively. The Wilcoxon Rank Sum test was used to compare paired MABP and VIS values between baseline and 3 hours and PELOD-2 between AT-II initiation and discontinuation. Continuous ΔVIS and MABP values are depicted as smoothed conditional means modeled using locally estimately scatterplot smoothing (LOESS) non-linear regression with the line of best fit and the 95% confidence interval estimated. Statistical tests were considered significant where $p < 0.05$. Statistical analysis was performed with SPSS version 25 (Armonk, NY) and R version 4.2.2 (Vienna, Austria) including the *ggplot2* package.

Results

A total of 25 pediatric patients were identified as receiving an AT-II infusion during the study period. Six patients were excluded for lack of continuous hemodynamic data, 4 patients had incomplete or inaccessible continuous hemodynamic data, and 1 patient had AT-II discontinued prior to the 3-hour response evaluation. Fourteen patients had complete continuous hemodynamic data suitable for the primary analysis. The median age and weight were 11.6 years (range, 13 days–16.8 years) and 34.6 kg (range, 2.9–76.8), respectively. Ten patients (71%) received AT-II for the management of septic shock and received stress-dose hydrocortisone prior to AT-II initiation. One patient (7%) received 1 vasopressor, 6 (43%) received 2 vasopressors, and 7 (50%) received 3 vasopressors prior to AT-II initiation; the median baseline VIS of 50 reflected a correspondingly high vasopressor dose requirement. Additional demographic and baseline clinical characteristics are presented in Table 1.

The median duration of AT-II infusion for the cohort was 32 hours (range, 3.1–72.4). The median starting and maximum dose of AT-II were 5 ng/kg/min (range, 2.5–10) and 80 ng/kg/min (range, 20–80), respectively. The median time to maximum dose was 58 minutes (range, 17–434). At 3 hours, the median ΔMABP was

Table 1. Baseline Clinical Characteristics*

	(N = 14)
Age, yr	11.6 (0.04–16.8)
Male sex, n (%)	7 (50)
Weight, kg	34.6 (2.9–76.8)
PRISM-III score	11 (0–37)
PELOD-2 score at ICU admission	7.5 (0–25)
PELOD-2 score at AT-II initiation	16.5 (4–25)
Cause of vasodilatory shock, n (%)	
Septic shock	10 (71)
Vasoplegic shock	4 (29)
Vasopressor use at AT-II initiation, n (%)	
Epinephrine + norepinephrine + vasopressin	7 (50)
Epinephrine + vasopressin	4 (29)
Norepinephrine + vasopressin	1 (7)
Norepinephrine + epinephrine†	1 (7)
Norepinephrine†	1 (7)
VIS at AT-II initiation	50 (28–220)
Stress-dose hydrocortisone use at AT-II initiation, n (%)	10 (71)
Mechanical ventilation during ICU admission, n (%)	13 (93)
ECMO during ICU admission, n (%)	5 (36)
RRT at AT-II initiation, n (%)	6 (43)

AT-II, angiotensin II; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PELOD, pediatric logistic organ dysfunction; PRISM, pediatric risk of mortality; RRT, renal replacement therapy; VIS, vasoactive-inotropic score

*Data reported as median (range), unless otherwise noted.
†Received AT-II prior to implementation of institutional protocol.

significantly higher than baseline by 7 mm Hg (range, −5 to 40) (p = 0.04) and the VIS was significantly decreased at −4.5 (range, −100 to 15) (p = 0.01). A total of 10 patients (71%) were categorized as responders. Figure 1 shows the trend in VIS and percent change in MABP between groups. Of the responding patients, 5 (50%) met response criteria based on a decrease in VIS of >10 and 6 (60%) met response criteria based on a positive ΔMABP of >10 mm Hg and/or 15% increase with a stable VIS (1 patient met both criteria). As expected, change in VIS was significantly higher in responders at 3 hours of therapy (−12 vs −1; p = 0.02). Supplemental Figure S1 depicts the best-fit lines and 95% CI modeled by using LOESS nonlinear regression for the complete treatment period. Responders were significantly older (p = 0.002) and had a significantly higher baseline VIS (p = 0.008) than nonresponders (Table 2). Despite similar baseline PRISM-III and PELOD-2 scores, nonresponders had over a threefold higher mortality rate during the AT-II infusion and at 30 days; however, these differences were not statistically significant (Table 2). Due to this higher

Table 2. Patient Characteristics Based on Response to AT-II*

	Responders n = 10	Nonresponders n = 4	p value
Age, yr	12.5 (2.4–16.8)	0.4 (0.04–1.8)	0.002
Weight, kg	44.2 (10–76.8)	5.1 (2.9–12)	0.004
PRISM-III score	13 (3–34)	9 (0–37)	0.73
PELOD-2 score at ICU admission	8 (2–23)	11 (0–25)	1
PELOD-2 score at AT-II initiation	17 (4–23)	19 (14–25)	0.54
Septic shock, n (%)	6 (60)	4 (100)	0.251
Baseline VIS	56 (34–220)	33 (28–37)	0.008
Time on vasopressors prior to AT-II initiation, hr	16.6 (6.1–113.2)	23.6 (5.1–27.1)	0.84
Vasopressin use, n (%)	8 (80)	4 (100)	1
Stress-dose hydrocortisone use, n (%)	6 (60)	4 (100)	0.25
ΔMABP at 3 hr, mm Hg	9 (−3.5 to 40.4)	3.6 (−4.8 to 10.3)	0.64
ΔVIS at 3 hr	−12 (−100 to 0)	−1 (−3 to 15)	0.02
Time to max AT-II dose, minutes	56.5 (17–413)	74.5 (21–434)	0.539
Left ventricular fractional shortening, %	38 (19–43)†	43 (30–45)	0.35
Lactate at AT-II initiation, mg/dL	10 (5.5–19)	7.5 (2.6–22)	0.64
ARDS classification, n (%)			
None	1 (10)	0 (0)	0.66
Mild	3 (30)	2 (50)	
Moderate	4 (40)	2 (50)	
Severe	2 (20)	0 (0)	
Renal dysfunction, n (%)			
AKI stage 2	2 (20)	0 (0)	1
AKI stage 3	8 (80)	4 (100)	
ECMO during ICU admission, n (%)	4 (40)	1 (25)	1
RRT at AT-II initiation, n (%)	3 (30)	3 (75)	0.25
Mortality during AT-II administration, n (%)	2 (20)	3 (75)	0.09
Mortality at day 30, n (%)	3 (30)	4 (100)	0.07

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AT-II, angiotensin II; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PELOD, pediatric logistic organ dysfunction; PRISM, pediatric risk of mortality; RRT, renal replacement therapy; ΔVIS, vasoactive-inotropic score; ΔMABP, change in mean arterial blood pressure

*Data reported as median (range), unless otherwise noted.
†Data available for 6 patients.

mortality rate, an assessment of PELOD-2 scores during AT-II administration could only be performed in the responder group. Of the 8 patients in the responder group who survived during the AT-II infusion (1 died after stopping the AT-II, but prior to 30 days), there was a significant decrease in the PELOD-2 score from AT-II initiation to AT-II discontinuation (median, 17; range, 4–23 vs median, 11; range, 2–17; p = 0.01). All other characteristics were similar between responders and nonresponders (Table 2).

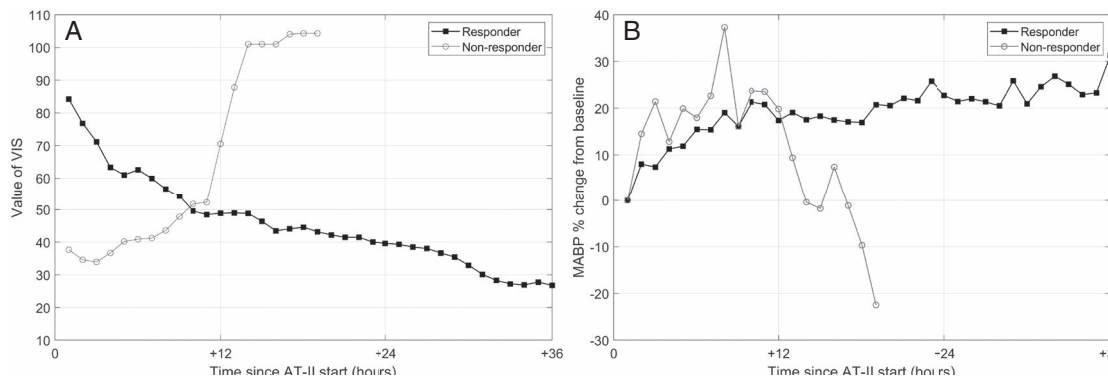
Two patients (14%) had a documented thrombosis, but both were identified prior to AT-II initiation. One patient (7%) experienced ischemia of the right lower extremity, which did not result in AT-II discontinuation. None of the patients in our cohort received pharmacologic VTE prophylaxis during the AT-II infusion. Three patients (21%) were already receiving therapeutic anticoagulation with either bivalirudin or unfractionated heparin. Ten patients (71%) had contraindications to anticoagulation, including 8 patients (57%) with thrombocytopenia and 2 patients (14%) with coagulopathy. Non-pharmacologic VTE prophylaxis with sequential compression devices were used in 2 patients (14%). No other adverse effects were documented.

Discussion

To date, this is the only study to describe response to AT-II, using high-fidelity hemodynamic trends in a pediatric population. Despite the high degree of critical illness within this cohort, treatment with AT-II resulted in a positive acute hemodynamic response in most patients. Classification of response was equally distributed between patients who had a positive ΔMABP or a decrease in VIS at hour 3 of the AT-II infusion. Baseline VIS was higher in those patients with an acute hemodynamic response to AT-II initiation. Our study is also the first to assess severity of illness in pediatric patients across the duration of the AT-II infusion, showing a significant decrease in PELOD-2 score in responders, indicating improved organ function and reduced mortality risk. Documented adverse effects were infrequent and did not require discontinuation of AT-II.

Angiotensin II has robust evidence evaluating efficacy, safety, and predictors of response in the adult population. Angiotensin II effectively increased MABP compared with placebo in adults with vasodilatory shock who were unresponsive to high-dose multimodal vasopressor therapy in the ATHOS-3 trial.[7] *Post hoc* analyses of ATHOS-3 documented a more profound response to AT-II therapy in patients with AKI requiring RRT and decreased mortality with initiation of AT-II at lower doses of other vasopressors.[7,18,19] A subsequent retrospective, multicenter, adult study demonstrated a significant association between favorable hemodynamic response and lower baseline lactate concentrations.[20] Informed by these trials, we explored clinical factors predictive of response to AT-II in pediatric patients. We were unable to reproduce these findings in our small pediatric cohort. However, we evaluated several pediatric-specific characteristics, including age, weight, and left ventricular fractional shortening percentage, and found that responders to AT-II were significantly older with correspondingly higher weights (p = 0.002 and p = 0.004, respectively). We are unable to attribute this difference in response to myocardial maturity because all patients in our cohort with available data (n = 10) had normal left ventricular fractional shortening percentages (Table 2). Using a less specific definition of response, Tezel et al[10] similarly found no difference in clinical characteristics, including need for ECMO, RRT, and steroid use, between survivors and those who died after AT-II infusion. Interestingly, although our time to AT-II initiation was less in the responder group, responders had a significantly

Figure 1. Median vasoactive-inotropic scores (A) and percent change in mean arterial blood pressures (B) in responders vs nonresponders to AT-II. Plots are censored when ≥50% of the subgroup has missing data due to attrition.



AT-II, angiotensin II; MABP, mean arterial blood pressure; VIS, vasoactive-inotropic score.

higher VIS (p = 0.008) than nonresponders. Tezel et al[10] similarly showed a numerically lower time on vasopressors in pediatric patients who survived but with a correspondingly lower NED; however, in both evaluations this difference was not statistically significant.

Data supporting the efficacy and safety of AT-II in the pediatric population are limited to small case series and a single center cohort study.[8–10] Although these studies demonstrated an increase in MABP and/or decrease in requirement for vasopressor support with the use of AT-II, definition of hemodynamic response was subjectively determined and results are limited by intermittent blood pressure assessments collected retrospectively from the EMR. In our study, we used high-fidelity, continuous hemodynamic assessment with retrospective clinical information to categorize response to AT-II in a critically ill pediatric population. We modified previously used adult response definitions to account for criteria not directly applicable to pediatric patients, including varying blood pressure goals for age and use of a validated pediatric vasopressor equivalence score. More specifically, we adapted the definition of blood pressure response used in the ATHOS-3 trial (increase in MABP from baseline of at least 10 mm Hg or an increase to at least 75 mm Hg) to account for young pediatric patients with lower goal blood pressures (increase in MABP from baseline of at least 10 mm Hg or 15%). We defined a clinically meaningful change in VIS of >10 to correlate with a NED change of >0.1 mcg/kg/min, which was the change in background vasopressor criteria used in ATHOS-3 to continue use of study medication.[7] Our definition of response, using both a ΔMABP/% change and ΔVIS at 3 hours, may provide better feedback than either blood pressure response or change in vasopressor requirement alone for clinicians and researchers evaluating AT-II in pediatrics. Consideration of both variables in the first 3 hours of AT-II administration, in addition to patient-specific characteristics, may help with intensivist assessment of response and decisions regarding continuation of treatment. Use of similar criteria should be considered for AT-II response assessment in future prospective studies. Additionally, use of automated, high-fidelity, continuous hemodynamic data obtained from invasive monitoring devices improved precision in identification of response to AT-II in the pediatric population (Figure 1).

The largest pediatric cohort study (Tezel et al[10]) described the use of AT-II in 23 critically ill pediatric patients with catecholamine-resistant vasodilatory shock. Guidelines for use of AT-II were similar between our institutions, resulting in patient populations with comparable PELOD-2 scores at AT-II initiation, rates of invasive mechanical ventilation, use of steroids, and a primary etiology of sepsis. Tezel et al[10] documented an increase in median MABP of 6.5 mm Hg and decrease in the median NED by 18%, 3 hours after initiation of AT-II. We saw a comparatively positive median ΔMABP in our entire cohort of 7 mm Hg at 3 hours with a smaller decrease in median VIS of 9%. While both the VIS in our cohort and the NED in the cohort presented by Tezel et al[10] represent a high vasoactive burden on their respective scales, it is difficult to directly compare NED and VIS given differences in their calculations. Most notably the weight of vasopressin varies drastically; whereas VIS escalates consistently with weight-based titrations common to pediatric practice, NED assumes flat dosing based on adult data and practice and application of this ratio to titratable doses increases the influence of vasopressin on the score.[21] For this reason and given current data supporting validated use in the pediatric population, we opted to use VIS in the current report.[16,17]

Similar to previous pediatric cohorts, mortality in the current study was high; however, this is unsurprising given our use criteria, baseline vasopressor requirements, and PELOD-2 score at AT-II initiation. While the difference in patient ages between responders and nonresponders in this cohort is concerning, it is important to recognize the known worse outcomes in younger patients with septic shock, which could account for the mortality trends observed between groups.[22] Furthermore, this difference may be attributed to ontogenetic changes in the renin-angiotensin-aldosterone system. Endogenous AT-II levels are generally elevated in early infancy, but they decrease with age. This age-related shift may present a potential for therapeutic use of exogenous AT-II, though current data on endogenous AT-II concentrations in infants and children show considerable variability.[23] We believe that age-related differences may have pathophysiologic feasibility and demonstrate the necessity of future studies of the very young. Safety data for AT-II also exist primarily in adult literature indicating a potential for tachyarrhythmias, peripheral ischemia, and deep-vein thrombosis.[7] Among 23 pediatric patients in a recent case series, a single occurrence of digital ischemia and a peripherally inserted central catheter associated thrombus were reported.[10] These reports, in addition to our single report of peripheral ischemia, are unable to establish direct causality given their retrospective design, high baseline vasoactive burden, and inadequate sample size to reliably detect rare adverse effects.

Additional limitations of this cohort study should be noted. Use of medication guidance criteria resulted in many patients receiving AT-II as a last-line therapy as demonstrated by an increasing PELOD-2 score and high VIS at AT-II initiation. This prevents evaluation of a defined place in treatment for AT-II, may confound the number of responders and mortality rate reported, and limits applicability of our results to less critically ill patients. Furthermore, the individualized titration practices of AT-II by each physician may have influenced the response rate, although 79% of patients reached their maximum AT-II dose prior to the 3-hour efficacy mark and there was no difference in time to achieve maximum AT-II dose between responders and

nonresponders (Table 2). Additionally, the retrospective design of this study limited our ability to evaluate adequacy of the volume resuscitation component of the use criteria because it was determined at the discretion of the attending physician. Although we collated vasopressor dose titrations from multiple documentation sources, vasopressor dosing was not collected from an infusion pump integrated with the electronic health record, and therefore calculated VIS scores are limited by manual charting. Similarly, adverse effect reporting relied on physician documentation and association of adverse effects with AT-II was highly subjective.

Conclusions

Angiotensin II has a potential role in the management of pediatric patients with vasodilatory shock based on improvement in MABP observed in adult studies and emerging pediatric data. This study used high-fidelity, continuous hemodynamic monitoring to contribute additional data on the acute hemodynamic response to AT-II in pediatric patients with fluid and vasopressor refractory shock, documenting a positive response in 71% of patients corresponding with a significant decrease in the PELOD-2 scores. While a difference in age, weight, and baseline VIS were noted in our cohort, patient-specific predictors of response to AT-II warrant further exploration.

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 international guidelines on human experimentation and have been approved by the appropriate committees at our institution (Washington University in St. Louis; IRB approval No. 202209151, June 2022). However, given the nature of this study, informed consent was not required by our institution.

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References

1. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. *Pediatr Crit Care Med.* 2020;21(2):e52–e106.
2. Russell JA, Gordon AC, Williams MD, et al. Vasopressor therapy in the intensive care unit. *Semin Respir Crit Care Med.* 2021;42(1):59–77.
3. Wallner M, Duran JM, Mohsin S, et al. Acute catecholamine exposure causes reversible myocyte injury without cardiac regeneration. *Circ Res.* 2016;119(7):865–879.
4. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Crit Care Med.* 2018;46(9):1411–1420.
5. Zimmerman JJ, Williams MD. Adjunctive corticosteroid therapy in pediatric severe sepsis: observations from the RESOLVE study. *Pediatr Crit Care Med.* 2011;12(1):2–8.
6. Bitterman Y, Hubara E, Hadash A, et al. Methylene blue administration for distributive shock states in critically ill children. *Isr Med Assoc J.* 2020;22(7):404–408.
7. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med.* 2017;377(5):419–430.
8. Bailey DM, Chima RS, Tidmarsh GF, Williams MD. Synthetic human angiotensin ii in pediatric patients with vasodilatory shock: a report on two patients. *Crit Care Explor.* 2019;1(8):e0036.
9. Yunge M, Petros A. Angiotensin for septic shock unresponsive to noradrenaline. *Arch Dis Child.* 2000;82(5):388–389.
10. Tezel O, Hutson TK, Gist KM, et al. Utilization of synthetic human angiotensin II for catecholamine-resistant vasodilatory shock in critically ill children: a single-center retrospective case series. *Crit Care Explor.* 2023;5(9):e0978.
11. Mitchell HK, Reddy A, Montoya-Williams D, et al. Hospital outcomes for children with severe sepsis in the USA by race or ethnicity and insurance status: a population-based, retrospective cohort study. *Lancet Child Adolsesc Health.* 2021;5(2):103–112.
12. Pollack MM, Dean JM, Butler J, et al. The ideal time interval for critical care severity-of-illness assessment. *Pediatr Crit Care Med.* 2013;14(5):448–453.

13. Leteurtre S, Duhamel A, Salleron J, et al. PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *Crit Care Med.* 2013;41(7):1761–1773.
14. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl*. 2012;2(1):1–138.
15. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med.* 2015;16(5):428–439.
16. Perizes EN, Chong G, Sanchez-Pinto LN. Derivation and validation of vasoactive inotrope score trajectory groups in critically ill children with shock. *Pediatr Crit Care Med.* 2022;23(12):1017–1026.
17. McIntosh AM, Tong S, Deakyne SJ, et al. Validation of the vasoactive-inotropic score in pediatric sepsis. *Pediatr Crit Care Med.* 2017;18(8):750–757.
18. Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Crit Care Med.* 2018;46(6):949–957.
19. Wieruszewski PM, Bellomo R, Busse LW, et al. Initiating angiotensin II at lower vasopressor doses in vasodilatory shock: an exploratory post-hoc analysis of the ATHOS-3 clinical trial. *Crit Care.* 2023;27(1):175.
20. Wieruszewski PM, Wittwer ED, Kashani KB, et al. Angiotensin II infusion for shock: a multicenter study of postmarketing use. *Chest.* 2021;159(2):596–605.
21. Goradia S, Sardaneh AA, Narayan SW, et al. Vasopressor dose equivalence: a scoping review and suggested formula. *J Crit Care.* 2021;61:233–240.
22. Ruth A, McCracken CE, Fortenberry JD, et al. Pediatric severe sepsis: current trends and outcomes from the Pediatric Health Information Systems database. *Pediatr Crit Care Med.* 2014;15(9):828–838.
23. Sussenbach FK, Burckhardt BB. Levels of angiotensin peptides in healthy and cardiovascular/renal-diseased paediatric population—an investigative review. *Heart Fail Rev.* 2019;24(5):709–723.

JPPT | Single-Center Retrospective Study

Evaluation of Methicillin-Resistant *Staphylococcus aureus* Eradication in People With Cystic Fibrosis

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OBJECTIVE People with cystic fibrosis (pwCF) have impaired bacterial mucociliary clearance, which can result in colonization with pathogens like *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) in the lower airway. Although guidelines for the eradication of *P. aeruginosa* in CF are well-established, MRSA eradication guidelines are lacking. This study aimed to determine the rates of MRSA eradication in pwCF based on a prescribed antibiotic regimen.

METHODS This retrospective chart review included pwCF with a first lifetime positive MRSA respiratory culture or first positive MRSA respiratory culture after at least 1 year of MRSA negativity (minimum of 4 negative respiratory cultures) obtained at Nationwide Children's Hospital between August 1, 2012, and February 28, 2022. Secondary outcomes assessed the impact of adding topical decontamination on MRSA eradication and the time to a subsequent MRSA-positive respiratory culture after completing the eradication regimen.

RESULTS Sixty-two patients were included, and 16% achieved MRSA eradication. Intravenous vancomycin transitioned to oral trimethoprim-sulfamethoxazole achieved the highest eradication rate of 75% ($p = 0.008$). Antibiotics consisting of dual therapy with rifampin and topical decontamination had a higher rate of eradication (25%) compared with antibiotics alone, antibiotics with topical decontamination, or no antibiotics. Four patients had no subsequent MRSA-positive cultures, including 2 patients who did not receive antibiotics.

CONCLUSIONS The transition from intravenous vancomycin to oral trimethoprim-sulfamethoxazole had the highest rate of MRSA eradication. Overall rates of MRSA eradication at 12 months in patients CF using antibiotics with or without topical decontamination are low.

ABBREVIATIONS CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ETI, elexacaftor/tezacafor/ivacaftor; MRSA, methicillin-resistant *Staphylococcus aureus*; NCH, Nationwide Children's Hospital; pwCF people with cystic fibrosis; Pa, *Pseudomonas aeruginosa;* TMP-SMX, trimethoprim-sulfamethoxazole

KEYWORDS antibiotics; cystic fibrosis; eradication; methicillin-resistant *Staphylococcus aureus*

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Introduction

Impaired bacterial mucociliary clearance caused by the production of abnormally thick, sticky mucus in the respiratory tract is a key clinical feature of cystic fibrosis (CF). In healthy individuals, the lower respiratory tract supports minimal bacterial replication. Owing to the changes in the airway environment caused by the defect in the CF transmembrane conductance regulator (CFTR) protein, people with CF (pwCF) can host microorganisms in the lower airway, including pathogens capable of colonization and long-term survival, such as *Pseudomonas aeruginosa* (Pa) and methicillin-resistant *Staphylococcus aureus* (MRSA).[1,2]

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Based on the 2022 Cystic Fibrosis Foundation patient registry, 26% and 15.6% of pwCF had positive respiratory cultures for Pa and MRSA, respectively.[2] Chronic infection with Pa and MRSA in CF is associated with poor outcomes, including increased morbidity and mortality.[3,4] Eradication of colonized bacteria may prevent chronic infection in pwCF. There are well-established guidelines for the eradication of Pa, yet MRSA eradication guidance is lacking.[5] United States guidelines do not address the eradication of MRSA.[6] The United Kingdom Cystic Fibrosis Trust recommends attempting to eradicate MRSA, although it states that the optimal eradication method remains unclear.[7]

The STAR-too randomized trial is considered the first randomized trial in the United States studying a MRSA eradication regimen in pwCF.[8] Forty-five pwCF

between the ages of 4 and 45 years with a positive MRSA respiratory culture were randomized to receive either observation or undergo an eradication protocol. The eradication protocol included the following: oral trimethoprim-sulfamethoxazole (TMP-SMX) or minocycline plus rifampin for 2 weeks; nasal mupirocin and whole-body cleansing with chlorhexidine wipes for 5 days; twice daily gargling with 0.12% chlorhexidine gluconate for 14 days, and enhanced household cleaning. The primary endpoint was MRSA eradication by day 28.[8] The study found that 82% of patients in the treatment group had MRSA-negative respiratory cultures compared with 26% in the observation group on day 28, with a difference of 52% after adjusting for interim reviews ($p < 0.001$). On day 84, 54% of the treatment group were MRSA negative compared with 10% in the observation group.[8]

The duration of the endpoints in the STAR-too trial may not be adequate for assessing the long-term clinical response of MRSA eradication attempts. In comparison, the endpoints of trials evaluating Pa eradication in pwCF are considerably longer than the STAR-too trial. The EPIC and ELITE trials followed patients over 18 and 27 months after initiation of treatment, respectively.[9,10] The ability of a pwCF to sustain long-term eradication may lead to improved outcomes. A cohort study of children in the EPIC trial found that patients who were Pa-free in all quarterly cultures in the preceding 12 months, defined as sustained eradicators, had improved microbiologic outcomes, increased time to *Pa* chronic infection, and increased time to developing mucoid Pa.[11]

The CF Center at Nationwide Children's Hospital (NCH) is a Cystic Fibrosis Foundation–accredited cystic fibrosis center serving more than 500 pediatric and adult pwCF. At our center, the incidence of methicillin resistance within CF respiratory cultures growing *S. aureus* has decreased from 45% (555/1228) in 2012 to 25% (214/862) in 2022. NCH does not have a standardized MRSA eradication protocol in CF, although many providers will follow part or all of the STAR-too protocol. This study aimed to determine the rates of MRSA eradication within 12 months after treatment based on the prescribed antibiotic regimen.

Materials and Methods

Study Design and Participants. This retrospective study included pwCF with an index MRSA isolation from a respiratory culture obtained at NCH between August 1, 2012, and February 28, 2022. An index MRSA culture was defined as the first lifetime positive MRSA respiratory culture or first positive MRSA respiratory culture after at least 1 year of MRSA negativity. Patients included after at least 1 year of MRSA negativity were required to have a minimum of 4 negative respiratory cultures during that period. Respiratory cultures included bronchoalveolar lavage and CF respiratory cultures (expectorated or oropharyngeal). Patients were excluded if the index culture was a small colony variant or TMP-SMX resistant MRSA, if they received systemic antibiotics with MRSA coverage within 30 days before index culture, if they received antibiotics their MRSA isolate was resistant to, if they had less than 1 year of documented follow-up, or if the index MRSA culture was identified from outside of the NCH electronic health record. Antibiotics considered as having MRSA susceptibility included TMP-SMX, minocycline, doxycycline, linezolid, and vancomycin. As this study was intended to demonstrate the ability to achieve routine MRSA eradication, TMP-SMX resistance was chosen as an exclusion criterion because it indicates a MRSA strain would be a small colony variant and, therefore, difficult to eradicate.

Measures. This study aimed to determine the rates of MRSA eradication within 12 months after treatment based on the prescribed antibiotic regimen. Antibiotics with MRSA susceptibility received within 1 year of the index culture, whether prescribed for intentional MRSA eradication or received incidentally for CF exacerbation, were recorded. Antibiotics with MRSA susceptibility were defined as previously listed in the exclusion criteria. If no antibiotics with MRSA sensitivity were prescribed within 1 year of the index culture, patients who otherwise met inclusion criteria were included to assess for rates of self-eradication. Eradication was defined as at least 4 consecutive MRSA-negative respiratory cultures within a minimum of 12 months. Secondary objectives included the eradication rates with the addition of topical decontamination (nasal mupirocin, chlorhexidine mouthwash, or chlorhexidine body wipes or wash) and time to subsequent positive MRSA respiratory culture after completion of the initial eradication regimen. An exploratory analysis examined the likelihood of eradication associated with patient age, type of *CFTR* mutation, *CFTR* modulator therapy, and timing of treatment in relation to the index culture.

Data were obtained through retrospective chart review within the NCH electronic health record. Demographics collected at the date antibiotics were prescribed included age and *CFTR* modulator therapy. If a patient was not prescribed antibiotics, age and *CFTR* modulator therapy were collected on the date of index MRSA culture. The authors also collected data on sex assigned at birth, *CFTR* gene profile, duration of antibiotics, addition of rifampin to the eradication regimen, addition of topical decontamination to the eradication regimen, results of respiratory cultures 12 months after antibiotics for MRSA eradication, and time to a subsequent MRSA-positive respiratory culture after antibiotics for MRSA eradication.

Statistical Analysis. Descriptive statistics are reported as mean ± SD, median (IQR), or total number and percentage. For the group comparisons, a 2-sample *t*-test or Wilcoxon sum rank test was used for the continuous variables, and X^2 or Fisher's exact test were used for the proportions as appropriate. The

significance level was set at $\alpha \leq 0.05$. The data were analyzed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

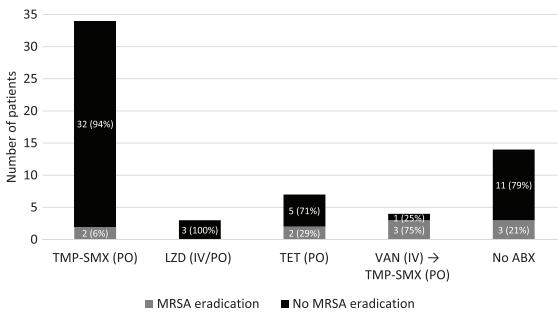
Results

Demographics. There were 74 patients who met inclusion criteria with an index MRSA respiratory culture between August 1, 2012, and February 28, 2022. Twelve patients were excluded for having less than 1 year of follow-up (n = 8), receipt of antibiotics with MRSA coverage within 30 days before index culture (n = 3), or having an index culture that was a small colony variant or TMP-SMX–resistant strain (n = 1). Lung transplant patients were not specifically excluded; however, none were identified. Of patients, 47% were assigned male at birth. The median patient age was 9 years (IQR, 4–23) at the time of antibiotic receipt, with a range of 1 month to 65 years. *CFTR* gene profiles included F508del homozygous (n = 31, 50%), F508del heterozygous (n = 22, 35%), other (n = 8, 13%), and unknown (n = 1, 2%). Of patients, 74% (n = 46) were not prescribed a *CFTR* modulator at the time of the MRSA index culture positivity.

Antibiotic Regimen. Forty-eight patients (77%) received antibiotics with MRSA susceptibility, and 14 (22%) did not receive antibiotics. Antibiotic regimens prescribed included oral TMP-SMX (n = 34), oral and intravenous linezolid (n = 3), oral tetracycline (minocycline and doxycycline; n = 7), and intravenous vancomycin transitioned to oral TMP-SMX (n = 4). Figure 1 shows eradication rates stratified by the prescribed antibiotic regimen. The overall MRSA eradication rate at 1 year was 16%. The antibiotic regimen with the highest rate of eradication was intravenous vancomycin, which was followed by oral TMP-SMX, yielding a 75% eradication rate (p = 0.008). These patients received a range of 4–12 days of vancomycin therapy, with a median duration of 8.5 days before transitioning to oral TMP-SMX. Of 48 patients who received antibiotics, 25 (52%) were prescribed antibiotics for the intentional eradication of MRSA, and 23 (48%) received antibiotics with MRSA susceptibility incidentally for a CF exacerbation. Antibiotics used for intentional MRSA eradication were as follows: TMP-SMX (n = 21), oral linezolid (n = 1), oral minocycline (n = 1), and intravenous vancomycin transitioned to oral TMP-SMX (n = 2). The eradication of those who intentionally received antibiotics for MRSA eradication was 12% (n = 3) compared with 17% (n = 4) in those who received antibiotics for a CF exacerbation. The median duration of antibiotics was 14 days (IQR, 14–14) and did not differ between those who intentionally received antibiotics for eradication compared with those who received antibiotics incidentally for a CF exacerbation. All but 8 patients received 14 days of antibiotics.

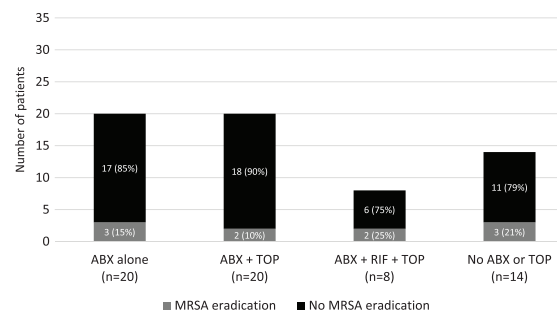
Rifampin and Topical Decontamination. Figure 2 outlines the eradication rates based on the addition of rifampin and topical decontamination. Patients who underwent intentional MRSA eradication (n = 25) were prescribed individual topical products at varying rates as follows: 100% were prescribed nasal mupirocin (n = 25), 84% were prescribed chlorhexidine body wash or wipes (n = 21), and 40% were prescribed chlorhexidine mouthwash (n = 10). Eight patients (32%) were prescribed rifampin and topical decontamination as part of their antibiotic regimen consistent with the STAR-too protocol. These patients received TMP-SMX (n = 7) and minocycline (n = 1).

Figure 1. Number of patients who did or did not achieve MRSA eradication stratified by antibiotic regimen. MRSA eradication was defined as MRSA negativity at 12 months after initiation of antibiotic treatment with a minimum of 4 consecutive MRSA-negative respiratory cultures.



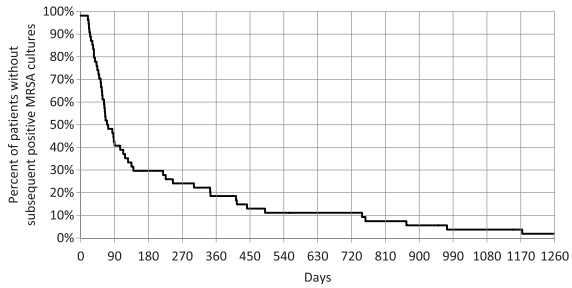
ABX, antibiotics; IV, intravenous; LZD, linezolid; TET, tetracycline; TMP-SMX; trimethoprim-sulfamethoxazole; PO, oral.

Figure 2. Number of patients who did or did not achieve MRSA eradication stratified by antibiotics with or without the addition of rifampin or topical decontamination. Topical decontamination is reported as the addition of at least 1 of the following: nasal mupirocin, chlorhexidine mouthwash, or chlorhexidine body wash/wipes. MRSA eradication was defined as MRSA negativity at 12 months after initiation of antibiotic treatment with a minimum of 4 consecutive MRSA-negative respiratory cultures.



ABX, antibiotics; RIF, rifampin; TOP, topical decontamination

Figure 3. Kaplan-Meier curve of the percentage of patients without subsequent positive MRSA cultures following the index culture.



Time to Subsequent MRSA-Positive Respiratory Culture. Patients had a median follow-up of 4.4 years (IQR, 3.1–7.5) from their index MRSA culture. Figure 3 depicts MRSA culture negativity survival after index MRSA culture. Four patients had no follow-up cultures that were positive for MRSA, including 1 patient who received vancomycin and transitioned to oral TMP-SMX, 1 patient who received oral minocycline, and 2 patients who did not receive any antibiotics.

Exploratory Analysis. The exploratory analysis in the Table assessed MRSA eradication rates stratified by age, *CFTR* gene profile, and *CFTR* modulator therapy. Overall, MRSA eradication rates were found to be higher in patients aged ≥ 18 years of age, those with *F508del* heterozygosity, and those on either ivacaftor or elexacaftor/tezacaftor/ivacaftor (ETI), although the differences were not statistically significant.

Discussion

Despite increased mortality and morbidity from MRSA infection in pwCF, the optimal regimen for MRSA eradication remains unclear. Our study retrospectively evaluated the rates of MRSA eradication at 12 months, based on the antibiotics used in clinical practice. The primary endpoint of 12 months was chosen to assess sustained MRSA eradication, which may be more relevant than initial early eradication (ie, 28 days) to morbidity and mortality outcomes of chronic MRSA infection. The STAR-too protocol uses TMP-SMX or minocycline plus rifampin as the antibiotic regimen for MRSA eradication.[8] Most patients included in our study received oral TMP-SMX (55%) and tetracycline derivatives (11%). Eradication rates with these antibiotics were 6% and 29%, respectively. The transition from intravenous vancomycin to oral TMP-SMX had the highest eradication rate of 75% (n = 4). During the study period, vancomycin therapeutic drug monitoring utilized within our institution targeted serum trough concentrations of 15–20 mcg/mL in pwCF. Area under the curve/minimum inhibitory concentration monitoring for vancomycin was not performed. All vancomycin therapy was initiated while inpatient. Other studies have found varying success in using nebulized vancomycin in combination with oral antibiotics and topical decontamination for MRSA eradication. However, evidence for intravenous vancomycin for MRSA eradication is lacking.[12,13]

In our study, 8 patients followed regimens comparable to the STAR-too protocol. The 12-month eradication rate for these patients was 25%. In comparison, Belarski et al[14] found that the percentage of negative cultures at 12 months in 10 CF patients who completed MRSA eradication using the STAR-too protocol was 70%. The feasibility of using all components of the STAR-too protocol has been impacted by the development of *CFTR* modulator therapy as a standard of care in pwCF. Rifampin is a strong inhibitor of CYP3A4, which induces the metabolism of CFTR modulators, including ETI.[15] Concurrent use of rifampin with *CFTR* modulators

Table. Exploratory Analysis of Factors Impacting MRSA Eradication

Demographics	Number of Patients (N = 62)		p value
	Achieved Eradication (n = 10)	Did Not Achieve Eradication (n = 52)	
Age			
<18 yr	5 (12%)	34 (87%)	0.19
≥18 yr	5 (21%)	18 (78%)	
***CFTR* gene profile**			
F508del homozygous	3 (10%)	28 (90%)	0.358
F508del heterozygous	6 (27%)	16 (72%)	
Other	1 (13%)	7 (87%)	
Unknown	0 (0%)	1 (100%)	
***CFTR* modulator therapy**			
None	5 (11%)	41 (89%)	0.076
Ivacaftor	3 (43%)	4 (57%)	
Lumacaftor/ivacaftor	0 (0%)	3 (100%)	
Tezacaftor/ivacaftor	0 (0%)	1 (100%)	
Elexacaftor/tezacaftor/ivacaftor	2 (40%)	3 (60%)	

is not recommended.[15] Patients in our study more commonly received single antibiotic regimens (not including rifampin) with topical decontamination than antibiotics consisting of dual therapy with rifampin and topical decontamination, which had a lower eradication rate (10% vs 25%). The more frequent use of a single antibiotic regimen at our institution was likely due to our study period largely preceding the publication of the STAR-too trial in 2017. Before this, no MRSA eradication protocol was used at our CF center, and MRSA eradication attempts were not routinely attempted. Cunningham et al[16] published a protocol for the STARter trial, which compared MRSA negativity at 28 days between a treatment group given 2 courses of a single oral antibiotic regimen (without rifampin) plus nasal mupirocin and the control group from the STAR-too trial. At the time of publication, the results of this study were not yet available, and additional studies may help determine the optimal eradication regimen for pwCF on *CFTR* modulator therapy.

Of note, the results of our study call into question the effectiveness of antibiotics in eradicating MRSA. The overall rates of sustained MRSA eradication at our center at 12 months were quite low. Only 10 patients (16%) achieved eradication by any method according to our study's definition. Of these 10 patients, 3 received no antibiotics with MRSA susceptibility within 1 year of their index MRSA culture. Self-eradication was identified in the STAR-too study, as 5 of 19 patients (26%) in the observational group were MRSA negative at day 28.[8] Patients in both our study and the STAR-too trial may have had a transient MRSA infection, which is thought to impact up to 30% of patients with MRSA positive culture.[17] In addition, the use of ETI, a highly effective *CFTR* modulator, may impact a patient's ability to self-eradicate or could prevent MRSA colonization altogether. ETI has been found to have a positive impact on MRSA respiratory cultures in pwCF. A retrospective chart review revealed that patients initiated on ETI experienced a decrease in MRSA culture positivity from 31% to 24% (−6.5%, p = 0.0963) 12 months after starting ETI.[18] Another prospective cohort study found that the rate of MRSA-positive cultures decreased from 43.8% at baseline to 27.5% (−37.2%, p = 0.003) 12 months after ETI initiation.[19] Of 3 patients who self-eradicated within our study, 1 was not receiving a *CFTR* modulator at the time of the index MRSA culture, 1 was prescribed ivacaftor, and 1 was prescribed ETI. Our study was unable to fully describe the impact of *CFTR* modulators on MRSA eradication. Only 23% of index cultures occurred after the approval of ETI in our study. Before that, very few patients would have been eligible for highly effective ivacaftor therapy. Last, it is important to note that although it has been established that chronic MRSA infection leads to a decline in lung function in pwCF, there is a lack of data to show that achieving MRSA eradication improves long-term clinical outcomes. Our study did not assess the clinical impact of achieving or sustaining MRSA eradication, and larger database studies are needed to determine the long-term effects of MRSA eradication in pwCF.

Limitations of this study include its retrospective chart review design and small sample size. The dose and frequency of antibiotic regimens were not assessed. Antibiotic regimens were recorded based on prescriptions within the electronic health record; however, it was not determined whether the prescriptions were filled or picked up by the patient. Evidence of therapeutic vancomycin trough levels was not assessed. It is unknown in our study if patients may have received antibiotics during this period that were not documented in the NCH electronic health record. Adherence to recommended environmental decontamination strategies could not be determined. Our study did not assess for clinical outcomes associated with MRSA eradication or adverse effects of MRSA eradication therapies.

Conclusions

The transition from intravenous vancomycin to oral TMP-SMX had the highest rate of MRSA eradication in our single-center, retrospective study. Future studies are needed to determine the impact of intravenous versus oral antibiotic regimens on MRSA eradication. Patients presenting with an index MRSA culture during an acute pulmonary exacerbation should be treated according to exacerbation guidelines and be considered as having completed a MRSA eradication attempt. Of note, the overall rates of MRSA eradication in pwCF using antibiotics with or without topical decontamination are low. The lack of long-term effectiveness studies supports the need to weigh the risks and benefits when considering antibiotics for eradication following the patient's first MRSA culture, especially in patients on ETI who may be able to achieve self-eradication. More data are needed to determine the impact of *CFTR* modulator therapies on their ability to prevent initial MRSA colonization, enhance MRSA self-eradication, and achieve sustained MRSA eradication with an optimal protocol.

Article Information

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study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors attest to meeting the four criteria recommended by the ICMJE for authorship of this manuscript.

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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References

1. Bhagirath AY, Li Y, Somayajula D, Dadashi M, et al. Cystic fibrosis lung environment and Pseudomonas aeruginosa infection. *BMC Pulm Med*. 2016;16(1):174.
2. Cystic Fibrosis Foundation Patient Registry. 2022 Annual Data Report. 2023. Accessed April 5, 2024. https://www.cff.org/medical-professionals/patient-registry.
3. Emerson J, Rosenfeld M, McNamara S, et al. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol*. 2002;34(2):91–100.
4. Dasenbrook EC, Checkley W, Merlo CA, et al. Association between respiratory tract methicillin-resistant Staphylococcus aureus and survival in cystic fibrosis. *JAMA*. 2010;303(23):2386–2392.
5. Mogayzel PJ, Jr., Naureckas ET, Robinson KA, et al. Cystic fibrosis foundation pulmonary guideline. Pharmacologic approaches to prevention and eradication of initial Pseudomonas aeruginosa infection. *Ann Am Thorac Soc*. 2014;11(10):1640–1650.
6. Saiman L, Siegel JD, LiPuma JJ, et al. Infection prevention and control guideline for cystic fibrosis: 2013 update. *Infect Control Hosp Epidemiol*. 2014;35 Suppl 1:S1–S67.
7. Cystic Fibrosis Trust. Methicillin-resistant staphylococcus aureus (MRSA): report of the UK cystic fibrosis trust infection control working group. Accessed June 3, 2023. https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/MRSA.pdf
8. Muhlebach MS, Beckett V, Popowitch E, et al. Microbiological efficacy of early MRSA treatment in cystic fibrosis in a randomised controlled trial. *Thorax*. 2017;72(4):318–326.
9. Treggiari MM, Retsch-Bogart G, Mayer-Hamblett N, et al. Comparative efficacy and safety of 4 randomized regimens to treat early Pseudomonas aeruginosa infection in children with cystic fibrosis. *Arch Pediatr Adolesc Med*. 2011;165(9):847–856.
10. Ratjen F, Munck A, Kho P, Angyalosi G. Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial. *Thorax*. 2010;65(4):286–291.
11. Mayer-Hamblett N, Kloster M, Rosenfeld M, et al. Impact of sustained eradication of new Pseudomonas aeruginosa infection on long-term outcomes in cystic fibrosis. *Clin Infect Dis*. 2015;61(5):707–715.
12. Dezube R, Jennings MT, Rykiel M, et al. Eradication of persistent methicillin-resistant Staphylococcus aureus infection in cystic fibrosis. *J Cyst Fibros*. 2019;18(3):357–363.
13. Kiefer A, Bogdan C, Melichar VO. Successful eradication of newly acquired MRSA in six of seven patients with cystic fibrosis applying a short-term local and systemic antibiotic scheme. *BMC Pulm Med*. 2018;18(1):20.
14. Belarski E, Pettit R. Outcomes of a methicillin-resistant Staphylococcus aureus (MRSA) eradication protocol in pediatric cystic fibrosis (CF) patients. *Pediatr Pulmonol*. 2020;55(3):654–659.
15. Purkayastha D, Agtarap K, Wong K, et al. Drug-drug interactions with CFTR modulator therapy in cystic fibrosis: Focus on Trikafta®/Kaftrio®. *J Cyst Fibros*. 2023;22(3):478–483.
16. Cunningham F, Caldwell E, Mayer-Hamblett N, et al. Eradication of early MRSA infection in cystic fibrosis: a novel study design for the STAR-ter trial. *ERJ Open Res*. 2022;8(4):00190–02022.
17. Bell SC, Flume PA. Treatment decisions for MRSA in patients with cystic fibrosis (CF): when is enough, enough? *Thorax*. 2017;72(4):297–299.
18. Beck MR, Hornick DB, Pena TA, Singh SB, Wright BA. Impact of elexacaftor/tezacaftor/ivacaftor on bacterial cultures from people with cystic fibrosis. *Pediatr Pulmonol*. 2023;58(5):1569–1573.
19. Sheikh S, Britt RD, Jr., Ryan-Wenger NA, et al. Impact of elexacaftor-tezacaftor-ivacaftor on bacterial colonization and inflammatory responses in cystic fibrosis. *Pediatr Pulmonol*. 2023;58(3):825–833.

JPPT | Education Survey

Evaluation of Research and Scholarship Activities with a Pediatric Curricular Track in a Doctor of Pharmacy Program

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OBJECTIVE The University of Oklahoma College of Pharmacy created the Pediatric Degree Option Program (PDOP) to enhance the knowledge and skills of students in pediatric pharmacy. The purpose of the study was to identify the pediatric-focused research and scholarship activities and outcomes of PDOP graduates.

METHODS This was a retrospective study of PDOP graduates from 2011-2022. The primary objective was to identify the overall number of activities conducted during the PDOP. Secondary objectives included the overall number of peer-reviewed and non-peer reviewed publications, and comparison of the median number of scholarship activities per PDOP graduate between those who did and did not complete a PGY1 residency. Inferential statistics were performed using Mann-Whitney U and Chi-square or Fischer's exact test as appropriate, with an *a priori* p value <0.05.

RESULTS Fifty-two PDOP graduates completed the program. Following graduation, 23 (44.2%) individuals completed a postgraduate year-one (PGY1) residency. PDOP graduates completed a total of 53 research and scholarship activities. The majority (n=44; 83.0%) were original research projects, and 41 (77.4%) graduates published ≥1 manuscript. There was a significant difference in manuscript authorship between graduates who did and did not complete a residency (18 versus 7, p<0.001). Seventeen (26.2%) of the PDOP scholarship projects involved collaboration with a PGY1/postgraduate year-two (PGY2) resident.

CONCLUSIONS This study demonstrated that students enrolled in a curricular track were exposed to various aspects of the research and scholarship process. Many of the activities resulted in a publication or presentation for the PDOP graduate.

ABBREVIATIONS APPE, advanced pharmacy practice experience; IRB, institutional review board; OU, University of Oklahoma; PDOP, Pediatric Degree Option Program; PGY1, postgraduate year one; PGY2, postgraduate year two

KEYWORDS pediatrics; pharmacy; research; manuscripts; curricular track

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Introduction

Children <18 years of age account for approximately 25% of the United States population.[1] Pharmacists play a significant role in the care of pediatric patients. A 2013 white-paper including members of the American College of Clinical Pharmacy Pediatric Practice and Research Network and the Pediatric Pharmacy Association highlighted the impact that pharmacists have on the care of pediatric patients including prevention of medication errors, improvement in quality of life, and economic outcomes, and these findings are still relevant today.[2] Despite the vital role that pediatric pharmacists have, Prescott and colleagues[3] noted that pharmacy students in Doctor of Pharmacy programs only receive a median of 16 hours of pediatric didactic content within pharmacy curricula and only about 20% of students complete an advanced pharmacy practice experience (APPE) rotation in pediatrics. As a result, there remains limited opportunities to provide the knowledge and skills for pharmacy students to expose them to a future career in pediatric pharmacy. In 2020, a joint statement on pediatric education in Doctor of Pharmacy programs was published and provided recommendations on ways colleges of pharmacy could enhance their professional programs.[4] One recommendation was the creation of pediatric pharmacy concentrations or curricular tracks within Doctor of Pharmacy programs. Pediatric curricular tracks provide students with in-depth training in pediatrics, often including at least one didactic elective in pediatric pharmacy, an independent study involving pediatric research, and at least one pediatric focused APPE.[4]

Few programs across the United States offer a pediatric curricular track within their Doctor of Pharmacy program. In 2010, the University of Oklahoma (OU) College of Pharmacy initiated its curricular track, called the Pediatric Degree Option Program (PDOP), with the first graduate of the program in 2011.[5,6] A detailed description of the PDOP that describes the overall purpose, the admission requirements for students, and primary faculty and adjunct support preceptors involved have been described in the literature.[5] One element that was included within the OU College of Pharmacy PDOP was a focus on research and scholarship in pediatric patients. The emphasis on research and scholarship in pediatric patients is important because off-label use of medications in children is common. Petkova and colleagues[7] conducted a systematic review of studies across the world evaluating the incidence of off-label medications in pediatric patients and noted that the number of off-label medications in the United States ranged from 36-57%, depending upon the patient population. Thus, pediatric pharmacists should develop the skills necessary to conduct medication use evaluations and literature searches to investigate the efficacy and safety of medications. As part of the program, PDOP graduates had the opportunity to complete research and scholarship activities. Johnson and colleagues[5] conducted an evaluation on the impact of the PDOP on pediatric-focused APPEs and faculty scholarly productivity. Between 2011-2016, all 30 graduates completed pediatric-focused scholarly activities, defined as participation in original institutional review board (IRB)-approved projects and/or quality improvement activities focused on the pediatric population, as a co-author on a peer-reviewed or non-peer-reviewed manuscript, and as a presenter at a conference on clinical research.[5] At the time the study was conducted, the PDOP program had only been in existence for five years. Additional data has since been collected and can be used to evaluate the types of research and scholarship activities graduates have completed in the PDOP. The purpose of the study was to identify the pediatric-focused research and scholarship activities and outcomes of PDOP graduates over a 12-year timeframe.

Research and Scholarship Activities in the Pediatric Degree Option Program

The PDOP has included 2 different tracks that students can complete to meet the 16 credit hour requirements of the program, track 1 (6 hours of didactic coursework and three APPE rotations) and track 2 (8 hours of didactic course work and two APPE rotations). At the OU College of Pharmacy, these APPE rotations were completed over 1 calendar month and consisted of 4 credit hours per APPE rotation. The requirements of the PDOP from 2011-2022 are listed in Table 1.

From 2010-2014, PDOP graduates completed didactic courses on the Oklahoma City or Tulsa campuses which were delivered synchronously, and pediatric APPE rotations could be completed in the Oklahoma City or Tulsa area. Beginning in 2015, the OU College of Pharmacy underwent a programmatic change where all graduates would complete the Doctor of Pharmacy program on the Oklahoma City campus. The PDOP graduating class of 2018 was the last class to have students on both campuses. As a result of these programmatic changes, the number of pediatric faculty and the overall Doctor of Pharmacy students class size declined.

Graduates in the 2010-2018 classes were given the option to participate in research and scholarship activities. The PDOP directors identified students interested in research and scholarship during one-on-one meetings to discuss each student's individual plan of study. Research and scholarship projects were identified from OU College of Pharmacy faculty and adjunct support preceptors who participated in the PDOP. To complete the research and scholarship activities, students were enrolled in a self-paced, independent study for didactic credit during their second or third professional year and/or one research APPE rotation during their fourth professional year. Alternatively, students could also complete these activities in a volunteer capacity associated with no elective credit during their second, third, or fourth professional year. In addition, students were given the opportunity to participate as research assistants on ongoing IRB-approved research projects. These projects were OU College of Pharmacy faculty and/or adjunct support preceptor-led projects, some of which were assigned as postgraduate year one (PGY1) Pharmacy or postgraduate year two (PGY2) Pediatric pharmacy resident projects. They were also given the opportunity to participate in the development and execution of a new original IRB-approved study or other scholarly manuscripts (i.e., case reports and review articles). To minimize the burden on the OU College of Pharmacy faculty and/or adjunct support preceptors, multiple students may have been assigned to a single project.

Graduates from 2019-present are required to complete track 1. In addition, a decision was made to require all students to participate in an original IRB-approved research project. These PDOP graduates participated in all phases of the research process, including development and submission of an IRB protocol, in a structured manner like the conduct of research with PGY1 Pharmacy residents. As mentioned above, more than one student may have been assigned to a single project. Based on their interests, students may have also volunteered to participate as a research assistant in another ongoing IRB-approved project and/or scholarly manuscript.

Table 1. Didactic and Pediatric-Focused Advanced Pharmacy Practice Experiences in the Pediatric Degree Option Program from 2011-2022

Course	Brief Description	Credit Hours	Required Course During Time Period (Yes, Optional, Not available)	
			2011-2018	2019-2022
Didactic Electives				
Pharmacotherapy considerations in pediatrics	Case-based delivery focusing on ambulatory care topics (hypertension, community acquired pneumonia) and acute care topics (cystic fibrosis exacerbations, septic shock)	3	Yes	Yes
Introduction to pediatric pharmacotherapy	Lecture-based content delivery focusing on drug development, various self-care topics, problem solving, counseling tips, and palatability of medications	2	Optional[a]	Not available[b]
Pediatric medication safety	Discussion-based delivery focusing on best practice for pediatric prescriptions and including hands-on review of prescriptions and utilization of drug information sources	2	Optional[a]	Not available
Independent study	Self-paced course with one-on-one teaching with a faculty member on a quality improvement or research project	1-3	Optional[a]	Yes[c]
APPEs				
In-patient rotations (general pediatrics, PICU, CICU, infectious disease, NICU, hematology/ oncology)	Students participate in multidisciplinary rounds with teaching teams. Activities include medication reconciliation, therapeutic drug monitoring, medication counseling, and provision of drug therapy recommendations.	4	Yes[d]	Yes[d]
Nephrology/kidney transplant	Students participate in rounds with the nephrology in-patient team and attend the renal transplant clinic approximately 1-2 half days per week. Activities include drug information responses, medication reconciliation, medication counseling, provision of drug therapy recommendations, therapeutic drug monitoring, and renal dose adjustment	4	Optional[e]	Optional[e]
Ambulatory care	Students attend various out-patient clinics approximately 5 half-days per week. Activities include disease state management, drug information responses, medication reconciliation, medication counseling, provision of drug therapy recommendations and prescription insurance assistance	4	Optional[e]	Optional[e]
Diabetes camp	Students participate as a counselor for both day-camp and a week-long overnight camp for children with diabetes. Activities include monitoring for, preventing, and treating hypoglycemia and hyperglycemia, carbohydrate counting, calculating insulin doses, administering insulin, assisting with insulin dose adjustments, and administering other medications.	4	Optional[e]	Optional[e]
Research	Student completes a concentrated rotation focused in completion of an ongoing research project and/or scholarly article. Activities include data collection, data entry, data analysis, and/or completion of writing assigned sections of an article	4	Optional[e]	Yes

APPE = Advanced pharmacy practice experiences; CICU = Cardiac intensive care unit; NICU = Neonatal intensive care unit; PICU = Pediatric intensive care unit

[a] Students could select from these courses in order to meet the didactic credit hour requirement for track 1 (6 hours of didactic course work) and track 2 (8 hours of didactic course work)

[b] Course no longer offered beginning with 2019 PDOP graduates

[c] Beginning with the PDOP graduates in 2019, the independent study course was approved for 3 credit hours and took place in the Fall semester of the 3rd year of the Doctor of Pharmacy program.

[d] Students had to complete ≥1 in-patient rotation.

[e] Students could select the remaining 1-2 APPE rotations based on the track that the PDOP graduate completed (i.e., track 1 required three APPE rotations and track 2 required two APPE rotations), preceptor availability, and the PDOP graduate's interests.

Table 2. Overview of the Research and Curriculum within the Pediatric Degree Option Program Beginning with the PDOP Graduating Class of 2019

Course	Year of the Professional Program	Description of Research and Scholarship Activities	Topics Covered
Independent study didactic elective	Third	• As part of the content for the course, students complete research training required by the IRB and additional topics regarding clinical research • Students are assigned a pediatric pharmacy research project during the independent study and work on the development of the IRB protocol and present the presentation of the research-in-progress at the end of the semester	• CITI/IRB training • Overview of clinical research design • Developing a great research question • Working with your research team • Ethical considerations in research • Off-label use of medications • Expanded access/compassionate use of medications • How to deliver a poster/platform presentation
Research APPE rotation	Fourth	• The students complete the assigned research project from their independent study course • Activities include data collection, data entry, data analysis, completion of writing assigned portions of their research article, and completion of a peer-review of manuscript submitted for publication with a preceptor • Students are assigned additional topic discussions for medical writing and peer-review	• Medical writing • Abstract writing • Peer-review of manuscripts

APPE = Advanced pharmacy practice experiences; CITI = Collaborative Institutional Training Initiative; IRB = Institutional review board

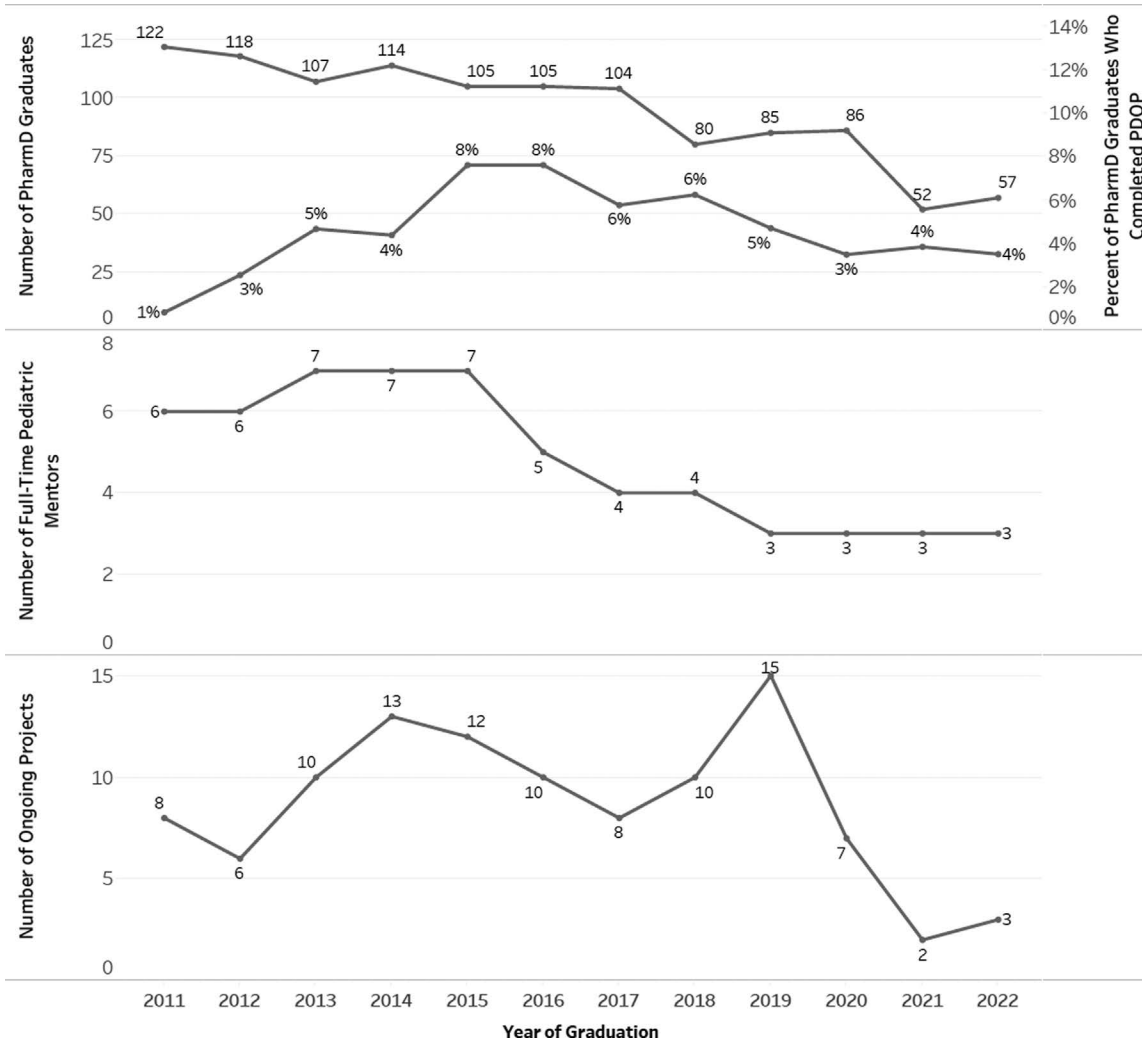
For all research and scholarship activities, one of the OU College of Pharmacy faculty served as the research mentor. Depending on the research and scholarship project, other OU College of Pharmacy faculty or other adjunct support preceptors participated as members of the research team. Additional OU College of Pharmacy faculty or staff were employed to assist with the qualitative or quantitative analyses. To prepare PDOP students for work on research and scholarship activities, they participated in several topic discussions throughout their experiences. Beginning with the 2019 PDOP graduates, these topic discussions were more formalized. Table 2 describes an overview of the research and scholarship activities and topics that were covered through their required coursework. It should be noted that all students participating in original IRB-approved research projects were required to complete the required IRB training through the Collaborative Institutional Training Initiative.[8]

Materials and Methods

Study Design. This study was a retrospective cohort study of OU College of Pharmacy PDOP graduates from 2011-2022. Graduating students were identified by records maintained by the PDOP director that contain the name of the student, graduating year, research and scholarship activities, coursework completed, and initial position after graduation, and these records were utilized to provide ongoing reports to the OU College of Pharmacy Dean's Office and the Curriculum and Assessment Committees for accreditation reports. The 2022 end date was selected for the study to allow time for publication, as previous studies have identified the mean time to publication of research projects by pharmacy trainees is approximately 2 years after initiation of the project.[9,10] IRB approval was waived for this study as it was based on de-identified data that was maintained in the existing database for the PDOP.

Data Collection and Study Objectives. Data collection included the PDOP track completed, the type of APPE rotations and didactic courses that students completed, the graduation year, and types of research and scholarship activities. Specific data collected for each project included type of research and scholarship activity (i.e., original IRB-approved research, case report/case series, or review article), if a manuscript was published, the type of presentation given (platform, poster, or both), and if the project received an award. The number of active ongoing projects per year were collected and included a count of projects in any phase of development (e.g., protocol development, data collection, manuscript preparation). If a project spanned more than one year, it would be included in the count for subsequent years.

Figure 1. Overview of Pediatric Degree Option Program (PDOP) Graduates, Projects, and Number of Pediatric Faculty Members Per Year



The primary objective was to identify the overall number of pediatric-focused research and scholarship activities. Research and scholarship activities were defined as participation in original IRB-approved pediatric focused projects, as a co-author on a peer-reviewed or non-peer-reviewed manuscript, and as a presenter at a conference on clinical research.[5] Any involvement on an original IRB-approved research or scholarly manuscript (i.e., case report/case series, or review article) were counted as one project. For example, development of an IRB protocol and data collection on the same project counted as one project. Projects that were not submitted for IRB-approval (e.g., drug monographs, formulary projects) were not included as part of this definition since they did not meet the definition for human-subjects research. Secondary objectives included the overall number of original IRB-approved research projects, peer-reviewed and non-peer reviewed publications, and authorship and contributor roles on peer-reviewed and non-peer-reviewed publications. Contributors on manuscripts were defined as those who do not meet the four criteria for authorship as proposed by the International Committee of Medical Journal Editors and were acknowledged as participants in published manuscripts.[11] Other secondary objectives included the overall number of poster and platform presentations, the initial position of each PDOP graduate after graduation and whether they collaborated on a PGY1 Pharmacy or PGY2 Pediatric pharmacy resident project, and a comparison in the median number of scholarship activities per PDOP graduate between those who completed a PGY1 Pharmacy residency versus those who did not.

Statistical Analyses. Descriptive statistics were employed. Continuous data were compared using Wilcoxon rank-sum test. Categorical data were compared

Table 3. Overview of Track Completed and Research Coursework in PDOP Graduates from 2011-2018 and 2019-2022 (n=52)

Variables	2011-2018 (n=41)[a]	2019-2022 (n=11)[b]
	Number (%)	
Track completed		
Track 1	35 (85.4)	11 (100)
Track 2	6 (14.6)	—
Involvement in research	36 (87.8)	11 (100)
Research coursework completed:		
Independent study for self-directed learning	32 (78.0)	11 (100)
APPE research rotation	32 (78.0)	11 (100)
Either independent study didactic elective or APPE research rotation	39 (95.1)	11 (100)
Both independent study didactic elective and APPE research rotation	25 (61.0)	11 (100)

APPE = Advanced pharmacy practice experience

[a] From 2011-2018, the number of graduates per year were 2011 (n=1), 2012 (n=3), 2013 (n=5), 2014 (n=5), 2015 (n=8), 2016 (n=8), 2017 (n=7), and 2018 (n=4).

[b] From 2019-2022, the number of graduates per year were 2019 (n=4), 2020 (n=3), 2021 (n=2), and 2022 (n=2).

using Chi-square tests or Fisher's Exact tests, as appropriate. Data analysis was performed using SAS v9.4 (Statistical Analysis System; Cary, North Carolina), with the a priori alpha being set at $p<0.05$.

Results

Demographics of PDOP Graduates. There was a total of 52 students evaluated that were enrolled in the PDOP between the years of 2011 to 2022, including 41 graduates from 2011-2019 and 11 graduates from 2019-2022. Figure 1 provides an overview of the total number of the OU College of Pharmacy Doctor of Pharmacy graduates per class, and the percentage of PDOP graduates per Doctor of Pharmacy class from 2011-2022. The majority of PDOP graduates completed track 1 (n=46; 88.5%). Table 3 provides an overview of the track completed and the research coursework that PDOP graduates completed. Forty-seven students (90.4%) participated in at least one research or scholarship activity. The remaining five students were PDOP graduates between the timeframe of 2011-2018. Three of these five students completed an independent study didactic elective where they worked on non-IRB-approved projects. The majority (n=35; 67.3%) of PODP graduates completed both an independent study didactic elective and an APPE research rotation. Figure 1 provides the number of full-time pediatric faculty mentors per year from 2011-2022.

Table 4. Description of Pediatric Research and Scholarship Activities (Projects) (n=53)

Variable	Number (%) or Median (IQR)
Type of project:	
Original IRB-approved research	44 (83.0)
Review article	3 (5.7)
Case report/case series	6 (11.3)
PGY1 Pharmacy or PGY2 Pediatric pharmacy resident project:	
Original IRB-approved research	15 (28.3)
Case report/case series	2 (3.8)
Manuscript published	41 (77.4)
Presentation given	29 (54.7)
Presentation type:	
Platform	1 (1.9)
Poster	26 (49.1)
Both	2 (3.8)
Award received for project	5 (9.4)
Number of students per project	1.0 (1 to 2)

IRB = Institutional review board; PGY1 = Postgraduate year one; PGY2 = Postgraduate year two

Twenty-three (44.2%) completed a PGY1 residency after graduation. For the remaining 29 (54.7%) PDOP graduates 19 (36.5%) took a position practicing in community pharmacy, 9 (17.3%) took a position in a health-system, and 1 (1.9%) took a position as a certified specialist at a poison information center.

Research and Scholarship Activities. A total of 53 unique pediatric-focused research and scholarship activities were identified. A summary of these projects can be found in Table 4. Figure 1 also provides the number of ongoing active research and scholarship projects per year from 2011-2022. The median [interquartile range (IQR)] number of ongoing research and scholarship projects per year was 9 (6.8-10.5). The number of PDOP graduates who worked on each activity varied with a median of one PDOP graduate per project. Twenty (37.7%) projects had ≥1 PDOP graduate on the project, and the maximum number of PDOP graduates working on a project was six. The most common activity was an original research IRB-approved project (n=44; 83.0%). Of these 44 projects, 24 (54.5%) involved voluntary participation by the PDOP graduates on a project in progress, including 15 (34.1%) that were an assigned pharmacy resident project and nine that (20.4%) were OU College of Pharmacy faculty and/or adjunct support preceptor project. The remaining 20 (45.5%) were a project that was developed specifically for the PDOP graduates, and they were involved throughout the entire development and execution of the project.

Most projects (n=41; 77.3%) were published (Table 4). PDOP graduates delivered 29 (54.7%) presentations as

a platform and/or poster presentation at various professional conferences both locally and nationally. Only three of these presentations involved a research and scholarship activity that was not ultimately published. Of the 17 resident projects, five (29.4%) had PDOP graduate co-authors on the published peer-reviewed manuscript and six (35.3%) had PDOP graduate co-authors on the platform and/or poster presentations. Five (13.9%) of the 36 projects that were non-PGY1 or PGY2 pharmacy resident projects received a local or national research award.

Comparison of Research and Scholarship Activities. Table 5 provides a comparison of research and scholarship activities per PDOP graduate who did and did not complete a PGY1 Pharmacy residency. There was not a significant difference in the types of projects between those who did and did not complete a PGY1 Pharmacy residency, nor was there a significant difference in manuscript publication. A greater number of PDOP graduates who completed a PGY1 Pharmacy residency were co-authors on a manuscript versus those who did not complete a PGY1 Pharmacy residency (18 versus 7, p<0.001). In contrast, a greater number of PDOP graduates that did not complete a PGY1 Pharmacy residency were listed as contributors on manuscripts in comparison to those that completed a PGY1 Pharmacy residency, 15 versus 6, p=0.06. There were significantly more PDOP graduates that completed a PGY1 Pharmacy residency who presented an original IRB-approved research project at local (9 versus 3, p<0.001) and national (21 versus 14. p<0.014) conferences versus those who did not complete a residency.

Discussion

This study evaluated the research and scholarship output of students enrolled in the pediatric-focused curricular tracks or concentrations over a 12-year period. Our findings demonstrate that the majority (n=47; 90.4%) of PDOP graduates were successfully engaged in various aspects of the research process, resulting in meaningful scholarly contributions to the field of pediatric pharmacy. Several studies have described outcomes of curricular tracks or concentrations within Doctor of Pharmacy programs.[5,6,12–20] To our knowledge, there are only 3 pediatric pharmacy curricular tracks or concentrations offered within Doctor of Pharmacy programs.[5,6,19,21] All three programs involve students in pediatric research. Given the number of medications that are used off-label in pediatrics and the concerns for establishment of pediatric medication safety and efficacy, the goal would be that these original IRB-approved research studies and scholarly manuscripts completed by students would fill gaps in the literature.

Most of these other studies evaluating outcomes of curricular tracks or concentrations have focused on other clinical specialties (e.g., adult acute care, critical care, psychiatry, geriatrics), leadership/pharmacy business management, and global health and have not included a focus on development of research skills. Parsons and colleagues[12] conducted a survey of curricular tracks or concentrations within 134 Doctor of Pharmacy programs and had 65 (48.5%) respondents. Sixteen (11.9%) respondents offered 38 curricular tracks or concentrations. Only seven (18.4%) of the 38 curricular tracks or concentrations required a project, but it was not apparent if this project was a research or scholarship activity, or if it was a non-IRB-approved project that was not intended to be published or presented outside of the institution. Volger and colleagues[19] reported on their experience with a pediatric curricular track or concentration at Southern Illinois University Edwardsville School of Pharmacy. Their program required all students to complete a clinical research project within an independent study course during their third professional year. These findings align with the current OU College of Pharmacy PDOP graduate requirements that were implemented in 2019. However, their study did not provide specific details on the outcomes of their projects, so it is difficult to compare to our study.

The OU College of Pharmacy PDOP graduates completed or assisted with 44 original IRB-approved research projects. In the previous eight studies describing their curricular track or concentration, six mentioned that they offered students opportunities to participate in original IRB-approved projects.[13–20] It is difficult to compare these studies with our study because not all of them provided a specific number of original research projects completed, and some of the studies only included an evaluation 1-3 years after initiation of their program. We found no statistical difference in the number of original IRB-approved projects between those who did and did not complete a PGY1 pharmacy residency. Four of the other studies evaluating curricular tracks or concentrations did report the number of students who went on to complete a PGY1 Pharmacy residency after graduation, but they did not compare differences in those who did and did not complete a residency program.[16–19] Given that until 2019 participation in research was an option with the PDOP, our findings seem to suggest that students who are not residency bound still seek out opportunities for participation in research activities. It is plausible that their participation in these activities may help foster critical thinking and time management skills that may aid students no matter their postgraduate career paths.

Within the OU College of Pharmacy PDOP program, several of our projects involved "layered learning" with other PDOP students or pharmacy residents. Fifteen (34.1%) of our 44 original IRB-approved research projects were an assigned residency project, and one-third had ≥1 student working on the same project. Involving multiple students and residents on one project is a "layered learning" approach that could help ensure

Table 5. Comparative Analysis of Aggregate and Individual Research and Scholarship Activities Among PDOP Graduates with and without a PGY1 Residency (n=52)

Variable	Overall (N=52)	Residency (n=23)	No Residency (n=29)	P-value
	Number (%) and Median (IQR)			
Projects				
Types of projects:				
Original IRB-approved research	33 (63.5)	17 (73.9)	16 (55.2)	0.16
Review article	4 (7.7)	3 (13.0)	1 (3.4)	0.31
Case report/case series	8 (15.4)	5 (21.7)	3 (10.3)	0.44
Manuscripts				
Published ≥1 manuscript	38 (73.1)	19 (82.6)	19 (65.5)	0.168
Manuscript type:				
Peer-reviewed	38 (73.1)	19 (82.6)	19 (65.5)	0.17
Non peer-reviewed	1 (1.9)	1 (4.3)	--	0.44
Role on manuscript:				
Author	25 (48.1)	18 (78.3)	7 (24.1)	<0.001
Contributor	21 (40.4)	6 (26.1)	15 (51.7)	0.06
Total number of manuscripts	1 (1 to 2)	2 (1 to 2)	1 (1 to 1)	0.40
Presentations				
Presented at a conference	35 (67.3)	21 (91.3)	14 (48.3)	0.001
Presentation type:				
Platform	3 (5.8)	2 (8.7)	1 (3.4)	0.58
Local poster	12 (23.1)	9 (39.1)	3 (10.3)	<0.001
National poster	33 (63.5)	21 (91.3)	12 (41.4)	0.014
Total number of presentations	2 (2 to 3)	3 (2 to 3)	2 (1 to 3)	0.03

IRB = Institutional review board

timely completion of the research project. Coons and colleagues[17] developed a Pharmacotherapy Scholars program at the University of Pittsburg School of Pharmacy that focused on preparation for postgraduate residency training from 2013-2019. They noted 60 students completed the program and reported that they had as many as eight students on one research project. Most of our projects had 1-2 students, but we did have one large project in which six students were working on data collection. The "layered learning" approach may provide pharmacy residents with opportunity for mentorship and co-precepting responsibilities.

The majority of PDOP graduates in our program published ≥1 manuscript with their original IRB-approved research project or scholarly manuscript (n=41; 77.4%) and presented their research project at a research conference (n=29; 54.7%). Other studies evaluating curricular tracks or concentrations evaluated both metrics and reported that students presented their research at conferences and several students were able to publish their findings.[16–20] However as noted previously, the total number of projects was not reported, and the timeframe for some of these studies was only 1-3 years after inception. So, it would be difficult to compare the findings to our study. In our study, we did find that a significantly higher number of PODP graduates who completed a PGY1 Pharmacy residency were an author on a published manuscript versus those who did not complete a residency. None of the other studies evaluating curricular tracks or concentrations evaluated this metric. These results suggest that those who are focused on postgraduate training may be more motivated to complete all phases of a research or scholarship activity that may lead to publication to enhance their competitiveness as a PGY1 Pharmacy resident.

Aside from the impact on the individual PDOP graduates, the research and scholarship activities did help increase scholarly productivity for the faculty mentors. Johnson and colleagues[5] evaluated the number of scholarship activities pre- (2005-2010) versus post-implementation (2011-2016) of the PDOP program for the first five years of the program. In this study, they found that implementation of the PDOP program allowed for twice the number of scholarship projects for participating faculty compared to baseline. The number of faculty members did decline over time with the programmatic change that occurred with the OU College of Pharmacy beginning in 2014. However, for most projects, there was more than one faculty member who served as a mentor on these projects, so

this helped offset the time commitment of a particular faculty member. Unfortunately, in this study, we were unable to quantify the number of mentorship hours that faculty spent to provide guidance to the PDOP graduates on their projects and teaching activities related to research. To help streamline delivery of teaching content, a standardized research curriculum was implemented (Table 2).

This study has several limitations. First, this was a single-center study, so the results may not be generalizable to all Doctor of Pharmacy programs as they may not have a pediatric curricular track or concentration, and/or they may not have a required research and scholarship component as part of their curricular track or concentration. Second, for our PDOP, there were anywhere from 3-7 OU College of Pharmacy pediatric-focused faculty and 2-4 adjunct support preceptors in addition to the OU College of Pharmacy faculty/staff who helped with data analysis during the 12-year timeframe and were able to serve as a mentor for research and scholarship activities. Our results would have likely been different if we did not have this level of support to guide the PDOP graduates on their research and scholarship activities. Third, there was a reduction in the number of Doctor of Pharmacy students did decrease over the 2011-2022 timeframe. However, the percentage of PDOP graduates per Doctor of Pharmacy class ranged from was between 3-8% from 2011-2022. Fourth, as noted, graduates in the PDOP were not required to participate in research until the 2019 graduating class, and graduates from 2019-2022 were required to complete Track 1 with more formalized research topic discussions. However, as we noted, 90% of PDOP graduates participated in ≥1 research or scholarship activity, and most (67%) completed Track 1 including an independent study and APPE research rotation. Last, the retrospective nature of the study limits our ability to assess the quality of the research experiences or the long-term impact on graduates' careers. Bennett and colleagues[22] surveyed pharmacy residents who participated in a team-based research program associated with the OU College of Pharmacy and found that participation in a structured research program was associated with future participation in clinical research after residency graduation and overall confidence in mentoring of students and residents in clinical research. However, it is unclear if we would note similar findings with PDOP graduates, as their experiences were within a Doctor of Pharmacy program rather than a postgraduate training experience.

Conclusion

This study demonstrates that a structured pediatric curricular track with a strong emphasis on research can successfully engage pharmacy students in meaningful scholarship activities. The high rates of project completion and output in terms of publication and presentation suggest that such programs can contribute significantly to students' research skills and to the broader field of pediatric pharmacy. Future efforts should focus on further optimizing research curricula within Doctor of Pharmacy programs and evaluating the long-term impact on graduates' careers and contributions to pediatric medication use and safety.

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 has been approved by our institution review board. Given the nature of this study, informed consent and assent were not required.

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References

1. Childstats.gov. POP2 children as a percentage of the population: persons in selected age groups as a percentage of the total US population, and children ages 0–17 as a percentage of the dependent population, 1950–2022 and projected 2023–2050. Accessed October 22, 2024. http://www.childstats.gov/americaschildren/tables/pop2.asp
2. Bhatt-Mehta V, Buck ML, Chung AM, et al. Recommendations for meeting the pediatric patient's need for a clinical pharmacist: a joint opinion of the Pediatrics Practice and Research Network of the American College of Clinical Pharmacy and the Pediatric Pharmacy Advocacy Group. *Pharmacotherapy*. 2013;33(2):243–251.
3. Prescott WA, Woodruff A, Prescott GM, Albanese N, Bernhardi C, Doloresco F. Introduction and assessment

of a blended-learning model to teach patient assessment in a Doctor of Pharmacy Program. *Am J Pharm Educ*. 2016;80(10):176.
4. Cox CL, Todd TJ, Lubsch L, et al. Joint Statement on pediatric education at schools of pharmacy. *Am J Pharm Educ*. 2020;84(8):ajpe7892.
5. Johnson PN, Gildon BL, Condren M, et al. Description of a pediatric degree option program in a doctorate of pharmacy curriculum and its impact on pediatric-focused advanced pharmacy practice experience rotations and faculty scholarly productivity. *Curr Pharm Teach Learn*. 2018;10(5):627–636.
6. Johnson PN, Gildon BL, Condren M, Miller JL, Hagemann TM, Lewis TV, John B, Farmer KC. A survey of Pediatric Degree Option Program graduates in a doctor of pharmacy curriculum: confidence and initial employment position. *Curr Pharm Teach Learn*. 2019;11(12):1296–1302.
7. Petkova V, Georgieva D, Dimitrov M, Nikolova I. Off-label prescribing in pediatric population—literature review for 2012-2022. *Pharmaceutics*. 2023;15(12):2652
8. Collaborative Institutional Training Initiative Program. Accessed December 6, 2024. https://about.citiprogram.org/
9. Miller JL, Lewis, TV, Walling J, O'Donnell A, Neely SB, Johnson PN. Publication rates of pediatric-focused resident research projects presented at the Pediatric Pharmacy Association Burce Parks Memorial Residency Showcase. *J Pediatr Pharmacol Ther*. 2021;26(2):163–171.
10. Olson K, Holmes M, Dang C, et al. Publication rates of abstracts presented by residents at the Western States Conference. *Am J Health-Syst Pharm*. 2012(1);69:59–62.
11. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Accessed October 23, 2024. www.icmje.org/icmje-recommendations.pdf
12. Parsons KA, Nemec EC, Maynard KM, Welch B. Specialization within pharmacy education: a survey of curricular track or concentration offerings. *Curr Pharm Teach Learn*. 2018;11(4):1296–1302.
13. New J, Garner S, Ragucci K, Spencer A. An advanced clinical track within a Doctor of Pharmacy program. *Am J Pharm Educ*. 2012;76(3):43.
14. Brahm NC, Davis TS. Development of a psychiatric pharmacy elective track. *Curr Pharm Teach Learn*. 2012;4(4):267–272.
15. Smith MJ, Wilson J, George DL, Laster K, Filippo C, Spies A. Emotional intelligence scores among three cohorts of pharmacy students before and after completing the University of Oklahoma College of Pharmacy's Leadership Degree Option Program. *Curr Pharm Teach Learn*. 2018;10(7):911–917.
16. Slazak EM, Prescott GM, Doloresco F, Woodruff AE, Prescott WA. Assessment of a scholars program designed to enhance pharmacy students competitiveness for postgraduate residency training. *Am J Pharm Educ*. 2020;84(7):7728.
17. Coons JC, Benedict N, Seybert A, et al. A pharmacotherapy scholars program to provide intensive training to enhance students' postgraduate readiness. *Am J Pharm Educ*. 2019;83(9):7327.
18. Morbitzer KA, McLaughlin JE, Ozawa S, et al. Implementation and initial evaluation of a research and scholarship training pathway in a doctor of pharmacy curriculum. *Am J Pharm Educ*. 2021;85(1):8079.
19. Vogler C, Sheley J, Lubsch L. Clinical pharmacy specializations at a school of pharmacy: development and implementation. *Curr Pharm Teach Learn*. 2023;15(12):1040–1045.
20. Smith SE, Newsome AS, Hawkins A, et al. Teaching research skills to student pharmacists: a multi-campus multi-semester applied critical care research elective. *Curr Pharm Teach Learn*. 2020;12(6):735–740.
21. University of Connecticut School of Pharmacy. Pediatric Track. https://pharmacy.uconn.edu/pharm-d-degree/pediatric-track/. Accessed October 23, 2024.
22. Bennett KK, Fox A, Miller JL, Neely SB, Dennis V, Johnson PN. A survey of post-graduate pharmacy residency graduates involved in a team-based research programme: involvement and confidence in research and scholarship activities. *Pharmacy Education*. 2023;23(1):430–439.

JPPT | Retrospective Single Center Study

Retrospective Evaluation of Dosing Effects of Bumetanide Continuous Infusions in the Pediatric Cardiac Intensive Care Unit

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OBJECTIVE Bumetanide is commonly used to achieve diuresis and alleviate fluid overload in pediatric cardiac intensive care unit (PCICU) patients. This study aims to describe the dosing, efficacy, and safety of bumetanide continuous infusion (CI) regimens used in PCICU patients.

METHODS This single center, retrospective study included patients <6 years of age, admitted to the PCICU who received a bumetanide CI for at least 6 hours. The primary outcome was identifying doses and the total duration of bumetanide CI regimens. Secondary efficacy outcomes were determined by the ability to achieve negative fluid balance within 24 hours and the time to reach negative fluid balance. Secondary safety outcomes were based on the prevalence of electrolyte imbalances and renal impairment.

RESULTS Data from 90 pediatric patients represented 106 hospital encounters in this study. The median age of our study population was 137 days, with a median weight of 4.3 kg. The dose ranged from 0.005 mg/kg/hr to 0.3 mg/kg/hr, with a median dose of bumetanide of 0.046 mg/kg/hr and a median duration of 5.8 days. The change in serum electrolytes and creatinine during baseline and peak infusion rates was not clinically significant.

CONCLUSION This study remains the largest pediatric study to date describing the dosing, efficacy, and safety concerns of bumetanide CI in the PCICU population. However, using a high-dose bumetanide drip >0.1 mg/kg/hr may not improve the overall outcome, and future studies can explore specific advantages of its use in neonates undergoing cardiac surgery.

ABBREVIATIONS AVSD, atrioventricular septal defect; CI, continuous infusion; CRRT, continuous renal replacement therapy; CV, cardiovascular; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; IV, intravenous; PCICU, pediatric cardiac intensive care unit; PD, peritoneal dialysis; SCr, serum creatinine; VA, venoarterial; VAD, ventricular assist device

KEYWORDS bumetanide; cardiac intensive care unit; continuous infusion; critically ill; pediatrics

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Introduction

The pediatric cardiac intensive care unit (PCICU) plays a critical role in managing pediatric patients with complex congenital heart defects and those undergoing cardiac surgery. One challenge often encountered in these patients is fluid overload, which can lead to compromised cardiac function, respiratory distress, and other adverse clinical outcomes.[1] Effective fluid management strategies are essential to achieving optimal hemodynamic stability and improving patient outcomes in the PCICU setting.[1]

Loop diuretics, such as bumetanide, are commonly used to achieve diuresis and alleviate fluid overload in these patients owing to their rapid onset of action and potent diuretic effects. These agents are indicated in various clinical conditions, including generalized edema, heart failure, and oliguria.[2] Owing to inadequate response to furosemide or furosemide plus a thiazide diuretic and limited intravenous (IV) drug compatibility seen with furosemide, bumetanide continuous infusions (CIs) have been increasingly used at our institution, particularly within our PCICU. While bumetanide is often administered intermittently, CI administration has gained increasing attention as a potential strategy to provide more constant and predictable drug exposure, potentially leading to more controlled diuresis and fewer fluctuations in fluid balance.[3] Currently, bumetanide is not approved by the US Food and Drug Administration

for administration in pediatric patients, even though it has been used consistently for more than a decade. Compared with furosemide, bumetanide has greater bioavailability and potency, with a conversion rate of 20:1 for IV furosemide to IV bumetanide and 40:1 when converting oral furosemide to IV bumetanide.[4] Based on the established furosemide CI doses of 0.05 to 0.4 mg/kg/hr and having this conversion in mind, bumetanide CI dosing regimens generally range from 0.00125 to 0.01 mg/kg/hr.[4] We started at a slightly higher dose given resistance of loop diuretics over time, inadequate response to increasing furosemide doses, and propensity for renal insufficiency in patients with significant cardiac disease.

Bulkley and colleagues[5] were the first to evaluate bumetanide CIs in critically ill neonates and children and reported mean doses of 0.05 mg/kg/hr. McCallister and colleagues[6] also reviewed the use of bumetanide CI in critically ill pediatric patients, where 58% of patients were admitted to the PCICU, and mean doses up to 0.01 mg/kg/hr were used. These studies reported significant variations in mean doses of bumetanide CI. Owing to the limited data available to support a definitive dosing regimen of bumetanide CI, specifically in the pediatric patient population, the purpose of this study was to describe the dosing, efficacy, and safety of bumetanide CI regimens used in PCICU patients.

Materials and Methods

Study Design. This was a single center, descriptive, retrospective study performed at the University of Florida (UF) Health Shands Hospital in Gainesville, FL. Our PCICU unit is a quaternary care center with 23 beds for patients with complex congenital heart disease. Electronic health records were used to identify pediatric patients admitted to the PCICU who received a bumetanide CI.

Inclusion criteria were met if patients were younger than 6 years, admitted to the PCICU, and received bumetanide CI for at least 6 hours as part of their clinical management between January 1, 2018, and September 1, 2022. The age cutoff 6 years was used to allow for a more homogenous patient population and to evaluate the dosing effects in younger children, because previous studies that included pediatric patients up to 18 years of age have reported significant variations in dosing regimens.[5] Patients with incomplete or missing medical records were excluded from the study. If a patient had multiple admissions during the study time frame, each encounter with bumetanide CI was assessed as an individual occurrence.

Data Collection. A comprehensive review of medical records was conducted. Historical patient data were collected by manual chart review, and bumetanide CI was determined by clinical documentation on the medication administration record. Data collection included relevant demographic information (i.e., age, sex, weight); admitting cardiac problem or diagnosis; dosing regimens, including doses and duration of CI; previous use of furosemide; concomitant diuretics; fluid balance measurements (every 12 hours); weight measurements obtained 24 hours before and after bumetanide infusion and laboratory parameters (i.e., serum electrolytes; renal function biomarkers, namely blood urea nitrogen and serum creatinine every 12 and 24 hours); hemodynamic or mechanical circulatory support; and respiratory support and oxygen requirements, defined as any support other than room air to mechanical ventilatory and circulatory support requirements. Inadequate response to furosemide is defined as not reaching negative fluid balance.

Outcomes. The primary outcome was identifying doses and total duration of bumetanide CI regimens. Secondary efficacy outcomes were determined by the ability to achieve negative fluid balance within 24 hours and time to reach negative fluid balance defined as the net cumulative balance of inputs and outputs with variables including but not limited to oral/IV fluids, medications, blood products, daily urine output, stool, and other bodily output (e.g., chest tube, gastrostomy, gastric or ostomy outputs) as recorded after initiation of bumetanide infusion. Secondary safety outcomes were based on the prevalence of electrolyte imbalances and renal impairment. Electrolyte imbalances were predefined as serum potassium concentration less than 3 mEq/L, serum chloride concentration less than 90 mEq/L, and serum bicarbonate concentration greater than 35 mEq/L. Renal impairment was predefined as increased serum creatinine (SCr) by 0.3 mg/dL within 48 hours or 1.5 times the baseline, or urine output <0.5 ml/kg/hr for at least 6 hours.[7,8] Laboratory values were obtained upon admission (or within 1 week of life for neonates) and within 12 hours of bumetanide peak infusion rates.

Subgroup analyses were performed to evaluate bumetanide regimens, based on patients' overall cardiovascular (CV) history and risk. This evaluation included patients who required extracorporeal membrane oxygenation (ECMO) and those with an implanted ventricular assist device (VAD). Exploratory outcomes in the *post hoc* analysis included survival to discharge, mortality rates observed from peak bumetanide infusion rates, and dosing regimens used at the time of death.

Statistical Analysis. Descriptive statistics (e.g., medians, IQRs, and frequencies) were used to summarize the study population's patient demographic and clinical characteristics. The Wilcoxon signed rank test was used to test the statistical significance of continuous variables, and a chi-square test was used to analyze categorical data. All tests were 2-tailed, with an overall alpha level of 0.05 for statistical significance. To generate these findings, statistical analyses were performed by using appropriate statistical software, JMP Pro 17.

Results

Baseline Characteristics. Ninety-four patients were identified for study eligibility; however, 4 patients were excluded because they received continuous bumetanide infusions for less than 6 hours. Ninety patients were included in the final analysis; however, to account for patients having multiple hospital admissions, the total number of 106 hospital encounters was analyzed (Figure). Baseline patient demographics for all encounters, including age, sex, weight, and admitting cardiac problems, are summarized in Table 1. Most patients included were female and younger than 8 months (65 patients making up 72%). Eighty-six percent of the patients receiving bumetanide CI transitioned from furosemide with inadequate response to furosemide as defined by no negative fluid balance (Supplemental Table S1). Of note, 91% of patients received concomitant diuretics during bumetanide CI, with the highest use seen with chlorothiazide, followed by acetazolamide and spironolactone (Supplemental Figure). The most common admitting cardiac problem was hypoplastic left heart syndrome (HLHS), followed by cardiomyopathy and atrioventricular septal defect (AVSD).

Primary Outcome. Table 2 highlights bumetanide dosing regimens observed in the PCICU during the study period. The median initial starting dose of bumetanide was 0.03 mg/kg/hr, ranging from 0.005 to 0.2 mg/kg/hr. The median dose of bumetanide was 0.046 mg/kg/hr, with a median duration of CI of 5.8 days. Median maximum doses of bumetanide were 0.075 mg/kg/hr, with doses as high as 0.3 mg/kg/hr being used in 2 patients.

Efficacy Outcomes. The secondary efficacy endpoints for optimal diuresis are displayed in Table 3, with 83% of patients achieving negative fluid balance within 24 hours of bumetanide CI initiation and a median time to reach negative fluid balance of 13.4 hours.

Figure. Study inclusion flow diagram.

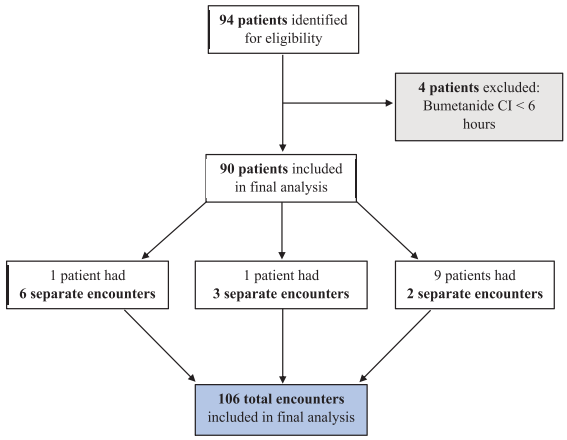

Table 1. Baseline Patient Demographics for All Encounters (N = 106)*

Age, days	137 [49, 276]
Female	57 (53.8)
Weight, kg	4.3 [3.2, 7.0]
Hypoplastic left heart syndrome	47 (44.3)
Cardiomyopathy	15 (14.2)
Atrioventricular septal defects	7 (6.6)
Other diagnosis	37 (34.9)
Other diagnosis breakdown	
Double outlet right ventricle	6
Tetralogy of Fallot	5
Tricuspid atresia	5
Ventricular septal defects	4
Coarctation of aorta	3
Truncus arteriosus	2
Transposition of great arteries	2
Total anomalous pulmonary venous return	2
Partial anomalous pulmonary venous return	2
Pulmonary atresia intact ventricular septum	2
Aortic stenosis	1
Double inlet left ventricle	1
Interrupted aortic arch	1
Pulmonary stenosis	1

* Categorical data reported as counts (%); continuous data reported as median [IQR].

Table 2. Bumetanide Dosing Regimen*

Initial dose, mg/kg/hr	**0.03** [0.01, 0.05] (0.005–0.2)
Maximum dose, mg/kg/hr	**0.075** [0.05, 0.1] (0.01–0.3)
Median dose, mg/kg/hr	**0.046** [0.03, 0.07] (0.005–0.16)
Cumulative dose, mg/kg	**6.02** [2.07, 21.82] (0.2–40)
Duration of CI, hrs	**140** [51, 381] (9–585)

CI, continuous infusion

* Continuous data reported as median [IQR] or median [IQR] (range).

The urine output was collected for 24 hours for our study population with a median of 1.36 mL/kg/hr. To account for inconsistent or incomplete documentation on 18 encounters concerning weight, a weight comparative analysis was performed on 88 individuals before and 24 hours after starting a bumetanide CI. Before bumetanide initiation, the median weight was 5.0 kg compared with 4.9 kg after the start of bumetanide, which was statistically significant (p = 0.009).

Safety Outcomes. Safety was analyzed by using the previously defined criteria for electrolyte imbalances and renal impairment. Seventy-three percent of patients experienced hypokalemia, 32% experienced hypochloremia, and 36% experienced hypercarbia (Table 4). Based on SCr elevations, 51% of patients had some renal impairment. Significant changes in serum electrolytes and renal function biomarkers were noted between all laboratory values measured at baseline and during median peak infusion rates but were not clinically significant (Table 5).

Exploratory Outcomes. Epinephrine (45.2%), milrinone (34.4%), dopamine (8.6%), vasopressin (7%), norepinephrine (3.2%), and phenylephrine (1.6%) were the choices of vasopressor and inotropic support that required hemodynamic support for hemodynamic stability. Supplemental Table S2 includes additional clinical characteristics that were analyzed to assess patients' CV history and risk. Eighteen percent of individuals were supported while on venoarterial (VA) ECMO, whereas 19% of patients had an implanted VAD using the Berlin Heart (Woodlands, TX, USA) EXCOR for additional mechanical circulatory support. When looking at heart transplant status, 34% of patients were awaiting heart transplants, whereas 12% had a history of heart transplants. Seventeen patients were supported by dialysis: 9 patients needing continuous renal replacement therapy (CRRT) and 8 patients requiring peritoneal dialysis (PD). Of the 17 patients, 13 were non-survivors, 8 received CRRT, and 5 were on PD. Of the 4 survivors, 1 was on CRRT, and 3 were on PD. Respiratory support and oxygen requirements varied substantially, with 75% of patients needing mechanical ventilation at some point during a bumetanide CI.

When assessing survival to discharge, 31 non-survivors were reported at the time of discharge. Of the non-survivors, 61% were receiving maximum bumetanide doses of 0.1 mg/kg/hr or greater (Supplemental Table S3). When stratifying this group further, based on maximum bumetanide doses (<0.1 vs ≥0.1 mg/kg/hr), there was a significant increase in deaths recorded with doses ≥0.1 mg/kg/hr (12 vs 19 patients; p = 0.0085). Doses observed at the time of death were 0.1 mg/kg/hr, ranging up to 0.3 mg/kg/hr (Supplemental Table S3).

A subgroup analysis of bumetanide regimens and survival to discharge, based on the CV history and risk, is presented in Supplemental Table S4. Patients with HLHS received higher doses of bumetanide and had

Table 3. Efficacy Secondary Endpoints (N = 106)*

Negative fluid balance within 24 hr	88 (83)
Overall net negative volume, mL	151.5 [83.8, 257.8]
Urine output over 24 hr after initiation, mL/kg/hr	1.36 [0.74, 2.35]
Time to reach negative fluid balance after initiation, hr	13.4 [9.5, 19.1]

* Categorical data reported as counts (%); continuous data reported as median [IQR].

Table 4. Prevalence of Safety Secondary Endpoints (N = 106)*

Electrolyte Imbalances	
K^+ <3 mEq/L	77 (72.6)
Cl^- <90 mEq/L	34 (32.1)
CO_2 >35 mEq/L	38 (35.9)
Renal Impairment	
SCr increase ≥0.3 mg/dL within 48 hr or ≥1.5× baseline	54 (50.9)
BUN[15] >20 mg/dL	83 (78.3)

BUN, blood urea nitrogen; Cl^-, chloride; CO_2, carbon dioxide; K^+, potassium; SCr, serum creatinine

* Categorical data reported as counts (%).

Table 5. Comparison Between Laboratory Values at Baseline and During Peak Infusion Rates*

	Baseline	During Peak Infusion Rate	p value†
K^+, mEq/L	4.0 [3.6, 4.6]	3.3 [2.9, 3.6]	<0.0001
Cl^-, mEq/L	104 [100, 107]	100 [94, 105]	0.0028
CO_2, mEq/L	24 [21, 26]	28 [24, 32]	<0.0001
SCr, mg/dL	0.36 [0.25, 0.48]	0.42 [0.28, 0.70]	0.0006
BUN, mg/dL	16 [11, 21]	22 [14, 35]	0.0008

BUN, blood urea nitrogen; Cl^-, chloride; CO_2, carbon dioxide; K^+, potassium; SCr, serum creatinine

* Continuous data reported as median [IQR]
† Wilcoxon signed rank test.

higher mortality than those with cardiomyopathy and AVSD. Patients with a VAD in place received higher doses and had higher mortality rates than those without a VAD. This finding was also consistent among individuals on VA ECMO. Because several patients had multiple admissions, we analyzed these data from the number of encounters. For patients with multiple encounters, compared with those with a single encounter, we observed shorter durations of bumetanide CI (92 vs 161 hours; p = 0.3032) and increased survival to discharge (78% vs 68%; p = 0.3527). However, these results did not reach statistical significance.

Discussion

In this single center retrospective study, we reviewed 106 encounters of patients admitted to the PCICU who received a bumetanide CI for at least 6 hours. This review provides valuable insights and real-world evidence into bumetanide's dosing, efficacy, and safety in managing fluid overload in critically ill pediatric cardiac patients. The findings of this study demonstrate that bumetanide CI led to improvements in diuresis and fluid balance in pediatric patients undergoing or awaiting cardiac surgery within the PCICU. We suggest a starting dose of 0.005 mg/kg/hr and a maximum dose of 0.1 mg/kg/hr to maximize benefits with a minimal side effect profile that can be easily managed. The reason for choosing this maximum dose is that in our subgroup analysis no patient survived when the doses were above 0.1 mg/kg/hr, suggesting that a patient's underlying condition and hemodynamic profile cannot be reversed with high-dose diuretics.

The analysis of urine output, weight, and fluid intake/output records revealed favorable responses to treatment, suggesting that bumetanide CI provides a sustained diuretic effect. This aligns with the rationale for using bumetanide CI in this patient population, because it allows for more precise titration and potentially avoids the rapid fluctuations in diuresis that may be experienced with intermittent dosing. Bumetanide offers additional potential benefits when compared with furosemide. Previous adult studies have suggested that bumetanide may potentially cause less potassium excretion,[9] ototoxicity,[10] and bilirubin displacement[11] when compared with furosemide and may have a reduction in seizure burden.[12] These last 2 findings are significant and beneficial to consider in the neonatal patient population, who typically present with hyperbilirubinemia in the first few days of life and have a higher propensity for seizures with neonatal cardiac surgery.[13] We had 18 neonates in our study, but we did not focus on evaluating these and hope to explore this in future studies.

It is crucial to note that our analysis also identified electrolyte imbalances and renal impairment in patients receiving bumetanide CI. These findings are consistent with previous studies highlighting the potential risks and complications of loop diuretic therapy in critically ill patients.[14] Electrolyte imbalances, including hypokalemia and hypochloremia and resulting contraction alkalosis, can have significant clinical consequences and require careful monitoring and management in these patients.

Additional key findings indicate that sicker patients received higher doses of bumetanide CI. The subgroup and exploratory analyses found higher doses were being used with longer duration of infusions, specifically in patients on ECMO and those with an implanted VAD. However, it should be noted that the observed increased mortality risk may be attributed to several factors, including but not limited to the severity of illness, underlying cardiac pathology, or the development of treatment-resistant fluid overload.

These adverse effects highlight the need for close monitoring and cautious administration of this treatment approach. The risks observed in this retrospective review underscore the importance of considering individual patient factors, such as baseline renal function, electrolyte status, and overall clinical condition, when deciding on the appropriateness and dosage of bumetanide CI. Furthermore, a multidisciplinary approach involving collaboration between the PCICU team, pediatric cardiology specialists, and pharmacists is crucial to ensure adequate patient selection, appropriate dosing strategies, and proactive management of potential complications.

Limitations of Study

By analyzing a comprehensive set of patient data, this study contributes to our understanding of the use of bumetanide CI and its implications for clinical practice. However, it is essential to consider the limitations inherent in a retrospective chart review when interpreting these results. The study's retrospective nature introduces the risk of selection biases and limitations in the data collection process due to incomplete documentation of medical records. The lack of a control group hinders the ability to directly compare the outcomes of bumetanide CIs with alternative treatment strategies, such as intermittent dosing or other loop diuretic agents. Considering all this, it is challenging to attribute these findings directly to continuous bumetanide infusions. Therefore, these findings should be interpreted cautiously and considered hypothesis generating rather than definitive evidence of causality.

A large percentage of patients receiving concomitant diuretics may also confound the results. However, this can be expected in clinical practice with critically ill patients. Patients who are admitted to the PCICU often have poor heart function at baseline, which can contribute to hypoperfusion to vital organs and worsening clinical outcomes. Additionally, electrolyte replacement and supplementation data were not included or analyzed owing to variable provider practices. Lastly, the inclusion of patients who received bumetanide CI may introduce a bias toward patients with more severe fluid overload or those who were deemed less responsive to

intermittent dosing. This could potentially overestimate the efficacy of bumetanide CI as compared with a randomized controlled trial or prospective study.

Despite these limitations, this study remains the largest pediatric study describing dosing, efficacy, and safety concerns of bumetanide CI in this specific patient population. Our comprehensive data collection and analysis provide detailed insights into the clinical outcomes and highlight existing knowledge gaps in the literature.

Conclusion

This study contributes to the growing body of evidence on bumetanide CI regimens in pediatric patients admitted to the PCICU. We identified positive outcomes in diuresis and fluid balance by comprehensively analyzing bumetanide CI in our population. However, using a high-dose bumetanide drip >0.1 mg/kg/hr may not improve the overall outcome, and there may be advantages to specific use in neonates undergoing cardiac surgery, which needs to be explored. We emphasize the importance of further research, including prospective, randomized controlled trials, to assist clinicians in making informed decisions, aiming to improve patient outcomes and enhance care in this critical setting.

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Ethical Approval and Informed Consent. This retrospective chart review evaluated existing data using interventions that have already occurred. There was no risk to the patients involved, nor were there any associated costs. The study protocol was approved by the University of Florida Institutional Review Board (IRB), and patient informed consent was waived owing to the retrospective design of the study.

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References

1. Hazle MA, Gajarski RJ, Yu S, et al. Fluid overload in infants following congenital heart surgery. *Pediatr Crit Care Med*. 2013;14(1):44–49.
2. Huxel C, Raja A, Ollivierre-Lawrence MD. Loop diuretics. In: *Stat Pearls*. Treasure Island, FL: Stat Pearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK546656/
3. Salvador DRK, Punzalan FE, Rey NR, et al. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. *Cochrane Database Syst Rev*. 2005;2005(3):CD003178.
4. Bumetanide [pediatric drug information]. *Lexicomp*. Hudson, OH: Wolters Kluwer Clinical Drug Information Inc. Accessed September 9, 2022. http:/www.online.lexi.com
5. Bulkley CF, Johnson PN, Henry E, et al. Bumetanide continuous-infusion dosing in critically ill pediatric patients. *Am J Health Syst Pharm*. 2012;69(17):1458–1461.
6. McCallister KM, Chhim RF, Briceno-Medina M, et al. Bumetanide continuous infusions in critically ill pediatric patients. *Pediatr Crit Care Med*. 2015;16(2):e19–e22.
7. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179–c184.
8. Bellomo R, Ronco C, Kellum JA, et al; Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204–R212.
9. Dunn FG, Kerr IC, McQueen MJ, et al. Comparison of intravenous bumetanide and frusemide during open heart surgery. *Postgrad Med J*. 1975;5(suppl 6):72–76.
10. Tuzel IH. Comparison of adverse reactions to bumetanide and furosemide. *J Clin Pharmacol*. 1981;21(11):615–619.
11. Turmen T, Thom P, Louridas AT, et al. Protein binding and bilirubin displacing properties of bumetanide and furosemide. *J Clin Pharmacol*. 1982;22(11–12):551–556.
12. Soul JS, Bergin AM, Stopp C, et al; Boston Bumetanide Trial Group. A pilot randomized, controlled, double-blind trial of bumetanide to treat neonatal seizures. *Ann Neurol*. 2021;89(2):327–340.
13. Naim MY, Gaynor JW, Chen J, et al. Subclinical seizures identified by postoperative electroencephalographic monitoring are common after neonatal cardiac surgery [discussion in J Thorac Cardiovasc Surg. 2015;150(1):178–180]. *J Thorac Cardiovasc Surg*. 2015;150(1):169–178.
14. Greenberg A. Diuretic complications. *Am J Med Sci*. 2000;319(1):10–24.
15. Gowda S, Desai PB, Kulkarni SS, et al. Markers of renal function tests. *N Am J Med Sci.* 2010;2(4):170–173.

JPPT | Single-Center Retrospective Study

Evaluation of Institution-Specific Strategy for Converting Dexmedetomidine to Clonidine in a Pediatric Cardiac Intensive Care Unit

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OBJECTIVE This study aimed to evaluate the success and safety of an institution-specific strategy for converting dexmedetomidine to clonidine in the cardiac intensive care unit at a tertiary care pediatric hospital.

METHODS This retrospective descriptive study included pediatric patients under 18 years of age receiving at least 7 days of dexmedetomidine infusion before conversion to clonidine between January 1, 2018, and October 1, 2023. A successful conversion was defined as dexmedetomidine infusion discontinuation in the absence of therapy reinitiation within 36 hours after the initial enteral clonidine dose; no dose increases greater than 15% within 36 hours of initial clonidine dose, and no requirement for supplemental doses. Patients with dexmedetomidine discontinuation before completing stepwise conversion were evaluated for adverse drug events (ADEs). Descriptive statistics were used to analyze the data.

RESULTS A total of 148 episodes of conversion from dexmedetomidine to clonidine were evaluated for 134 patients. Patient demographics and treatment characteristics included a median age at conversion of 4.6 months (IQR, 1.5–7.1), a median duration of dexmedetomidine exposure of 19 days (IQR, 12–34), a median initial clonidine dose of 9.3 mcg/kg/day (IQR, 7.2–10), and a median time to discontinuation of 19 hours (IQR, 17–36) after the first dose of clonidine. Successful conversion occurred in 99 (67%) of episodes evaluated, and no ADEs were identified.

CONCLUSION The conversion allowed for most patients to tolerate the conversion to clonidine, and no ADEs were identified.

ABBREVIATIONS ADE, adverse drug event; CICU, cardiac intensive care unit; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; PICU, pediatric intensive care unit

KEYWORDS clonidine; dexmedetomidine; sedation; pediatric; withdrawal; cardiac intensive care unit

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Introduction

Dexmedetomidine is a centrally acting alpha-2 adrenoreceptor agonist commonly used in intensive care unit (ICU) settings as a sedative, anxiolytic, and analgesic.[1,2] Its use has increased because of its minimal effects on respiratory drive and reduced risk of delirium.[3,4] The Pain, Agitation, Neuromuscular Blockade, and Delirium in Critically Ill Pediatric Patients with Consideration of the ICU Environment and Early Mobility Guidelines recommend dexmedetomidine as a primary sedative in critically ill pediatric patients requiring mechanical ventilation and in postoperative pediatric cardiac surgery patients to decrease the risk of tachyarrhythmias.[4]

Prolonged intravenous (IV) infusions of dexmedetomidine increase the potential for tolerance and, subsequently, the risk of withdrawal after therapy discontinuation. Withdrawal symptoms include hypertension, tachycardia, diaphoresis, anxiety, fever, and delirium upon abrupt discontinuation.[2,4,5] To facilitate dexmedetomidine discontinuation and decrease the risk of withdrawal, clonidine, an enterally available alpha-2 adrenoreceptor agonist, has been used.[3–9] Reported dosing regimens of clonidine for attenuating withdrawal ranged from 4 to 19 mcg/kg/day, divided every 6, 8, or 12 hours.[6–8] Prior studies also describe inconsistent conversion practices and methods for detecting the impact of clonidine. This variability highlights the need for further research to establish optimal dosing regimens based on patient characteristics, clinical contexts, and safety considerations.

The study institution's pediatric cardiac intensive care unit (CICU) developed a strategy for converting dexmedetomidine infusions to enteral clonidine in

divided doses starting in 2018. At the time of developing this approach, there was no previous literature describing how to do this conversion. Therefore, this practice was developed in close collaboration between CICU pharmacists and physicians, informed by historical experience, physician preference, existing literature, and typical dose ranges and pharmacokinetic properties of both drugs.

The adopted institution-specific strategy for converting a patient from dexmedetomidine to clonidine involves calculating the clonidine dose (mcg/kg/day) by multiplying the rate of dexmedetomidine infusion at the time of conversion (mcg/kg/hr) by 10 (a 1:10 ratio). It is recommended to divide the daily clonidine dose every 6 hours, unless the individual dose falls below the minimum measurable volume set by the institution. Clonidine is administered concomitantly with dexmedetomidine until the fourth dose of clonidine is given. The decision to overlap therapy while decreasing the dexmedetomidine dose was guided by the onset of action of clonidine and the half-lives of clonidine and dexmedetomidine.[5,10,11] This allows clonidine sufficient time to reach therapeutic levels while dexmedetomidine is weaned to discontinuation. For example, dexmedetomidine 1 mcg/kg/hr is converted to enteral clonidine 10 mcg/kg/day divided every 6 to 12 hours. Clonidine is administered in the form of tablets or extemporaneously compounded suspension (0.1 mg/mL). The preferred frequency of clonidine was a daily dose divided every 6 hours unless the volume was less than 0.05 mL (0.005 mg), which is the minimum measurable volume determined by the institution to ensure the accuracy of doses drawn up. To facilitate the conversion from dexmedetomidine to clonidine, the institution-specific strategy recommends that the dexmedetomidine infusion rate be decreased by half 30 minutes after the second and third doses of enteral clonidine and discontinued 30 minutes after the fourth clonidine dose (Table 1).

Table 1. Example of Institution-Specific Strategy for Converting a Dexmedetomidine Infusion to Enteral Clonidine

Example: Dexmedetomidine IV 1 mcg/kg/hr	
Step 1	Administer the first dose of enteral clonidine 10 mcg/kg/day divided every 6–12 hr
Step 2	Decrease dexmedetomidine IV rate to 0.5 mcg/kg/hr 30 min after administering second dose of enteral clonidine
Step 3	Decrease dexmedetomidine IV rate to 0.25 mcg/kg/hr 30 min after administering third dose of enteral clonidine
Step 4	Discontinue dexmedetomidine IV 30 min after the fourth dose of enteral clonidine

IV, intravenous

This study aimed to address the gaps in current literature by focusing on patients converted to clonidine using this standardized conversion approach and outlining specific criteria for achieving successful conversion. The purpose of this study was to describe the conversion of dexmedetomidine to clonidine to evaluate the success and tolerability of this institution-specific strategy.

Materials and Methods

This retrospective descriptive study was performed at a 600-bed freestanding children's hospital with a 36-bed CICU. Patients were identified for inclusion if they had orders for dexmedetomidine and clonidine between January 1, 2018, and October 1, 2023. Patients less than 18 years of age, admitted to the CICU, who received dexmedetomidine infusions for at least 7 days and were converted to clonidine using the institution-specific strategy, were included. Patients were excluded if they were administered any alpha-2 adrenoreceptor agonists (i.e., clonidine or guanfacine) as a maintenance medication before dexmedetomidine initiation, received an initial clonidine dose that deviated greater than 15% of the calculated dose, were intubated at the time of conversion, received extracorporeal membrane oxygenation and/or continuous renal replacement therapy, became nothing by mouth status and could not receive enteral medications within 36 hours of the initial dose of clonidine and/or were transferred to another facility at the time of conversion (to account for any missing information that may occur outside the institution), or expired within 36 hours of the initial dose of clonidine. Patients with greater than 1 conversion episode were included in this evaluation.

Baseline demographic data, including age and weight at the time of conversion, sex, and race, were collected. Data related to treatment characteristics, including the number of episodes, initial and maximum dexmedetomidine infusion rate (mcg/kg/hr), total dexmedetomidine infusion duration (days), dexmedetomidine infusion rate at the time of conversion (mcg/kg/hour), clonidine dose at time of conversion (mcg/kg/day), time between the administration of the first dose of clonidine and dexmedetomidine discontinuation (hours), were collected.

The primary endpoint was the rate of successful conversion from dexmedetomidine to clonidine, defined as: (1) dexmedetomidine infusion discontinuation within 36 hours of the initial clonidine dose, (2) lack of dexmedetomidine infusion restart within 36 hours after infusion discontinuation, (3) absence of clonidine dose adjustments greater than 15% of the recommended dose within 36 hours of initial clonidine dose given, and (4) no requirement for supplemental intermittent

doses of dexmedetomidine or clonidine within 36 hours of initial clonidine dose.

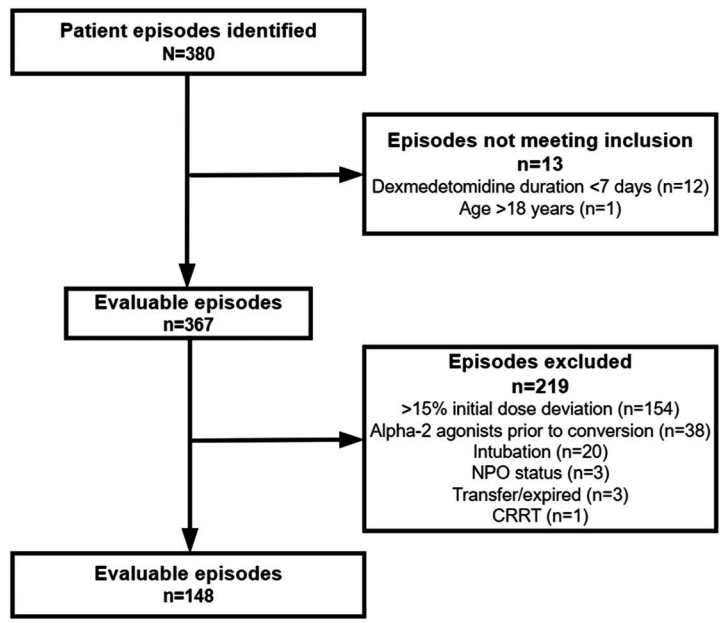
The secondary endpoint was the safety of this conversion strategy, focusing on the number of adverse drug events (ADEs) that occurred during conversion. The 2 ADEs of interest were hypotension and bradycardia that occurred as a result of the conversion. To assess this, the institution's internal safety reporting system was reviewed for any reported ADEs linked to the conversion. Hospital staff are trained to recognize and report ADEs using a standardized definition, which classifies an ADE as any harm experienced by a patient as a result of medication exposure.[12] Acknowledging that only 10% to 20% of these events are likely reported, steps were taken to ensure ADEs potentially associated with this conversion were captured.[13] If the patient, after receiving at least 1 dose of clonidine following conversion, subsequently had their clonidine therapy discontinued or its dose reduced within 36 hours of the initial clonidine dose, or if dexmedetomidine was discontinued within 18 hours of the initial clonidine dose, further investigation to assess for possible ADEs as causation for deviation from the standard conversion protocol was completed. This assessment included reviewing the attending physician's daily progress notes for any mention of common ADEs related to conversion, using keywords of bradycardia and/or hypotension. Vital signs during conversion were also examined to determine whether patients experienced bradycardia or hypotension, defined as any occurrences in which the patient's measured vital sign fell below the normal age-related values as specified by the institution.

Descriptive statistics were used to analyze the data, with nominal data expressed as a percentage and continuous data expressed as median with IQR. A Shapiro-Wilks test was performed on all continuous data to test for normality.

Results

A total of 134 patients with 148 episodes of conversion from dexmedetomidine to enteral clonidine were evaluated (Figure 1). Thirteen patients experienced more than one conversion episode, with 12 having 2 episodes, and 1 patient having 3 episodes. The Shapiro-Wilks test demonstrated significant departure from normality for all continuous data points ($p > 0.05$). For baseline demographics (Table 2), the median age at conversion was 4.6 months (IQR, 1.5–7.1), the median weight at conversion was 4.7 kg (IQR, 3.5–6.7), 72 (54%) patients were male sex at birth, and 76 (56.7%) of the patients were White or Caucasian. The median duration of dexmedetomidine exposure before conversion was 19 days (IQR, 12–34). The median dexmedetomidine infusion rate at the time of the conversion to clonidine was 1 mcg/kg/hr (IQR, 0.7–1) at the time of conversion to clonidine. The median initial clonidine dose at conversion was 9.3 mcg/kg/day (IQR, 7.2–10) and was administered at a frequency of every 6 hours for 135 (91%) of episodes. Dexmedetomidine was discontinued a median of 19 hours (IQR, 17–36) following administration of the first dose of clonidine. Information

Figure. CONSORT diagram. *CRRT, continuous renal replacement therapy, NPO, nothing by mouth.*



regarding the remaining treatment characteristics is available in Table 3.

Of the total 148 episodes evaluated, 99 (67%) met the conditions for successful conversion. Episodes may have had more than 1 reason qualifying for unsuccessful conversion, and the total of each reason is displayed in Table 4. In 76 episodes where dexmedetomidine was infused for less than the median of 19 days, 23 (30%) resulted in unsuccessful conversions. In comparison, 72 episodes with infusions lasting more than 19 days had 26 (36%) unsuccessful conversions. In 31 patients, dexmedetomidine was discontinued within 18 hours of the initial clonidine dose, which prompted a review for any ADEs. Clonidine was neither discontinued nor dose-reduced because of ADEs within 36 hours of its initiation. No ADEs were reported during the study period.

Table 2. Baseline Demographics

Total Patients		**N = 134**
Male sex, n (%)		72 (54)
Age at conversion, mo, Median (IQR)*		4.6 (1.5–7.1)
Weight at conversion, kg, Median (IQR)*		4.7 (3.5–6.7)
Race† n (%)	White or Caucasian	76 (56.7)
	Unknown	29 (21.6)
	Black or African American	25 (18.7)
	Asian	2 (1.5)
	Hispanic or Latino White	2 (1.5)

* Total number of episodes: 148.
† As documented in the electronic health record.

Table 3. Treatment Characteristics for Conversion From Dexmedetomidine to Clonidine

Total Episodes N = 148	
Total dexmedetomidine treatment duration, days	19 (12–34)
Initial dexmedetomidine rate, mcg/kg/hr	0.5 (0.3–0.5)
Maximum dexmedetomidine rate, mcg/kg/hr	1.2 (1–1.5)
Dexmedetomidine rate at time of conversion to clonidine, mcg/kg/hr	1 (0.7–1)
Initial clonidine dose, mcg/kg/day	9.3 (7.2–10)
Initial clonidine frequency, n (%)	Every 6 hours: 135 (91) Every 8 hours: 8 (5) Every 12 hours: 5 (3)
Time between clonidine initiation and dexmedetomidine discontinuation, hr	19 (17–36)

Nonparametric continuous data presented as median (IQR); nominal data presented as n, (%)

Discussion

This study aimed to assess the success and safety of an institution-specific conversion strategy from dexmedetomidine to clonidine used within the CICU. The decision to restrict to this patient population was driven by the fact that the conversion practice described is specific to the CICU at the study institution and aimed to minimize variability in the patient population. The motivation behind conversion to enteral clonidine is to facilitate de-escalation from ICU-level care by allowing for expedited discontinuation of dexmedetomidine infusions, while minimizing the risk of withdrawal symptoms. Although previous studies have investigated the role of clonidine for attenuating withdrawal symptoms in patients transitioning from dexmedetomidine, these studies do not focus on CICU patients, there is variability in dosing recommendations, and limited consensus on the most effective approach.[5–9]

Liu et al[6] conducted a retrospective analysis involving 24 episodes of converting dexmedetomidine to clonidine in patients admitted to a pediatric intensive care unit (PICU) rather than in CICU patients evaluated in the present study. In contrast to the present

Table 4. Dexmedetomidine to Clonidine Conversion Effectiveness

Total Episodes N = 148	
Successful conversion, n (%)	99 (67)
Counts of Individual Reasons for Unsuccessful Conversion, n = 64*	
Dexmedetomidine continuation for >36 hr following clonidine initiation, n (%)	35 (55)
Scheduled clonidine dose increased (>15% of recommended dose) within 36 hr of dexmedetomidine discontinuation, n (%)	19 (30)
As needed clonidine rescue administration within 36 hr of clonidine initiation, n (%)	7 (11)
Dexmedetomidine restarted within 36 hr of clonidine initiation, n (%)	3 (5)

* Unsuccessful conversion may occur for >1 reason per episode.

study, where the dexmedetomidine rate determined the dose of clonidine, the enteral clonidine dose was based on age, with 8 mcg/kg/day for patients younger than 6 months of age or 16 mcg/kg/day for patients 6 months and older. The stepwise conversion approach in the current study was similar to the approach used in the study, but dexmedetomidine was discontinued after the third dose rather than the fourth. The median dexmedetomidine treatment duration was 3.8 days, which is shorter than the median 19 days in the present study. Eight conversion episodes (33%) demonstrated withdrawal that required additional support during conversion, similar to the proportion of episodes requiring additional sedation in the present study. The median overlap of clonidine and dexmedetomidine was 18.2 hours, which is comparable to the overlap observed in the present study. Additionally, 2 episodes (8%) had bradycardia or hypotension requiring intervention.

Another analysis by Lee et al[7] evaluated 39 conversion episodes from dexmedetomidine to clonidine in patients admitted to the PICU. The median dexmedetomidine duration was 7.6 days, which is less than half of the median duration observed in this evaluation. Unlike the institution in the current study, there was no standardized conversion practice. The median initial clonidine dose was 7.8 mcg/kg/day and was typically given every 8 or 12 hours. Of note, 5% of episodes were converted using transdermal clonidine which was not employed in the present study. Similar to the present study, the conversion from dexmedetomidine to clonidine occurred over a median of 19.2 hours. In terms of outcomes, 14 (37%) conversion episodes resulted in elevated Withdrawal Assessment Tool (Version 1) scores of 3 or greater. However, only 7 (18%) in their study required an increase in sedation, compared with the higher intervention rate observed in the present study, which could be attributed to the shorter duration of dexmedetomidine exposure. Additionally, adverse cardiovascular events attributed to conversion occurred in 4 patient episodes (10%).

Crabtree et al[8] conducted a study involving 105 PICU patients who received dexmedetomidine infusions for at least 24 hours, with clonidine administered within 72 hours of discontinuation of dexmedetomidine. Unlike the present study, which did not collect data on other sedatives, their study excluded patients receiving other continuous infusion sedatives besides dexmedetomidine. A notable difference in their approach was that not all patients were converted with dexmedetomidine, which overlapped with clonidine. For those with dexmedetomidine infusion exceeding 5 days, enteral clonidine was initiated at 15 mcg/kg/day, divided every 8 hours, rather than the approach in the present study, where the clonidine dose was scaled to the dexmedetomidine rate at the time of clonidine initiation. Although both the present and Crabtree et al[8] study used a stepwise conversion process, dexmedetomidine was discontinued after the second dose compared with the fourth dose in the present study. The median cumulative duration of dexmedetomidine infusion in this group was 5.5 days, approximately one-third the duration in this study. This may explain, in part, why withdrawal symptoms requiring modifications to the planned conversion occurred in only 12 (18%) of patients rather than the 33% of episodes requiring additional support during conversion in this evaluation.

By adhering to the conversion practice used in this study's CICU, dexmedetomidine should be discontinued 30 minutes after the fourth dose of clonidine. This should occur between 18 and 36 hours after the first dose of clonidine, depending on the frequency of clonidine administration. Therefore, a period of 36 hours for dexmedetomidine discontinuation was chosen as a condition for conversion success providing sufficient time to complete the conversion and allowing for additional buffer time to account for medical rounds, ordering and verification, medication preparation, and administration.

The use of strict inclusion and exclusion criteria played a role in controlling for potential confounding variability for the conversion process. It is noteworthy that episodes were excluded most frequently for an initial clonidine dose deviation greater than 15% from the standard conversion guidance. This dose deviation threshold was chosen to help ensure accuracy of volume measurement based on syringe size and associated barrel graduations in conjunction with dose rounding logic within the institution's computerized physician order entry system. Patients intubated at the time of conversion were excluded because they had a higher likelihood of receiving other sedatives to facilitate mechanical ventilation. Typically, other sedatives are rapidly weaned in preparation for extubation, which is why episodes in intubated patients were excluded. Patients on extracorporeal membrane oxygenation and/or continuous renal replacement therapy were excluded as a measure to prevent potential confounding effects due to pharmacokinetic impact from any extracorporeal circuitry.

This evaluation found that most episodes were successfully converted from dexmedetomidine to clonidine according to the predefined criteria. This indicates that the conversion practice used in this study is clinically feasible by achieving the intended therapeutic goal of dexmedetomidine discontinuation. The absence of ADEs identified among episodes included is reassuring and underscores the safety profile of our conversion practice.

The remaining episodes that did not meet the criteria for successful conversion required additional support during the conversion process, such as extended dexmedetomidine infusion, dose increases

of clonidine, or rescue doses of either clonidine or dexmedetomidine. This can be compared with the studies detailed above, where 18% to 33% of patients required modification or an increase in sedation during conversion.[6–8] It is noteworthy that episodes in this study had greater dexmedetomidine exposure than previously reported.

This study has limitations, including an absence of a comparator group and data on other sedatives used at the time of conversion. Details regarding the reason for admission or specific cardiac defects were not collected because of feasibility concerns. Patients at the study institution's CICU often have complex surgical histories, resulting in a heterogeneous patient population that would have been difficult to categorize. Although collecting information on the concomitant administration of other sedatives would help limit the confounding of the effects of this conversion, excluding patients who were intubated at the time of conversion ensured that the patients evaluated were less likely to have undergone significant changes to sedation at the time of conversion. Information on other medications that may impact blood pressure was not collected. However, given this retrospective review was of patients in a CICU, the use of such medications could have confounded the assessment of hemodynamics.

It is also important to note that in practice, this conversion would not be attempted unless the patient were clinically stable for at least 24 hours and not experiencing significant withdrawal or excessive sedation requiring active titration of concomitant sedatives. Given that data collection was retrospective and the safety reporting system is voluntary, there is a potential for underdetection or underreporting of ADEs.[13] Data on dexmedetomidine use at other facilities could not be reliably reported for patients started before transfer to the study institution. Therefore, dexmedetomidine exposure was only reflective of what was administered at the study institution.

Additionally, there is variability and subjectivity to the elements of withdrawal, which cannot be adequately accounted for retrospectively. Differences in provider preferences for conversion and weaning strategies may explain why a significant number of episodes were excluded because of dose deviations. This variability in practice may also introduce bias, as successful conversions may not have been captured due to deviations from the guidance provided by the institution-specific conversion strategy.

Conclusion

The conversion practice investigated allowed for most patients to tolerate the transition from a dexmedetomidine infusion to clonidine, and no ADEs were identified. Future studies should assess the safety and efficacy of converting from dexmedetomidine to clonidine.

Article Information

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References

1. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent)*. 2001;14(1):13–21.
2. Precedex [package insert]. Lake Forest, IL: Hospira, Inc; 2022.
3. Thompson RZ, Gardner BM, Autry EB, et al. Survey of the current use of dexmedetomidine and management of withdrawal symptoms in critically ill children. *J Pediatr Pharmacol Ther*. 2019;24(1):16–21.
4. Smith HAB, Besunder JB, Betters KA, et al. 2022 Society of Critical Care Medicine Clinical Practice Guidelines on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. *Pediatr Crit Care Med*. 2022;23(2):e74–e110.
5. Haenecour AS, Seto W, Urbain CM, et al. Prolonged dexmedetomidine infusion and drug withdrawal in critically ill children. *J Pediatr Pharmacol Ther*. 2017;22(6):453–460.
6. Liu J, Miller J, Ferguson M, et al. The impact of a clonidine transition protocol on dexmedetomidine withdrawal in critically ill pediatric patients. *J Pediatr Pharmacol Ther*. 2020;25(4):278–287.
7. Lee MM, Caylor K, Gockenbach N. Evaluating the transition from dexmedetomidine to clonidine for the prevention of withdrawal in critically ill pediatric patients. *J Pediatr Pharmacol Ther*. 2020;25(2):104–110.
8. Crabtree MF, Sargel CL, Cloyd CP, Tobias JD, Abdel-Rasoul M, Thompson RZ. Evaluation of an enteral

clonidine taper following prolonged dexmedetomidine exposure in critically ill children. *J Pediatr Intensive Care*. 2021;11(04):327–334.
9. Beitz ER, Seabury R, Miller CD, Darko WQ, Probst LA, Steidl KE. Clonidine for dexmedetomidine withdrawal in pediatric patients: a single center's experience. *J Pediatr Pharmacol Ther*. 2019;24(6):542–543.
10. Buck ML. Dexmedetomidine use in pediatric intensive care and procedural sedation. *J Pediatr Pharmacol Ther*. 2010;15(1):17–29.
11. Klein RH, Alvarez-Jimenez R, Sukhai RN, et al. Pharmacokinetics and pharmacodynamics of orally administered clonidine: a model-based approach. *Horm Res Paediatr*. 2013;79(5):300–309.
12. Patient Safety Network. Medication Errors and Adverse Drug Events. 2019. Accessed September 14, 2024. https://psnet.ahrq.gov/primer/medication-errors-and-adverse-drug-events
13. Griffin FA, Resar RK. IHI Global Trigger Tool for Measuring Adverse Events. 2nd ed. Cambridge, MA: Institute for Healthcare Improvement; 2009. Accessed September 6, 2025. https://www.ihi.org/library/white-papers/ihi-global-trigger-tool-measuring-adverse-events

Stability Study of Lorazepam Oral Solution Repackaged in Amber Colored ENFit Oral Syringes

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OBJECTIVE Lorazepam is a benzodiazepine drug that hospital pharmacies commonly dispense to treat patients with severe anxiety and seizure disorders. Lorazepam oral concentrate, a marketed oral formulation of lorazepam, contains polyethylene glycol and propylene glycol in a solution (2 mg/mL). At Strong Memorial Hospital nurses draw patient-specific doses from a 30mL bulk bottle of lorazepam oral concentrate for administration. This study aims to investigate the stability of lorazepam when stored in repackaged amber-colored ENFit Oral syringes under typical hospital pharmacy conditions (stored at ambient temperature), to reduce waste.

METHODS Stability indicating HPLC assay was established to investigate the degradation profile of lorazepam treated at ambient temperature (~25°C) and hot conditions (60°C) under acidic (1N HCL), basic (1N NaOH), and oxidative (H_2O_2) stress conditions. This HPLC assay established a robust calibration curve to check the stability of the repackaged lorazepam ENFit Oral Syringes. The repackaged syringes were stored at Strong Memorial Hospital's Inpatient Pharmacy at ambient temperature (72 ± 4°F) for 182 days and samples were taken to investigate the stability of the repackaged formulation.

RESULTS After 182 days, both volumes (0.25 mL and 0.5 mL) of lorazepam repackaged formulation in the ENFit oral syringes, exhibited no visible changes and remained within the acceptable concentration range (100 ± 10%) when stored at ambient temperature (72 ± 4°F). The stability data demonstrated that lorazepam repackaged in amber-colored ENFit Oral Syringes remained stable at room temperature for up to 90 days.

CONCLUSION This study represents a 30-day extension in the stability compared with the previously reported 60-day stability period for the repackaged lorazepam oral syringes.

ABBREVIATIONS ACN, acetonitrile; DI, deionized water; HCl, hydrochloric acid; H_2O_2, hydrogen peroxide; HPLC, High-Performance Liquid chromatography; IM, intramuscular; IV, intravenous; LOD, limit of detection; LOQ, limit of quantitation; NaOH, sodium hydroxide; RT, retention time; TFA, trifluoroacetic acid; USP, United States Pharmacopoeia; URMC, University of Rochester Medical Center; %CV, percentage coefficient of variance

KEYWORDS compounding formulation; oral syringes; stability; stability indicating; lorazepam

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Introduction

Lorazepam belongs to the benzodiazepine class of molecules that are used for the treatment of central nervous system disorders such as anxiety, seizures, insomnia, and others. It is also used to manage anxiety-related depressive symptoms. In single high dosages, lorazepam has a tranquilizing action on the central nervous system. Lorazepam is readily absorbed in the body with an absolute bioavailability of 90% making it a viable drug candidate for delivery through the oral route. Peak plasma concentrations of lorazepam occur in the body at 2 hours after administration. It is recommended that the dosage of lorazepam be individualized according to the patient's clinical condition, age, and the patient's response to therapy.[1,2] For instance, LORAZEPAM doses may range from 1 mg/day to 10 mg/day, divided into smaller doses throughout the day as needed.[2]

Strong Memorial Hospital Inpatient Pharmacy of the University of Rochester Medical Center (URMC), serves both pediatric and adult patients and used lorazepam doses ranging from 0.04 mg/dose to 8 mg/dose. When an oral liquid form of lorazepam is required, a 30-mL multidose bottle of lorazepam oral concentrate 2 mg/mL is dispensed. The bottle of lorazepam oral concentrate that is stored in a CII Safe refrigerator until dispensed to the nursing unit, then the bottle is stored at room temperature in a Pyxis machine with a 90-day expiration. Nurses draw the required patient-specific volumes from the multidose bottle based on the ordered dosing needs. When the lorazepam

oral solution order is discontinued, the bulk bottle is returned to the CII Safe, until any remaining contents are destroyed, leading to significant waste over time. Repackaging the lorazepam oral solution concentrate in small doses may help solve this problem.[3] Brown et al[3] recently demonstrated that repackaged lorazepam solution from lorazepam oral concentrate into 1-mL oral syringes retains stability for 60 days, showing a steady stability profile. Lorazepam oral concentrate stored in glass syringes remained stable for over 200 days at both refrigerated and ambient temperatures.[4] It was also recommended to investigate the stability of small-volume aliquots (e.g., 0.5 mL) of repackaged lorazepam solution for extended durations.[3] Therefore, this study investigated the extended stability of low-volume aliquots of repackaged amber-colored ENFit oral syringes of lorazepam oral concentrate.

Materials and Methods

Lorazepam oral syrup (Intensol, NDC 0054-3532-44, expiration date April 2025) was procured commercially by Strong Memorial Hospital Inpatient Pharmacy for performing repackaging. All chemicals used in the study were analytical grade. Trifluoro acetic acid (TFA) (Acro organics, lot: A0426846), acetonitrile (Fisher Scientific, lot: 219305), hydrochloric acid (HCl)1N solution (Fisher Scientific, lot: 206701), sodium hydroxide (NaOH) pellets (Sigma Aldrich, lot: 07406LE), hydrogen peroxide (H_2O_2), 30% v/v (Thermo Scientific, lot: B0546098A), and all other chemical reagents used in the study were purchased from Fisher Scientific (Fair Lawn, NJ). Lorazepam standard 1 mg/mL in methanol (Sigma Aldrich, lot: FE03272008) was procured as standard. Two sizes (0.5 mL and 1 mL) of ENFit amber oral syringes (Amber, NeoMed NeoConnect) were procured by Strong Memorial Hospital Pharmacy.

HPLC Conditions for Lorazepam Run. All chromatographic runs were performed using the Shimadzu HPLC system (LC-2010AHT), with a UV detector. Data were recorded using LC Solution Version 1.24 SP1. Separations were performed using the Kinetex C18 column (S/N: H21-169476, 5µ, 100Å, 150 × 4.6 mm) was used for the analysis. The flow rate of the system was 1 mL/min and run time for the method was 15 minutes and gradient flow ramping for 10 minutes for the ACN (with 0.1% v/v TFA) and water (with 0.1% v/v TFA) is shown in Table 1. Column eluents were monitored at 254 nm wavelength and column temperature was maintained at 30°C. The injection volume for all the standards and samples was 10 µL.

Table 1. Gradient Run for the HPLC Run

Time (min)	A (Water, 0.1% TFA)	B (ACN, 0.1% TFA)
0.01	90%	10%
10	30%	70%
10.01	90%	10%
15	Stop	

ACN, acetonitrile; HPLC, high-performance liquid chromatography; TFA, trifluoroacetic acid

Calibration Curve Development and Validation. The calibration curve for the lorazepam was established in the concentration range of 2 µg/mL to 200 µg/mL. All the standards were analyzed n = 2 × 2 configuration, that is 2 sets were injected (to determine intraday variation) on 2 different days (to determine interday variation). The % coefficient of variance (%CV) and % accuracy of each concentration were determined to assess the robustness of the analytical assay. Acceptance limits of the calibration curve were defined as follows (1) % accuracy in the range of 80% to 120%, and (2) % coefficient of variance (%CV) of ≤ 20%.[5,6] A manual approach was used to set the limit of quantitation (LOQ) and limit of detection (LOD) of the method to effectively analyze the lorazepam samples.

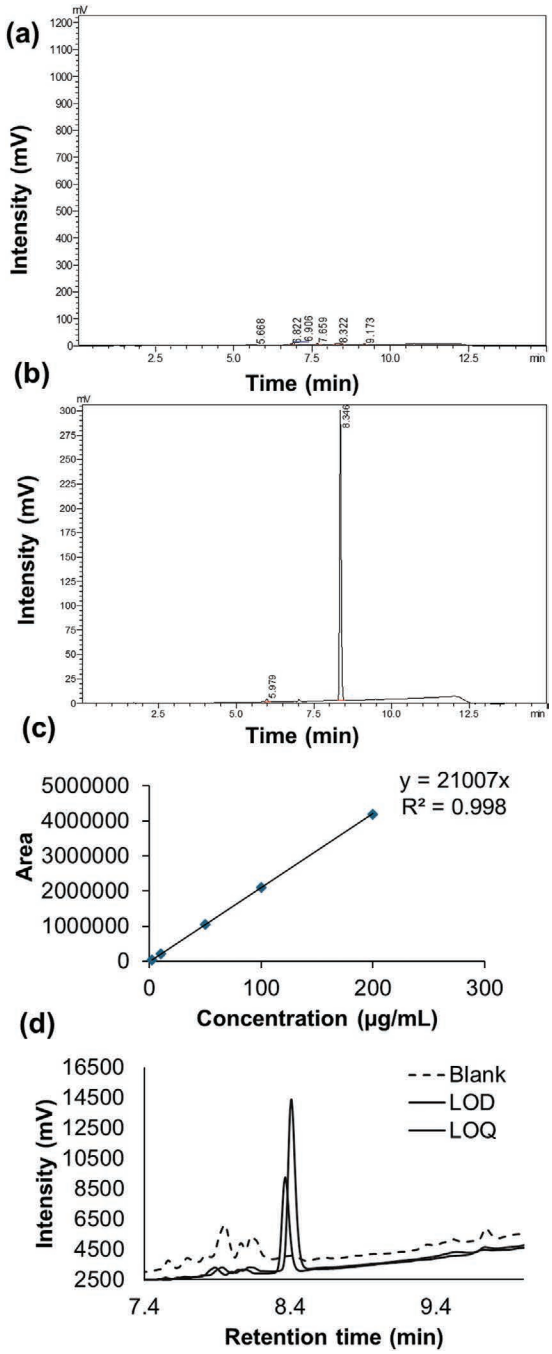
Stability Indicating Assay. A standard stock of lorazepam (50 µg/mL) was prepared in 50:50 Water: ACN and treated with 1N HCl, 1N NaOH, and H_2O_2. Such that pH of the solution with acid, and basic treatments were titrated to pH 2 and 12, respectively. The final concentration of H_2O_2 in the oxidative-treated lorazepam was 3% v/v. Acid, base, and peroxide-treated samples were divided into 2 aliquots and exposed to (a) ambient temperature (~21 to 25°C) and (b) 60°C (kept on shaking using an orbital shaker at 130 rpm). Samples were drawn at specific time points from each temperature condition for acid, base, and peroxide treatments for degradation peak investigation using the HPLC method.

Lorazepam Stability Assay. Lorazepam stability assay was performed using the HPLC method discussed in the previous section. Here we have discussed the method for repacking, stability conditions, and sample preparation for performing a stability study of the repackaged lorazepam oral solution.

Repackaging and Storage of ENFit Syringes Filled With Lorazepam in the CII Safe of Strong Memorial Hospital's Inpatient Pharmacy. At the Strong Memorial Hospital Inpatient Pharmacy of the URMC, lorazepam oral concentrate, 2 mg/mL solution was re-packaged as per the United States Pharmacopoeia (USP) <795> standards as follows: (1) 0.25 mL lorazepam oral solution was re-packaged into a 0.5-mL amber color ENFit oral syringe, and (2) 0.5 mL lorazepam oral solution was re-packaged into a 1-mL amber color ENFit oral syringe.

Stability Study of Repackaged Oral Syringes and Acceptance Criteria. Repackaged ENFit syringes were stored at ambient room (72 ± 4°F) temperature in the Strong Memorial Hospital Inpatient Pharmacy CII Safe for 182 days. Samples were taken from the

Figure 1. (a) Representative high-performance liquid chromatography (HPLC) chromatogram of blank (50:50 Water: ACN) sample shows background peaks and absence of lorazepam peak at approximately ~8.3 minutes. (b) Representative HPLC chromatogram of lorazepam showing a peak at ~8.3 minutes, 50 µg/mL. (c) Standard calibration curve of lorazepam assay. (d) The overlay of the lower limit of detection (LOD) as 1 µg/mL and quantitation (LOQ) as 2 µg/mL.



hospital inpatient pharmacy at specific time points (0, 4, 7, 14, 35, 63, 91, and 182 days), diluted with Water: ACN (50:50) only such that the final concentration was 50 µg/mL and evaluated for drug content using the HPLC method.

Data Analysis. The stability analysis of lorazepam was determined by calculating the percentage change of drug remaining from the initial amounts. The data were presented as mean with SD.

Results

Standard Curve and Method Validation. As compared with blank deionized water (Figure 1a), the chromatography of lorazepam shows a retention time (RT) peak at ~8.3 min (Figure 1b). Table 2 shows the list of system suitability parameters that were used for the HPLC method development for effective detection and quantitation of lorazepam. All the injections for system suitability were made using standard lorazepam (concentration 85 µg/mL) made in 50:50 water: ACN only. No peak was observed in the blank solvent as compared with the drug lorazepam. This RT peak was used for performing further method development. The calibration curve shown in Figure 1c, suggests robust linearity in the concentration range of 2 µg/mL to 200 µg/mL. The coefficient of determination (r^2) was found to be 0.99. The %CV and % accuracy for the intra and interday variability were found to be within the acceptable limit of < 5% and 100 ± 10% (Table 3). Further, acceptable %CV and % accuracy were also observed for the freeze-thaw cycle of the 3 random concentrations for intra- and interday validation runs (Table 4). Further, LOD and LOQ were also set (by manually checking chromatography peaks) for the given assay for the robust detection of lorazepam (Figure 1d).

Stability Indicating HPLC Method. The current HPLC method for lorazepam met all the requirements for the robust detection and quantitation of standard lorazepam solutions. It is also important for the HPLC assay to effectively detect the degradation peaks for

Table 2. System Suitability Parameters Used for Lorazepam HPLC Method Development*

System Suitability Parameters	Values
RT	8.3 ± 0.050 min
Tailing Factor	1.31 ± 0.010
%CV	2.150
%Accuracy	103 ± 2.210

HPLC, high-performance liquid chromatography; RT, retention time; %CV, percentage coefficient of variance

* All injections were made using 85 µg/mL (n = 5 injections) in Water: acetonitrile and the data are presented as average with SD.

Table 3. %CV and %Accuracy for Lorazepam Calibration Standards for Inter- and Intraday Runs

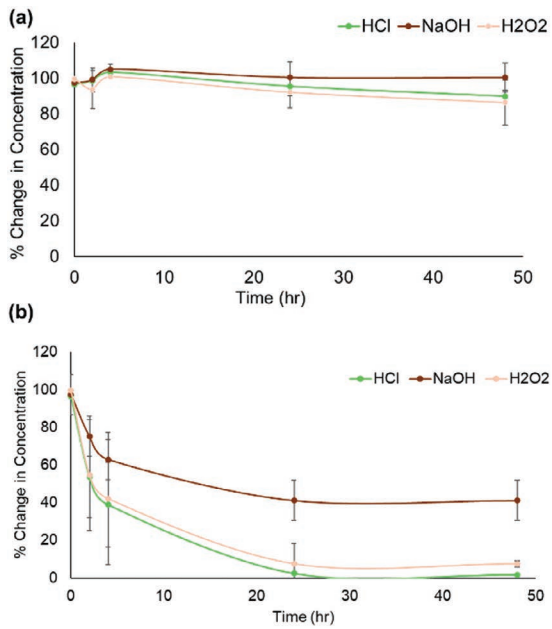
Conc. (µg/mL)	Interday		Intraday	
	%CV	%Accuracy	%CV	%Accuracy
2	2.393	95.114	4.031	95.412
10	1.163	99.272	1.556	98.636
50	0.413	100.426	0.604	100.598
100	0.441	100.446	0.440	100.757
200	0.813	99.861	0.129	100.562

%CV, percentage coefficient of variance

Table 4. %CV and %Accuracy of the Validation Runs Conducted After Freeze-Thaw Cycles of Standard Lorazepam Using 3 Random Concentrations on the Calibration Curve

Conc. (µg/mL)	Interday		Intraday	
	%CV	%Accuracy	%CV	%Accuracy
80	0.494	104.544	0.046	104.110
90	0.275	104.109	0.092	103.899
180	0.142	100.047	0.189	100.019

Figure 2. Degradation profile of lorazepam after treatment with acid, base, and peroxide treatment at (a) ambient temperature (~21°C to 25°C), and (b) 60°C. Data show relatively higher degradation in the first 4 hours of exposure to acid, base, and peroxide conditions at 60°C.



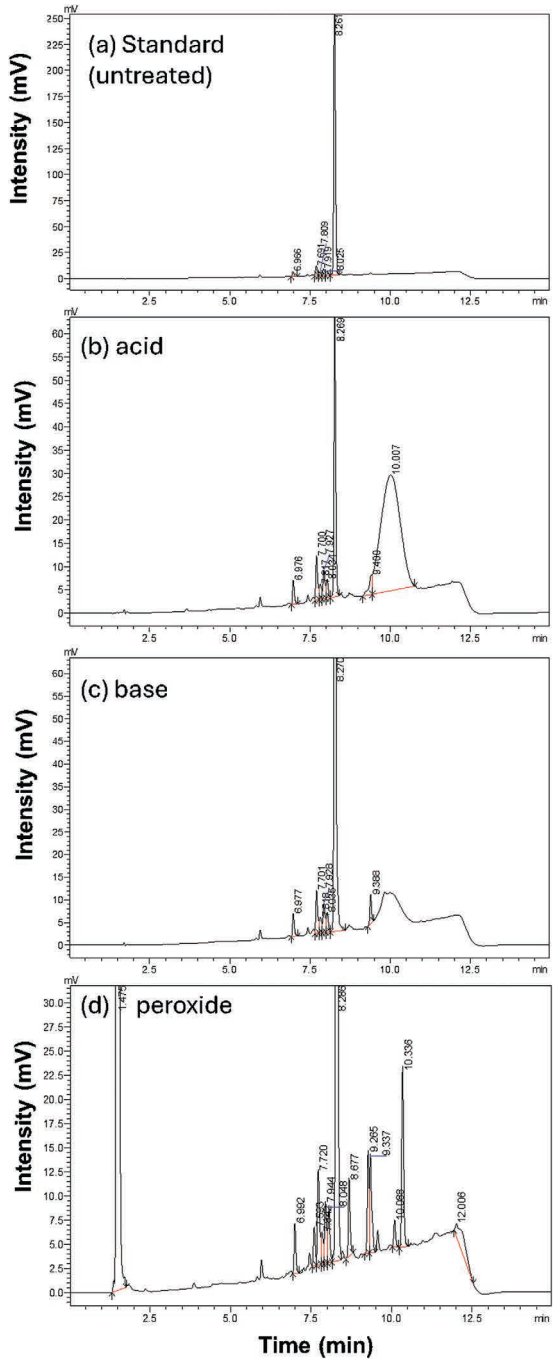
being used in studying the stability of the repackaged lorazepam formulations. Hence, the HPLC method was evaluated for the detection of the forced degradation rate and degradation peaks of the standard lorazepam solution (50 µg/mL) exposed to acidic, basic, and oxidative stress conditions at ambient temperature (~21°C to 25°C) and at 60°C (Figure 2a and b).

Data show that the lorazepam remains relatively stable under acid, base, and peroxide stress conditions at ambient temperature conditions. After 48 hours, under ambient temperature, acidic and oxidative stress causes drug concentration to fall to 89.76% and 86.41%, respectively. Whereas the shock of 60°C, for acidic and oxidation-treated lorazepam causes complete degradation of the drug by the end of 24 hours. This observation was confirmed by checking the presence of degradation peaks in lorazepam at ambient temperatures and 60°C.

Degradation peaks of the lorazepam after 4 hours of exposure to acidic, basic, and oxidative stress under 60°C heat shock are shown in Figure 3b–d as compared with standard untreated lorazepam with RT around 8.3 minutes (Figure 3a). Moreover, Table 5 shows the list of the unique degradation peaks that are produced due to acidic, basic, and oxidative stress. Chromatographic data (Figure 3) for the 4-hour exposure (at 60°C) clearly shows the separation of degradation peaks. We are unable to confirm the purity or the identity of the degradation peak due to the limitation of the HPLC assay. Hence, it is difficult to know which type of degradation product is being formed during the degradation

process. However, chromatography data show that the degradation products do not interact with the parent peak (~8.3 minutes). This shows that the established HPLC assay is stability-indicating and can be used for investigating the stability of lorazepam repackage oral syringes.

Figure 3. Representative chromatograms of the degradations after exposure at 60°C. (a) Standard (untreated), (b) acidic, (c) basic, and (d) peroxide conditions after 4 hours of heat exposure.



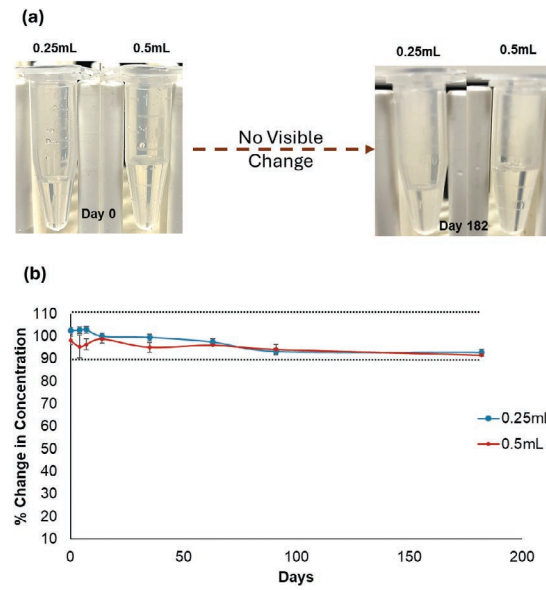
Physical Evaluation and Drug Content Analysis for Repackaged Amber Color ENFit Oral Syringes. There was no physical change observed in the formulation. No precipitation was seen at the end of 182 days for both types (0.25 mL and 0.5 mL) of oral syringes (Figure 4a). This shows that the formulation was physically stable in the CII Safe (storage facility) at Strong Memorial Hospital Inpatient Pharmacy.

At predetermined intervals, 3 independent samples from 2 types of repackaged syringes (0.25 mL and 0.5 mL) were collected and analyzed using the established HPLC method. The final concentration was set to 50 µg/mL for accurate quantitation with the stability-indicating assay. The lorazepam concentration remained within 90% to 100% of the labeled claim. This finding suggests that the repackaged ENFit oral

Table 5. Degradation Peaks Observed After 4-Hour Exposure to 60°C Under Acid, Base, And Peroxide Stress Conditions

Sample Type	Retention Time Peaks (min)
Acid	10.007
Base	9.388
Peroxide	8.677, 9.266, 9.337, 10.336

Figure 4. (a) Visual appearance of samples (0.25 mL and 0.5 mL volume) drawn from repackaged oral syringes (of sizes 0.5 mL and 1 mL). Images show no physical or visual change over 182 days when stored at ambient temperature. (b) % Change in concentration of lorazepam suggests that the repackaged oral formulation was found to be stable for 182 days. Data are presented as average (n = 3 individual runs), with SD.



syringes can be stored at ambient room temperature (72 ± 4°F) for at least 182 days (Figure 4b).

Discussion

Lorazepam is commonly used to treat anxiety and seizure disorders. Lorazepam oral concentrate is dispensed by Strong Memorial Hospital's Inpatient Pharmacy. When an oral liquid form of lorazepam is needed, a 30-mL multidose bottle of lorazepam oral concentrate 2 mg/mL is dispensed. Nurses draw the required patient-specific volumes from the bulk bottle based on the ordered doses. There is a significant amount of lorazepam oral concentrate wastage over time due to fractional dosing of the preparation from a 30-mL bulk bottle, with an expiration date of 90 days. Repackaging the lorazepam oral solution in small doses was carried out to solve this problem.[3]

A robust HPLC method was developed for detecting and quantifying lorazepam from a commercial non-aqueous oral lorazepam concentrate for studying the stability of repackaged solutions in the amber-colored ENFit oral syringes. All chromatograms of the standard lorazepam solutions met the system suitability parameters. This reverse phase gradient elution HPLC method was used to establish a calibration curve for lorazepam, effectively quantifying its concentration with a %CV of <10% and inter- and intraday accuracy of 100 ± 10%. The lower limit of detection (LOD) and lower limit of quantitation (LOQ) were 1 µg/mL and 2 µg/mL, respectively (Figure 1d). The method was simple and effective for lorazepam detection and comparable to previously reported HPLC methods.[7–9] Studies have shown the use of HPLC methods for detecting lorazepam in both solid and liquid dosage forms.[7,10] However, previous methods had lower sensitivity, with LOQs ranging from 150 µg/mL to 50 µg/mL.[3,7,9] Therefore, we developed a similar but more sensitive HPLC method with a higher sensitivity (LOQ of 2 µg/mL) gradient chromatography for stability studies.

Previous reports indicated that lorazepam experienced over 10% degradation after 48 hours of exposure to acidic and peroxide stress at ambient temperature. In our current study, we confirmed that no degradation of lorazepam occurred at room temperature when exposed to acid, base, and peroxide within the first 4 hours at ambient temperature (~21°C to 25°C). Our data also support previous findings (Figure 2a) of lorazepam degradation around 48 hours under acidic, basic, and peroxide conditions at ambient temperature.[3,11] Additionally, our robust gradient method detected degradation peaks within the first 4 hours of heat (60°C)-treated acidic, basic, and peroxide-treated standard lorazepam (Figure 2b; Figure 3b–d), which was not previously shown.[3] We also confirmed that both acid and peroxide treatments cause maximum degradation of lorazepam within 2 to 4 hours of exposure at 60°C. This is likely due to the high sensitivity of our gradient chromatography method established for studying the stability of the repackaged oral formulation.

Given the ordered doses at Strong Memorial Hospital, the stability of 0.25 mL and 0.5 mL volumes is particularly beneficial. It is estimated that Strong Memorial Hospital may use approximately 7200 syringes of repackaged 0.5 mg/0.25 mL syringes and about 6300 syringes of repackaged 1 mg/0.5 mL syringes annually. Data on estimated waste per month for bulk lorazepam oral concentrate stored in the CII Safe and dispensed in low volumes (0.25 mL and 0.5 mL), as well as yearly waste from these sources, is shown in Figure 5a and b. It is estimated that the current workflow for repackaging 0.25 mL and 0.5 mL syringes at Strong Memorial Hospital may generate about 950 mL of waste per year. Due to the lack of data on packaging and storage for low-volume repackaged preparations, the wastage in the CII Safe is nearly 6000 mL per year.

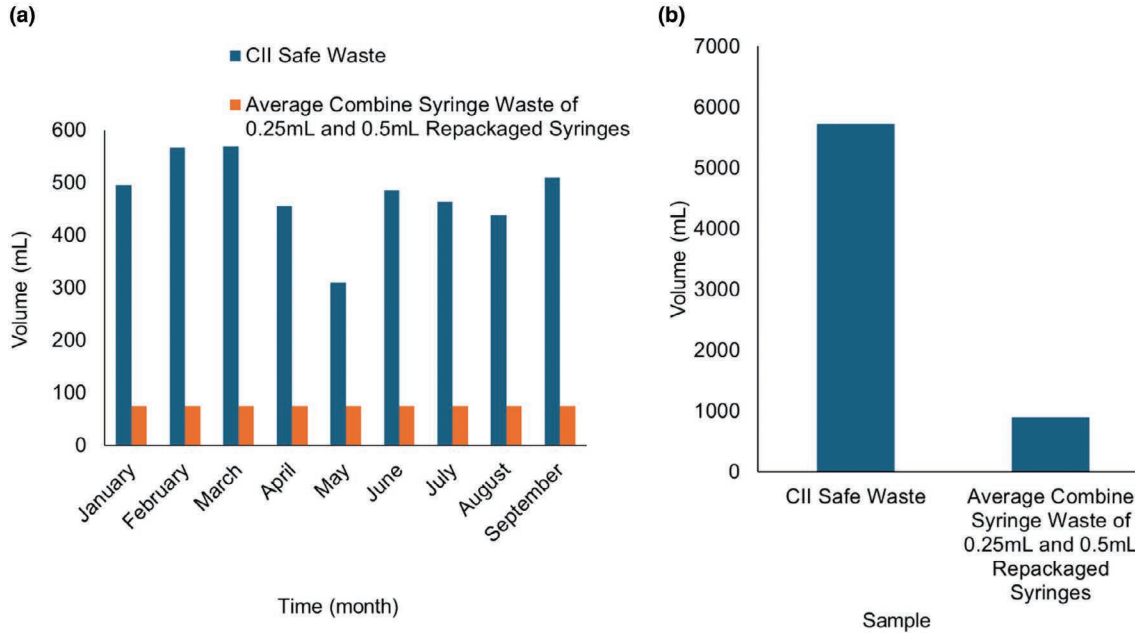
In today's health care environment, cost savings are a priority for many departments. While this change may seem minor, it represents a workflow that hospital pharmacies can integrate to support cost-saving initiatives. Additionally, dispensing lorazepam in ready-to-use oral syringes, rather than bulk bottles, reduces the potential for drug diversion. Accurately accounting for waste with bulk bottles is challenging due to spillage, product loss when the plunger is inserted, and other factors. Using repackaged oral syringes can improve the efficiency of patient-specific dose dispensing of lorazepam from bulk doses and enable a more accurate waste process, thereby reducing the opportunity for diversion. Therefore, a stability study for lorazepam repackaged in amber-colored, tamper-proof ENFit oral syringes was conducted at Strong Memorial Hospital Inpatient Pharmacy to address this issue and improve patient compliance.

We used our stability-indicating HPLC assay to investigate the stability of repackaged lorazepam solution in the amber-colored ENFit oral syringes over 182 days. Visible observations showed no precipitation or particulate matter at the end of the study (Figure 4a). The lorazepam concentration was 93.21% ± 2.04 (for 0.25 mL syringes) and 94.21% ± 2.13 (for 0.5 mL syringes) at the 91-day mark. At 182 days, the concentrations were 92.78% ± 0.86 (for 0.25 mL syringes) and 91.18% ± 0.45 (for 0.5 mL syringes). Both results were within the acceptable range of 100 ± 10% variation. This data supports the extended stability of lorazepam oral concentrate repackaged in ENFit oral syringes for 90 to 182 days. It not only confirms recent findings but also provides additional extended stability data that may be useful for hospital pharmacies.[3]

Conclusion

Lorazepam oral concentrate was repackaged into 0.25 mL and 0.5 mL tamper-proof ENFit oral syringes at Strong Memorial Hospital Inpatient Pharmacy. This study aimed to investigate the percentage

Figure 5. (a) Estimated waste per month compared with projected waste per month after repackaging, and (b) current average waste per year compared with projected average waste per year after repackaging.



concentration change over time to evaluate the stability of these syringes at ambient temperature (72 ± 4°F) using a robust stability-indicating HPLC assay. A robust HPLC assay with an $r^2 > 0.99$, %CV < 5%, and accuracy of 100 ± 10% for inter- and intraday variations was developed. The RT of lorazepam under the current HPLC conditions was 8.3 ± 0.05 minutes. The HPLC method was stability-indicating, as degradation peaks under stress conditions (acidic, basic, and oxidative) did not interfere with the parent peak. Native lorazepam solution showed significant degradation at 60°C under chemical stressors, with acidic and oxidative stress having a notable impact compared with ambient conditions. This stability-indicating HPLC assay was applied to study the stability of repackaged amber-colored ENFit oral syringes containing 0.25 mL and 0.5 mL of lorazepam (2 mg/mL) stored under ambient (72 ± 4°F) conditions at Strong Memorial Hospital Inpatient Pharmacy, Rochester, NY. After 182 days, both volumes of lorazepam showed no visible changes, and the percentage concentration change remained within the 100 ± 10% variation when stored at ambient temperature. This suggests that lorazepam repackaged in tamper-proof amber-colored ENFit oral syringes may have extended stability at ambient temperatures for 90 to 182 days.

Article Information

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References

1. Ghiasi N, Bhansali RK, Marwaha R. Lorazepam. Treasure Island, FL: StatPearls; 2024.
2. Hikma Pharmaceuticals. Lorazepam solution, concentrate. NIH: 2021. Accessed February 2, 2025.

https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=5ff82103-cc57-4af9-9362-82a7c686271d&type=display%202024
3. Brown SD, Sergent S, Morris S, et al. Chemical stability of lorazepam oral solution repackaged in plastic oral syringes at room and refrigerated temperatures. *Hosp Pharm*. 2024;59(4):471–475.
4. Gottwald MD, Akers LC, Liu PK, et al. Prehospital stability of diazepam and lorazepam. *Am J Emerg Med*. 1999;17(4):333–337.
5. Rochani A, Nguyen V, Becker R, et al. Stability-indicating LC-MS Method for determination of stability of extemporaneously compounded buprenorphine oral syringes for neonatal abstinence syndrome. *J Pediatr Pharmacol Ther*. 2021;26(4):395–404.
6. Rochani A, Nguyen V, Becker R, Kaushal G. Stability-indicating HPLC method to determine the stability of extemporaneously prepared vancomycin oral solution cups. *Am J Health Syst Pharm*. 2022;79(1):e34–e40.
7. Lee WM, Lugo RA, Cash J, et al. The accuracy and precision of measuring lorazepam from three liquid preparations. *J Pediatr Pharmacol Ther*. 2005;10(1):36–42.
8. Chinna P, Prakash MS, Ramakrishna RA, et al. Quantification of genotoxic impurities by HPLC in active pharmaceutical ingredient lorazepam. *J Analytical Chem*. 2023;78(4):514–521.
9. Orlovic D, Radulovic D, Ivanovic D, Vujic Z. HPLC determination of lorazepam and lorazepam-related compounds in pharmaceutical formulations. *Chromatographia*. 2000;52(11):732–734.
10. van der Vossen AC, van der Velde I, Smeets OS, et al. Formulating a poorly water soluble drug into an oral solution suitable for paediatric patients; lorazepam as a model drug. *Eur J Pharm Sci*. 2017;100:205–210.
11. Michelle Tubolino SS, Brown S, Coffey T. *Stability Indicating HPLC-UV Method for Quantification of Lorazepam in Oral Solution*. East Tennessee State University; 2023.

JPPT | Single Center Retrospective Study

Real-World Tocilizumab Use in Pediatric Inpatients

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OBJECTIVES Primary objective: to quantify tocilizumab (TCZ) use in pediatric inpatients. Secondary objectives: to explore safety and clinical outcomes.

METHODS This retrospective cohort study took place in a free-standing, 564-bed children's hospital. Pediatric inpatients who received intravenous TCZ from January 2016 to May 2021 were included. Data collected included demographics, indication, dose, number of administrations, safety events on days 0 to 7 after TCZ, use of extracorporeal support (ES), presence of concurrent infection, and survival to discharge. Exploratory analyses assessed characteristics associated with mortality.

RESULTS A total of 103 TCZ courses (n = 87 patients) were analyzed. Median age was 14 years. Tocilizumab indications included cytokine release syndrome (CRS; 56%), autoimmune disease (27%), graft-versus-host disease (GVHD; 5%), and COVID-19 (4%). The median TCZ dose was 8 mg/kg (IQR, 7.9–11.9), 18% of courses were administered during active infection, and ES was used in 15% of courses. New-onset alanine transaminase (ALT) or aspartate transaminase (AST) levels >3 times upper limit of normal (ULN) occurred in 53% and 60% of courses, respectively. Of 29 courses with evaluable hematologic data, 10% resulted in new-onset neutropenia and 3% in severe thrombocytopenia. Overall survival to discharge was 83%. In multivariable analyses, independent associations with mortality were found for the use of ES (OR, 8.68; 95% CI, 1.85–4.87), oncologic diagnosis (OR, 7.07; 95% CI, 1.14–89.29), and post-TCZ infection (OR, 11.17; 95% CI, 1.50–138.13).

CONCLUSIONS Tocilizumab is used for many pediatric inpatient indications, most commonly CRS. Newly identified transaminitis was common following TCZ administration. Risk factors for mortality are likely confounded by illness severity. Administration during active infection was not independently associated with increased mortality.

ABBREVIATIONS ALT, alanine transaminase; aOR, adjusted OR; AST, aspartate transaminase; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ECMO, extracorporeal membrane oxygenation; ES, extracorporeal support; FDA, US Food and Drug Administration; GVHD, graft-versus-host disease; ICU, intensive care unit; IL, interleukin; IV, intravenous; ONC/M, oncologic diagnosis or receiving myelosuppressive therapy; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; TCZ, tocilizumab; ULN, upper limit of normal

KEYWORDS cytokines; evidence-based medicine; interleukin-6; patient safety; pharmacology

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Introduction

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody targeted against the interleukin (IL)–6 receptor that inhibits IL-6–mediated signaling.[1] Tocilizumab is currently approved for the treatment of rheumatoid arthritis, giant cell arteritis, and systemic sclerosis–associated interstitial lung disease in adult patients. Additionally, it carries US Food and Drug Administration (FDA) approval for systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, and cytokine release syndrome (CRS) following chimeric antigen receptor (CAR) T-cell therapy in patients 2 years of age and older.[2]

In June 2021, the FDA granted emergency use authorization for TCZ in patients 2 years of age and older who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[3] The outbreak of the SARS-CoV-2 pandemic in December 2019 brought renewed attention to the off-label use of TCZ for patients with hyperinflammatory conditions, including critically ill patients. At least 15 studies have assessed the impact of TCZ use in adult patients with severe COVID-19, with an overall signal of decreased mortality.[4–7] Importantly, multiple studies have found no increase in secondary infection among adult patients with severe COVID-19 who received TCZ.[8–12]

While additional uses for TCZ are being explored, it is critical to balance any potential benefit with the known risks of the drug. Tocilizumab carries several warnings in its package labeling, including increased risk of infection, hepatotoxicity, and thrombocytopenia.[2] The current literature surrounding TCZ in pediatric patients is sparse and is largely centered on FDA-approved indications.[1,2,13–15] We therefore designed a retrospective, single center study to describe intravenous (IV) TCZ use patterns for on- and off-label indications in hospitalized children. We also tested the exploratory hypothesis that clinical characteristics could be identified that are associated with mortality in hospitalized children who receive IV TCZ.

Materials and Methods

A retrospective chart review was performed at a free-standing, 564-bed children's hospital. All patients who received TCZ from January 2016 to May 2021 were identified via query of pharmacy medication orders. Patients were excluded from analysis if TCZ was ordered but not administered, TCZ was administered in an ambulatory setting, or any route of administration other than IV was used. Only patients receiving IV TCZ were included because initial feasibility assessments indicated nearly 98% of inpatient TCZ orders during the inclusion period were administered via the IV route. Each individual patient could contribute more than 1 TCZ course if they were discharged and readmitted to the hospital. All analysis was performed based on TCZ courses unless specified.

Data collected via chart review included demographics, comorbid conditions, TCZ indication, TCZ dose, number of doses administered during hospitalization (i.e., course of therapy), whether TCZ was administered during an active infection, TCZ administration location (intensive care unit [ICU] or general ward), receipt of any extracorporeal therapy during hospitalization (ECMO or any dialysis modality), and survival to discharge. Active infection was defined as a positive microbiologic finding with ongoing organism-directed therapy at time of TCZ administration. Additional safety data collected included new-onset neutropenia, severe thrombocytopenia, transaminitis, or new infection within 7 days after TCZ administration. Neutropenia was defined as an absolute neutrophil count <1500 cells/μL, severe thrombocytopenia as a platelet count <50 K/μL, and transaminitis as either aspartate transaminase (AST) or alanine transaminase (ALT) levels >3 times the upper limit of normal (ULN) for age. New-onset laboratory abnormalities were defined as having the above laboratory values within the normal range for age for the 7 days prior to TCZ administration, followed by subsequent fulfillment of new-onset abnormality criteria. New infection was defined as a positive microbiologic test result within the 7 days following TCZ administration that received organism-directed therapy for >72 hours. For patients who died, data on whether death was deemed due to infection or other cause by the clinical team were also collected.

Statistical analysis was performed with R 3.6.3 (R Core Team, 2021). Descriptive data are reported as median (IQR). Categorical data were analyzed by using the Fisher exact test and continuous data by using the Kruskal-Wallis test. To test associations with mortality, univariable analysis was performed on physiologically plausible and clinically available characteristics and outcomes, using the Fisher exact test. Multivariable binomial logistic regression was then performed with characteristics found to be statistically significant on univariable analysis with a p value < 0.05.

Results

A total of 103 TCZ courses, administered to 87 patients, were included for analysis (Table 1). Seventy-five patients received a single dose of TCZ, 10 patients received 2 doses, and 2 patients received 4 doses. The median age was 14.1 years (IQR, 7.1–18.7), and median weight was 50 kg (IQR, 23.3–64.8). The median dose of TCZ administered was 8 mg/kg/dose (IQR, 7.9–11.9) and each course consisted of a median of 1 dose (IQR, 1–2).

Tocilizumab was administered for the treatment of CRS, primary autoimmune disease, graft-versus-host disease (GVHD), and a small number of other indications. The most common indication for TCZ was CRS (56.3%), with 48 (82.7%) of these courses administered on-label in patients who underwent CAR T-cell therapy. The 10 off-label administrations for CRS-related indications included cytokine release secondary to flotetuzumab, dinutuximab, and cytotoxic T-lymphocyte infusions. Of the 26 TCZ courses administered for an autoimmune indication, 20 (76.9%) were for off-label indications including neuromyelitis optica, acute disseminated encephalomyelitis, and Takayasu arteritis. Tocilizumab was administered to patients with a primary oncologic diagnosis or who had received myelosuppressive treatment (ONC/M) in 68 (66%) courses, and 50 (48.5%) TCZ courses were administered in an ICU. There were 19 courses where at least 1 dose was administered during an active infection, and 15 courses where the patient received some form of ECMO during the hospital admission (Table 1).

Evaluable safety data are presented in Table 2 with hematologic data available for 29 (28.2%) TCZ courses. Of those, 3 (10.3%) demonstrated new-onset neutropenia, and 1 (3.4%) new-onset severe thrombocytopenia. Additionally, 45 courses had evaluable pre- and post-TCZ ALT data, with 24 (53.3%) courses demonstrating new-onset ALT elevation. Of the 53 courses with evaluable pre- and post-TCZ AST data, 32 (60.4%) demonstrated new-onset AST elevation. Of these courses with evaluable transaminase data, 13 demonstrated new-onset elevation of both ALT and AST. There were no significant differences between

Table 1. Demographics*

Characteristic	All Courses (N = 103)	Survived (n = 85)	Deceased (n = 18)
Age, yr	14.1 (7.1–18.7)	14.3 (7.1–19.1)	11.9 (7.1 –17.2)
Weight, kg	50 (23.3–64.8)	50 (22.8–63.8)	53 (23.2–65.4)
Active oncologic diagnosis or received myelosuppressive treatment	68 (66%)	52 (61%)	16 (88.9%)
• Acute lymphocytic leukemia	50 (48.5%)	43 (50.6%)	7 (38.9%)
• Acute myeloid leukemia	9 (8.7%)	5 (5.9%)	4 (22.2%)
• Other	9 (8.7%)	4 (4.7%)	5 (27.8%)
Tocilizumab dose, mg/kg	8 (7.9–11.9)	8 (7.9–11.8)	8 (8–12)
Number of doses received	1 (1–2)	1 (1–2)	1 (1–3)
Indication for tocilizumab			
• CRS	58 (56.3%)	47 (55.3%)	11 (61.1%)
• GVHD	5 (4.9%)	3 (3.5%)	2 (11.1%)
• Primary autoimmune	26 (25.2%)	25 (29.4%)	1 (5.6%)
• COVID-19	4 (3.9%)	3 (3.5%)	1 (5.6%)
• Other	10 (9.7%)	7 (8.2%)	3 (16.7%)
Received any extracorporeal therapy	15 (15%)	5 (5.8%)	10 (55.6%)
• ECMO only	1	1	0
• CRRT only	8	4	4
• ECMO + CRRT	6	0	6
Received tocilizumab in an ICU	50 (48.5%)	35 (41.2%)	15 (83.3%)
Received tocilizumab during active infection†	19 (18.4%)	12 (14.1%)	7 (38.9%)
• Bacterial	8 (7.8%)	5 (5.9%)	3 (16.7%)
• Viral	15 (14.6%)	9 (10.6%)	6 (33.3%)
• Parasitic	2 (1.9%)	1 (1.2%)	1 (5.6%)

CRRT, continuous renal replacement therapy; CRS, cytokine release syndrome; ECMO, extracorporeal membrane oxygenation; GVHD: graft-versus-host disease; ICU, intensive care unit

*Data are reported as median (IQR) or n (%).
†Two subjects had concurrent bacterial and viral infections, and 2 subjects had concurrent bacterial, viral, and parasitic infections.

survivors and non-survivors for these outcomes. There were 9 courses, all in different patients, determined to have post-TCZ infections. Of these 9 courses, 2 patients (22.2%) survived to discharge and 7 (77.8%) died. There were 4 courses overall where the cause of death was deemed by the clinical team to be infection, 2 of which had confirmed post-TCZ infections per study criteria.

Overall survival to discharge occurred for 85 (83%) TCZ courses. Clinical characteristics associated with mortality on univariable analysis included receipt of extracorporeal support (ES) (OR, 18.93; 95% CI, 4.62–90.53), ONC/M diagnosis (OR, 5.01; 95% CI, 1.07–47.77), new-onset post-TCZ infection (OR, 24.92; 95% CI, 4.10–273.74), administration of TCZ during active infection (OR, 3.81; 95% CI, 1.04–13.52), and TCZ administration in an ICU (OR, 7.01; 95% CI, 1.80–40.62). On multivariable analysis receipt of ES (adjusted OR [aOR], 8.68; 95% CI, 1.85–44.87), ONC/M diagnosis (aOR, 7.07; 95% CI, 1.14–89.29), and post-TCZ infection (aOR, 11.17; 95% CI, 1.50–138.13) remained as significant risk factors for death (Table 3).

Discussion

Targeted immunomodulation is increasingly being investigated as a therapeutic approach to a range of inflammatory diseases in adult and pediatric patients,

Table 2. Safety Outcomes*

Outcome of Interest	Evaluable Courses	Occurrence of Outcome	Survived	Deceased	p value
New infection in 7 days after TCZ	103	9 (8.7%)	2 (22.2%)	7 (77.8%)	<0.001
New-onset ANC <1500 cells/μL after TCZ	29	3 (10.3%)	–	–	–
New-onset platelets <50K cells/μL after TCZ	29	1 (3.4%)	–	–	–
New-onset ALT >3× ULN after TCZ	45	24 (53.3%)	20 (83.3%)	4 (16.7%)	NS
New-onset AST >3× ULN after TCZ	53	32 (60.4%)	26 (81.3%)	6 (18.8%)	NS

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; NS, not significant; TCZ, tocilizumab; ULN, upper limit of normal

*New onset: values within normal range for age for 7 days prior to TCZ administration followed by noted abnormality within 7 days after TCZ administration.

from COVID-19 to inborn errors of immunity to autoimmune encephalopathies.[10–12,16,17] However, the potential efficacy of TCZ in these novel patient populations must be balanced with a safety assessment for off-label use. This study is the first to describe the real-world use and safety of TCZ across a range of pediatric inpatients, including critically ill children with and without active infection at the time of TCZ administration. Our study demonstrates a wide range of on- and off-label uses of TCZ in pediatric inpatients and suggests that being on extracorporeal life support, having an ONC/M diagnosis, and occurrence of post-TCZ infection represent independent risk factors for mortality in the context of receiving TCZ. Notably, the presence of active infection at the time of TCZ administration was not independently associated with mortality.

In the present study, 19 (18.4%) TCZ courses were administered in the setting of active infection. Most of these courses (78.9%) were administered during an active viral infection. The SARS-CoV-2 pandemic and resultant studies of acute COVID-19–associated respiratory failure demonstrate a role for targeted immunosuppression in acutely infected patients. A recent meta-analysis of 27 clinical trials describing 10,930 adults hospitalized with COVID-19 showed lower mortality in the TCZ-treated subjects (n = 6449; OR, 0.86 [95% CI, 0.79–0.95]; p = 0.003) with no increased risk of secondary infection in the TCZ group (OR, 0.95; 95% CI, 0.77–1.16).[18] Importantly, among studies that failed to show a mortality benefit of TCZ in adults with COVID-19, the use of TCZ in acutely SARS-CoV-2–infected subjects did not demonstrate harm.[7,10,19]

Our results complement these studies in the pediatric population, assessing off-label use and clinical characteristics associated with mortality, including administration during active infection. Our finding of a significant association between the use of extracorporeal therapy and mortality suggests that critical illness itself is likely a driver of mortality in our cohort. Similarly, the finding that an ONC/M diagnosis was associated with mortality may be driven by the underlying disease in that population, specifically with TCZ frequently administered for CRS. Like the association found between ES and mortality, the degree of underlying illness likely contributes to this finding, but additional study is warranted given the increasing use of IL-6 blockade in hyperinflammatory states. Finally, the association between post-TCZ infection and mortality emphasizes the need for infection prevention as well as optimized anti-infective therapy in immunocompromised populations.

While our study could not assess the impact of TCZ use on mortality, we were able to address several important safety outcomes. Adverse events associated with administration of TCZ are well described in prior clinical studies.[2] Depending on the indication, incidence of AST and ALT elevation >3 times ULN ranged from <1% to 5% and 1.7% to 13%, respectively. This transaminitis was not associated with clinically significant increases in direct bilirubin or clinical evidence of hepatitis or hepatic insufficiency. Additionally, transaminitis resolved with either dose reduction or discontinuation of TCZ. Neutropenia (neutrophil count <1500 cells/μL) incidence was reported as high as 15.4% overall, with an incidence of 25.9% in the subgroup of patients <30 kg with polyarticular juvenile idiopathic arthritis. Thrombocytopenia (platelet count <100 K/μL) was reported in 1.7% of patients. Because of these adverse events, the package labeling for TCZ includes recommendations to avoid use in patients with an absolute neutrophil count below 2000 cells/μL, platelet count below 100 K/μL, or those who have AST or ALT levels >1.5 times ULN. The labeling also importantly states that the decision to administer TCZ must consider potential benefits of treating severely ill patients (e.g., those with CRS) versus the risk of short-term TCZ use.[2]

Our study population's incidence of new-onset neutropenia, thrombocytopenia, and transaminitis was significantly higher than that reported in the package labeling for TCZ. This labeling acknowledges that patients with severe CRS often have cytopenias or transaminitis due to previous chemotherapy or CRS

Table 3. Univariable and Multivariable Analysis of Mortality Risk Factors

Risk Factor	Survived (n = 85)	Deceased (n = 18)	Univariable Analysis OR (95% CI)	Multivariable Analysis aOR (95% CI)
Received any extracorporeal therapy	5 (5.8%)	10 (55.6%)	**18.93 (4.62–90.53)**	**8.68 (1.85–44.87)**
Active oncologic diagnosis or received myelosuppressive treatment	52 (61%)	16 (88.9%)	**5.01 (1.07–47.77)**	**7.07 (1.14–89.29)**
Post-tocilizumab infection	2 (2.4%)	7 (38.9%)	**24.92 (4.10–273.74)**	**11.17 (1.50–138.13)**
Received tocilizumab during active infection	12 (14.1%)	7 (38.9%)	**3.81 (1.04–13.52)**	2.98 (0.67–12.80)
Received tocilizumab in an ICU	35 (41.2%)	15 (83.3%)	**7.01 (1.80–40.62)**	1.60 (0.34–8.60)

aOR, adjusted OR; ICU, intensive care unit

Bolded values represent statistically significant variables

itself, which we attempted to control for by evaluating only patients without preexisting laboratory abnormalities in the 7 days prior to TCZ administration. Laboratory monitoring was not protocolized in our study, with laboratory testing being performed at the discretion of the treating clinicians. Subjects who underwent laboratory testing may therefore have had a higher pre-test probability of having laboratory abnormalities that those for whom testing was not performed. The higher rate of adverse events identified in this study emphasizes the need for additional studies specifically focused on identifying the incidence of these adverse events in critically ill children.

The package labeling for TCZ recommends laboratory monitoring every 2 to 8 weeks, depending on indication, starting with the second dose. Based on the results of our study, it may be prudent to increase monitoring in the period immediately following administration of the first dose, particularly in critically ill children. While reassuring that the primary adverse effects of TCZ resolved in previous studies with either dose reduction or discontinuation, an individualized risk-benefit analysis must be made in patients at high risk of adverse events secondary to TCZ or with preexisting laboratory abnormalities that may be further exacerbated.

Anti-cytokine therapies have been studied extensively in adults with sepsis, including IL-1 pathway inhibitors, anti–tumor necrosis factor-α therapies, and bradykinin antagonists.[20–25] These trials nearly uniformly failed to show a mortality benefit, though secondary analyses have repeatedly suggested benefit in the subset of subjects with the most severe systemic inflammation.[26,27] The REMAP-CAP study, an 803-subject prospective, adaptively randomized study of TCZ in critically ill adults with COVID-19, showed the greatest efficacy of TCZ in subjects in the highest tercile of serum C-reactive protein concentrations.[28] It is unclear if a biomarker-driven approach to TCZ use, with TCZ being reserved for patients with marked elevations in IL-6, could further enhance the safety and efficacy of TCZ in hospitalized children. This is a topic deserving of further study.

Limitations of Study

Our study has several limitations, first of which is its single center, retrospective nature. This design, as well as the lack of a non-TCZ comparator group, prevents causal inferences from being drawn. While multivariable analysis was performed to help account for confounders inherent in any retrospective study, other unmeasured confounders may have influenced our results. Post-TCZ laboratory data were also not available for all patients and data that were available were not collected in a standardized fashion, reducing power to identify safety signals. Additionally, combined analysis of ICU and non-ICU inpatients may suppress safety signals present in either population alone. However, this was done to increase power owing to the limited number of TCZ courses with available data, and patients receiving TCZ for the treatment of CRS were well balanced between the ICU and ward.

Conclusions

Tocilizumab is used for a broad range of indications in pediatric inpatients, the most common being CRS. We found no independent association between administration of TCZ during active infection and mortality, though laboratory abnormalities including transaminase elevation were common. Post-TCZ infection and conditions associated with underlying critical illness, however, were associated with mortality. Based on our findings, surveillance for early transaminitis and neutropenia is warranted in acutely ill children receiving IV TCZ. Future studies of targeted immunomodulation should be considered, focusing on the safety and efficacy of TCZ in pediatric patients with severe inflammation, and these studies should include surveillance for early neutropenia and liver injury.

Article Information

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References

1. Le R, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor t cell-induced severe or life-threatening cytokine release syndrome. *Oncologist*. 2018;23(8):943–947.
2. ACTEMRA (tocilizumab) [package insert]. San Francisco, CA: Genentech Inc; September 2021.
3. Coronavirus (COVID-19) update: FDA authorizes drug for treatment of COVID-19. US Food and Drug Administration. Published June 28, 2021. Accessed September 1, 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19
4. Zhao J, Cui W, Tian B-p. Efficacy of tocilizumab treatment in severely ill COVID-19 patients. *Crit Care*. 2020;24(1):524.
5. Selvaraj V, Khan MS, Bavishi C, et al. Tocilizumab in hospitalized patients with COVID-19: a meta analysis of randomized controlled trials. *Lung*. 2021;199(3):239–248.
6. Snow TAC, Saleem N, Ambler G, et al. Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials. *Intensive Care Med*. 2021;47(6):641–652.
7. Albuquerque AM, Eckert I, Tramujas L, et al. Effect of tocilizumab, sarilumab, and baricitinib on mortality among patients hospitalized for COVID-19 treated with corticosteroids: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2023;29(1):13–21.
8. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181(1):24.
9. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med*. 2020;383(24):2333–2344.
10. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. *N Engl J Med*. 2021;384(16):1503–1516.
11. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181(1):32.
12. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med*. 2021;384(1):20–30.
13. Bielak M, Husmann E, Weyandt N, et al. IL-6 blockade in systemic juvenile idiopathic arthritis—achievement of inactive disease and remission (data from the German AID-registry). *Pediatr Rheumatol*. 2018;16(1):22.
14. Grönlund MM, Remes-Pakarinen T, Kröger L, et al. Efficacy and safety of tocilizumab in a real-life observational cohort of patients with polyarticular juvenile idiopathic arthritis. *Rheumatology*. 2020;59(4):732–741.
15. Si S, Teachey DT. Spotlight on tocilizumab in the treatment of CAR-T-cell-induced cytokine release syndrome: clinical evidence to date. *Ther Clin Risk Manag*. 2020;16:705–714.
16. Abani O, Abbas A, Abbas F, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637–1645.
17. Koh JC, Murugasu A, Krishnappa J, Thomas T. Favorable outcomes with early interleukin 6 receptor blockade in severe acute necrotizing encephalopathy of childhood. *Pediatr Neurol*. 2019;98:80–84.
18. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Domingo P, Mur I, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA*. 2021;326(6):499.
19. Aziz M, Haghbin H, Abu Sitta E, et al. Efficacy of tocilizumab in COVID-19: a systematic review and meta-analysis. *J Med Virol*. 2021;93(3):1620–1630.
20. Calandra T, Glauser MP, Schellekens J, Verhoef J. Treatment of Gram-negative septic shock with human IgG antibody to Escherichia coli J5: a prospective, double-blind, randomized trial. *J Infect Dis*. 1988;158(2):312–319.
21. Fisher CJ. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome: results from a randomized, double-blind, placebo-controlled trial. *JAMA*. 1994;271(23):1836.

22. Opal SM, Fisher CJ, Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial: The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med*. 1997;25(7):1115–1124.
23. Fisher CJ, Balk RA, Benjamin E. Treatment of septic shock with the tumor necrosis factor receptor:fc fusion protein. *N Engl J Med*. 1996;334(26):6.
24. Abraham E, Anzueto A, Gutierres G, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock: NORASEPT II Study Group. *Lancet*. 1998;351(9107):929–933.
25. Fein AM. Treatment of severe systemic inflammatory response syndrome and sepsis with a novel bradykinin antagonist, deltibant (CP-0127): results of a randomized, double-blind, placebo-controlled trial. *JAMA J Am Med Assoc*. 1997;277(6):482.
26. Panacek EA, Marshall JC, Albertson TE, et al. Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. *Crit Care Med*. 2004;32(11):2173–2182.
27. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of the macrophage activation syndrome: re-analysis of a prior Phase III trial. *Crit Care Med*. 2016;44(2):275–281.
28. The REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med*. 2021;384(16):1491–1502.

JPPT | Single Center Survey Study

Knowledge and Awareness of Caregivers About Using Paracetamol in Children in Al-Baha Region: a Cross-sectional Study

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OBJECTIVE This study aimed to assess parents' knowledge, attitudes, and practices regarding the use of paracetamol in children.

METHODS A cross-sectional study was conducted in the in Al-Baha region. A self-administered electronic questionnaire was constructed and distributed by the research team using a simple random sampling method. The questionnaire included sections regarding the sociodemographic data, knowledge, practices and attitudes regarding pediatrics' paracetamol use. Parents or children's caregivers were targeted by the study.

RESULTS 41.9% of 1000 survey respondents reported administering paracetamol to their children. Parents reported administering paracetamol based on experience with similar symptoms in their children (27.2%). One-third of the respondents (33.3%) believes that the maximum amount to be administered in 1 time is a single dose, 58.8% are aware that overdose of paracetamol can harm the child, 60.8% had never administered adults' paracetamol to their children, 26% measure doses using a graded cup or a teaspoon, 61.3% preferred paracetamol syrup, and 56.9% store the drugs in the refrigerator. Re-administration of pediatric paracetamol, as per instructions of the manufacturer, is practiced by 40%. Physicians are the source of drug information in 48.1% of cases. Physician's prescriptions are the source of obtaining paracetamol in 51.1% of cases.

CONCLUSION A parental knowledge gap exists regarding the correct use of paracetamol for children in Al-Baha region. Educational programs should focus on the risks of overdose and the importance of following recommended dosages. Educational programs should also recommend limiting OTC dispensing of pediatric medications. Health care professionals should educate parents during clinical visits. Social media can be utilized to disseminate correct drug information. Narrowing of these gaps in parents' knowledge and practices improves safety and efficacy of paracetamol yielding better health outcomes.

ABBREVIATIONS ED, emergency department; IBM SPSS, International Business Machines Statistical Package for the Social Sciences; KSA, Kingdom of Saudi Arabia; NIS, New Israeli Shekel; OTC, over-the-counter; SAR, Saudi Riyals.

KEYWORDS Al-Baha region; parental awareness; pediatric paracetamol; OTC drugs; self-medication

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Introduction

Over-the-counter (OTC) paracetamol, also known as acetaminophen, is regularly used for children's pain relief and as an antipyretic due to its efficacy, relative safety, and availability in a range of pharmaceutical forms that includes syrups, drops, suppositories, etc. However, previous research has shown that parents frequently unintentionally give their children an incorrect amount of paracetamol.[1] In this study, we aimed to assess parents' knowledge, attitudes, and practices regarding the use of paracetamol, as well as their awareness of items containing the active ingredient. According to reports, paracetamol is the most prevalent pharmaceutical agent involved in overdoses, especially in children under age 6.[2] The variable dosing schedules and strengths of the various formulations of paracetamol pose a serious risk of overdose in children and infants.[2]

Paracetamol is commonly used for fever which is demonstrated to be a reason for anxiety among parents. Fever accounts for up to 22% of visits to emergency

departments (ED).[3] Fifty percent of parents treat their child's fever with the wrong medication dosage.[3] Many parents endorse simultaneous utilization of ibuprofen and paracetamol, to lower fever because they dread it excessively.[3] Paracetamol poisoning can result from attempted suicide or accidental overdose in children.[4] Accidental child poisoning in Jeddah was mostly connected with medicinal drugs, with a reported frequency of 23.3%.[5] Parental education and understanding played a significant influence in decreasing the incidence of child poisoning.[5] In a survey of 300 parents, most of the caregivers polled (87%) were females (mothers). Approximately half of the parents (50.9%) reported having used paracetamol as an antipyretic in children under the age of 6.[5] One-quarter (25.4%) favored syrup forms, whereas 33.8% chose suppository dose forms. Roughly half of the caregivers (51.2%) relied mostly on medical staff for information. The average knowledge score for paracetamol was 2.1 (SD = 1.4) out of 6, with a median of 2.0 and an IQR of 1.0 to 3.01. [6] Given the lack of existing studies related to our topic and our emphasis on Al-Baha city, our main goal is to assess the level of parental knowledge and awareness regarding the utilization of paracetamol among children in Al-Baha. It is essential to assess parental knowledge to establish whether parents are aware of the correct usage, dosages, potential side effects, and other safety precautions while their children are receiving treatment with paracetamol. This knowledge will add a new perspective to the discourse that could be beneficial to health providers, authorities, and educational programs aiming to ensure the safe administration of drugs to the pediatric populations in Al-Baha city, Saudi Arabia.

Materials and Methods

Study Design. A cross-sectional study was conducted in in the in Al-Baha region (including Al-Baha city and a few nearby villages). We collected data from pediatrics and primary health care centers, where parents went to vaccinate their children regularly and then focused on dates when we could obtain the needed sample. Most of the patients that come to these clinics do not have serious symptoms. Data was collected over an 8-week period from April 1, 2024 in the spring to May 31, 2024.

Inclusion and Exclusion Criteria. Al-Baha area residents who are parents or caregivers who have legal custody of children between the ages of 0 and 18 years were the target sample group for the study. Persons without children were excluded. Health care providers with children have been included to serve as internal controls.

Sample Size. The sample size was calculated by utilizing the Qualtrics calculator with a confidence level of 95%; the proposed sample size was 384.

Method for Data Collection and Instrument. A self-administered electronic questionnaire was constructed and distributed by the research team using a simple random sampling method to parents and health care providers at the clinics. The health care providers included physicians, nurses, and pharmacists. Prior to participation, informed consent was obtained from all respondents, ensuring their voluntary agreement and understanding of the study's purpose and procedures. The survey took 8 weeks' time. The questionnaire utilized a modified validated survey from a similar study conducted in Palastine.[7] It included 4 sections regarding the sociodemographic data, the awareness regarding paracetamol products among participants, parents' knowledge of paracetamol use, and parents' paracetamol-related practices and attitudes (see Supplemental Table).

Statistical Analysis

The relationship and incidence of the event have been assessed using the χ^2. Analysis was performed using the software package IBM SPSS Statistics (SPSS Inc, version 25.0). Differences were considered statistically significant at $p \leq 0.05$.

Results

All those approached by the questionnaire agreed to participate in the survey after understanding of the study's purpose and procedures. Their total number was 1000 participants. The demographic characteristics of the participants in the study are shown in Table 1. The responses reported by physicians were not significantly different from the responses of the parents. Most of the respondents (45.8%) exist in the age range of 18 to 29 years.

Some health features of the children studied in the present work are shown in Table 2. 41.9% of parents and 50.8% of physician parent respondents reported administering OTC paracetamol to their children. 27.2% of the parents related this OTC use to their previous experience with similar symptoms in their children.

The dosing and administration knowledge and practices of parents are shown in Table 3. One-third of the respondents (33.3%) think that the maximum amount to be administered is a 1-time single dose (as opposed to repeated doses for persistent fever); and that the dose quantity is determined by the age of the child, 58.8% think that overdose of paracetamol can harm the child, 60.8% had never administered adult paracetamol pharmaceutic forms to their children, and approximately 26% measure doses using a graded cup or a teaspoon. The parents' medication preferences and practices are shown in Table 4. A majority (61.3%) of respondents preferred paracetamol syrup over other pharmaceutical forms for their children, 56.9% store the drugs in the refrigerator, 41.2% reported that their children refuse to take medications; 58.3% persuaded their children by encouragement and motivation to take medications. Re-administration of pediatric paracetamol is practiced by 40% of the parents according to the severity of the condition. Physicians were source of drug information

Table 1. Demographic Characteristics of the Participants in a Cross-sectional Study About Knowledge and Awareness of Parents About Using Paracetamol in Children in Al-Baha Region KSA

Item	Total Population N = 1000 n (%)	Physician n = 65 n (%)	Parent* n = 935 n (%)
Age range of the respondent (yr)			
18–29	499 (49.9)	41 (63.1)	458 (49)
30–39	193 (19.3)	9 (13.8)	184 (19.7)
40–49	234 (23.4)	13 (20)	221 (23.6)
50–59	57 (5.7)	2 (3.1)	55 (5.9)
>60	17 (1.7)	0	17 (1.8)
Education level of the respondent			
Not educated	1 (0.1)	0 (0)	1 (0.12)
Elementary	20 (2)	0 (0)	20 (2.1)
Intermediate	25 (2.5)	0 (0)	25 (2.6)
Secondary	176 (17.6)	0 (0)	176 (18.8)
University	721 (72.1)	45 (69.2)	676 (67.6)
Postgraduate degree	57 (5.7)	20 (30.8)	37 (4)
Relationship to investigated children			
Father	120 (12.0)		
Mother	328 (32.8)		
Brother	76 (7.6)		
Sister	236 (23.6)		
Grandfather	8 (0.8)		
Grandmother	12 (1.2)		
Other	220 (22.0)		
Education level of the mother			
Not educated	53 (5.3)	1 (1.5)	
Elementary	51 (5.1)	5 (7.7)	
Intermediate	67 (6.7)	4 (6.2)	
Secondary	204 (20.4)	13 (20)	
University	550 (55.0)	30 (46.2)	
Postgraduate degree	75 (7.5)	12 (18.5)	
Education level of the father			
Not educated	28 (2.8)	1 (1.5)	
Elementary	49 (4.9)	7 (10.8)	
Intermediate	76 (7.6)	6 (9.2)	
Secondary	219 (21.9)	8 (12.2)	
University	515 (51.5)	27 (41.5)	
Postgraduate degree	113 (11.3)	16 (24.6)	
Family Income per month (in SAR)			
<5K	102 (10.2)	4 (6.2)	98 (10.5)
5K–10K	277 (27.7)	20 (30.8)	257 (27.5)
10K–20K	389 (38.9)	22 (33.8)	367 (39.3)
>20K	232 (23.2)	19 (29.2)	213 (22.8)
Marital status			
Single	432 (43.2)	36 (55.4)	396 (42.4)
Divorced	46 (4.6)	5 (7.7)	41 (4.4)
Widowed	24 (2.4)	0 (0)	24 (2.6)
Married	498 (49.8)	24 (37)	474 (50.7)
No. of children			
One child	223 (22.3)	20 (3.1)	203 (21.7)
2–4 children	480 (48.0)	32 (49.2)	448 (52.2)
More than 4	297 (29.7)	13 (20)	284 (30.4)

SAR, Saudi Arabia Riyals

* Includes person with legal custody.

Table 2. Comparison Between Physician and Global Population (Including Physicians) Regarding Some Health Features of the Children Studied in a Cross-sectional Study About the Knowledge and Awareness of Parents About Using Paracetamol in Children in Al-Baha Region KSA

Response	Global Study Population N = 1000 n (%)	Participants Physicians n = 65 n (%)
Children visits to doctor in the past 6 mo		
None	159 (15.9)	11 (16.9)
Once	237 (23.7)	14 (21.5)
Twice	255 (25.5)	25 (38.5)
More than 2 times	222 (22.2)	13 (20)
I don't remember	127 (12.7)	2 (3.1)
Children self-treatment at home in the past 6 mo		
None	140 (14)	9 (13.8)
Once	198 (19.8)	15 (23.1)
Twice	205 (20.5)	17 (26.2)
More than 2 times	314 (31.4)	18 (27.7)
I don't remember	143 (14.3)	6 (9.2)
Administration of paracetamol to children without prescription		
No	321 (32.1)	22 (33.8)
Yes	419 (41.9)	33 (50.8)
I don't know (what paracetamol is)	260 (26)	10 (15)
Indication of paracetamol administration to children without prescription (n = 935)		
I didn't use it without prescription	377 (40.3)	20 (30.8)
Experience with similar symptoms	254 (27.2)	12 (18.5)
Expensive doctor charges	23 (2.5)	2 (3.1)
Lack of confidence in the health care system	18 (1.9)	7 (10.8)
No need to visit doctor	112 (12)	17 (26.2)
Other	151 (16.1)	7 (10.8)
Children ever been hospitalized before (Yes), n (%)	762 (76.2)	50 (76.9)

with reference to pediatric paracetamol use and dosing in 48.1% of cases; source of obtaining paracetamol itself was physicians' prescriptions in 51.1% of cases. Thirty-seven percent never share pediatric paracetamol, while 41.4% share the drug among other children of the family.

The participant's response, regarding the febrile indication of pediatric paracetamol without prescription, is shown in Figure 1. 31.2% estimated 38°C as the febrile point for administration of paracetamol to their children.

The response of participants, regarding the dosing interval of pediatric paracetamol preparations, is shown in Figure 2. 48.9% estimated the dosing interval at 4 to 6 hours.

Discussion

Socio-demographic factors, and family caregivers' psychosocial status, are among the influencing factors on parental pediatric paracetamol administration practices.[6] The demographic characteristics of the participants in the present study has 2 merit features compared with similar previous investigations; a larger study sample (n = 1000), and a detailed description of the sample. Both contribute to the reliability of the results. A Palestinian cross- sectional study of similar interest, that included 300 participants, reported 87% of the sample being females.[1] This is higher than our female participants of 57.6% of the study sample wherein 32.8% were mothers, 23.6% were sisters and 1.2% were grandmothers. The diversity of caregivers in the family, and the involvement of all family members in the health care of the family children, shows the strength of relationships within the local community. Most of our respondents (72.1% total, 55% of mothers and 51.5% of fathers) are university graduates. 5.7%, including 7.5% of the mothers and 11.3% of the fathers, hold postgraduate degrees. 0.1% of the respondents were non-educated, moreover, 5.3% of the mothers and 2.8% of the fathers of the children are non-educated. Considering that the sample was random and cross-sectional, these results indicate the wide dissemination of education in the local community and contribute to the reliability of the results which depends on understanding and honest questionnaire responses. The educational level of participants in our study is different from that in the Palestinian report, where 55.3% of the mothers reported completing high school education as their highest level of education. They also reported 75.3% of respondents

Table 3. Dosing and Administration Knowledge and Practices of Parents in a Cross-sectional Study About the Knowledge and Awareness of Parents About Using Paracetamol in Children in Al-Baha region KSA*

Item	Study Population Response, n (%)	
	Rectal Suppositories	5-mL Teaspoon
Maximum doses of pediatric paracetamol/day (N = 1000)		
1	333 (33.3)	427 (42.7)
2	172 (17.2)	152 (15.2)
3	69 (6.9)	69 (6.9)
4	29 (2.9)	35 (3.5)
5	9 (0.9)	17 (1.7)
I don't know	388 (38.8)	300 (30)
Pediatric paracetamol dose is determined according to (N = 1000)		
Previous experience	66 (6.6)	
Age of the child	333 (33.3)	
Weight of the child	238 (23.8)	
Severity of the condition	103 (10.3)	
Pharmaceutical manufacturer instructions	130 (13)	
Other	130 (13)	
Overdose of pediatric paracetamol can cause harm (N = 1000)		
No	94 (9.4)	
I don't know	318 (31.8)	
Yes	588 (58.8)	
Drug poisoning	137 (13.7)	
Renal injury	144 (14.4)	
Hepatic injury	130 (13)	
Immunosuppression	77 (7.7)	
Gastric upset	80 (8)	
Other	234 (23.4)	
Paracetamol syrup expiration following bottle opening (N = 1000)		
3 mo	380 (38)	
6 mo	119 (11.9)	
Until expiration date	175 (17.5)	
I don't know	326 (32.6)	
Ever administered adult paracetamol preparations to your children (N = 1000)		
No	608 (60.8)	
I don't know	232 (23.2)	
Yes	160 (16)	
Cause of administration of adult paracetamol preparations to your children (N = 407)		
More safe	66 (6.6)	
More effective	93 (9.3)	
Didn't have pediatrics form	60 (6)	
Other	188 (18.8)	
Adult dose modification done to fit your children (N = 424)		
Administration of half the adult dose	93 (9.3)	
Calculated dose	74 (7.4)	
No modification needed	96 (9.6)	
Other	161 (16.1)	
Instrument used to measure the dose (N = 831)		
Graded cup	267 (26.7)	
Syringe	195 (19.5)	
Tablespoon	100 (10)	
Teaspoon	269 (26.9)	
Other	169 (16.9)	

* Expiration date according to the respondent own thoughts.

Table 4. Parents' Medication Preferences and Practices in a Cross-sectional Study About the Knowledge and Awareness of Parents About Using Paracetamol in Children in Al-Baha region KSA

Item	Study Population Response, n (%)
Preferred pediatric paracetamol dosage form (N = 1000)	
Rectal suppositories	101 (10.1)
Tablets	67 (6.7)
Syrup	613 (61.3)
Rectal suppositories or syrup	186 (18.6)
Drops	33 (3.3)
Reason for preferring paracetamol rectal suppositories (N = 482)	
Children age	94 (19.5)
Ease of administration	81 (16.8)
Effectiveness	90 (18.7)
Affordable price	27 (5.6)
Doctor-'s advice	54 (11.2)
Pharmacist's advice	19 (3.9)
Friends' recommendation	4 (0.8)
Other	113 (23.4)
Source of mastering suppositories administration technique (N = 457)	
Physicians' instructions	122 (26.7)
Pharmacists' instructions	41 (9)
Nurses' demonstration	68 (14.9)
Previous personal experience	123 (26.9)
Other	103 (22.5)
Storage of paracetamol rectal suppositories (N = 496)	
In the refrigerator	282 (56.9)
In the deep freezer	64 (12.9)
At room temperature	53 (1.1)
Other	97 (19.6)
Difficulties in administering paracetamol to the children (N = 1000)	
Children uncooperative because of illness	122 (12.2)
Children sleeping at dosing time	56 (5.6)
Children refuses to take medications	412 (41.2)
No difficulties	243 (24.3)
Other	167 (16.7)
Method used to convince children to take medications (N = 1000)	
Children encouragement and motivation to take medications	583 (58.3)
Children enforcement to take medications	63 (6.3)
Administration of suppositories in replacement for syrups	76 (7.6)
Mixing medications with juice or food	69 (6.9)
Mixing medications with juice or food or use of suppositories	28 (2.8)
Asking for medical counseling	31 (3.1)
Replacing medicines with non-pharmacologic methods	15 (1.5)
Other	135 (13.5)
Repeated re-administration of pediatric paracetamol depends on (N = 1000)	
Physicians' counseling/consultation	254 (25.4)
Pharmacists' recommendations	46 (4.6)
Children age	66 (6.6)
Children weight	54 (5.4)
Children severity of condition	400 (40)
Pharmaceutical manufacturer instructions	46 (4.6)
Other	134 (13.4)
Source of drug information with reference to pediatric paracetamol (N = 1000)	
Physicians	481 (48.1)
Pharmacists	144 (14.4)
Pharmaceutical manufacturer medicine leaflet	86 (8.6)
Friends and relatives	24 (2.4)
Previous experience	64 (6.4)
Personal knowledge	64 (6.4)
Other	137 (13.7)

(Table cont. on page 651)

Table 4. Parents' Medication Preferences and Practices in a Cross-sectional Study About the Knowledge and Awareness of Parents About Using Paracetamol in Children in Al-Baha region KSA *(cont.)*

Item	Study Population Response, n (%)
Source of getting pediatric paracetamol (N = 1000)	
Physicians' prescription	511 (51.1)
Pharmacy without prescription (over the counter)	249 (24.9)
From friends and relatives	28 (2.8)
From previously used and stored at home	43 (4.3)
Via electronic marketing suppliers	21 (2.1)
Other	148 (14.8)
Re-administration or sharing of pediatric paracetamol for similar symptoms (N = 1000)	
I don't share medicines with others	370 (37)
I share medicines between my children if they develop similar symptoms	414 (41.4)
I share medicines with my friends/relative if their children develop similar symptoms	61 (6.1)
I re-use pediatric paracetamol for the same child if it develops similar symptoms	155 (15.5)

Figure 1. The response percent, regarding the febrile indication (in Celsius degrees) of OTC pediatric paracetamol, of participants in a cross-sectional study about knowledge and awareness of parents about using paracetamol in children in Al-Baha region KSA, n = 1000.

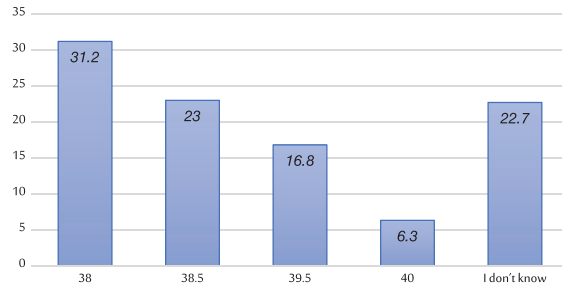
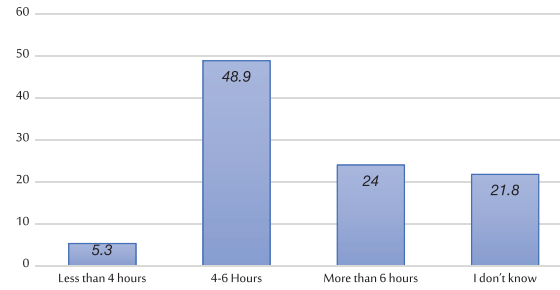


Figure 2. The response percent, regarding the dosing interval of pediatric paracetamol preparations, of participants in a cross-sectional study about knowledge and awareness of parents about using paracetamol in children in Al-Baha region KSA, n = 1000



fell into the age range of 19 to 30 years old, whereas only 49.9% of our respondents were in this age range.[1] With age, mothers are expected to collect a build-up of experience pertaining to childcare. Slightly less than half of our sample (48%) have 2 to 4 children, 22.3% have 1 child, and 29.7% have more than 4 children. These determinations are partially consistent with the previous determinations that 33.0% had 2 children below 18 years of age, and 50% had 2 children below 6 years of age.[1] It has been found that 43.2%, 4.6%, 2.4%, and 49.8% of those approached by the study are single, divorced, widowed, or married, respectively. The family monthly income was reported as less than 5K, 5 to 10K, 10 to 20K, or more than 20K SAR for 10.2%, 27.7%, 38.9%, and 23.2% of them respectively. The latter finding is higher than the findings in similar previous investigation in Palestine in which 64% of their sample has a family monthly income of 2K to 5K NIS, that is, 2.066K to 5.165K SAR.[7] Both the former and latter findings contribute to family stability and general child welfare including health issues.

Among the children included in our sample, it has been determined that 23.7%, 25.5%, and 22.2% (total of 71.4%), have visited a doctor once, twice, or more than 2 times, respectively within the past 6 months. These results indicate that a majority of families rely on health services for their children's welfare. This percentage is greater than the previous determination that 43.7% of the children had 1 doctor visit in the last 6 months.[1] The frequency of parental treatment of children at home in the past 6 months was 23.7%, 25.5%, 22.2%, for 1 time, twice, or more than 2 times, respectively, compared with none (15.9%). Administration of paracetamol to children without prescription was at 41.9%. The justification of this drug administration was experience with similar symptoms (27.2%),

expensive doctor charges (2.5%), lack of confidence in the health care system (1.9%), and denial of the need to visit a doctor (12%). These findings are consistent with those reported by previous studies that 73.4% self-medicated their children without medical advice; that 50.7% self-medicated their children with paracetamol without medical advice; and that the reason for this administration was either having parental experience of treating their children (54.6%) or ascertaining of the child's illness from symptoms (49.2%)[7]. These findings reflect a high incidence of OTC paracetamol potentially being used incorrectly by parents which poses potential hazards to this especially vulnerable patient population. Earlier investigators had raised alarm against over-the-counter medication for pediatrics, particularly regarding parents' misinterpretations medications' labels.[8] Indiscriminate home medication of non-specific symptoms such as fever should not be encouraged in the presence of remote health care facilities. The available access to these services is confirmed by the present finding that 76.2% of the subject children have been hospitalized before.

As it has been initially proposed, there is an awareness gap regarding paracetamol pediatric use. This is significant regarding the wide use and the ease of access to the drug. Most respondents think that the maximum dose is 1 suppository or a teaspoon-full syrup. This finding is consistent with the previous finding that 61% of the investigated community specify paracetamol dosing interval as 4 to 6 hours.[1] However, there is still a notable number of participants who either believe a shorter or longer time frame is appropriate or are unsure. Most of the respondents (56.1%) think that pediatric paracetamol dose is determined according to age or weight of the child regardless of other determinant variables such as the clinical indication. A previous study had reported similar findings (52.6%).[1] 58.8% think that overdose of pediatric paracetamol can cause harm, wherein only 13% correctly assigned that harm to hepatic injury. This result is consistent with the previous reports that 50.9% of the investigated community is aware of the potential harm of an overdose of the drug[1]; that 67.4% of the investigated community believe that paracetamol self-medication is potentially lethal in overdose[7]; or that 25.8% were aware of liver damage as a side effect of paracetamol.[9] Wherein 16% had previously administered adult paracetamol to their children, 9.3% attributed that misuse to its effectiveness compared with pediatric forms, 9.6% used the full adult dose while 9.3% gave half of the adult dose. This determination is less than a previous report where most parents believed that, for all pills, when split in half, they provide precisely half of the therapeutic dose.[7] Of those who used a calculated dose (7.4%), only 46.2% used a graded instrument. This finding is less than the previous determination that 64% used a syringe or a graded cup to adjust the dose of paracetamol syrup,[1] and far less than the finding that most 93.8% of the parents indicated their use of the measurement tool available in the medicine packet.[7] Pertaining to expiration of paracetamol syrup following bottle opening, most of the respondents (38%) assigned the period of 3 months, contrary to an earlier determination of assigning this to the manufacturer expiration date on the bottle by 44% of the investigated sample.[1]

The preferred pediatric paracetamol dosage form was syrup (62.3%) followed by rectal suppositories (10.1%). This finding is different from a previous report wherein suppository preference (33.8%) predominated over syrup (25.4%).[1] In an earlier study, it was determined that 33.8%, 25.4%, or 1.7% preferred suppositories, syrup, or drops, respectively.[9] This finding may be determined by child age group, with suppositories being more commonly indicated for toddlers and infants, while syrups are more appropriate for school age children. 18.6% reported preferring, both forms equally, and only 3.3% preferred neonatal drops. Of the respondents, 19.5%, 16.8%, 11.2%, and 18.7%, owed their preference of rectal suppositories to the age of the child, ease of administration, the doctor's advice, or effectiveness, respectively. The last finding signals a gap of awareness since the different dosage forms are usually bioequivalent. A similar finding has been reported in a previous study, where 32.8% owed their preference of suppositories to its therapeutic efficacy compared with other dosage forms.[1] It is worth mentioning that the efficacy of this dosage form depends largely on mastering administration technique and the storage of suppositories. Health care instructions, or demonstration (50.6%) had been the source of mastering the technique, and 56.9% kept the medicine stored in the refrigerator. In the instances that children refused to take the medication 41.2% the predominant method used to convince the child to take the medication was encouragement and motivation to take the medicine (58.3%) among other methods. Approximately 7% of respondents reported mixing medication with juice or food which can lead to unanticipated food and/or drug interactions. Former investigators found that 26.5% revert to coaxing and encouraging the reluctant children (36.2%), compared with 24% shifting to suppositories, or 18.8% using force with the child.[1] The latter method (e.g., using force) may lead to more serious outcomes as aspiration pneumonia, physical trauma, or aggrandizement of psychological trauma. The respondents assess severity of the children's illness (40%) rather than physicians' consultation (25.4%) for repeated re-administration of pediatric paracetamol. These determinations are consistent with the previous report that 36.9% of parents relay on severity of illness rather than physicians' consultation (15.1%) for repeating paracetamol administration.[1]

Among other sources, physicians are the main source of drug information with the reference to be pediatric

paracetamol (48.1%). This finding is greater than a previous finding that 33.4% identified physicians as their source of drug information.[1] Friends and relatives constitute a source for drug information to 2.4% of our respondents. However, non-medically trained friends and relatives are an unreliable source of information, compared with other sources such as the pharmaceutical manufacturer leaflet and can pose hazards to the subject children. Over-the-counter acquirement of pediatric paracetamol is common to 24.9% of our sample, together with another 2.1% obtaining the drug from electronic marketing suppliers. The findings that 51.1% of our sample get the drug after issuance of a prescription order does not ameliorate the seriousness of the situation. It is an important finding that 63% share the drug between their children, for the same child, and relatives and friends' children once they developed the same symptoms. Similar findings were reported in Palestine,[7] Korea,[10] India,[11] and Yemen.[12] Fever can be presenting symptom for a variety of conditions, the management of each depends slightly on the underlying cause of fever. Regarding the body temperature that indicates administration of pediatric paracetamol, the response of 77.5% of the caregivers was variable between 38°C and 40°C, while 22.5% were unsure. Similar response variations have been reported by previous Malaysian[2] and Italian[13] researchers.

Limitations

Limitations of our study include the study type being a cross-sectional study which provides the least level of evidence. Interventional cohort studies may produce stronger evidence pertaining to the same research question. Our study was limited to a single local community, expanding to a greater region and expanding to additional special populations (e.g., geriatric patients) would strengthen the validly of the results. A new questionnaire must be designed and validated to include new domains. Correlation between demographic and respondent responses should have been conducted using logistic regression with a view to find any beneficial association that may aid in clarifying some issues regarding the area under investigation.

Conclusion

A gap exists in parents' knowledge regarding the rational use of paracetamol for children in Al-Baha region. In as much as paracetamol is widely used, many parents are unaware of the essential drug information. A considerable number of parents depend on non-medical sources for these information. It has been shown that while most parents use paracetamol for their children, a notable number of them do so without medical advice, or share the drug with other patients. Some parents use incorrect dosages, or are unaware of the potential harm of overdose. This shows the need for educational programs to enhance parent's knowledge and safe use of paracetamol. Educational programs should focus on the risks of overdose and the importance of following recommended dosages. Our data suggest that the OTC dispensing of drugs should be limited until education of their safe use is expanded. Health care professionals roles are important in educating parents during clinical visits. Social media is, yet, an effective tool that can be utilized to disseminate correct drug information is received. If these gaps in parents' knowledge and practices are narrowed, the safety and efficacy of paracetamol use will be enhanced and better health outcomes will be obtained in Al-Baha region.

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 international guidelines on human experimentation and have been approved by the appropriate committees at our institution (Al-Baha University Faculty of Medicine; No. REC/PHA/BU-FM/2024/37).

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References

1. Daifallah A, Jabr R, Al-Tawil F, et al. An assessment of parents' knowledge and awareness regarding paracetamol use in children: a cross-sectional study from Palestine. *BMC Public Health.* 2021;1(1):21.
2. Yeoh ET, Goh AWL, Chong CP. Evaluation of the practices of using paracetamol among parents in treating

their children in Penang, Malaysia. *J Appl Pharm Sci*. 2022;12(1):120–130.
3. Kloeden B, Tham D, Oakley E, et al. Community use of paracetamol and ibuprofen in children with fever. *J Paediatr Child Health*. 2021;57(10):1640–1644.
4. Shivbalan S, Sathiyasekeran M, Thomas K. Therapeutic misadventure with paracetamol in children. *Indian J Pharmacol*. 2010;42(6):412–415.
5. Fareed AS, Al-Raddadi R, Khaled AH. Children drug poisoning in Jeddah: Prevalence, pattern and mother's practice. *J Community Health Management*. 2019;6(1):12–20.
6. Cheng L, Wang L, He M, et al. Perspectives of children, family caregivers, and health professionals about pediatric oncology symptoms: a systematic review. *Support Care Cancer*. 2018;26(1):2957–2971.
7. Zyoud S, M Shtaya R, Q Hamadneh D, et al. Parental knowledge, attitudes, and practices towards self-medication for their children: a cross-sectional study from Palestine. *Asia Pacific Family Medicine*. 2020;18(1):1.
8. Lokker N, Sanders L, Perrin EM, et al. Parental misinterpretations of over-the-counter pediatric cough and cold medication labels. *Pediatrics*. 2009;123(6):1464–1471.
9. Kamel F, Magadmi R, AbuOuf NM, et al. Knowledge, attitude, and practice of paracetamol and ibuprofen administration among caregivers of the pediatric age group in Jeddah. *Cureus*. 2021;13(1):e12460.
10. You MA, Nam SM, Son YJ. Parental experiences of medication administration to children at home and understanding of adverse drug events. *J Nurs Res*. 2015;23(3):189–196.
11. Sontakke S, Magdum A, Jaiswal K, et al. Evaluation of parental perception about self-medication and other medicine use practices in children. *Eur J Pharm Med Res*. 2015;2(7):179–185.
12. Mohanna M. Self-medication with antibiotic in children in Sana'a city, Yemen. *Oman Med J*. 2010;25(1):41–43.
13. Lubrano R, Paoli S, Bonci M, et al. Acetaminophen administration in pediatric age: an observational prospective cross-sectional study. *Ital J Pediatr*. 2016;42(1):20.

JPPT | Single Center Retrospective Study

Effectiveness and Safety of Outpatient Monoclonal Antibody Use for the Treatment of COVID-19 in Children and Adolescents: Single Center Study

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OBJECTIVE Monoclonal antibody therapy has been used to treat COVID-19, with paucity of literature about its use in children. This retrospective study sought to evaluate the effectiveness of preventing hospitalization and safety of monoclonal antibody (mAb) treatment (bamlanivimab-etesevimab and casirivimab-imdevimab) for COVID-19 in patients ≤18 years of age.

METHODS Between January 1 and December 31, 2021, patients were selected for mAb therapy, based on the referring provider's clinical assessment of high risk for progression to severe COVID-19. The choice of mAb was determined by drug availability, compounding feasibility, and documented *in vitro* activity against circulating SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) variants. All patients received a single-dose infusion. Primary outcomes included hospital readmissions and emergency department (ED) visits within 90 days of treatment. The secondary outcome was safety/adverse events.

RESULTS Of 141 patients who received mAbs in 2021, only 3 experienced ongoing COVID-19 symptoms. Only 1 patient necessitated escalated care owing to persistent COVID-19 symptoms post infusion. There were no infusion-related side effects or hospitalizations in the 90 days post infusion.

CONCLUSION Monoclonal antibodies appear to be safe and effective in preventing hospitalizations in COVID-19–positive children.

ABBREVIATIONS Bam-Ete, bamlanivimab-etesivimab; Cas-Imd, casirivimab-imdevimab; ED, emergency department; mAb, monoclonal antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

KEYWORDS COVID-19; immunotherapy; monoclonal antibodies; pediatrics

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Introduction

The COVID-19 pandemic demanded the timely development of new therapeutics for prevention and treatment of COVID-19 infection. Aside from new vaccines, and few antivirals, monoclonal antibodies (mAbs) emerged as alternative treatment of COVID-19 in selected patients.[1] Monoclonal antibodies were approved for treatment of mild to moderate COVID-19 disease by the US Food and Drug Administration under emergency use authorization. The first mAb treatment to receive approval was bamlanivimab alone in November 2020 and later for the combination bamlanivimab-etesevimab (Bam-Ete) in February 2021. This was followed by authorization of casirivimab-imdevimab (Cas-Imd) months later.[2] Bamlanivimab is an immunoglobulin G1 antibody that binds to the receptor-binding domain of the spike protein of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).[3] The antibody was approved for use in patients ≥12 years of age; however, the trials investigating bamlanivimab's efficacy included only patients ≥18 years of age at the time of randomization. Combination treatment with Bam-Ete (which also targets SARS-CoV-2 spike protein receptor-binding domain) was approved to treat younger pediatric patients including newborns in December 2021.[4]

Casirivimab and imdevimab (Cas-Imd), 2 additional mAbs targeting the spike protein of SARS-CoV-2, were also approved in November 2020. Again, the mAbs were approved for patients ≥12 years of age, because early investigations of Cas-Imd included only patients of this age group.[5–7]

There has been scarcity of systematic studies reporting the safety and effectiveness of these treatments in the pediatric population. We aim to describe the safety and effectiveness of mAb use in patients aged 18 years and younger who had at least 1 risk factor for progression to severe COVID-19 disease.

Materials and Methods

Patients 18 years and younger who received bamlanivimab, Bam-Ete, or Cas-Imd for treatment of mild to moderate COVID-19 disease at Tampa General Hospital were identified retrospectively through pharmacy records and by electronic medical record review. Disease categorization was based on the Centers for Disease Control and Prevention classification of COVID-19 severity in children—mild: requiring no specific medical care or treatment; moderate: potentially needing outpatient care, oxygen, or other medical support; or severe: involving hospitalization, intensive care unit admission, or mechanical ventilation.[8] Patients' medical records were reviewed from January 1, 2021, to December 31, 2021.

Examples of risk factors considered to increase the risk of progression to severe COVID-19 included obesity (body mass index >30), use of immunosuppression medications, immunodeficiency diseases, chronic kidney disease (estimated glomerular filtration rate <90 mL/min/1.73 m^2), solid organ transplant, congenital heart disease, chronic respiratory disease (including asthma), neurodevelopmental disorder, and dependence on a gastrostomy or tracheostomy tube. Of note, owing to the high volume of patients infused with mAb at our site, as well as some patients being referred for mAb therapy from outside our hospital system, the high-risk indication for mAb was not readily documented for all patients. The specific mAb agent administered was dependent on drug inventory and allocation, ease of compounding to accommodate high-infusion clinic volumes, and documented pseudoviral, *in vitro* mAb activity against the predominant circulating variant at the time of each surge. Dosing was a single infusion provided at the infusion clinic within the hospital; the infusion would last 30 to 60 minutes. Patients were monitored for an hour post administration for any side effects.

Data on age, sex, race, underlying condition, and COVID-19 screening were collected. Our primary outcomes were readmission rates and emergency department (ED) visits within 90 days. The secondary outcome was safety. Descriptive statistics were used to analyze the population demographics and outcomes.

Results

A total of 141 pediatric patients received a single infusion of mAb during the study period. Five patients (3.6%) received bamlanivimab, 9 (6.4%) received Bam-Ete, and 127 (90.1%) received Cas-Imd. The mean age was 15 years and ranged between 10 months and 18 years (IQR = 13.6-17; SD = 2.3). More than half of the patients self-identified as White (n = 82; 58.2%), 16 (11.4%) as African American, 16 (11.4%) as Hispanic, 8 (5.7%) as other race, and 19 (13.5%) declined to disclose their race. Two patients below age 12 years received mAb under compassionate use. The majority (n = 103; 73.0%) had antigen-confirmed COVID-19 infection, while 38 subjects (27.0%) underwent SARS-CoV-2 polymerase chain reaction testing. The most common underlying condition was asthma (n = 38; 27.0%), followed by obesity (n = 29; 20.6%), and immunocompromised state (n = 9; 6.4%) (Table 1).

None of the patients were hospitalized for 90 days post infusion. There were no significant variations identified in clinical response according to race/ethnicity. Within 90 days of receiving mAb, only 3 patients (2.1%) experienced ongoing COVID-19 symptoms (Table 2). All 3 received Cas-Imd. Two patients phoned in to report symptoms: one experienced continuous vomiting for 3 days post infusion and the second experienced nausea and vomiting. The third patient visited the ED 1 day after infusion with worsening COVID-19 symptoms. Chest x-ray was performed, leading to a diagnosis of bacterial pneumonia, and the patient was treated with amoxicillin-clavulanate. No infusion-related side effects, including rashes, urticaria, or anaphylaxis, were observed in any of the patients during infusion or after standard observation period. The 2 patients receiving mAbs under compassionate use were hospitalized. The 8-year-old patient receiving chronic immunosuppression therapy (prednisone, mycophenolate, and cyclosporine) owing to kidney transplant was admitted for the infusion, had no adverse infusion-related events, and required no escalation of care. The 10-month-old with ornithine transcarbamylase deficiency was admitted for treatment of hyperammonemia and COVID-19. He had no adverse infusion-related events and needed no escalation of care for COVID-19 symptoms but was hospitalized for 13 days owing to hyperammonemia.

Discussion

Our study found that no patients were hospitalized within 90 days of single-dose mAb administration and that mAbs were safe for treatment of COVID-19 in pediatric patients. Overall, patients in our study tolerated mAb infusions with less side effects than other authors have reported in the literature and had a lower rate of escalation of care. This may be due to healthier starting population.

Santos et al[9] reported that of 44 pediatric patients with risk factors of obesity and/or asthma who received bamlanivimab, Bam-Ete, or Cas-Imd, 38 experienced improvement of COVID-19 symptoms, 2 did not improve clinically, 3 did not keep their follow-up appointment, and 1 did not complete infusion owing to infusion-related adverse events. Two patients were evaluated at the ED within 28 days of infusion. One had shortness of breath and received treatment with albuterol and the other had cervical lymphadenitis. Both were discharged home. The patient who had infusion-related adverse events had shortness of breath and flushing that resolved after administration

Table 1. Demographics and Clinical Characteristics

Patient Characteristics	n (%)		
	Cas/Imd (n = 127)	Bam/Ete (n = 9)	Bam (n = 5)
Age, mean ± SD, yr	15.25 ± 2.0	16.15 ± 1.0	15.32 ± 1.5
Sex			
Male	69 (54.3)	6 (66.7)	2 (40)
Female	58 (45.7)	3 (33.3)	3 (60)
Race			
White	76 (59.8)	3 (33.3)	2 (40)
African American	13 (10.2)	2 (22.2)	0
Hispanic	12 (9.4)	2 (22.2)	2 (40)
Other	4 (3.1)	1 (11.1)	1 (20)
Unknown	18 (14.2)	1 (11.1)	0
No underlying condition	75 (59.1)	5 (55.6)	0
Underlying condition(s)	52 (40.1)	4 (44.4)	5 (100)
Asthma	24 (18.9)	2 (22.2)	3 (60)
Obesity (BMI >30)	13 (10.2)	3 (33.3)	1 (20)
Immunocompromised	7 (5.5)	0	2 (40)
Chronic kidney disease	1 (0.8)	0	0
COVID-19 screening			
Antigen-confirmed COVID-19	95 (74.8)	5 (55.6)	1 (20)
PCR-confirmed COVID-19	30 (23.6)	4 (44.4)	4 (80)
No test done	1 (0.8)	0	0

Bam/Ete, bamlanivimab-etesivimab; BMI, body mass index; Cas/Imd, casirivimab-imdevimab; PCR, polymerase chain reaction

of diphenhydramine and dexamethasone, and infusion was stopped. In comparison, our study had a lower percentage of participants with obesity (80% vs 20.6%) and asthma (43% vs 27.0%).[9]

Compared with our study, other published studies that included higher proportions of immunocompromised pediatric patients suggest that mAbs were less effective and safe for these populations. Despite this, most of their patients experienced improvement of COVID-19 symptoms with mAb infusion. Bahakel et al[10] reported a study of 94 patients ranging in age from 12 to 25 years with a higher percentage of immunocompromised patients than in our study (73% vs 5.7%). However, the percentage of patients with obesity was similar in both studies (26.9% and 20.6%). Of note, mAb therapy had greater efficacy in our population, with escalation of care necessary for only 1.4% of our population, compared with 12.7% of their patients. Patients in our cohort did not experience infusion-related adverse events, compared with a reported 10.1% of patients in their study.[10]

Another study, by Sherman et al,[11] included 142 patients, with 32% classified as immunosuppressed and 39% classified as obese. They had a higher rate in escalation of care than in our study (6% vs 0.7%). In the study of Sherman et al,[11] 4 of the 8 patients admitted in the 30 days post infusion were immunocompromised, while the other 4 had other underlying conditions. None of these patients went to the intensive care unit or died. Our population did not experience infusion-related adverse events as previously mentioned.

Blind et al[12] included 182 patients ranging in age from 10 months to 21 years with a higher proportion of participants (25%) classified with "severe immunosuppression," while our study had 5.7% of participants with immunocompromised status. In their cohort, 15 patients experienced ongoing COVID-19 symptoms in the 30 days after infusion—13 sought medical attention (2 went to their primary care provider, 3 received care in the ED, and 8 were hospitalized). One patient died from COVID-19 complications 23 days post infusion. This patient was actively receiving chemotherapy and was severely immunosuppressed. Blind et al[12] also reported 7 patients (4%) with infusion-related adverse events, but all completed their infusion therapy.

The evolution of the pandemic necessitated changes in the guidelines for mAb use. At the time of this writing, mAbs are no longer recommended for treatment of COVID-19 owing to the high mutability of later viral variants. However, these data remain valuable as a bridge in the knowledge gap of how children and adolescents respond to mAb treatment for this viral illness.

Limitations

Limitations of our study include its retrospective design, single center, small sample size, and lack of information regarding subjects' COVID-19 vaccination status. The analysis did not take into consideration

Table 2. Treatment-Related Adverse Events and Escalation of Care

Age, yr	mAb Received	Primary Underlying Condition	Event
17	Casirivimab-imdevimab	None	Severe vomiting × 3 days post infusion; reported via telephone
12	Casirivimab-imdevimab	Asthma	Nausea and vomiting; reported via telephone within 1 wk after infusion
12	Casirivimab-imdevimab	Asthma, immunocompromised due to azathioprine (taken for Behcet syndrome)	Emergency department visit; diagnosed with bacterial pneumonia 1 day post infusion

mAb, monoclonal antibody

circulating variants of SARS-CoV-2. Additionally, we did not include sotrovimab, an additional mAb approved for treatment of COVID-19.

Conclusions

In summary, single doses of mAb infusion included in our study were well-tolerated therapies for children and adolescents infected with COVID-19 who have at least 1 risk factor for progression to severe disease in our population. Our data suggest that mAbs are safe for use in children and adolescents, as demonstrated through the low rate of adverse events and absence of hospitalizations. It also demonstrates that mAb therapy is effective in preventing hospitalizations and progression of the disease, as only 1 patient required escalation of care due to unresolved COVID-19 symptoms after infusion. It is important to continue surveillance and data collection to monitor the long-term safety and effectiveness of mAb therapies in pediatric patients with COVID-19, particularly in the context of evolving viral variants and treatment guidelines.

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References

1. Taylor PC, Adams AC, Hufford MM, et al. Neutralizing monoclonal antibodies for treatment of COVID-19. *Nat Rev Immunol.* 2021;21(6):382–393.
2. San Filippo S, Crovetto B, Bucek J, et al. Comparative efficacy of early COVID-19 monoclonal antibody therapies: a retrospective analysis. *Open Forum Infect Dis*. 2022;14(4):ofac080.
3. Shrestha J, Sherchan R. Bamlanivimab. In: StatPearls [serial online]. Treasure Island, FL: StatPearls Publishing. January 2023. Accessed April 15, 2022. https://www.ncbi.nlm.nih.gov/books/NBK576376/#
4. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *N Engl J Med*. 2021;385(15):1382–1392.
5. Wolf J, Abzug MJ, Anosike BI, et al. Updated guidance on use and prioritization of monoclonal antibody therapy for treatment of COVID-19 in adolescents. *J Pediatr Infect Dis Soc*. 2022;11(5)177–185.
6. Recovery Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet.* 2022;399(10325):665–676.
7. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med*. 2021;384(3):238–251.

8. Centers for Disease Control and Prevention. COVID-19. Accessed September 12, 2022. https://www.cdc.gov/covid/hcp/clinical-care/for-pediatric-hcp.html
9. Santos JL, Bhisitkul D, Carman M, et al. The use of monoclonal antibody therapy in pediatric patients with COVID-19: a retrospective case series. *Int J Emerg Med*. 2022;15(1):9.
10. Bahakel H, Murphy C, Frenck RW, et al. Single site experience of the use of monoclonal antibodies for the treatment of COVID-19 in high-risk pediatric and young adult patients. *Pediatr Infect Dis J*. 2022;41(12):985–988.
11. Sherman G, Lamb GS, Sharma TS, et al. Monoclonal antibody use for coronavirus disease 2019 in pediatric patients: a multicenter retrospective study. *J Pediatr Infect Dis Soc*. 2023;12(3):152–155.
12. Blind JE, Sapko M, Killough A, et al. Implementation and patient outcomes of a pediatric COVID-19 monoclonal antibody program. *J Pediatr Infect Dis Soc*. 2022;11(12):565–574.

Assessing Confidence in Adolescent Mental Health Pharmacotherapy in Pediatric Medical Residents

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OBJECTIVE The objective of this study was to assess first through third year pediatric medical residents' confidence levels surrounding first-line pharmacotherapy for common mental health conditions in the pediatric patient population and identify areas of need in resident education initiatives.

METHODS From April 2024 through June 2024, 68 pediatric medical residents participating in a pediatric residency program at an academic tertiary medical center were invited to complete a self-assessment questionnaire. Residents rated their confidence in developing a treatment plan, prescribing, and counseling on medications for pediatric mental health conditions, general physical health conditions, and pharmacotherapy using a 5-point Likert scale.

RESULTS A total of 28 pediatric medical residents (41% response rate), ranging from postgraduate year 1 to year 3, completed the survey. Compared with physical health conditions, pediatric mental health conditions were associated with lower confidence scores in medical residents in the areas of developing a treatment plan (mean 3.31 vs 4.28, $p < 0.001$), prescribing medication (mean 2.77 vs 4.02, $p<0.001$), and counseling on medication side effects (mean 2.94 vs 4.01, $p < 0.001$).

CONCLUSIONS This study highlights significant gaps in medical residents' confidence in managing pediatric mental health pharmacotherapy compared with physical health conditions within a single institution's residency program.

ABBREVIATIONS PGY, postgraduate year

KEYWORDS adolescent; medical education; mental health; pediatric; surveys and questionnaires

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Introduction

Mental health conditions are common among pediatric and adolescent populations. The Centers for Disease Control and Prevention's Annual Youth Risk Behavior Survey demonstrated that 40% of high school students reported persistent feelings of sadness or hopelessness for weeks in a row, leading to a cessation of usual activities.[1] Furthermore, mental health conditions are one of the most common causes of hospitalization among adolescents.[2] The recent increase in the prevalence and severity of mental health conditions and psychotropic prescribing led to the declaration of a national emergency in child and adolescent psychiatry in the United States in 2021.[3] Not only are mental health conditions common, but many patients do not receive care. In 2021 and 2022, approximately half of children with a treatable mental health condition did not receive mental health care when needed in the United States.[4] In addition, prescribers recognize there are barriers to patients receiving adequate care, as a survey conducted in 2017–2018 revealed that more than 85% of health practices surveyed reported it was difficult to obtain pediatric behavioral health advice and services for patients.[5] Overall, there is an imminent need to provide adequate education regarding pediatric mental health care to future pediatricians, as pediatricians have a growing role in pediatric mental health care.

Pediatric medical residency programs in the United States are structured to provide broad and intensive training across various pediatric care areas. In addition to being certified by the American Board of Pediatrics or the American Osteopathic Board of Pediatrics, pediatrician candidates must complete a program requiring at least 36 months of residency practice.[6,7] According to the Accreditation Council for Graduate Medical Education, pediatric medical residency training must include at least 40 weeks dedicated to pediatric ambulatory care and 40 weeks focused on pediatric and neonatal inpatient care.[6,7] The mental health training component of the program comprises a small proportion of the overall requirements, with

only 4 weeks specifically allocated to the mental health specialty.[6] This limited exposure contrasts with the more intensive training provided in other disciplines, such as within psychiatry residency programs. It may impact residents' confidence and preparedness in pediatric mental health care.

Currently, the focus on pediatric mental health within the educational program for medical residents is limited because of the overall educational requirements imposed by the American Board of Pediatrics. Residents complete the required 4 weeks of mental health-focused rotations in both outpatient and inpatient settings and see patients with mental health conditions within general inpatient and outpatient rotations. However, the pharmacotherapy education may be overshadowed by the other physical health conditions treated during these rotations. This study aims to assess pediatric medical residents' confidence levels surrounding pharmacotherapy for common mental health conditions in the pediatric patient population. These factors that influence confidence levels and to help identify areas of need in medical resident education initiatives.

Methods

This study was conducted in a pediatric hospital system located in Texas, providing a broad range of medical services to children from 46 counties. The center is recognized for its comprehensive specialty care, including general and highly specialized medical services. The hospital serves a diverse group of pediatric patients, including many who require specialized care for mental health conditions treated in dedicated behavioral health units and throughout the hospital. This institution trains approximately 70 pediatric medical residents annually, offering hands-on experience in various medical disciplines in both inpatient and outpatient settings, with a mental health specialty practice provided during two 2-week inpatient rotations. The pediatric medical residents spend time in both the behavioral health unit, where the psychiatric team serves as the primary team, and with the consulting psychiatric team on the general floors. Pharmacists play a crucial role in training these pediatric medical residents, contributing their expertise in medication management and therapeutic strategies for various mental health and physical health disease states through multidisciplinary rounding. Currently, there is 1 pediatric psychiatric clinical pharmacist who serves the hospital in the behavioral health unit and the psychiatric consult team.

The primary objective of this study was to assess the confidence levels of pediatric medical residents in prescribing, counseling, and making treatment plans for mental health conditions. Secondary objectives were to quantify previous psychiatry experiences, identify areas of greatest need or potential gaps in education, and quantify interest in educational initiatives. A comprehensive electronic survey was developed using the Qualtrics platform to assess the confidence levels of residents in their knowledge of pediatric mental health pharmacotherapy and care planning. Survey questions were developed in alignment with previously conducted surveys in the literature. They were reviewed and adjusted based on feedback from local content experts, including a pediatric psychiatric pharmacist and a pediatric hospitalist.[8,9] The final draft of the survey included questions that rated residents' confidence in prescribing medications, developing treatment plans, and counseling patients for common pediatric mental health conditions, as well as other common pediatric medical conditions.

The 17-question survey, shown in Table 1, consisted of multiple-choice questions, open-ended queries, and Likert scale items. The survey addressed participants' current roles, anticipated practice settings, past experiences in pediatrics and psychiatry, resource usage for pediatric mental health treatment, and confidence in pharmacotherapeutic treatment planning, prescribing, and counseling. Confidence was self-assessed on a 5-point Likert scale (none [1], poor [2], fair [3], good [4], and excellent [5]).

The survey was distributed to postgraduate year 1 (PGY1), PGY2, and PGY3 pediatric medical residents via email and in-person printed QR codes, with 68 medical residents targeted for survey participation. The survey was open from April 2, 2024, through June 21, 2024. Descriptive statistics were employed to summarize demographic information, and open-ended responses were subject to qualitative analysis to extract meaningful insights based on trends in the responses. Likert scale responses were analyzed to quantify participant confidence levels of each disease state or medication class. The aggregate mean for all mental health portions of each section was compared with the aggregate mean for all physical health conditions using the Wilcoxon Signed Ranks test with an alpha level $\alpha = 0.05$ for significance.

Results

The survey was completed by 28 residents (response rate 41%) over the course of the survey period. Characteristics of the residents who completed the survey can be seen in Table 2. Of the residents who completed the survey, the majority were in the first year of their program and had a prior psychiatry rotation during medical school, residency, or both periods of time. Most residents (75%) reported spending 1 to 4 weeks in psychiatry rotations during their residency. During medical school rotations, the duration varied, with 57% of residents spending 1 to 4 weeks and 39% spending 5 to 8 weeks. Over half (54%) of the residents also reported personal or family experience with medications for mental health conditions. A slightly greater proportion of residents anticipate participating in an

Table 1. Survey Questions

Question #	Question	Answer Choices
1	Which of the following best describes your current role?	• PGY1 • PGY2 • PGY3
2	Where do you anticipate practicing in the future?	• Inpatient • Outpatient • Other
3	What prior experience do you have in psychiatry? (Select all that apply)	• None • Psychiatry rotation (medical school) • Psychiatry rotation (residency) • Personal/family experience with medications for mental health conditions • Work experience
3a	How many weeks of prior psychiatric rotation experience in medical school do you have?	• 1–4 wk • 5–8 wk • >8 wk
3b	How many weeks of prior psychiatric rotation experience in residency do you have?	• 1–4 wk • 5–8 wk • >8 wk
3c	How many weeks of prior work experience in psychiatry do you have?	• 1–4 wk • 5–8 wk • >8 wk
4	Please rate your confidence in DEVELOPING A TREATMENT PLAN for the following mental health conditions in pediatric populations: anxiety, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), behavioral/conduct disorders, depression	• None • Poor • Fair • Good • Excellent
5	Please rate your confidence in DEVELOPING A TREATMENT PLAN for the following medical conditions in pediatric populations: asthma, diabetes, community-acquired pneumonia, skin/soft tissue infection, constipation	• None • Poor • Fair • Good • Excellent
6	Please rate your confidence in PRESCRIBING the following medication classes for mental health indications in pediatric populations: antipsychotics (eg, risperidone), SNRIs (eg, duloxetine), SSRIs (eg, escitalopram, fluoxetine), stimulants (eg, amphetamines, methylphenidate), mood stabilizers (eg, lamotrigine, lithium)	• None • Poor • Fair • Good • Excellent
7	Please rate your confidence in PRESCRIBING the following medication classes for medical indications in pediatric populations: anti-asthmatics (eg, albuterol, fluticasone), insulin, antimicrobials (eg, penicillin, vancomycin), stimulant laxatives/stool softeners (eg, bisacodyl, senna, docusate, polyethylene glycol)	• None • Poor • Fair • Good • Excellent
8	Please rate your confidence in COUNSELING ON SIDE EFFECTS of following medication classes for mental health indications to pediatric populations and their caregivers: antipsychotics (eg, risperidone), SNRIs (eg, duloxetine), SSRIs (eg, escitalopram, fluoxetine), stimulants (eg, amphetamines, methylphenidate), mood stabilizers (eg, lamotrigine, lithium)	• None • Poor • Fair • Good • Excellent

(Table cont. on page 663)

Table 1. Survey Questions *(cont.)*

Question #	Question	Answer Choices
9	Please rate your confidence in COUNSELING ON SIDE EFFECTS of following medication classes for medical indications to pediatric populations and their caregivers: anti-asthmatics (eg, albuterol, fluticasone), insulin, antimicrobials (eg, penicillin, vancomycin), stimulant laxatives/stool softeners (eg, bisacodyl, senna, docusate, polyethylene glycol)	• None • Poor • Fair • Good • Excellent
10	What resources do you use currently in regard to pediatric mental health treatment? (Select all that apply)	• Internal guidelines • American Academy of Child and Adolescent Psychiatry (AACAP) • American Academy of Pediatrics (AAP) • Tertiary Database (Lexicomp, UpToDate) • Texas Health and Human Services Psychotropic Medication Use Parameter Guidelines • Other
11	What other pediatric mental health conditions/medication classes do you want to know more about?	Free-text response
12	Which of the following do you believe could enhance your education about pediatric mental health treatment in the residency program? (Select all that apply)	• Lectures • Online modules • Additional rotations • None • Other
13	What suggestions do you have for improving education about pediatric mental health treatment in your program?	Free-text response
14	How likely are you to participate in additional training or educational sessions related to pediatric mental health, if offered?	• Not at all • Slightly • Moderately • Very, Extremely

PGY, postgraduate year

outpatient practice site (46%) compared with an inpatient site (39%) in the future, with some reporting the intention to practice in both settings (14%).

The survey results reveal varying levels of confidence among medical residents in developing treatment plans, prescribing medications, and counseling patients across different disease states and drug classes, as shown in Table 3 and the Figure. When comparing aggregate data from all physical health conditions surveyed to all mental health conditions, mental health conditions overall were associated with lower confidence scores in the areas of developing a treatment plan (mean 3.31 vs 4.28, $p < 0.001$), prescribing medication (mean 2.77 vs 4.02, $p < 0.001$), and counseling on medication side effects (mean 2.94 vs 4.01, $p < 0.001$).

Confidence levels for managing physical health conditions, such as asthma, community-acquired pneumonia, and skin/soft tissue infections, were consistently higher than those for developing a treatment plan for mental health conditions, such as depression, anxiety, and autism spectrum disorder, as shown in Table 3. Confidence in prescribing medications for mental health conditions, such as antipsychotics, mood stabilizers, antidepressants, and stimulants, was lower, with 29% of residents rating their confidence as" good" or excellent" compared with 78% for physical health condition medications, such as antimicrobials, inhalers, and stimulant laxatives/stool softeners. Additionally, confidence levels for counseling on medication side effects were lower for mental health medications compared with physical health condition medications. Specifically, medication counseling confidence ratings of "good" or "excellent" were given by 87% of respondents for physical health condition treatments (excluding diabetes). In comparison, only 31% of respondents rated their confidence as "good" or "excellent" for mental health medications.

When asked how likely they were to participate in additional training or educational sessions, 47% of residents selected "very" or "extremely likely," with 39% selecting "moderately" likely. Residents were also asked questions about their preferred methods for enhancing their pediatric mental health education.

Table 2. Study Sample Characteristics

Characteristic	*N* = 28 n (%)
Role	
PGY1	13 (46)
PGY2	8 (29)
PGY3	7 (25)
Anticipated practice site	
Inpatient	11 (39)
Outpatient	13 (46)
Other*	4 (14)
Prior psychiatry experience	
None	0 (0)
Psychiatry rotation (medical school)	27 (96)
Psychiatry rotation (residency)	21 (75)
Personal/family experience with medications for mental health conditions	15 (54)
Work experience	2 (7)

PGY, postgraduate year

* Those that indicated "other" planned to practice in both inpatient and outpatient sites.

Table 3. Confidence Ratings for Specific Pediatric Mental Health and Physical Conditions

	N = 28 Mean ± SD		*N* = 28 Mean ± SD
Developing a treatment plan			
Mental Health		Physical Conditions	
Anxiety	3.64 ± 0.621	Asthma	4.5 ± 0.577
ADHD	3.82 ± 0.67	Diabetes	3.61 ± 0.832
Autism spectrum disorder	2.96 ± 0.838	Community Acquired pneumonia	4.46 ± 0.576
Behavioral conduct disorders	2.29 ± 0.46	Skin/soft tissue infections	4.39 ± 0.629
Depression	3.79 ± 0.568	Constipation	4.43 ± 0.573
Prescribing medication			
Mental Health Medications		Physical Conditions Medications	
Antipsychotics	1.89 ± 0.497	Anti-asthmatics	4.43 ± 0.573
SNRI	2.64 ± 0.731	Insulin	2.93 ± 1.016
SSRI	3.75 ± 0.701	Antimicrobials	4.39 ± 0.629
Stimulants	3.68 ± 0.819	Stimulant laxatives/stool softener	4.32 ± 0.612
Mood stabilizers	1.89 ± 0.685		
Counseling on side effects of medication			
Mental Health Medications		Physical Conditions Medications	
Antipsychotics	2.5 ± 0.962	Anti-asthmatics	4.18 ± 0.723
SNRI	2.71 ± 0.976	Insulin	3.64 ± 0.911
SSRI	3.64 ± 0.951	Antimicrobials	4.11 ± 0.737
Stimulants	3.75 ± 0.928	Stimulant laxatives/stool softener	4.11 ± 0.832
Mood stabilizers	2.07 ± 0.979		

ADHD, attention-deficit/hyperactivity disorder; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors

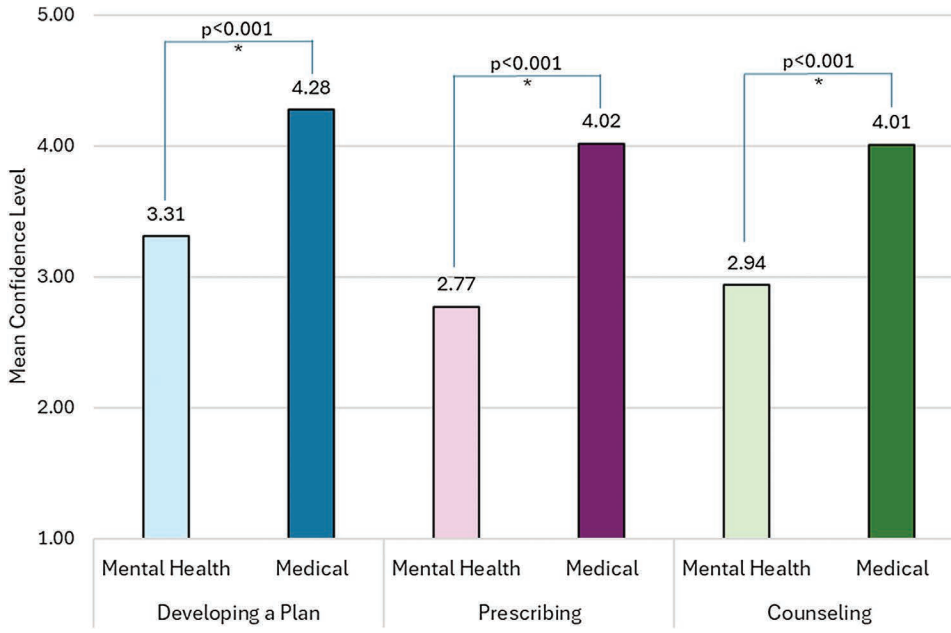
Likert scale confidence: 1 = none; 2 = poor; 3 = fair; 4 = good; 5 = excellent.

Participants were able to select as many choices as they wished. Lectures were the most commonly selected educational method (n = 22), followed by online modules (n = 12) and additional rotations (n = 11). None of the respondents selected "none" in response to this question. When asked in an open-ended format about other pediatric mental health conditions or medication classes, the residents were interested in knowing more about the following topics: obsessive-compulsive disorder, oppositional defiant disorder, conduct or behavioral disorders, agitation, antipsychotics, and serotonin-norepinephrine reuptake inhibitors.

Discussion

This study highlights a disparity in medical residents' confidence levels between managing pediatric mental health conditions and physical health conditions. Pediatric residents report lower confidence in their ability to develop treatment plans, prescribe medications, and counsel patients regarding mental health pharmacotherapy compared with other disease states, including asthma and infectious diseases. Confidence in insulin and diabetes management was lower than in other medical conditions, likely due to the endocrinology team serving as the primary team managing these medications, with less resident involvement in ordering and counseling of insulin. The discrepancy in treatment confidence in mental health conditions could potentially be attributed to the limited guidelines and resources for mental health conditions compared with the wide variety of guidelines and resources available

Figure. Overall average medical resident confidence levels for developing a treatment plan, prescribing, and counseling on side effects of medications for common mental health conditions compared with medical conditions in pediatric populations.



Likert scale confidence: 1 = none; 2 = poor; 3 = fair; 4 = good; 5 = excellent.

* $p < 0.05$ is statistically significant.

for common medical conditions surveyed. In addition, it is important to note that pharmacotherapy is often not first-line therapy for mental health conditions, which could lead to decreased confidence in the pharmacotherapy used in these conditions.[10] Given the substantial role that pediatricians often play in addressing mental health needs due to lack of access and shortages in psychiatric specialists, closing this gap is key to increasing the provision of pediatric mental healthcare.[11,12]

A vast majority of the residents in this study had previous exposure to mental health or psychiatric training, with 96% of respondents reporting the completion of a psychiatric rotation during medical school training, and 75% disclosing having a rotation during residency before taking this survey. Notably, there is a disconnect between exposure to psychiatric training and effectively managing mental health conditions, as resident comfort in managing and prescribing common psychotropic medications remains low. This insight illustrates that the current structure and content of psychiatric training may be insufficient in providing the necessary knowledge to ensure residents feel adequately prepared for optimizing patient outcomes as it relates to mental health. While residents are exposed to mental health training, the duration and intensity of their training may be fragmented and less likely to foster the requisite skills needed for the effective management of pediatric mental health conditions. This is evident at the study institution, where residents' mental health exposure is conducted in 2-week sections, which, according to the results of this study, may not be an adequate amount of time to instill confidence. At the study institution, residents are trained in various areas with access to robust online guidelines, resources, and simulations to practice different skills. At present, there are limited mental health guidelines available on the facility's internal intranet, and physical health conditions may overshadow mental health conditions treated in the inpatient setting during bedside rounds teaching.

These findings are consistent with previously conducted studies that have explored the efficacy of different training models in enhancing residents' confidence and competence in mental health care.[13,14] This study distinguishes itself by focusing on the pharmacological aspects of mental health conditions, specifically examining individual medications and drug classes in comparison to physical health conditions and their associated medications. Previous research has generally taken a broader approach, emphasizing the management of conditions, diagnosis, and overall medication titration, without concentrating on specific drugs. Other studies suggest that medical residents have low confidence in treating pediatric mental health conditions and have suggested ways to help improve

these confidence levels. One such study demonstrated that an integrated mental health training model, where mental health specialists either provided independent care in the same building or collaborated with the medical residents, resulted in a notable increase in confidence in prescribing psychotropic medications.[13] Additionally, it has been shown that introducing a curriculum that includes a multidisciplinary, case-based, active learning approach to covering mental health conditions increases resident confidence and retention related to the pharmacologic management of mental health disease states.[14]

In previously conducted studies regarding resident preferences for education, bedside teaching and hands-on learning were preferred over other types of education.[15,16] For this study, the goal was to explore additional teaching methods that could be offered to supplement the bedside learning that is already provided to residents. Although bedside learning was not offered as a preferred learning strategy in our survey, bedside learning should still be considered and optimized alongside didactic education. Additionally, of the 28 responses, no residents selected "none" when asked about their preferred education method, indicating a strong interest in improving their education. The information gained from this study can be leveraged to develop educational programs that align with residents' preferences by incorporating a mix of didactic lectures and additional resources, thereby providing a more comprehensive and effective training experience.

Given previous studies showing the benefit of a multidisciplinary approach in improving resident confidence levels, pharmacists can play a crucial role in addressing the confidence gap among medical residents by leveraging their expertise in pharmacotherapy. Studies have shown that pharmacist-led didactic educational sessions can significantly increase medical residents' pharmacotherapy knowledge.[17] Therefore, pharmacists are vital to educational efforts in both didactic settings and experiential teaching models (eg, multidisciplinary rounding). At the study institution, pharmacists already collaborate closely with residents during rounds and have various educational handouts for physical health conditions, but mental health conditions are currently less emphasized. To address this, pharmacists can develop targeted educational sessions and materials focused on mental health pharmacotherapy, covering medication management, monitoring side effects, and providing patient counseling. By providing practical, case-based learning opportunities and fostering a supportive learning environment, pharmacists can help residents gain the necessary skills to effectively manage pediatric mental health conditions and ensure they are well-prepared to address the mental health needs of pediatric patients.

This study highlights the gap in the confidence levels of pediatric medical residents regarding mental health pharmacotherapy, particularly in developing treatment plans and prescribing pharmacotherapy. This confidence gap may exacerbate the ongoing adolescent mental health crisis, as providers may be less equipped to address these patients or may unintentionally develop suboptimal treatment plans. It could be extrapolated that discomfort in counseling may correlate with discomfort in mental health pharmacotherapy prescribing, which can ultimately lead to reduced patient satisfaction and trust in their provider to plan their care. This also emphasizes the role of the pharmacist to provide appropriate medication counseling, as some physicians may not feel equipped to provide robust education on medications for mental health conditions. The marked improvements observed in prior studies with integrated and scenario-based training models indicate that these approaches could be essential for bridging the current confidence gap.[13–16] This implies that residency programs may consider incorporating more hands-on, longitudinal training experiences to ensure residents gain the repeated exposure and reinforcement necessary to build and sustain their confidence in managing pediatric mental health conditions.

Limitations

The study findings are limited by their focus on pediatric medical residents from a single hospital system, which may not be generalizable to other settings. Because this study was conducted on PGY1 through PGY3 residents with a relatively low response rate, there could be a skew in the data based on the residents' varying experiences before taking this survey. Additionally, the survey's reliance on self-reported confidence levels may not accurately reflect competency. The use of a survey instrument that has not been validated also introduces limitations, as it may compromise the reliability and accuracy of the findings. Future research is needed to explore the impact of enhanced training programs confidence and clinical outcomes in pediatric mental health care. As this study focused on child and adolescent mental health, these results may not be generalized to adult psychiatry education.

Conclusion

This study finds that pediatric residents have lower confidence levels in managing pediatric mental health pharmacotherapy compared with physical health conditions within a single institution's medical residency program. Owing to the requirements set by the Accreditation Council for Graduate Medical Education, this may be a similar challenge among pediatric residents at other programs. The survey results highlight the need for enhanced and targeted educational interventions to improve residents' skills and confidence in pediatric mental health pharmacotherapy. This highlights an area where pharmacists can make a substantial impact

through various initiatives, given the pharmacotherapy expertise they bring to a multidisciplinary approach.

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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. All participants provided written informed consent at survey initiation.

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References

1. Centers for Disease Control and Prevention. Youth risk behavior survey data summary & trends report: 2013–2023. Accessed September 2, 2024. https://www.cdc.gov/yrbs/dstr/index.html.
2. Weiss AJ, Liang L, Martin K. *Overview of Hospital Stays Among Children and Adolescents, 2019*. Rockville, MD: Agency for Healthcare Research and Quality; 2022. HCUP Statistical Brief #299.
3. Data Resource Center for Child and Adolescent Health. 2020-2021 National Survey of Children's Health (NSCH) data query. Accessed September 22, 2023. http://www.childhealthdata.org.
4. Meng JF, Wiznitzer E. Factors associated with not receiving mental health services among children with a mental disorder in early childhood in the United States, 2021–2022. *Prev Chronic Dis*. 2024;21:24106.
5. Chien AT, Leyenaar J, Tomaino M, et al. Difficulty obtaining behavioral health services for children: a national survey of multiphysician practices. *Ann Fam Med*. 2022;20(1):42–50.
6. Accreditation Council for Graduate Medical Education (ACGME). ACGME Program Requirements for Graduate Medical Education in Pediatrics. Chicago, IL: 2024. Accessed September 2, 2024. https://www.acgme.org/specialties/pediatrics/program-requirements-and-faqs-and-applications/
7. Accreditation Council for Graduate Medical Education (ACGME). ACGME Program Requirements for Graduate Medical Education in Psychiatry. Chicago, IL: 2024. Accessed September 2, 2024. https://www.acgme.org/specialties/psychiatry/overview/
8. Green C, Leyenaar JK, Turner AL, Leslie LK. Competency of future pediatricians caring for children with behavioral and mental health problems. *Pediatrics*. 2020;146(1):e20192884.
9. Hess BJ, Johnston MM, Lynn LA, et al. Development of an instrument to evaluate residents' confidence in quality improvement. *J Comm J Qual Patient Saf*. 2013;39(11):502–510.
10. Foy JM, Green CM, Earls MF, et al. Mental health competencies for pediatric practice. *Pediatrics*. 2019;144(5):e20192757.
11. Kim WJ; for the The American Academy of Child and Adolescent Psychiatry Task Force on Workforce Needs. Child and adolescent psychiatry workforce: a critical shortage and national challenge. *Acad Psychiatry*. 2003;27(4):277–282.
12. Iskra W, Deane FP, Wahlin T, Davis EL. Parental perceptions of barriers to mental health services for young people. *Early Interv Psychiatry*. 2018;12(2):125–134.
13. McLaurin-Jiang S, Cohen GM, Brown CL, et al. Integrated mental health training relates to pediatric residents' confidence with child mental health disorders. *Acad Psychiatry*. 2020;44(3):299–304.
14. Kiger ME, Fowler L, Eviston M, et al. A case-based, longitudinal curriculum in pediatric behavioral and mental health. *MedEdPORTAL*. 2024;20:11400.
15. Pan GC, Zheng W, Liao SC. Qualitative study of the learning and studying process of resident physicians in China. *BMC Med Educ*. 2022;22(1):460.
16. Knapp KE, Townsend NL, Hanley SP, et al. Resident learning styles: are we maximizing learning opportunities for today's resident learner? *Open J Anesthesiol*. 2015;5(7):177–182.
17. Hamilton LA, Behal ML, Metheny WP. Impact of pharmacist education on incoming medical residents. *Hospital Pharmacy*. 2022;57(4):442–447.

JPPT | Case Report

High Anion Gap Metabolic Acidosis (HAGMA) After Levetiracetam Administration in an 11-Year-Old Boy With Laminin-α2-Deficiency-Associated Muscular Dystrophy and Epilepsy

Piet Erik Beusker, MD; Doortje Marieke Mehrtens, MD; Eckard Hamelmann, MD; and Georg Classen, MD

Congenital muscular dystrophy type 1A (MDC1A), an autosomal recessive disorder, is one of the most prevalent forms of congenital muscular dystrophy, characterized by the loss of Laminin-α_2 subunit (Merosin). Approximately one-third of affected patients experience epileptic seizures, typically manifesting around 8 years of age, with focal onset and secondary generalization, often with tonic-clonic semiology. Most reported cases show limited or no response to conventional treatment, though a subset responds to valproate or lamotrigine. The efficacy of levetiracetam in these patients remains insufficiently studied. Metabolic acidosis is not listed as a known adverse effect of levetiracetam in the medication's technical information. In this case, an 11-year-old male with MDC1A presented with nocturnal seizure equivalents and was started on levetiracetam therapy. Approximately 24 hours after receiving the loading dose, the patient's condition deteriorated significantly, and severe metabolic acidosis with an elevated anion gap was observed. The patient required transfer to the pediatric intensive care unit and received intensive intravenous hydration and potassium supplementation. Upon discontinuation of levetiracetam, the patient stabilized, and metabolic normalization was achieved within approximately 24 hours. There are very few reports in the literature that also point to the development of a high anion gap metabolic acidosis after levetiracetam administration. The underlying mechanism is hypothesized but not experimentally verified, and a causal relationship remains unproven. Nevertheless, this observation represents a potentially serious adverse event associated with a commonly used medication, warranting heightened clinical awareness. We therefore recommend actively highlighting this and considering safety monitoring based on the individual risk of the patients being treated.

ABBREVIATIONS EEG, electroencephalography; HAGMA, high anion gap metabolic acidosis; *LAMA2*, laminin-α_2

KEYWORDS levetiracetam; high anion gap metabolic acidosis; laminin α_2 deficiency- associated muscular dystrophy; epilepsy

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Information Box

What specific question(s) does this report address?

Could high anion gap metabolic acidosis be an adverse drug reaction caused by levetiracetam?

What does this report add to our current knowledge?

High anion gap metabolic acidosis must be considered as a rare but potentially severe adverse effect after levetiracetam administration, requiring intensive care monitoring and treatment.

Introduction

Laminin-α_2-Deficiency-Associated Muscular Dystrophy. Muscular dystrophy can be distinguished from other neuromuscular disorders by the following 4 mandatory characteristics: it is a primary myopathy with a genetic cause, exhibits a progressive course, and leads to the degeneration and death of muscle fibers at a certain stage of the disease.[1]

According to the German Society for Muscle Diseases, congenital muscular dystrophy type 1A is one of the most common forms of congenital muscular dystrophy. It is caused by mutations in the Laminin-α_2 (*LAMA2*) gene on chromosome 6 at locus 6q22-q23, resulting in a partial or complete absence of merosin (laminin subunit-α_2). Hence, this condition is also referred to as merosin-negative muscular dystrophy. A complete absence of merosin is most commonly observed, leading to disease onset at birth or within the first few months of life. The diagnosis is confirmed

by detecting 2 pathological mutations in the *LAMA2* gene (autosomal recessive inheritance) when clinically suspected. Characteristic features include generalized hypotonia and muscle weakness with ophthalmoplegia, as well as early joint contractures or hypermobility. Serum creatine kinase concentrations are typically markedly elevated (>1000 U/L). As the disease progresses, respiratory insufficiency and difficulties in feeding may also occur. Magnetic resonance imaging of the brain typically shows diffuse changes in the white matter consistent with leukodystrophy. Muscle biopsy reveals muscular dystrophy with merosin deficiency. Cerebral malformations may also occasionally occur. Patients with complete merosin deficiency may achieve the ability to sit independently, although walking ability is rarely attained. Approximately one-third of affected patients, including the case described here, experience epileptic seizures.[2]

The most extensive clinical investigations to date, conducted by Natera-de Benito et al and Geranmayeh et al.[4] observed epilepsy in approximately 36% of patients with a complete absence of the laminin subunit-α_2[3]. The data from these two studies were included in a review by the Department of Clinical and Experimental Medicine at the University of Pisa in Italy, which systematically examined 20 studies on "Epilepsy in *LAMA2*-Related Muscular Dystrophy."[5] A complete absence of merosin led to a significantly earlier onset of seizures compared with a partial absence. The average age at first seizure was 8 years, and, clinically, the seizures typically began focally with pronounced visual and autonomic symptoms, including vomiting. The seizures predominantly presented as generalized tonic-clonic seizures, irrespective of the onset of the disease and merosin expression. In contrast, focal seizures were less common and more frequently associated with cortical malformations. Electroencephalography (EEG) abnormalities mainly were observed bilaterally in the posterior cortical regions.[5]

Overall, there is limited information available on the efficacy of antiseizure drugs in these patients. In most cases described, most treatment approaches were minimally or not effective, while a small subset of patients responded to monotherapy with valproate or lamotrigine or to combination therapy with valproate and ethosuximide or carbamazepine. A correlation between brain structural defects and drug-resistant seizures is suspected, according to the authors of the review, as a smaller extent of cortical malformations was associated with a better response to antiseizure therapy in these patients. Overall, the data and the resulting recommendations for antiseizure therapy in epileptic seizures associated with *LAMA2*-related muscular dystrophy are considered weak due to the low incidence and limited reporting.[5]

Pharmacological Aspects of Levetiracetam. According to the Union Register of Medicinal Products for Human Use of the European Commission and the prescribing information from Sun Pharmaceuticals (as of June 2022), "Levetiracetam Sun 100 mg/mL" is primarily indicated for monotherapy of partial seizures with or without secondary generalization in adults and adolescents aged 16 years and older with newly diagnosed epilepsy. Additionally, it is approved as adjunctive therapy for partial seizures in patients aged 4 years and older. Common side effects include nasopharyngitis, somnolence, headache, fatigue, and dizziness. In children aged 4 to 16 years, vomiting, agitation, mood swings, emotional instability, aggression, abnormal behavior, and lethargy occur more frequently.[6]

The active ingredient levetiracetam belongs to the pharmacotherapeutic group of antiseizure drugs (ATC code: N03AX14) and is a pyrrolidone derivative. The exact mechanism of action is not fully understood. Studies indicate that levetiracetam influences intracellular calcium concentrations, leading to inhibition of calcium influx and a reduction in calcium release. It interacts with synaptic vesicle protein 2A, which is thought to contribute to its antiseizure effects.[6]

Levetiracetam is primarily metabolized through enzymatic hydrolysis, without affecting the cytochrome P450 isoforms in the liver. The main metabolite is pharmacologically inactive. Additional metabolites are produced through hydroxylation and opening of the pyrrolidone ring, while unidentified degradation products account for only 0.6% of the dose. Levetiracetam has minimal effects on certain liver enzymes (CYP1A2, SULT1E1, UGT1A1) but causes slight induction of CYP2B6 and CYP3A4.[6]

The plasma half-life of levetiracetam in adults is approximately 7 ± 1 hours and is not affected by dose, mode of administration, or repeated dosing. Approximately 95% of the administered dose is primarily excreted via urine, with 93% being eliminated within 48 hours. Only 0.3% is excreted through feces. Within the first 48 hours, 66% of the dose is excreted as levetiracetam and 24% as its primary metabolite, indicating glomerular filtration and tubular reabsorption. The elimination correlates with creatinine clearance.[6]

In patients with mild to moderate hepatic impairment, levetiracetam clearance is only slightly affected, but in cases of severe impairment, clearance is reduced by more than 50%. There are no data on intravenous administration in children (4–12 years), but it is assumed that the pharmacokinetics are comparable to oral administration. After oral administration of 20 mg/kg/day in children with epilepsy (6–12 years), the half-life is 6 hours, and total body clearance is approximately 30% higher than in adults. After repeated oral administration (20–60 mg/kg/day), levetiracetam is rapidly absorbed, with peak plasma concentrations occurring after 0.5 to 1 hour. The half-life is approximately 5 hours.[6]

Case Presentation

An 11-year-old male Caucasian patient weighing 35 kg with confirmed Laminin-α_2-deficiency-mediated muscular dystrophy was admitted with newly developed nocturnal cyanosis, oxygen desaturation, and gaze deviation. There were no other relevant preexisting conditions, and the patient was not on any regular medication. No allergies were reported, and there was no infection. Routine laboratory tests, including complete blood count, electrolytes, clinical chemistry, and coagulation parameters, at admission showed no abnormalities except for a previously known elevated creatine kinase concentration of 1020 U/L due to the underlying disease. In previous hospital stays between 2013 and 2021, creatine kinase concentrations fluctuated between 112 and 1584 U/L for this patient. EEG revealed bilateral frontal spike waves, bilateral synchronous spikes, and intermittent generalized slowing, leading us to interpret the nocturnal cyanosis and desaturation as seizure equivalents with hypopnea. Consequently, we initiated seizure-suppressing therapy with levetiracetam. On day 3 of hospitalization, an intravenous loading dose of 30 mg/kg was administered over 30 minutes. On day 4, approximately 12 hours after the loading dose, the patient received the first intravenous maintenance dose of 10 mg/kg over 30 minutes as well. The planned ongoing treatment regimen was 20 mg/kg/day in 2 divided doses. All doses administered were diluted in sodium chloride 0.9%.

Approximately 12 hours after administering the first levetiracetam maintenance dose, the patient's clinical condition deteriorated significantly, with the onset of tachypnea, tachycardia, increased sweating, and polyuria. Initial blood gas analysis revealed severe metabolic acidosis with a pH of 7.27 and a base excess of −19 mmol/L, with compensatory respiratory alkalosis (pCO_2 19 mm Hg). A concurrent hypokalemia of K^+ 3 mmol/L was also noted. Blood gas and electrolyte analysis (Na^+ 140 mEql/L, K^+ 3.06 mEq/L, Cl^- 107 mEq/L, HCO_3^- 12.6 mEq/L) indicated a high anion gap metabolic acidosis (HAGMA; anion gap 23.46 mmol/L). Laboratory evaluations ruled out other causes of HAGMA, such as diabetic ketoacidosis (blood glucose 84 mg/dL, lack of glucosuria), lactic acidosis (lactate 0.7 mmol/L), acute kidney injury (serum creatinine <0.17 mg/dL, blood urea 7 mg/dL), rhabdomyolysis (serum creatine kinase 277 U/L), and sepsis (C-reactive protein 25.1 mg/L, interleukin 6 3.5 pg/mL, procalcitonin 0.06 ng/mL). However, there was marked ketonuria (>80 mg/dL), which may have been influenced by reduced food intake in the preceding days.

The patient was transferred to the pediatric intensive care unit and received intensive intravenous hydration and potassium replacement. In total, the patient received isotonic electrolyte solution (Jonosteril, Fresenius Kabi) 360 mL, potassium chloride 7.45% 40 mL, Ringer's acetate 1320 mL, and pediatric semi-osmolar glucose electrolyte solution (Pediatric Infusion Solution 2, B. Braun Melsungen AG) 380 mL in the first 24 hours, resulting in a total intravenous volume of 60 mL/kg. Additionally, the patient received 4 nasogastric tube feedings (1.3 kcal/mL) of 50 mL each in the first 24 hours. Levetiracetam administration was discontinued immediately after the detection of acidosis. These interventions within the first 24 hours led to normalization of the patient's metabolic state with a pH of 7.43, base excess of −1.5 mmol/L, and potassium 3.8 mEq/L achieved approximately 24 hours later. Owing to persistent EEG changes, an alternative seizure-suppressing therapy with oral valproate 150 mg twice a day (8.5 mg/kg/day) was initiated. This was well tolerated by the patient, allowing for a successive increase to the target dose of 300 mg twice a day (17 mg/kg/day) without complications. Nocturnal hypopnea as a seizure component was observed for the last time 2 days after the start of valproate therapy. During the further observation period, no further seizure equivalents occurred, but residual EEG changes persisted even on day 15 after initiation of therapy. A condensed overview of the relevant events during the inpatient course is shown in the Figure.

The Naranjo score was 7, corresponding to a probable association.[7] To complete the scale, definitions for each of the 10 criteria outlined in the National Institute of Diabetes and Digestive and Kidney Diseases instructions for using the adverse drug reaction probability scale have been used.[8] The criteria and their evaluation in this case are shown in the Table.

Discussion

There are very few reports in the literature that point to the development of a high anion gap metabolic acidosis after levetiracetam administration. A Phase 4 clinical study conducted by eHealthMe, which analyzes

Figure. Extract of relevant events during the hospital stay, including the periods of levetiracetam administration, acidosis, and pediatric intensive care unit (PICU) treatment.

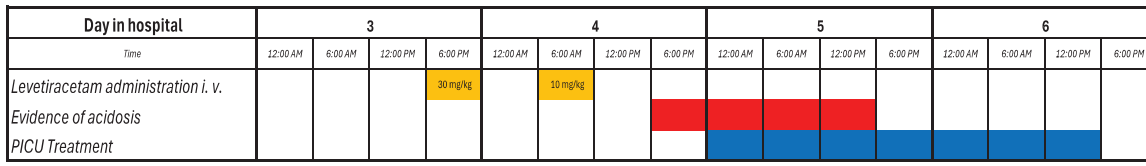

Table. Adverse Drug Reaction Probability Scale.

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was readministered?	+2	−1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	−1	+2	0	2
6. Did the reaction reappear when a placebo was given?	−1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
			Total Score: 7	

large Food and Drug Administration data sets with the help of big data-capable artificial intelligence models. It calculates frequencies over time and found metabolic acidosis in 412 of 74,747 patients (0.55%) who reported adverse effects while taking levetiracetam between 2001 and 2024. The majority of affected patients were male (51.1%), with the most common age groups being 20–29 years (25.4%) and 10–19 years (18.9%), the latter including the patient in this case report. Most cases (66.6%) occurred within less than a month of levetiracetam initiation, as was the case in this report.[9] However, caution is warranted in interpreting these data, as they are derived from patient self-reports rather than controlled, scientifically validated studies.

In contrast to the eHealthMe study, which relies on patient self-reporting, the literature contains only 1 similar physician-reported clinical case series involving 3 patients who developed high anion gap metabolic acidosis after levetiracetam administration. The authors postulate that the accumulation of the ketone-like acidic metabolite 2-pyrrolidone-N-butanoic acid might be the underlying mechanism. They support this hypothesis by referencing the incomplete understanding of levetiracetam's mechanism of action and the possibility that the accumulation of this metabolite might contribute to the drug's anticonvulsant effect like the widely used ketogenic diet.[10]

Ultimately, it remains unclear whether the initial administration of levetiracetam in our case was causative for the observed metabolic acidosis. Alternative causes that could, on their own, have caused HAGMA, such as diabetic ketoacidosis, lactic acidosis, acute kidney failure, rhabdomyolysis, and sepsis, were ruled out by the diagnostic report. However, the absence of other clinical factors that could have influenced the previously stable acid-base balance, as well as the more than 400 self-reported adverse events from Food and Drug Administration data, and the similar observations described by Megri et al,[10] suggest a likely causal relationship.[9] Nevertheless, this represents a potentially serious adverse effect of a commonly used medication, indicating a high degree of clinical relevance for this observation. We therefore recommend actively drawing attention to this and considering safety monitoring, including respiratory function and acid-base balance assessment, based on the individual risk of the patients being treated.

Conclusion

This case report documents a rare but potentially severe adverse effect requiring intensive care monitoring and treatment associated with a commonly used medication, underscoring the clinical significance of this observation. Although it remains uncertain whether the initial administration of levetiracetam was the cause of the observed metabolic acidosis in this case, the literature suggests a possible link. The underlying pathophysiological mechanism also remains unclear and warrants further investigation through experimental

preclinical and clinical studies. Nevertheless, it is important to repeatedly highlight the observed condition after levetiracetam administration and to indicate safety monitoring based on the individual risk of the patients being treated.

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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. Written informed consent for the scientific processing and publication of the patient's data was provided by the patient's caregivers and legal representatives.

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References

1. Kliegman RM, Nelson WE. *Nelson Textbook of Pediatrics*. Volume 2. 21 ed. Philadelphia, PA: Elsevier; 2020.
2. Gesellschaft für Muskelkranke. Kongenitale Myopathien. Accessed August 7, 2024. https://www.dgm.org/muskelerkrankungen/kongenitale-myopathien
3. Natera-de Benito D, Muchart J, Itzep D, Ortez C, González-Quereda L, Gallano P et al. Epilepsy in LAMA2-related muscular dystrophy: an electro-clinico-radiological characterization. *Epilepsia.* 2020;61(5):971–983.
4. Geranmayeh F, Clement E, Feng LH, et al. Genotype-phenotype correlation in a large population of muscular dystrophy patients with LAMA2 mutations. *Neuromuscul Disord.* 2010;20(4):241–250.
5. Salvati A, Bonaventura E, Sesso G, et al. Epilepsy in LAMA2-related muscular dystrophy: a systematic review of the literature. *Seizure*. 2021;91:425–436.
6. Levetiracetam [package insert] . Leverkusen, Germany: *Sun Pharmaceuticals Germany GmbH*. Accessed August 7, 2024. https://ec.europa.eu/health/documents/community-register/2021/20210318151210/anx_151210_en.pdf
7. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
8. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
9. eHealthMe.com. Levetiracetam and Metabolic acidosis - a phase IV clinical study of FDA data. Accessed August 7, 2024. https://www.ehealthme.com/ds/levetiracetam/metabolic-acidosis/
10. Megri MA, Abusnina WA, Bukamur HS, Shweihat YR. Levetiracetam as a cause of high anion gap metabolic acidosis. *Am J Respir Crit Care Med.* 2019;199:A4808.

JPPT | Case Report

Piperacillin Pharmacokinetics in a Pediatric Patient With Primary Hyperoxaluria Receiving High-Dose Continuous Dialysis Post Liver-Kidney Transplant

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Continuous kidney replacement therapy (CKRT) can influence pharmacokinetics (PK), including clearance (CL) of antibiotics like piperacillin (PIP). Both CKRT intensity, or "dialysis dose," and residual kidney function can alter PIP PK and pharmacodynamic (PD) target attainment (TA), defined by the percentage of time free PIP concentrations exceed the minimum inhibitory concentration (% *f*T > MIC). In existing reports, children receiving PIP and CKRT are usually oligoanuric, so PIP PK/PD in non-oligoanuric patients receiving high-intensity CKRT is unknown. This report analyzes free PIP PK/PD in a child with robust kidney function who received 30-minute infusions of 100 mg/kg PIP-tazobactam every 6 hours while on high-intensity CKRT after liver-kidney transplant for primary hyperoxaluria. Model-informed PK software was used to estimate PK/PD parameters for periods on and off CKRT. PIP CL on CKRT was 66% higher than off CKRT (5.59 L/hr vs 3.36 L/hr). Nearly 100% *f*T > 1xMIC (using 8 mg/L for Enterobacterales) was achieved whether on or off CKRT, but only 60% *f*T > 4xMIC was achieved on CKRT. CKRT CL was 40% of total CL on CKRT and 51% of the CKRT dialysis dose, suggesting PIP elimination was mostly renal despite high-intensity dialysis. Monitoring of free PIP concentrations may help ensure proper TA in non-oligoanuric patients receiving high-dose CKRT.

ABBREVIATIONS AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; CL, clearance; CL_{EC}, extracorporeal clearance; *f*T >, time free concentration exceeds; f_u, fraction unbound; MIC, minimum inhibitory concentration; MW, molecular weight; PD, pharmacodynamic; PH1, primary hyperoxaluria type 1; PIP, piperacillin; PK, pharmacokinetic; PTZ, piperacillin-tazobactam; Q, intercompartmental clearance; Q_{ef}, total effluent flow; Q_{uf}, ultrafiltration rate; TA, target attainment; TM_{50}, maturation half-life; UOP, urine output; V_d, volume of distribution; V_1, central volume of distribution; V_2, peripheral volume of distribution; % fT > MIC, percentage of time free PIP concentrations exceed the minimum inhibitory concentration

KEYWORDS continuous kidney replacement therapy; dialysis; pharmacodynamics; pharmacokinetics; piperacillin; primary hyperoxaluria

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Information Box

- What specific questions does this report address?
  - Appropriate piperacillin dosing for a pediatric patient receiving high-dose continuous kidney replacement therapy (CKRT) alongside significant intrinsic kidney function is unknown.
- What does this report add to our current knowledge?
  - While the patient was on high-dose CKRT, clearance of piperacillin was higher than while the patient was off CKRT, and residual kidney function contributed to a substantial proportion of clearance; therefore, stringent pharmacodynamic target attainment was inadequate when on high-dose CKRT.

Introduction

Continuous kidney replacement therapy, or CKRT, is a type of continuous dialysis typically used to support patients with severe acute kidney injury (AKI), intoxications, or fluid overload.[1] Patients who receive CKRT are often oligoanuric, but CKRT can be used in non-oligoanuric patients for supplemental toxin removal.[1] Extracorporeal clearance (CL_{EC}), or solute removal via CKRT, is possible when the solute is smaller than the pore size of the CKRT filter (molecular weight [MW] <35 kDa using modern CKRT filters[2]), has a low volume of distribution (V_d), and is not highly bound to plasma proteins. The solutes removed include toxins that accumulate with kidney dysfunction and some medications, including many antibiotics. Antibiotics are commonly administered to children receiving CKRT, as sepsis is a leading cause of AKI requiring CKRT,[3] and

the presence of an indwelling hemodialysis catheter predisposes to infection. However, there is a paucity of data regarding antibiotic pharmacokinetics (PK) and pharmacodynamics (PD) in children receiving CKRT, especially in patients who are non-oligoanuric.[4]

Piperacillin-tazobactam (PTZ) is a beta-lactam/beta lactamase inhibitor combination commonly used in critically ill children given its broad-spectrum activity, which includes anaerobic and antipseudomonal coverage.[5] Piperacillin (PIP), the active antimicrobial component, has a MW of 518 Da and is approximately 30% protein bound,[6] rendering it susceptible to CL_{EC} via CKRT. Optimal bactericidal activity of PIP depends on the percentage of time that free PIP concentrations are above the minimum inhibitory concentration, or MIC (% *f*T > MIC). A lack of consensus about precise PD targets exists due to limited data associated with clinical outcomes, but typically, more stringent PD targets are recommended for critically ill patients.[7] Expert reviews have suggested that targets such as 100% *f*T > 1xMIC and 100% *f*T > 4xMIC could be necessary for maximum efficacy of PIP and minimum emergence of resistance.[7,8]

Previous studies in adults have quantified the effects of CKRT on PIP PK. A review reported a median additional CL_{EC} of 1.43 L/hr, which contributed to a 66% increase in total clearance (CL) while on CKRT (median body CL = 2.76 L/hr). This review suggested that the use of continuous infusions could help attain stringent PD targets in the setting of this additional $CL_{EC.}$[9]

Pediatric data on PIP PK/PD in patients supported with CKRT are comparatively limited, with only 3 published reports to our knowledge. In a PIP PK and dose optimization study of 32 critically ill children receiving CKRT, Thy et al[10] created a population PK model to simulate different dosing regimens. Because only 53% of the patients were anuric, and 25% had urine output (UOP) >0.3 mL/kg/hr, they could only assess the effect of residual renal function on PIP PD target attainment (TA) to an oliguric threshold of 0.5 mL/kg/hr. Through simulating different levels of UOP up to 0.5 mL/kg/hr, they recommended using higher doses with continuous infusions for patients with modest residual renal function. A second population PIP PK study in critically ill children by Butragueño-Laiseca et al[11] included 13 (41% of total included) patients on CKRT. Only 3 of those patients had any residual UOP. Using the model that they created, they recommended PIP drug monitoring and either intermittent or continuous infusion dosing regimens for patients on CKRT. Finally, a case study on PIP PK in a child with liver failure who received concomitant molecular adsorbent recirculating system therapy and CKRT reported on PIP PK for 1 cycle of CKRT alone.[12] The authors found an increase in CL from baseline to during CKRT alone (2.0 L/hr vs 3.0 L/hr, 50% increase) and adequate TA on CKRT alone. Residual UOP was not reported. This last case report is the only one of the 3 articles that reported using free PIP concentrations. Measuring free concentrations directly obviates the need to rely on an assumption of a fixed percentage of protein binding, which is known to fluctuate in the context of critical illness.[13] Thus, there is a knowledge gap regarding free PIP PK in critically ill children receiving CKRT with significant residual kidney function.

Because blood flow rates are typically much faster than dialysis fluid flow rates in CKRT, the total effluent flow (Q_{ef}) is the main driver of solute removal in CKRT[1] and can affect antibiotic CL_{EC}. Q_{ef} can be considered the overall dialysis dose, and the standard pediatric dialysis dose is around 2000 mL/hr/1.73 m^2.[14] High-dose or high-intensity dialysis involves an effluent flow rate significantly above that standard. The aforementioned studies also do not elucidate the potential effect of high Q_{ef} on PIP CL or TA. Therefore, there also remains a knowledge gap in PIP PK regarding the effects of high-dose dialysis in the setting of preserved intrinsic kidney function.

This case study describes the unique PK/PD of free PIP in a child receiving high- dose CKRT for oxalate CL after combined liver-kidney transplant for primary hyperoxaluria who had intrinsic kidney function from the new allograft. We report CL, V_d, and TA, by estimating the percent time free PIP concentrations remain above 1x MIC (*f*T > 1xMIC) and 4x MIC (*f*T > 4xMIC).

Case Report

Patient Background. The 8-year-old, 23.5-kg (0.86 m^2) boy described here was enrolled in a larger PK/PD study of beta-lactam antibiotics in critically ill children that received institutional review board approval at our institution. The patient had received 1 prior kidney transplant owing to presumed renal dysplasia. He was thereafter diagnosed with primary hyperoxaluria type 1 (PH1) when his initial posttransplant course was complicated by severe persistent AKI.[15] PH1 is a rare genetic disorder that causes a deficiency of alanine-glyoxylate aminotransferase, a peroxisomal liver enzyme. This deficiency leads to the inability to properly metabolize glyoxylate, which is subsequently transformed into oxalate. The consequent oxalate excess results in toxicity to the kidneys, retina, bone, heart, and other organs.[16] His first allograft was salvaged with high-intensity CKRT and intermittent hemodialysis to remove excess oxalate along with lumasiran, a small interfering RNA that decreases hepatic oxalate production.[15–17] Despite these interventions, he developed posttransplant chronic kidney disease stage IV and subsequently received a combined liver-kidney transplant.

To minimize nephrotoxic effects from oxalate buildup in the new kidney allografts, the patient received high-dose CKRT (delivered Q_{ef} ~9000 mL/hr/1.73 m^2) during and immediately after transplant to augment renal oxalate CL. He had immediate good function of both the liver and paired kidney allografts, based on normal

hepatic synthetic function and robust urine output. He was prescribed PTZ as peri-transplant infection prophylaxis in alignment with the institution's standard liver transplant protocol.

Given the unique combination of high-dose CKRT alongside significant intrinsic renal function from the newly transplanted kidneys, we sought to characterize PIP PK in this patient.

Study Period PIP and CKRT Data. The patient was supported with continuous veno-venous hemodialysis, a modality of CKRT that can efficiently remove small molecules such as oxalate.[18,19] The filter used was the HF1000 (1.1 m^2; Baxter, Deerfield, IL), and the prescribed blood flow, dialysate flow, and replacement fluid flow rates were 150 mL/min, 4000 mL/hr, and 50 mL/hr, respectively. The patient had robust UOP, which averaged 2.26 mL/kg/hr during the study period. To ensure adequate perfusion of the new renal allograft, the CKRT was prescribed to remove only the volume of the calcium and citrate infusions provided for regional anticoagulation. This practice contrasts with the fluid removal strategy for patients with fluid overload or oligoanuria in which all fluids administered to the patient are typically removed during CKRT. The net volume removed is known as the net ultrafiltration rate (net Q_{uf}), which is calculated by subtracting the volume put into the circuit (priming volume) from the ultrafiltrate volume removed. The total dialysis dose, Q_{ef}, is the sum of dialysate flow rate, replacement fluid flow rate, and net Q_{uf}. The patient's average delivered Q_{ef} was 4406 mL/hr, approximately 4.5 times the typical pediatric dialysis dose when indexed to body surface area (8863 mL/hr/1.73 m^2 vs 2000 mL/hr/1.73 m^2).

At our institution, weight-based dosing is calculated for the PTZ combination, of which PIP comprises 89% of the total. Postoperatively, the patient was administered 100 mg/kg PTZ every 6 hours as a 30-minute infusion throughout the time he was on CKRT.

Methods

PK/PD Analysis. We analyzed free PIP concentrations immediately postoperatively and through the end of PTZ treatment, a period that spanned 7 days. Free PIP concentrations were measured from residual blood samples obtained from clinical samples through a random scavenged opportunistic sampling strategy.[20] Samples were stored at 4°C and centrifuged within 7 days for plasma extraction. Plasma was stored at −80°C until free drug was isolated with ultrafiltration, and free concentrations were measured by using a high-performance liquid chromatography assay previously validated by our group.[20]

PIP doses and free concentrations were entered into a precision dosing software, MwPharm++ (Mediware, Prague, Czech Republic), to estimate concentration vs time profiles as well as CL and central volume of distribution (V_1). To conduct the PK modeling for this patient, a previously published population PK model describing PIP in critically ill children,[21] adapted for free PIP by assuming 30% protein binding, was used because there is no available published model with free PIP concentrations at this time. Weight and post-menstrual age (PMA) are included as covariates in this model, and allometric scaling was used to scale the median body weight of 14 kg to 70 kg for use in MwPharm++. PMA was included as a maturation sigmoidal function $\left(F_{mat} = \frac{PMA^{HILL}}{TM_{50}^{HILL} + PMA^{HILL}}\right)$, though this was not influential on this patient's CL because he was significantly older than the maturation half-life (TM_{50}) of 61 weeks.[21] Intercompartmental CL (Q) and peripheral compartment V_d (V_2) were fixed to the population mean established by the model and adapted to free concentrations (Q = 13 L/hr/70 $kg^{0.75}$ and V_2 = 11.37 L/70 kg).

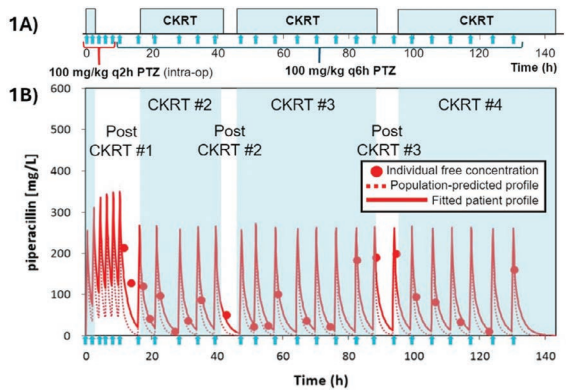
Analysis of the observed free concentrations was completed by using Bayesian estimation with an assay error of 5%, aligning with the test-retest variability of our clinical laboratory. Concentration vs time profiles were generated and used to find the CL and V_1 for each period on and off CKRT (Figure A). Serial fits were obtained by inputting all PIP doses prior to the period of interest, then fitting the concentration-time profile using only the concentrations available during the period of interest. Time-weighted arithmetic means of PK parameters were then calculated as based on the time the patient spent in each period to determine average PK parameters for time on- and off-circuit. These fits were also used to assess PD TA as % *f*T > 1xMIC and % *f*T > 4xMIC. The empiric selected MIC was 8 mg/L—the Clinical Laboratory and Standards Institute PIP breakpoint for Enterobacterales—because no bacteria were cultured from the patient.[22]

Clinical Data and Outcomes. Chart review of electronic medical record was conducted to obtain information about clinical history, demographics, potential infections, urine output, and kidney-/liver-related laboratory values. The initiation and cessation of CKRT periods were recorded in addition to blood flow, dialysate flow, and replacement fluid rates. Because creatinine is easily cleared by CKRT, creatinine was not a valid kidney function biomarker post-transplant, so serum creatinine data were not reported.

Results

Twenty-two free PIP concentrations were analyzed from scavenged plasma samples, 17 of which were obtained when the patient was receiving CKRT. The concentration-vs-time profile for the entire study period is displayed in Figure B. Each period on and off CKRT was analyzed individually, and the PK results are summarized in Table 1. Average urine outputs and albumin levels on each study day are reported in Table 2. The weighted mean PIP CL for all cycles when the patient was

Figure. Piperacillin concentration-time profile for periods on and off CKRT.



CKRT, continuous kidney replacement therapy; CL, clearance; PIP, piperacillin; PTZ, piperacillin-tazobactam; V_d, volume of distribution.

(A) The PTZ dosing regimen received by the patient relative to time 0, which represents the first dose of PTZ given. Times when the patient was on CKRT are indicated by light blue boxes. Each dose is represented by a blue arrow underneath the x-axis. (B) Concentration (PIP in mg/L) vs time (in hours) profile for the entire study period, with periods on and off CKRT labeled accordingly. Periods on CKRT are highlighted in light blue. The red circles are observed free concentrations. The dashed line is the population-predicted profile based on doses and covariates, while the solid line is the fitted individual-predicted line accounting for both the model and the concentrations with Bayesian estimation. For this figure, all the observed concentrations were fitted at once, but when estimating CL and Vd, the concentrations were fit phase by phase (e.g., post CKRT #1, CKRT #2).

on CKRT was 5.59 L/hr (13.1 L/hr/70 kg$^{0.75}$). The weighted mean PIP CL for all cycles off CKRT was 3.36 L/hr (7.88 L/hr/70 kg$^{0.75}$). Thus, mean CL_{EC} was 2.23 L/hr, increasing total CL by 66% while on CKRT vs while off CKRT (Table 3). This CL_{EC} was 40% of total patient CL while on CKRT and 51% of the total dialysis dose of ~4.4 L/hr.

The weighted mean PIP V_1 was larger while the patient was on CKRT vs off CKRT (18.25 L/70 kg vs 15.89 L/70 kg). Of note, the PIP V_1 for the first period off CKRT, immediately postoperatively, was elevated (18.20 L/70 kg) as compared with the estimated V_1 during other periods off CKRT (14.28 and 13.18 L/70 kg). The patient's net intake for the first period off CKRT was +4760.6 mL (366.2 mL/hr). PD results are summarized in Table 1. *f*T > 1xMIC approached or achieved 100% for all periods analyzed. *f*T > 4xMIC while the patient was on CKRT was 60% as compared with 97% when off CKRT.

Discussion

This case report of a child receiving high-dose CKRT after combined liver-kidney transplant demonstrates that CKRT was associated with higher PIP CL and decreased PD TA. For a target of 100% *f*T > 1xMIC, the target was achieved while off CKRT and nearly achieved while on CKRT. However, % *f*T > 4xMIC was much lower than 100% (60.3%) while on CKRT. Because the patient had immediate kidney allograft function post transplant, he had antibiotic elimination from both intrinsic kidney function and

Table 1. PK and Target Attainment Results From Each Period On and Off CKRT*

	Periods Off CKRT			Periods On CKRT		
Time of each period, hr	13.1	4.75	8.37	24.5	42.8	45.3
Total CL, L/hr (L/hr/70 kg$^{0.75}$)	3.35 (7.84)	3.91 (9.17)	3.08 (7.21)	5.19 (12.14)	5.65 (13.22)	5.76 (13.49)
	Weighted Mean: 3.36 (7.88)			**Weighted Mean: 5.59 (13.1)**		
V_1, L (L/70 kg)	6.11 (18.20)	4.80 (14.28)	4.42 (13.18)	5.57 (16.58)	6.71 (19.99)	5.88 (17.52)
	Weighted Mean: 5.33 (15.89)			**Weighted Mean: 6.13 (18.25)**		
% *f*T > 1xMIC	100	100	100	98.97	97.70	98.40
	Weighted Mean: 100			**Weighted Mean: 98.3**		
% *f*T > 4xMIC	100	91.62	100	67.70	60.60	55.98
	Weighted Mean: 98.5			**Weighted Mean: 60.3**		

CKRT, continuous kidney replacement therapy; CL, clearance; MIC, minimum inhibitory concentration; PIP, piperacillin; PK, pharmacokinetic; Q, intercompartmental clearance; V_1, central volume of distribution; V_2, peripheral volume of distribution; % fT > 1xMIC, percentage of time free PIP concentrations exceed 1x the minimum inhibitory concentration; % fT > 4xMIC, percentage of time free PIP concentrations exceed 4x the minimum inhibitory concentration

* CL, V_1, and fT > 1x-4xMIC for periods on and off CKRT. CL was allometrically scaled to body weight as dictated by the population PIP PK model for critically ill children.[21] V_2 (11.37 L/70 kg) and Q (13 L/hr/70 kg$^{0.75}$) were fixed according to the model population mean. Means are weighted as based on time of each period.

Table 2. Urine Output and Albumin Concentrations*

Study Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Mean
Urine output, mL/kg/hr	1.94	2.71	1.72	3.54	2.91	2.24	0.76	2.26
Albumin, g/dL	2.2	3.3	3.8	3.5	2.8	2.7	2.5	3.0

PTZ, piperacillin-tazobactam

* Average urine output (mL/kg/hr) and albumin levels (g/dL) for each day PTZ was administered. Note that the urine output far exceeded the threshold for oliguria (<0.5 mL/kg/hr).

Table 3. Comparisons of CL Provided by CKRT*

Weighted Mean CL While on CKRT, L/hr	Weighted Mean CL While off CKRT, L/hr	CL_{EC}, L/hr	Increase in Total CL With CKRT	CL_{EC}/Total CL While on CKRT	CL_{EC}/ CKRT Dose
5.59	3.36	2.23	66%	40%	51%

CKRT, continuous kidney replacement therapy; CL, clearance; CL_{EC}, extracorporeal clearance; PIP, piperacillin

* CKRT-provided PIP CL, or CL_{EC}, as calculated from the difference of PIP CL on vs off CKRT and compared with total CL while on CKRT and the total CKRT dose (about 4.5 L/hr).

from CKRT in the form of CL_{EC}. This additional CL_{EC} explains the lower PD TA for on-circuit periods. However, CL_{EC} was only 40% of total patient CL while on CKRT, suggesting that the majority of PIP elimination was from the patient's newly transplanted kidneys despite high-dose dialysis.

Because the dialysis dose (Q_{ef}) is the primary driver of solute removal in CKRT, and this patient was receiving a dose approximately 4½ times that of standard pediatric CKRT, it is interesting to note that PIP CL_{EC} was approximately half of the dialysis dose received (2.23 L/hr vs 4.4 L/hr). CL_{EC} in CKRT is sometimes estimated as the unbound fraction (f_u) multiplied by the Q_{ef} because only free solutes can pass through the CKRT filter. PIP has an f_u of ~70% (~30% protein binding), suggesting that CL_{EC} would be expected as ~70% of the Q_{ef}. The discrepancy between the observed and predicted CL_{EC} may exist because of decreased PIP availability for extracorporeal elimination due to intrinsic renal elimination. It also could be due to the limitations of using a predominantly diffusive, rather than convective, form of solute removal for CKRT CL,[1,18,23] as this patient was prescribed continuous veno-venous hemodialysis. This modality very effectively removes small molecules like oxalate, but less effectively clears molecules of middle MW (MW in the 500–50,000 Da range). With PIP's MW of 518 Da, it is considered a middle MW molecule despite being on the "small" end of the middle-MW range. Thus, PIP was perhaps less susceptible to CL_{EC} than would be expected from the prescribed effluent flow and degree of protein binding alone.

One additional change in PK/PD parameters in this patient over time is worth noting. PIP V_1 was likely elevated in the immediate postoperative period while the patient was off CKRT owing to the volume of fluids given immediately after the operation and the absence of much output (overall net fluid balance approximately +4.7 L during post CKRT period #1). This increase in V_1 did not appear to affect TA while the patient was off CKRT given the high percentage of *f*T > 1xMIC for all 3 off-CRKT periods. It is known that a larger V_d with a constant CL can increase half-life and thus time over MIC.[24,25]

Comparing these patient data directly to existing reports of PIP PK on CKRT is challenging in part because of differences in data reported and patients included. For example, Butragueño-Laiseca et al[11] reported only 3 patients with residual kidney function and did not explore the impact of residual diuresis. The case report by Tang-Girdwood et al[12] did not report UOP. While Thy et al[10] reported the impact of residual kidney function, they did not include UOP values for each patient or evaluations of UOPs above an oliguric level. In addition, the reports by Thy et al[10] and Butragueño-Laiseca et al[11] do not compare the CL on CKRT to the CL off CKRT for the patients in their studies, because their research is focused on PIP PK modeling.

Regardless, some comparisons regarding TA are apparent. The report by Tang Girdwood et al[12] found that CKRT provides a 50% increase in PIP CL while on CKRT vs off CKRT (3.0 L/hr vs 2.0 L/hr) in a 13-year-old, 42-kg patient with liver failure. This result is comparable to the 66% increase in PIP CL discussed in this article. Tang Girdwood et al[12] reported nearly 100% *f*T > 4xMIC for a MIC of 16 mg/L while on CKRT despite receiving a lower dose of 80 mg/kg every 8 hours while on CKRT and 48 mg/kg every 8 hours while off, which does not align with the 60% *f*T > 4xMIC for a MIC of 8 mg/L reported here. This discrepancy can be attributed to our patient's significant kidney function and high dialysis dose. Thy et al[10] simulated TA for a 15-kg patient on CKRT receiving

100 mg/kg of PTZ every 8 hours with a residual UOP of 0.5 mL/kg/hr and found approximately 75% *f*T > 4xMIC for a MIC of 8 mg/L. Butragueño-Laiseca et al[11] similarly reported PD TA of 78% fT > 4xMIC for a MIC of 8 mg/L in a simulated patient on CKRT weighing 10 to 30 kg and receiving 100 mg/kg of PTZ every 8 hours, though they could not explore the effect of residual kidney function. The TA for the patient in this study is lower, likely owing to both high-intensity CKRT and robust kidney function.

Because this was a single-patient case study, we cannot make broad generalizations regarding appropriate PTZ dosing in this patient population. That said, we simulated 3 dosing regimens that would achieve 100% *f*T > 4xMIC for on-circuit periods, assuming no change in CKRT or kidney CL: 110 mg/kg PTZ (98 mg/kg PIP) every 4 hours as a 30-minute infusion, 160 mg/kg PTZ (142 mg/kg PIP) every 6 hours as a 3-hour infusion, or 220 mg/kg/day PTZ (196 mg/kg PIP) as a continuous infusion. Concentration-time profiles for these simulated dosing regimens are available in Supplemental Figure A through C.

Limitations

This case study has limitations. Only 5 of the 22 concentrations were obtained when the patient was off CKRT. This is mainly because the patient was only off CKRT for short periods (mean of 9 hours vs mean of 38 hours on CKRT), but the paucity of data could result in less accurate estimates of PIP CL. Because this is a single-patient case report, we also cannot perform statistical inferential testing to examine the impact of patient- and CKRT-specific parameters in predicting PIP PK. We assume a fixed percentage of binding in the de Cock model used here, which may inaccurately represent the actual protein binding of PIP in this patient owing to his critical illness and fluctuating albumin levels. In addition, we did not collect urine or effluent PIP concentrations because the case study was subsumed under a parent study that only involved collection of scavenged opportunistic blood samples. Because piperacillin is known to have renal, hepatic, and extracorporeal clearance,[7,26,27] the absence of urine and effluent samples limited our ability to precisely quantify the contribution of each. Finally, because we do not have a validated assay for tazobactam at our institution, we could not perform tazobactam PK, which would have enriched this case report.

However, this report has strengths as well, especially owing to the unique nature of the patient case. To our knowledge, this is the first analysis of free PIP concentrations in a critically ill pediatric patient undergoing high-dose continuous dialysis. His significant intrinsic kidney function also adds to the novelty of the PK/PD results. The 17 free PIP concentrations available while the patient was on CKRT likely allowed for accurate estimates of PK parameters during those periods, as evidenced by the good fits of the observed concentrations while on CKRT.

Conclusions

This case report contributes valuable PIP PK data from a distinctive patient case to the sparse existing CKRT PK literature. We provide information about the potential effects of both the high dialysis dose and residual UOP above an oligoanuric level as is typically seen in children on CKRT. Clinical monitoring of free PIP concentrations may be warranted to better inform dosing in patients supported with CKRT, particularly given the discordance between dialysis dose and antibiotic elimination seen here. More frequent PIP dosing or prolonged or continuous infusions may be necessary to achieve stringent PD targets in this population, though more research is needed. Further analysis should be completed by using free PIP concentration data directly from critically ill pediatric patients receiving CKRT, including those with residual kidney function.

Article Information

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References

1. Teixeira JP, Neyra JA, Tolwani A. Continuous KRT: a contemporary review. *Clin J Am Soc Nephrol*. 2023;18(2):256–269.
2. Honore PM, Spapen HD. What a clinician should know about a renal replacement membrane? *J Transl Int Med*. 2018;6(2):62–65.
3. Hellman T, Uusalo P, Järvisalo MJ. Renal replacement techniques in septic shock. *Int J Mol Sci*. 2021;22(19):10238.
4. Stitt G, Dubinsky S, Edginton A, et al. Antimicrobial dosing recommendations in pediatric continuous renal replacement therapy: a critical appraisal of current evidence. *Front Pediatr*. 2022;10:1–8.
5. Schoonover LL, Occhipinti DJ, Rodvold KA, Danziger LH. Piperacillin/tazobactam: a new beta-lactam beta-lactamase inhibitor combination. *Ann Pharmacother*. 1995;29(5):501–514.
6. ZOSYN (piperacillin and tazobactam for injection, USP) [product information]. Philadelphia, PA: Pfizer; 2012. Accessed September 5, 2025. https://labeling.pfizer.com/ShowLabeling.aspx?id=502
7. Abdul-Aziz MH, Alffenaar JWC, Bassetti M, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper. *Intensive Care Med*. 2020;46(6):1127–1153.
8. Delattre IK, Taccone FS, Jacobs F, et al. Optimizing β-lactams treatment in critically-ill patients using pharmacokinetics/pharmacodynamics targets: are first conventional doses effective? *Expert Rev Anti Infect Ther*. 2017;15(7):677–688.
9. Selig DJ, DeLuca JP, Chung KK, et al. Pharmacokinetics of piperacillin and tazobactam in critically Ill patients treated with continuous kidney replacement therapy: a mini-review and population pharmacokinetic analysis. *J Clin Pharm Ther*. 2022;47(8):1091–1102.
10. Thy M, Urien S, Foissac F, et al. Piperacillin population pharmacokinetics and dosing regimen optimization in critically ill children receiving continuous renal replacement therapy. *Antimicrob Agents Chemother*. 2022;66(12):e0113522.
11. Butragueño-Laiseca L, Marco-Ariño N, Troconiz IF, et al. Population pharmacokinetics of piperacillin in critically ill children including those undergoing continuous kidney replacement therapy. *Clin Microbiol Infect*. 2022;28(9):1287.e9–1287.e15.
12. Tang Girdwood S, Arbough T, Dong M, et al. Molecular adsorbent recirculating system therapy with continuous renal replacement therapy enhanced clearance of piperacillin in a pediatric patient and led to failure to attain pharmacodynamic targets. *Pharmacotherapy*. 2020;40(10):1061–1068.
13. Morales Castro D, Dresser L, Granton J, Fan E. Pharmacokinetic alterations associated with critical illness. *Clin Pharmacokinet*. 2023;62(2):209–220.
14. Fuhrman DY, Gist KM, Akcan-Arikan A. Current practices in pediatric continuous kidney replacement therapy: a systematic review-guided multinational modified Delphi consensus study. *Pediatr Nephrol*. 2023;38(8):2817–2826.
15. Stone HK, VandenHeuvel K, Bondoc A, et al. Primary hyperoxaluria diagnosed after kidney transplant: a review of the literature and case report of aggressive renal replacement therapy and lumasiran to prevent allograft loss. *Am J Transplant*. 2021;21(12):4061–4067.
16. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med*. 2013;369(7):649–658.
17. Gang X, Liu F, Mao J. Lumasiran for primary hyperoxaluria type 1: what we have learned? *Front Pediatr*. 2023;10:1052625.
18. Macedo E, Mehta RL. Continuous dialysis therapies: core curriculum 2016. *Am J Kidney Dis*. 2016;68(4):645–657.
19. National Center for Biotechnology Information. PubChem Compound Summary for CID 71081, Oxalate. PubChem. 2024. Accessed August 5, 2024. https://pubchem.ncbi.nlm.nih.gov/compound/Oxalate
20. Tang Girdwood SC, Tang PH, Murphy ME, et al. Demonstrating feasibility of an opportunistic sampling approach for pharmacokinetic studies of β- lactam antibiotics in critically ill children. *J Clin Pharmacol*. 2021;61(4):565–573.
21. De Cock PAJG, van Dijkman SC, de Jaeger A, et al. Dose optimization of piperacillin/tazobactam in critically ill children. *J Antimicrob Chemother*. 2017;72(7):2002–2011.
22. US Food and Drug Administration. FDA rationale for piperacillin-tazobactam breakpoints for Enterobacterales. 2023. Accessed September 5, 2025. https://www.fda.gov/drugs/development-resources/fda-rationale-piperacillin-tazobactam-breakpoints-enterobacterales
23. Baxter. M60/M100/M150 AND ST60/ST100/ST150 sets with AN 69 membrane for CRRT powered by PrisMax and Prismaflex. 2020. Accessed September 5, 2025. www.baxter.com
24. Nehus EJ, Mouksassi S, Vinks AA, Goldstein S. Meropenem in children receiving continuous renal replacement therapy: clinical trial simulations using realistic covariates. *J Clin Pharmacol*. 2014;54(12):1421–1428.
25. Morales R, Mizuno T, Paice KM, et al. Impact of fluid balance on beta-lactam antibiotics target attainment: insights from a simulation-based meropenem study. *Int J Antimicrob Agents*. 2024;64(3):107267.
26. Westphal JF, Brogard JM, Caro-Sampara F, et al. Assessment of biliary excretion of piperacillin-tazobactam in humans. *Antimicrob Agents Chemother*. 1997;41(8):1636–1640.
27. Bulitta JB, Kinzig M, Jakob V, et al. Nonlinear pharmacokinetics of piperacillin in healthy volunteers–implications for optimal dosage regimens. *Br J Clin Pharmacol*. 2010;70(5):682–693.

JPPT | Case Report

Ertapenem Combined With Anti-*Staphylococcal* Beta-Lactam Therapy for the Treatment of Persistent *Staphylococcus Aureus* Bacteremia in a Child With Vertebral Osteomyelitis

Debbie-Ann Shirley, MD, MPH; Liliana Gutierrez, MD; Lisa Vuong, PharmD; and Shannon Moonah, MD, ScM

Staphylococcus aureus infection is one of the most common and serious infections that arises in children and is associated with high morbidity. *S. aureus* is the leading cause of acute hematogenous osteomyelitis in children. In the absence of concerns regarding resistance to methicillin, an anti-staphylococcal isoxazolyl penicillin, such as oxacillin or nafcillin, is the drug of choice for treatment of *S. aureus* osteomyelitis. However, first-generation cephalosporins, such as cefazolin, can also be used. There are limited antimicrobial options available for osteomyelitis and persistent or intermittent bacteremia when surgical intervention for source control is not indicated or feasible. Hence, there is a need to improve our knowledge of synergistic antimicrobial combinations to guide clinical practice and improve outcomes, particularly among children. We present the case of an 11-year-old child with persistence of acute hematogenous vertebral osteomyelitis with discitis and bacteremia, despite appropriate treatment with an anti-staphylococcal beta-lactam. Blood cultures were sterilized, and symptoms resolved after the addition of ertapenem 1 g daily for 7 days. To our knowledge, this is the first report of using ertapenem in combination with an anti-staphylococcal beta-lactam to specifically treat persistent methicillin-susceptible *S. aureus* (MSSA) vertebral osteomyelitis with bacteremia. Similar success has been reported using this combination to treat adults with persistent MSSA bacteremia and preterm low-birth-weight infants with late-onset neonatal sepsis; hence, our report provides further support for the benefit of this combination in staphylococcal infections.

ABBREVIATIONS MRI, magnetic resonance imaging; MSSA, Methicillin-sensitive *Staphylococcus aureus*; PBP, penicillin binding protein

KEYWORDS bacteremia; combination; ertapenem; pediatric; Staphylococcus

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Information Box

What specific question does this report address?

We describe clearance of methicillin-susceptible *Staphylococcus aureus* bacteremia in a child with hematogenous vertebral osteomyelitis and discitis using ertapenem combined with an anti-staphylococcal penicillin.

What does this report add to our current knowledge?

To our knowledge, this is the first report of using ertapenem combination therapy to treat a musculoskeletal infection with bacteremia in a child, further adding to the growing body of evidence supporting the benefits of this combination for staphylococcal infections.

Introduction

Staphylococcus aureus is the leading cause of osteomyelitis in children, accounting for more than three-fourths of infections.[1–3] Pediatric bone infections most commonly represent acute hematogenous infection. They can be associated with significant morbidity in this age group, resulting in potential sequelae, such as chronic infection, growth arrest, and pathologic fracture. Osteomyelitis is one of the most commonly implicated infections associated with either persistent bacteremia lasting 2 or more days or intermittently positive blood cultures.[4] Prolonged bacteremia, whether persistent or intermittent, requires prompt attention, as complications, such as septic emboli and metastatic infection, can arise if untreated. Each additional day of bacteremia in children, for example, is associated with 50% increased odds of bacteremia-related complications.[5] The mainstay of management in children with acute hematogenous osteomyelitis is antimicrobial therapy. Surgical debridement is additionally recommended for those with sepsis, rapidly progressive infection, or substantial abscess formation.[3]

Vertebral osteomyelitis is a less common form of bone infection in children compared with long bone involvement. It is also most likely to be caused by *S. aureus* infection when it does occur.[6] The mainstay of treatment is the administration of parenteral therapy or oral antibiotics that are highly bioavailable. Surgical intervention is usually reserved for those with progressive neurologic deficits, bone deformity, spinal instability, or persistent bacteremia despite appropriate antimicrobial management.[7]

The frequency of methicillin resistance among *S. aureus* bone infections varies widely by geographic location, but overall accounts for approximately one-third of cases by pooled reports. The first-line antibiotic choice for methicillin-susceptible *S. aureus* (MSSA) is an anti-staphylococcal penicillin, such as oxacillin or nafcillin; alternatively, a first-generation cephalosporin, such as cefazolin, can be used.[7] There are limited data on combination antimicrobial treatment options for patients with musculoskeletal infection and persistent *S. aureus* bacteremia, particularly in those who are not candidates for surgery.

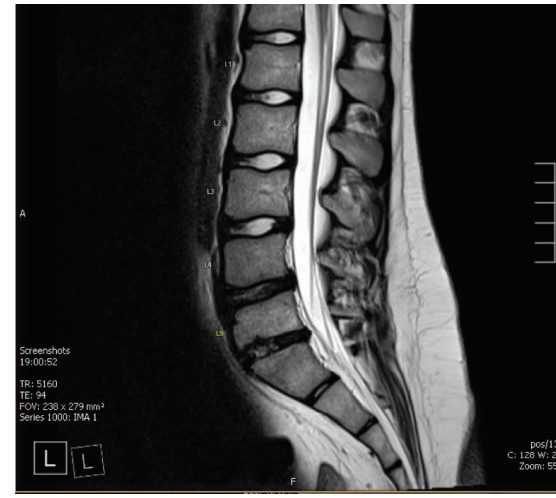
We report the case of a child with intermittent MSSA bacteremia and acute vertebral osteomyelitis with discitis successfully treated with a combination of oxacillin and ertapenem. To our knowledge, this is the first report of using ertapenem in combination with an anti-staphylococcal penicillin to clear intermittent bacteremia in a child with vertebral infection. Similar success has been reported using this combination in adult patients, however, to treat musculoskeletal infections.[8] This combination has also been used in low-birth-weight infants with persistent bacteremia.[9,10] Our report provides further support for the benefit of this combination for staphylococcal infections in children and summarizes pediatric cases reported to date.

Case

A previously healthy 11-year-old child presented to our hospital with a 3-day history of acute-onset back pain. On admission, vital signs revealed a fever of 39.3°C, tachycardia of 108 beats/min, and elevated blood pressure of 136/84 mm Hg with a normal respiratory rate of 20 breaths/min, oxygen saturations of 100% on room air, and admission weight of 65.9 kg. The physical examination was significant for point tenderness over the lumbar spine and paraspinal muscles, without overlying swelling or redness, and there was no focal neurologic deficit. Initial labs included mild leukocytosis of 12 × 10^9/L (8% bands and 51% neutrophils) with normal creatinine (0.6 mg/dL) and significantly elevated inflammatory markers (sedimentation rate >130 mm/hr and C-reactive protein 229 mg/L). Rhinovirus/enterovirus was detected by the respiratory pathogens multiplex molecular panel collected from the nasopharynx. Magnetic resonance imaging (MRI) of the thoracic and lumbar spine, done with and without contrast, revealed evidence of early vertebral osteomyelitis of the fifth lumbar vertebrae with surrounding discitis and associated small prevertebral fluid collection (Figure 1). The pediatric neurosurgery service was consulted, but no indication for surgical intervention was determined, given the lack of extension to the spinal canal or neural canals in the setting of an intact neurologic examination. The initial blood culture grew *S. aureus* after 18 hours of inoculation, and the *mecA/C* gene was not detected by rapid molecular diagnostic testing; therefore, the patient was started on 2 g of oxacillin administered intravenously every 4 hours.

The patient clinically improved with rapid defervescence and clearance of bacteremia the day after initiating antibiotic therapy. Oxacillin was adjusted to continuous intravenous infusion at 12 g/daily after insertion of a percutaneous intravenous central catheter, and the patient was discharged home after 6 days to complete a planned 6-week course of parenteral therapy. Therapeutic drug monitoring indicated this to be appropriate agent choice and dosing (Table 1 and Table 2); however, just before discharge, a repeat blood culture that was collected 4 days after starting antibiotic therapy became positive. As the patient was clinically improving, discharge home was still allowed, but the patient was readmitted 14 days after initiation of antibiotic therapy with the return of fever, chills, and

Figure 1. Initial magnetic resonance imaging of the lumbar and sacral spine, demonstrating early vertebral osteomyelitis and discitis.



Sagittal T2-weighted magnetic resonance image of the lumbar and sacral spine showing straightened lordotic curvature. There is preservation of vertebral body heights, but disc desiccation with disc space height loss is seen at L4-5 and L5-S1, associated with endplate contour irregularities and nodular contrast enhancement at the inferior endplate of L5. There is fatty stranding and phlegmonous changes in the prevertebral space at the level of L5. No intrinsic signal abnormality or abnormal enhancement of the spinal cord was noted.

Table 1. Antibiotic Susceptibility of *Staphylococcus Aureus* Initially Isolated From the Patient

a) Antibiotic Susceptibilities		
Antibiotic	**Minimal Inhibitory Concentration (mcg/mL)**	**Interpretation***
Ceftaroline	0.25	Susceptible
Ciprofloxacin	≤0.5	Susceptible
Clindamycin	0.25	Susceptible
Daptomycin	0.25	Susceptible
Erythromycin	≤0.25	Susceptible
Gentamicin	≤0.5	Susceptible
Levofloxacin	≤0.12	Susceptible
Linezolid	2	Susceptible
Minocycline	≤0.5	Susceptible
Moxifloxacin	≤0.25	Susceptible
Oxacillin	0.5	Susceptible
Penicillin	≥0.5	Resistant
Rifampin	≤0.5	Susceptible
Tetracycline	≤1	Susceptible
Trimethoprim/ sulfamethoxazole	≤10	Susceptible
Vancomycin	≤0.5	Susceptible

* Clinical and Laboratory Standards Institute Guidelines

Table 2. Therapeutic Drug Monitoring of Oxacillin 12 g IV q24 Hours Continuous Infusion With Therapeutic Goal of fCmin = 1 × MIC.

a) Oxacillin concentrations obtained during the first admission demonstrated patient was achieving pharmacokinetic target with fCmin = 1.2 × MIC		
Concentration 1	12.06 mcg/mL (**free drug 0.6 mcg/mL**)	Steady-state
Concentration 2	11.79 mcg/mL (**free drug 0.59 mcg/mL**)	Steady-state, drawn 6 hr after concentration 1
b) Oxacillin concentrations obtained on readmission with worsening infection demonstrated patient was still achieving pharmacokinetic target with fCmin = 1.3 × MIC		
Concentration 3	13.48 mcg/mL (**free drug 0.67 mcg/mL**)	Steady-state
Concentration 4	12.87 mcg/mL (**free drug 0.64 mcg/mL**)	Steady-state, drawn 3.5 hr after concentration 3

q, every; fCmin free minimum blood plasma concentration of oxacillin; MIC indicates minimal inhibitor concentration in milligrams per liter

Patient-specific pharmacokinetic parameters were not provided as they cannot be calculated while on a continuous infusion. Total and free oxacillin concentrations are provided for each measurement.

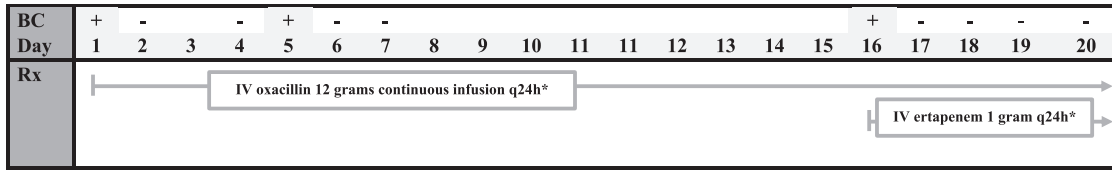
bacteremia. A repeat MRI showed the resolution of the prevertebral fluid collection, but 2 new phlegmons in the right anterior prevertebral soft tissue, posterior to the right common iliac vessels, along with extension of the osteomyelitis to the first sacral vertebrae and the L5-S2 disc spaces. No surgical intervention was again indicated after the surgical consultation. Susceptibility testing again showed oxacillin to be an appropriate choice. Oxacillin therapeutic drug monitoring was repeated, yielding similar results to the initial set of concentrations, confirming appropriate dosing (Table 2). Based on the good outcomes reported in published studies of combination therapy, intravenous ertapenem 1000 mg was administered every 24 hours for 7 days, followed by clinical improvement and clearance of bacteremia by the following day. The patient was subsequently allowed to return home (Figure 2).

In the ambulatory setting, the patient then developed a new rash along his waistline 3 weeks after discharge, with raised erythematous plaques, but no signs of angioedema, trouble swallowing, or respiratory symptoms. With concern for drug reaction, oxacillin was switched to cefazolin 6 g divided daily, given the low chance of cross-reactivity. His rash disappeared within 48 hours of the change. The patient was monitored closely with weekly blood counts, and routine chemistries, including tests for liver and renal function. No other adverse events emerged, and he tolerated the remainder of his therapy well. He completed 4 weeks of cefazolin, for a total of 8 weeks of parenteral antibiotic therapy, with resolution of clinical signs and normalization of inflammatory markers. A repeat MRI 3 months after completion of antibiotic therapy showed significant interval improvement. At 1 year of follow-up, the patient continued to do well with no further recurrences of bacteremia.

Discussion

We report the use of oxacillin combined with ertapenem to achieve clearance of MSSA bacteremia in a child with acute hematogenous vertebral osteomyelitis. Our case was treated with first-line isoxazolyl penicillin therapy for MSSA infection, using oxacillin. Cefazolin is an alternative, though the impact of the inoculum effect on cefazolin in persistent bacteremia

Figure 2. Timeline of initial antibiotic treatment and days of bacteremia.



*BC, blood culture; +. positive blood culture; -, negative blood culture; h, hours, q, every; Rx, treatment. *Treated with intravenous (IV) oxacillin × 4 weeks (Days 1–3 oxacillin: 2 g every 4 hr, then Day 3 onwards: oxacillin 12 g continuous infusion every 24 hr), switched to IV cefazolin on week 6 of therapy for 4 weeks due to rash, to complete 8 weeks of anti-staphylococcal beta-lactam therapy; treated with IV ertapenem for 7 days.*

remains to be determined. Despite an appropriate initial response based on in vitro susceptibility data and therapeutic oxacillin levels, his course was complicated by intermittent bacteremia, a return of fever, and the development of new areas of infection. He improved after the addition of ertapenem for a short interval, ultimately leading to a cure (Figure 2). Surgical intervention was not indicated, as no drainable collection was identified by imaging. When source control is not possible, medical management must rely solely on antimicrobial therapy. Combination therapy has been used to clear persistent bacteremia in such cases; however, data to guide optimal combinations and durations are sparse.[8,11–13] Checkerboard and time-kill assays using MSSA have demonstrated *in vitro* synergy when adding the penem antibacterial, ertapenem, to cefazolin or oxacillin.[11,14] The proposed synergistic mechanisms underlying dual beta-lactam combination therapy relate to either the saturation or complementary binding of penicillin-binding protein (PBP) sites, thereby inhibiting bacterial cell wall synthesis.[11] Complementary binding is observed in the preference of PBP-1 for ertapenem and PBP-2 for cefazolin. Similar to ertapenem, oxacillin also prefers PBP-1 but may also bind to PBP-2 and, to a lesser extent, PBP-3.[11,14,15] The proposed mechanisms for synergy in this combination could be complete saturation of PBP-1 or complementary binding of multiple PBPs. Potent *in vivo* activity against MSSA beyond that predicted *in vitro* has been shown in a rat model of endocarditis and mouse subcutaneous-infection model.[8,14] Reduction in the concentration of cefazolin required to eradicate *Staphylococcus* within biofilms and immunomodulatory effects through increased expression of interleukin-1b are other proposed mechanisms that may also contribute to the beneficial therapeutic effects of dual therapy noted in clinical reports.[16,17]

Our experience and review of successful outcomes in neonatal and adult literature provided the basis for trialing combination therapy in this case.[9,10,18,19] We previously reported on an encouraging observation using nafcillin plus ertapenem salvage combination therapy to clear persistent methicillin-susceptible *S. lugdunesnsis* bacteremia in a patient with infective endocarditis.[20] The decision to use dual combination beta-lactam therapy with an anti-staphylococcal agent and ertapenem was based on prior reports showing rapid clearance.[8,11–13] Our pediatric patient similarly experienced rapid clearance after the addition of ertapenem, with no further episodes of bacteremia, and the regimen was well tolerated. Similar successful outcomes have been noted in 3 neonatal reports.[9,10,18]*S. aureus* is a top cause of late-onset sepsis among infants receiving neonatal intensive care.[21] The risk of infection in the neonatal population increases inversely as gestational age and weight decrease, such that *S. aureus* accounts for 12% of episodes of late-onset sepsis episodes among infants born weighing less than 1000 g.[22] Mortality in this population is high, with fatality reported in 25% of infants under a birthweight of 1500 g infected with *S. aureus* meningitis or bacteremia.[23]

The first neonatal report of dual therapy describes a neonate born at 29 weeks, with persistent MSSA bacteremia for 9 days presumed to be secondary to umbilical catheter infection, treated initially with cefazolin monotherapy and bacteremia cleared within 1 day of adding ertapenem (Table 3).[9] In the second report, a preterm infant born at 27 weeks of gestation with a birthweight of 1105 g developed MSSA bacteremia presumed to be secondary to an infected umbilical catheter, followed by dissemination to the left finger. The infant was bacteremic for 6 days while being treated with oxacillin monotherapy and cleared within 1 day of adding ertapenem (Table 3).[10] Finally, the third report describes a case series of 3 premature low-birth-weight infants with persistent MSSA bacteremia, including a neonate with endocarditis and 2 with presumed catheter-related bloodstream infections, all initially being treated with cefazolin, and clearing within 3 days of the addition of ertapenem. Two infants survived, but 1 infant unfortunately experienced demise, though the reported cause of death was related to *Stenotrophomonas* sepsis, not MSSA infection.[18]

The risks of using antimicrobial combination therapy also bear consideration. Ertapenem has a favorable safety profile, particularly in comparison to other non–beta-lactam agents, such as vancomycin and gentamicin, which can be associated with nephrotoxicity.

Table 3. Patient Characteristics of Neonatal and Pediatric Patients with Persistent Methicillin-Susceptible *Staphylococcus Aureus* Bacteremia Treated With Dual Anti-Staphylococcal and Ertapenem Beta-Lactam Combination Therapy

Case (Ref)	Age	Comorbidity	Presumed Infection Source	Duration of Bacteremia Before Dual Beta-Lactams (Days)	Combination Intravenous Antibiotics	Duration of Bacteremia Post Dual Beta-Lactams (Days)	Duration of Ertapenem Combination Therapy (Days)	Clinical Outcome
Neonatal cases								
1[18]	5 d	Preterm 33 weeks gestation, 1539 g birthweight	Endocarditis	6	Ertapenem* and cefazolin	2	9	Survived without recurrence of bacteremia†
2[18]	23 d	Preterm 23 weeks gestation, 485 g birthweight	Catheter-related line infection	9	Ertapenem* and cefazolin	3	2‡	Demise on day 26 of life from *Stenotrophomonas maltophilia* sepsis
3[18]	9 d	Preterm 29 weeks gestation, 1510 g birthweight	Umbilical catheter infection	9	Ertapenem* and cefazolin	1§	14	Survived without recurrence of bacteremia
4[9]	9 d	Preterm 29 weeks gestation, 1510 g birthweight	Umbilical catheter infection	7	Ertapenem* and cefazolin¶	1	14	Survived without recurrence of bacteremia
5[10]	9 d	Preterm 27 weeks gestation, VLBW at 1105 g	Catheter related blood stream infection#	6	Ertapenem* and oxacillin	1	14	Survived without recurrence of bacteremia
Pediatric case								
6**	11 y	Previously healthy	Vertebral osteomyelitis	14††	Ertapenem‡‡ and oxacillin	1	7	Survived without recurrence of bacteremia

d, days old; y, years old; ref, reference

* 15 mg/kg IV q12h.
† Mitral valve was sterile at the time of valvuloplasty.
‡ Switched to meropenem for broader coverage after 2 days of ertapenem.
§ 30 hours.
¶ Was on nafcillin monotherapy prior to switching to dual combination therapy on day 8.
# Disseminated metastatic infection to left finger.
** our case
†† Intermittent bacteremia.
‡‡ 1000 mg/day.

Rifampin has traditionally been added to neonates with persistent *Staphylococcal* bacteremia, particularly those with coagulase-negative *Staphylococcus* or methicillin-resistant *S. aureus*.[24] The benefit of rifampin in other patient populations remains to be determined, and there are additional concerns related to drug-drug interactions and hepatotoxicity.[25] Hence, ertapenem holds promise as both a safe and effective choice for synergy with an anti-staphylococcal beta-lactam agent. However, clinical data are restricted to case series and case reports.[8–13,18,20] Comparator studies are still warranted to further inform clinical practice in children, including the optimal dosages and duration for dual therapy.

Conclusion

We report the case of a child being treated with oxacillin for acute MSSA vertebral osteomyelitis and intermittent bacteremia, experiencing clearance after the addition of ertapenem. This case adds to the pediatric experience of using this combination for salvage efforts.

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 are exempt from Institutional Review Board review at our institution. Given the nature of this study, informed consent was not required by our institution.

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References

1. Centers for Disease Control and Prevention. HAI pathogens and antimicrobial resistance report, 2018–2021. 2023. Accessed September 2, 2024 https://www.cdc.gov//nhsn/hai-report/index.html.
2. Yi J, Wood JB, Creech CB, et al. Clinical epidemiology and outcomes of pediatric musculoskeletal infections. *J Pediatr*. 2021;234:236–244.e232.
3. Woods CR, Bradley JS, Chatterjee A, et al. Clinical practice guideline by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: 2021 guideline on diagnosis and management of acute hematogenous osteomyelitis in pediatrics. *J Pediatric Infect Dis Soc*. 2021;10(8):801–844.
4. Cardenas-Comfort C, Kaplan SL, Vallejo JG, McNeil JC. Follow-up blood cultures in children with Staphylococcus aureus bacteremia. *Pediatrics*. 2020;146(6):e20201821.
5. Hamdy RF, Hsu AJ, Stockmann C, et al. Epidemiology of methicillin-resistant Staphylococcus aureus bacteremia in children. *Pediatrics*. 2017;139(6):e20170183.
6. Fernandez M, Carrol CL, Baker CJ. Discitis and vertebral osteomyelitis in children: an 18-year review. *Pediatrics*. 2000;105(6):1299–1304.
7. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis*. 2015;61(6):e26–e46.
8. Ulloa ER, Singh KV, Geriak M, et al. Cefazolin and ertapenem salvage therapy rapidly clears persistent methicillin-susceptible Staphylococcus aureus bacteremia. *Clin Infect Dis*. 2020;71(6):1413–1418.
9. Akers SM, Kinney K, Butcher MI, Moïse A. Clearance of persistent Staphylococcus aureus bacteremia in a preterm neonate with the use of combination cefazolin and ertapenem. *J Pediatr Pharmacol Ther*. 2020;25(6):547–551.
10. Hitchins M, O'Mara K, Edwards L, Bouchard J. Treatment of persistent methicillin-susceptible Staphylococcus aureus bacteremia and presumed osteomyelitis with oxacillin and ertapenem in a premature neonate. *Pharmacotherapy*. 2023;43(1):96–99.
11. El-Dalati S, Sridaran S, Uricchio M, et al. Oxacillin plus ertapenem combination therapy leads to rapid blood culture clearance and positive outcomes among patients with persistent MSSA bacteraemia: a case series. *JAC Antimicrob Resist*. 2021;3(3):dlab148.
12. Wilsey HA, Pisani B, O'Neill TJt. Oxacillin plus ertapenem rapidly clears persistent left ventricular assist device-related methicillin-susceptible Staphylococcus aureus bacteremia. *J Card Surg*. 2022;37(7):2127–2130.
13. Cardenas-Alvarez JL, Suarez J, Motoa G, et al. Cefazolin plus ertapenem and heart transplantation as salvage therapy for refractory LVAD infection due to methicillin-susceptible Staphylococcus aureus: a case series. *J Card Surg*. 2021;36(12):4786–4788.
14. Sakoulas G, Olson J, Yim J, et al. Cefazolin and ertapenem, a synergistic combination used to clear persistent Staphylococcus aureus bacteremia. *Antimicrob Agents Chemother.* 2016;60(11):6609–6618.
15. Dumitrescu O, Choudhury P, Boisset S, et al. Beta-lactams interfering with PBP1 induce Panton-Valentine leukocidin expression by triggering sarA and rot global regulators of Staphylococcus aureus. *Antimicrob Agents Chemother*. 2011;55(7):3261–3271
16. Gilbertie J, Ulloa ER, Daiker JC, et al. Potent activity of ertapenem plus cefazolin within staphylococcal biofilms: a contributing factor in the treatment of methicillin-susceptible Staphylococcus aureus endocarditis. *Open Forum Infect Dis*. 2022;9(5):ofac159.
17. Smelter D, Hayney M, Sakoulas G, Rose W. Is the success of cefazolin plus ertapenem in methicillin-susceptible Staphylococcus aureus bacteremia based on release of interleukin-1 beta? *Antimicrob Agents Chemother*. 2022;66(2):e0216621.
18. Hagmann SHF, Hodle T, Brennan M, et al. Cefazolin and carbapenem combination to treat persistent methicillin-sensitive Staphylococcus aureus bacteremia in preterm infants. *Pediatr Infect Dis J*. 2024;43(2):145–148.
19. Chastain DB, Covert KL, Tu PJ, et al. Therapeutic options for adult patients with persistent methicillin-susceptible Staphylococcus aureus bacteremia: a narrative review. *Ann Pharmacother*. 2023;57(11):1312–1327.
20. Sharma I, Hodges J, Moonah S, Shirley D-A. Clearance of persistent methicillin-susceptible Staphylococcus lugdunensis bacteremia using nafcillin plus ertapenem combination therapy. *Infect Dis Clin Pract*. 2023;31(4):1.
21. Kotloff KL, Shirley DT, Creech CB, et al. Mupirocin for Staphylococcus aureus decolonization of infants in neonatal intensive care units. *Pediatrics*. 2019;143(1):e20181565.

22. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002;110(2 Pt 1):285–291.
23. Shane AL, Hansen NI, Stoll BJ, et al. Methicillin-resistant and susceptible Staphylococcus aureus bacteremia and meningitis in preterm infants. *Pediatrics*. 2012;129(4):e914–e922.
24. Tan TQ, Mason EO, Jr., Ou CN, Kaplan SL. Use of intravenous rifampin in neonates with persistent staphylococcal bacteremia. *Antimicrob Agents Chemother*. 1993;37(11):2401–2406.
25. Thwaites GE, Scarborough M, Szubert A, et al. Adjunctive rifampicin for Staphylococcus aureus bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391(10121):668–678.

JPPT | Research Letter

Indicators of Antibiotic Use in Pediatric Care: A Prospective Observational Study

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ABBREVIATIONS DoT, days of therapy; DDD, defined daily dose

KEYWORDS antibiotics; infectious disease

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Misdiagnosis of infectious diseases has an impact on the health of the community, as well as the patients. This is because many infectious disorders are contagious. If they are disregarded or discovered too late, important steps to stop the spread of infectious agents may not be taken.[1]

A major inaccuracy in identifying an infectious illness occurs during the initial diagnosis, including the collection of a history and physical examination, recognizing urgency or complications, and testing.[2] One of the most misdiagnosed diseases is benign viral infections.[3]

Viral infections, particularly those of the upper respiratory tract infections, are frequently misdiagnosed as bacterial diseases, leading to unnecessary or ineffective antibiotic prescriptions.[4,5] While most respiratory tract infections in pediatrics are viral and self-limiting, there is substantial evidence that antibiotics are overused in treating respiratory disorders. Inappropriate antibiotic usage promotes the growth of resistant germs and exposes patients to unwanted side effects, which result in excessive expenses.[6]

Pediatric antimicrobial resistance is a growing global health threat, referring to the ability of bacteria, viruses, fungi, and parasites to resist the effects of antimicrobial drugs, thereby making infections more difficult to treat in children. While antibacterials can be highly effective in killing bacteria, their overuse or misuse can lead to bacterial resistance to multiple antibiotics.

To assess the use of antibiotics in the pediatric population, this study was conducted over a 6-month period from December 2022 to May 2023. Cases were collected from the pediatric inpatient departments until the day of discharge. Patients admitted to intensive care units and oncology departments were excluded from the study.

Data were collected using a well-structured electronic data collection form, which included patient demographics, infection type, prescribed antimicrobials, culture test results, patient medical and medication history, and interventions performed.

In this investigation, we examined the relationship between the antibiotics used and the days of consumption in pediatric inpatients. Categorical data were presented by number and percentage, and numerical data with mean ± SD. Univariate analysis of variance was the statistical tool used to identify the correlation between different factors. Type I error was determined as 5%, and a p value of < 0.05 was considered statistically significant.

Quantitatively assessing antibiotic consumption in pediatric patients based on using the recommended days of therapy (DoT) per 1000 Patient Days (PD), which will help to determine the number of antibiotics

Table 1. General Characteristics of Admitted Patients Aged Older Than 28 Days to 15 Years

Variable	Categories	Frequency
Total admissions		N = 185, %
Age*	Under 5	94, 50.8%
	Over 5	91, 49.2%
Patients treated with antibiotics†		n = 100, %
Sex	Male	56, 56%
	Female	44, 44%
Type of clinical diagnosis	Infectious disease	43, 43%
	Noninfectious disease	57, 57%
Age	Under 5	54, 54%
	Over 5	46, 46%
Length of hospital stay	≤5 days	41, 41%
	6–10 days	45, 45%
	> 10 days	14, 14%

* Age of patients categorized to under and above 5 years of age.
† Patients classified specifically based on receiving antibiotics.
‡ Clinical diagnosis classified based on infectious or noninfectious diagnosis.

Table 2. Antibiotics Used in Inpatients Aged Younger and Older Than 5 Years

Antibiotics	ATC Code*	DoT	DoT/1000 PD (Total PD = 1064)	Proportion of Patients Treated With the Antibiotic (n = 185, %)	Age	
					<5 yrs (n = 94, %)	≥5 yrs (n = 91, %)
Trimethoprim & Sulfamethoxazole	J01EE01	6	5.6	4, 2.1%	2, 2.1%	2, 2.1%
Ceftriaxone	J01DD04	283	265.9	55, 29.7%	32, 34.0%	23, 25.2%
Amoxicillin & Calvulanic	J01CR02	129	121.2	24, 12.9%	14, 14.8%	10, 10.9%
Azithromycin	J01FA10	51	47.9	10, 5.4%	8, 8.5%	2, 2.1%
Cefotaxime	J01DD01	72	67.6	16, 8.6%	8, 8.5%	8, 8.7%
Faropenem	J01DI03	7	6.5	2, 1.0%	1, 1.0%	1, 1.0%
Benzathine penicillin	J01CE08	2	1.8	2, 1.0%	0, 0	2, 2.1%
Doxycycline	J01AA02	16	15.0	2, 1.0%	1, 1.0%	1, 1.0%
Amikacin	J01GB06	39	36.6	7, 3.7%	4, 4.2	3, 3.2
Metronidazole	J01XD01	14	13.1	3, 1.6%	2, 2.1%	1, 1.0%
Amoxicillin	J01CA04	2	1.8	1, 0.5%	0, 0	1, 1.0%
Cefoperazone & Sulbactum	J01DD62	7	6.5	1, 0.5%	0, 0	1, 1.0%
Oxfloxacin	J01MA01	4	3.7	1, 0.5%	0, 0	1, 1.0%
Vancomycin	J01XA01	26	24.4	3, 1.6%	2, 2.1%	1, 1.0%
Ciprofloxacin	J01MA02	7	6.5	2, 1.0%	1, 1.0%	1, 1.0%
Piperacillin & Tazobactum	J01CR05	13	12.2	3, 1.6%	3, 3.1%	0, 0
Meropenem	J01BH02	19	17.8	3, 1.6%	2, 2.1%	1, 1.0%
Polymyxin B	A07AA05	3	2.8	1, 0.5%	0, 0	1, 1.0%
Clindamycin	J01FF01	7	6.5	1, 0.5%	1, 1.0%	0, 0
Aztreonam	J01DF01	7	6.5	1, 0.5%	0, 0	1, 1.0%
Cefexime	J01DD08	77	72.3	18, 9.7%	14, 14.8%	4, 4.3%

ATC, anatomical therapeutic chemical; DoT, days of therapy, PD, Patient Days

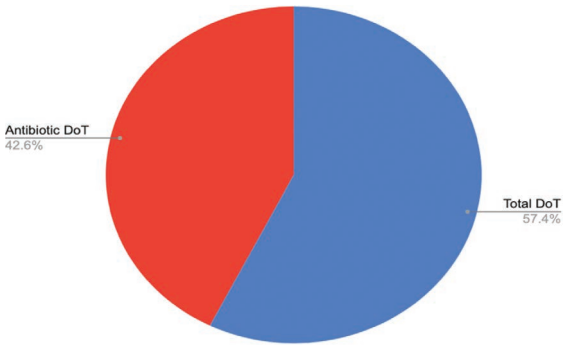
* The active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties.

used in the pediatric patients.[7] Because the defined daily dosage (DDD) is primarily meant for adults, it underestimates antibiotic intake in pediatrics due to weight variations. Pediatric-specific DDDs are lacking, and age-based dosing further complicates the applicability of DDDs in estimating antibiotic consumption accurately in the pediatric population. Therefore, we used DoT as an alternative for evaluating antibiotic usage density in pediatrics because it considers each drug and the number of days administered, allowing for independent contributions.[8]

A total of 185 individuals were accepted into the study, and 100 (54.1%) received at least 1 antibiotic (Table 1). Only 26% of patients receiving antibiotics underwent a microbiological culture test, whereas 74% of patients did not. Of the entire patient population, 52 (28.1%) had infectious disorders, while 133 (71.9%) had noninfectious ailments. Patients were administered antibiotics in such conditions, either suspecting that the underlying disease might lead to an infectious condition or thinking that an infectious condition can only lead to the current state of the patient's condition.

Within the group of patients on antibiotics, 43 of 100 (43%) were diagnosed with infectious diseases. Respiratory infections, such as pneumonia, bronchiolitis, and other upper and lower respiratory tract infections, were the most prevalent infections that were seen.

Figure 1. Distribution based on total days of treatment and days of treatment with antibiotics.



DoT, days of therapy.

Ceftriaxone, amoxicillin/clavulanic acid, cefixime, cefotaxime, and azithromycin were the 5 antibiotics that were the subject of the study (Table 2). With a DoT/1000 PD of 265.9, ceftriaxone had the highest consumption rate. Following that, the consumption rates for amoxicillin/clavulanic acid were 121.2 cefixime was 72.3, cefotaxime was 67.6, and azithromycin was 47.9 (Figure 1).

Our research found that 54.1% of the overall pediatric population received antibiotics. According to our study, ceftriaxone was the most frequently used antibiotic, with a DoT/1000 PD of 265.9 of 1064 total treatment days (accounting for 57.4% of total treatment time and antibiotic therapy consisted of 42.6% of the total DoT (Figure 2). This accounts for 29.7% of the total patients involved in the study, which serves as a warning to the healthcare profession about the increased use of third-generation cephalosporins, which may be a significant factor in the development of antimicrobial resistance in cephalosporins. A practice like this enables healthcare practitioners to optimize antibiotic therapy based on the precise identification of causative bacteria, supporting successful treatment and potentially minimizing antibiotic resistance problems.[9]

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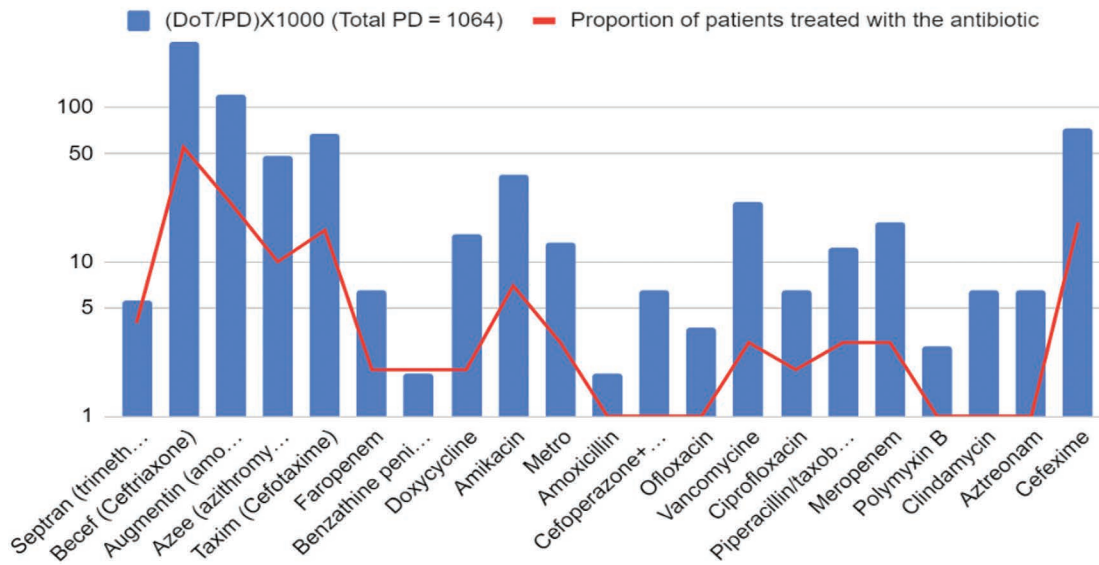
Figure 2. Distribution based on days of antibiotic therapy per 1000 patients to the proportion of patients treated with each antibiotic.



PD, Patient Days.

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References

1. Haddad M, Sheybani F, Naderi H, et al. Errors in diagnosing infectious diseases: a physician survey. *Front Med (Lausanne)*. 2021;8:779454.
2. Schiff GD, Hasan O, Kim S, et al. Diagnostic error in medicine: analysis of 583 physician-reported errors. *Arch Intern Med*. 2009;169(20):1881–1887.
3. Ely JW, Kaldjian LC, D'Alessandro DM. Diagnostic errors in primary care: lessons learned. *JABFM*. 2012;25(1):87–97.
4. Singh H, Schiff GD, Graber ML, et al. The global burden of diagnostic errors in primary care. *BMJ Qual Saf*. 2017;26(6):484–494.
5. Singh H, Thomas EJ, Wilson L, et al. Errors of diagnosis in pediatric practice: a multisite survey. *Pediatrics*. 2010;126(1):70–79.
6. Dekker ARJ, Verheij TJM, van der Velden AW. Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. *Fam Pract*. 2015:32(4):401–407.
7. Kreitmeyr K, von Both U, Pecar A, et al. Pediatric antibiotic stewardship: successful interventions to reduce broadspectrum antibiotic use on general pediatric wards. *Infection*. 2017;45(4):493–504.
8. Broyles MR. Impact of procalcitonin-guided antibiotic management on antibiotic exposure and outcomes: real-world evidence. *Open Forum Infect Dis*. 2017;4(4):ofx213.
9. Kizhakethil MM, Ranganathan JR, Gafoor TA, et al. Adverse drug reactions of antibiotics and it's management in a tertiary care hospital: a prospective observational study. *J Basic Pharmacol Toxicol*. 2020;4(1):10–15.

JPPT | Pediatric Pharmacy Association Position Paper Update

Continuing as Partners in Immunization: Updates to Practice and Legislation for Pediatric Pharmacy Immunizations

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ABBREVIATIONS CDC, Centers for Disease Control and Prevention

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Immunizations are an essential public health intervention for pediatric patients. Since the publication of the Pediatric Pharmacy Association's White Paper, Pharmacists as Partners in Pediatric Immunizations, in December 2024, many changes in state laws and federal processes have occurred.[1] In this paper, the members of the Pediatric Pharmacy Association's Immunizations Committee provide updated information and links to state resources to ensure that pediatric pharmacists and other healthcare providers understand some of the changes to provide the best care for their pediatric patients.

Pharmacists need to be familiar with state pharmacy practice laws, as these govern pharmacist immunization authority outside of the Public Readiness and Emergency Preparedness act. This act allows pharmacists to provide COVID-19 and influenza vaccines to children as young as 3 years old through December 2029.[2] The Table provides an update to the state specific pharmacist immunization regulation and adds information about state specific processes (eg, Centers for Disease Control and Prevention [CDC] schedule, follow state protocol, collaborative practice agreement) that pharmacists must follow to provide immunizations to children. It is important to note that all immunizations provided through the Vaccine for Children program must adhere to the CDC's immunization recommendations.[3] For additional evidence-based resources for the pharmacist, the American Academy of Pediatrics has released an independent 2025 immunization schedule and posted it as an open resource on their website.[4] Additionally, at the time of publication, it was noted that multiple states have announced changes to statewide pharmacist vaccine authority as it applies to COVID-19 vaccination.[5] As all states now provide pharmacists with some degree of immunization authority, and this area continues to expand, pharmacists must stay up to date on regulatory changes that impact their practice.

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References

1. Girotto JE, Klein KC, Cober MP, et al. Pharmacists as partners in pediatric immunizations: a white paper from the Pediatric Pharmacy Association. *J Pediatr Pharmacol Ther*. 2024;29(6):660–666.
2. Health and Human Services Department. 12th Amendment to Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19. 2024;89(238):99875–99883. Accessed June 20, 2025. https://www.federalregister.gov/documents/2024/12/11/2024-29108/12th-amendment-to-declaration-under-the-public-readiness-and-emergency-preparedness-act-for-medical#:~:text=The%20Public%20Readiness%20and%20Emergency%20Preparedness%20(PREP)%20Act%20authorizes%20the,relating%20to%2C%20or%20resulting%20from
3. National Center for Immunization and Respiratory Diseases (US) Immunization Services Division. Vaccine for Children (VFC) Program Operations Guide. 2024.

Table. Pharmacist Pediatric Immunization Authority and Regulation Resources

State*	Pharmacist Authorized to Provide at Least Some Immunizations to Persons <18 yr†	Pharmacist Authorized to Provide Immunizations Other Than COVID-19, Influenza, and/or Declared Emergency to Those as Young as 7 yr	Pharmacists Authorized to Provide Immunizations Other Than COVID-19 and/or Influenza as Young as 12 yr	Pharmacist Immunization CE Requirements	Requirements for Immunizing Pharmacists
Alabama	Yes	Yes	Yes	2 hr CE each cycle	ACIP
Alaska	Yes	Yes	Yes	1 hr CE annually	Independent prescribing
Arizona	Yes	Yes	Yes	2 hr CE each cycle	Per ACIP, Rx, or CPA
Arkansas	Yes	Yes	Yes	2 hr CE each cycle	Rx or CPA. Must participate in VFC, which requires following ACIP
California	Yes	Yes	Yes	1 hr CE each cycle	Rx or both FDA & ACIP
Colorado	Yes	Yes	Yes	—	Rx or CPA, needs to be per ACIP 2/3/2020
Connecticut	Yes	No	Yes	1 hr annually	On adult ACIP schedule, instructions on CDC website, or Rx. Must follow package insert or Rx
Delaware	Yes	Yes	Yes	2 hr CE each cycle	Rx or CPA
District of Columbia	Yes	Yes	Yes	2 hr CE each cycle	Rx or CPA either per ACIP or physician-patient relationship
Florida	Yes	No	No	3 hr CE each cycle (in addition to vaccines, must also include education on epinephrine)	CPA
Georgia	Yes	No	No	—	CPA
Hawaii	Yes	Yes	Yes	2 hr CE each cycle	ACIP
Idaho	Yes	Yes	Yes	1 hr CE annually	Independent prescribing
Illinois	Yes	Yes	Yes	2 hr CE each cycle	Rx or CPA
Indiana	Yes	No	Yes	—	State protocol, currently based on ACIP. If not on protocol can have Rx or CPA
Iowa	Yes	No	Yes, only final dose(s) HPV	1 hr CE each cycle	State protocol
Kansas	Yes	No	Yes	—	CPA

(Table cont. on page 693)

Table. Pharmacist Pediatric Immunization Authority and Regulation Resources *(cont.)*

State*	Pharmacist Authorized to Provide at Least Some Immunizations to Persons <18 yr†	Pharmacist Authorized to Provide Immunizations Other Than COVID-19, Influenza, and/or Declared Emergency to Those as Young as 7 yr	Pharmacists Authorized to Provide Immunizations Other Than COVID-19 and/or Influenza as Young as 12 yr	Pharmacist Immunization CE Requirements	Requirements for Immunizing Pharmacists
Kentucky	Yes	Yes	Yes	—	CPA, or in emergencies statewide protocol
Louisiana	Yes	No	Yes, but only at age 17+ yr	1 hr CE each yr	ACIP
Maine	Yes	Yes	Yes	2 hr CE each year on drug administration	Influenza based on rules of board, others based on ACIP
Maryland	Yes	Yes	Yes	2 hr CE per cycle	CPA that follows ACIP or FDA
Massachusetts	Yes	Yes	Yes	1 hr CE each yr	ACIP
Michigan	Yes	Yes	Yes	—	ACIP
Minnesota	Yes	Yes	Yes	—	ACIP
Mississippi	Yes	No	Yes	—	CPA
Missouri	Yes	Yes	Yes	2 hs per cycle	CPA
Montana	Yes	Yes	Yes	—	Independent prescribing – influenza; CPA that follows ACIP others
Nebraska	Yes	Yes	Yes	—	CPA
Nevada	Yes	Yes	Yes	2 hr CE each year or a course provided by the CDC	CPA
New Hampshire	Yes	No	No	—	Independent prescribing
New Jersey	Yes	No	No	2 hr CE each cycle	Rx or CPA
New Mexico	Yes	Yes	Yes	2 hr CE every cycle	State protocol that currently follows ACIP
New York	Yes	No	No	—	Rx or CPA
North Carolina	Yes	Yes	Yes	3 hr CE every cycle	ACIP for COVID & Influenza; others by Rx if follows ACIP
North Dakota	Yes	Yes	Yes	—	Statewide protocol that currently follows ACIP
Ohio	Yes	Yes	Yes	—	CPA

(Table cont. on page 694)

Table. Pharmacist Pediatric Immunization Authority and Regulation Resources *(cont.)*

State*	Pharmacist Authorized to Provide at Least Some Immunizations to Persons <18 yr†	Pharmacist Authorized to Provide Immunizations Other Than COVID-19, Influenza, and/or Declared Emergency to Those as Young as 7 yr	Pharmacists Authorized to Provide Immunizations Other Than COVID-19 and/or Influenza as Young as 12 yr	Pharmacist Immunization CE Requirements	Requirements for Immunizing Pharmacists
Oklahoma	Yes	Yes	Yes	2 hr CE per cycle	Pharmacists based on FDA approval or RX, but technicians must follow ACIP
Oregon	Yes	Yes	Yes	—	Rx, CPA, or statewide protocol. Statewide protocol currently references ACIP, but is made individually for each immunization
Pennsylvania	Yes	No	No	2 hr CE per cycle	CPA or Rx
Rhode Island	Yes	No	No	1 hr CE each yr	CPA or RX in line with manufacturers guidance, ACIP or AAP
South Carolina	Yes	Yes	Yes	1 hr CE each yr	Statewide protocol that currently states to ensure dosing is in line with labeling and ACIP
South Dakota	Yes	Yes	Yes	—	Rx or CPA
Tennessee	Yes	Yes	Yes	—	Independent prescribing for COVID & influenza; others per CPA
Texas	Yes	Yes	Yes	3 hr CE per cycle	CPA
Utah	Yes	Yes	Yes	2 hr CE per cycle	Statewide protocol which currently follows ACIP
Vermont	Yes	No	No	2 hr CE per cycle	Independent prescribing
Virginia	Yes	Yes	Yes	—	Statewide protocol that currently follows ACIP
Washington	Yes	Yes	Yes	—	CPA
West Virginia	Yes	Yes	Yes	2 hr CE each yr	ACIP
Wisconsin	Yes	Yes	Yes	—	Rx or ACIP
Wyoming	Yes	Yes	Yes	1 hr CE each yr	Manufacturers labeling

ACIP, Recommended by the Advisory Committee for Immunization Practices; CDC, Centers for Disease Control and Prevention; CE, continuing education; CPA, collaborative practice agreement; FDA, approved by the Food and Drug Administration; HPV, human papillomavirus vaccine; Rx, by prescription, VFC, Vaccines for Children

* Each state name is a hyperlink to state specific regulations. Links last updated June 27, 2025

† Includes states that only authorize pharmacists to provide 1 or 2 immunizations to this age group, such as COVID-19 or influenza.

Accessed June 20, 2025. https://www.cdc.gov/vaccines-for-children/media/pdfs/2024/08/vfc-ops-guide_version-4.0_july-2024_low-res-508-rev-2.pdf#page=10&zoom=100,46,746

4. American Academy of Pediatrics, Committee on Infectious Diseases. Immunization schedules. In: Kimberlin DW, Banerjee R, eds. *Red Book: Report of the Committee on Infectious Diseases 2024–2027*. Washington, DC: AAP; 2025. Accessed August 20, 2025 . https://publications.aap.org/redbook/resources/15585/AAP-Immunization-Schedule?autologincheck=redirected
5. Huang P. Concerned about federal vaccine policies, states are crafting their own. *NPR* Shots Health News, Accessed September 6, 2025. www.npr.org/sections/shots-health-news/2025/09/06/nx-s1-5532121/states-vaccine-guidance-washington-oregon-new-mexico.

JPPT | Commentary

A Structured Approach to Identifying and Addressing Drug Therapy Problems in Neonatal and Pediatric Critically Ill Patients: IN-DEPTH

Braydon Moore, PharmD; Peter N. Johnson, PharmD; and Jamie Miller, PharmD

Pharmacy students, residents, and new practitioners may feel overwhelmed with patients in the pediatric critical care setting due to the disease states, variation in acuity based on patient factors, and complex medication regimens. The FASTHUG MAIDENS mnemonic is a standardized and validated tool that was developed in 2011 for pharmacists to use when evaluating critically ill adult patients. However, there are no studies evaluating the use of this tool in pediatric critical care setting. This article aims to provide trainees and new practitioners with a new and distinct mnemonic tool, IN-DEPTH, to use when evaluating critically ill pediatric patients and identifying areas for treatment optimization. In addition, this article will provide rationale and examples to enhance the user's understanding of the components and subcomponents of the mnemonic. Ultimately, the goal of the IN-DEPTH mnemonic is to help provide some structure for pharmacy trainees or new practitioners that are less experienced with critical or pediatric care and provide the opportunity to have a meaningful impact in the care of critically ill pediatric patients.

ABBREVIATIONS AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices; APPE, advanced pharmacy practice experience; CICU, cardiac intensive care unit; eGFR, estimated glomerular filtration rate; EMR, electronic medical record; GT, gastrostomy tube; IV, intravenous; IVIG, intravenous immunoglobulin; IWS, iatrogenic withdrawal syndrome; NG, nasogastric; NICU, neonatal intensive care unit; NPO, *nil per os*; PANDEM, prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility; PICU, pediatric intensive care unit; PO, *per os*; RSV, respiratory syncytial virus; TOF, train of four; TPT, transpyloric tube

KEYWORDS critical care; drug-related problems; neonate; pediatrics

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Introduction

Pharmacy practice in pediatric critical care is intricate because of the vast range of patient ages and disease states, variation in acuity based on patient factors, and the complexity of medication regimens. Most students in Doctor of Pharmacy programs lack sufficient didactic or experiential exposure to pediatric pharmacy. Prescott et al[1] noted that Doctor of Pharmacy students only receive on average 21.9 hours of didactic content in the curriculum focused on pediatric patients, and that only 20% of Doctor of Pharmacy students took at least 1 advanced pharmacy practice experience (APPE) rotations. Additionally, Doctor of Pharmacy students also have limited exposure to some of the critical care disease states that may be seen in children and adults.[2] Pharmacy students, residents, and new practitioners are likely to feel overwhelmed when entering a rotation or new position in the pediatric critical care setting like the pediatric intensive care unit (ICU) (PICU), neonatal ICU (NICU), or the cardiac ICU (CICU).

Given the limited experience of pharmacy students and residents with both pediatrics and critical care, trainees and new practitioners may struggle with identifying a systematic way to identify and address drug therapy problems. There is a standardized and validated mnemonic tool, FASTHUG MAIDENS (Feeding; Analgesia; Sedation; Thromboembolic prophylaxis; Head of bed elevation; stress Ulcer prophylaxis; Glucose control; Medication reconciliation; Antibiotics/anti-infectives; Indications for medications; Dosing; Electrolytes, hematology, and other laboratory tests; No drug interactions, allergies duplication, or side effects; and Stop dates), that was developed in 2011 for pharmacists to use when evaluating critically ill adult patients.[3] Its purpose is to aid trainees and new practitioners in identifying drug-related problems in adult ICUs. The FASTHUG MAIDENS mnemonic could be

applied to pediatric patients. However, the guidance provided along with this tool lacks a comprehensive application to critically ill neonatal and pediatric patients due to additional information needed to assess drug therapy problems (e.g., weight-based dosing, dosage forms, parenteral and enteral nutrition considerations). In addition to this, not all components of the FASTHUG MAIDENS tool are relevant to pediatric patients. For example, the use of thromboembolic prophylaxis in all hospitalized pediatric patients is not routinely recommended whereas, this is a common practice in most hospitalized adult patients. To our knowledge, only one group adapted the FASTHUG BID (Bowel, Indwelling catheter, and Drug de-escalation) mnemonic for application to pediatric critical care, but it is important to note that no studies have explored the application of this mnemonic with pediatric critical care trainees.[4] Our goal was to develop an adapted mnemonic tool, IN-DEPTH, to assist pharmacy trainees and new practitioners in evaluating critically ill pediatric patients and identifying areas for treatment optimization (Table). This proposed tool could be applied to patients in the PICU, NICU, and/or CICU.

Description of IN-DEPTH components

I – Indications for Medications. There are 2 subcomponents to the "I" in IN-DEPTH. The first is matching indications to medications. Trainees and new practitioners should review the medication list and match each medication to an indication from the active problem list and/or past medical history. An assessment should then be made to determine if deprescribing or initiating new therapy is warranted.

The second subcomponent is performing a medication reconciliation upon transitions of care. Transitions of care can occur upon admission (either from a different facility or home), moving between units in the same institution, and upon discharge (to another facility or home). During the medication reconciliation process, allergies, medications prior to arrival (e.g., dose, route of administration, dosage form), and availability of those medications on the health-system's formulary should be assessed. An example of using this section cohesively is discontinuing acid suppression agents that were initiated in the PICU in a mechanically ventilated pediatric patient for stress ulcer prophylaxis upon transition to a general medicine floor. The acid suppression therapy would no longer have an indication and could be discontinued during a transition medication reconciliation. Another example would be when a clonidine extemporaneous oral suspension is continued from home, and the dose obtained upon medication reconciliation is mL/dose rather than mcg/dose. In this case, the trainee or new pharmacist should obtain the concentration of the clonidine extemporaneous oral suspension received prior to admission, and if this is different than the health-system's formulary extemporaneous oral suspension they would need to determine the mcg/dose that should be ordered.

N – Nutrition. Nutrition requires a large focus in the pediatric critical care arena. As such, there are 3 subcomponents to the "N" section of the mnemonic. The first component is review of enteral nutrition. It is important to determine the diet status such as *nil per os* (NPO), liquids only, or solid foods as tolerated. For infants, the type of enteral liquid feeds (i.e., human milk, formula) should be identified as this could result in the need for additional supplementation of vitamins or iron for some patients receiving human milk. Another consideration would be the route of administration of these enteral feeds such as *per os* (PO) or via a feeding tube [e.g., nasogastric (NG), transpyloric tube (TPT), or gastrostomy tube (GT)]. Trainees and new practitioners should assess the volume and frequency of enteral feeds. This information is important to determine when medication therapy can be switched from intravenous (IV) to enteral routes if the patient is tolerating the enteral nutrition goals for the patient.

The second component is consideration of parenteral nutrition. If enteral nutrition is not an option, the threshold to initiate parenteral nutrition would be dependent upon the age and nutritional status of the patient. If parenteral nutrition is initiated, it is important to identify fluid goals and determine if the patient has central or peripheral IV access, as this would determine the maximum amount of macronutrients (e.g., amino acids and dextrose) added as well as other micronutrients (e.g., potassium). In addition, trainees and new practitioners should assess the concentration of other continuous IV infusions to optimize the volume provided from these medications. This would allow for most of the total fluid goal to be provided with parenteral nutrition to maximize the macronutrient kilocalories for the patient. For more detailed discussion of considerations for enteral and parenteral nutrition in children, trainees may need to be referred to other references for greater understanding.[5]

The third subcomponent with nutrition management is consideration of nutrition monitoring parameters (e.g., glycemic status, electrolytes, triglycerides, alkaline phosphatase, or weight changes). More frequent monitoring of electrolytes and triglycerides may be needed with parenteral nutrition, specifically after adjustments in the formulation are made. It is also important to assess if any medications on the patient's medication list will alter serum electrolyte concentrations and could be anticipated, prevented, or corrected with adjustments in the parenteral nutrition formulation or addition of enteral electrolyte supplements. At the time of initiation of enteral or parenteral nutrition, risk factors for development of re-feeding syndrome should be assessed (e.g., history of eating disorder, recent large weight loss, cachexia) and a more conservative nutrition plan

Table. The Components of the IN-DEPTH Tool

Letter	Definition	Subcomponent	Description
I	Indications for medications	Matching indications to medications	• Identify problem list • Match medications with each problem • Determine appropriateness of medications • Assess for de-prescribing opportunities • Initiate medications for untreated or partially treated problems/conditions
		Perform medication reconciliation upon transitions of care	• Assess patient allergies • Identify medications and indications for use at each transition of care (e.g., dosage form, dosage regimen, concentration of oral liquids)
N	Nutrition	Assess enteral nutrition	• Determine diet status (NPO, clear liquids, solid foods) • Identify type of enteral feeds (formula, human milk) • Assess route of feeding (PO, NG/OG, TPT, GT) and method of delivery if applicable (continuous versus bolus) • Identify volume and frequency of enteral feeds • Assess for ability to change IV medications to PO if tolerating enteral feeds
		Assess parenteral nutrition	• Identify type of intravenous line access (i.e., central versus peripheral) • Identify patient's fluid goal and amount of fluid available for parenteral nutrition • Assess concentrations of other fluids to maximize fluids available for parenteral nutrition
		Monitor nutrition parameters	*Enteral and parenteral nutrition*: • Assess for hypo- and hyper-glycemia • Assess if medications affecting electrolytes would be added or discontinued • Assess for re-feeding syndrome when initiating nutrition with malnourished patients *Parenteral nutrition*: • Assess electrolyte changes to determine adjustments to parenteral nutrition • Periodic monitoring of parenteral nutrition labs (phosphorus, magnesium, triglycerides, direct bilirubin)
D	Dosing, dosage form, and drug interactions	Assess dosage regimen appropriateness	• Check appropriateness of dosing based on age, weight, body surface area for indication • Ensure dosing does not exceed maximum adult dose or pediatric dose for patients ≥40 kg • Determine need for hepatic and/or renal adjustment Evaluate the planned duration for non-anti-infectives if applicable
		Assess for dosage form appropriateness	• Assess availability/measurability of medications (i.e., measurable doses) • Determine appropriateness of dosage form
		Screen for drug interactions	• Assess for drug-disease interactions • Assess for drug-drug interactions • Assess for appropriateness of a medication based on age (KIDs list[7]) • Assess for drug-food interactions (e.g., warfarin, levothyroxine)

(Table cont. on page 699)

Table. The Components of the IN-DEPTH Tool *(cont.)*

Letter	Definition	Subcomponent	Description
E	Electrolytes, labs, vital signs, and ins & outs	Review laboratory findings	• Review pertinent labs based on medication list • Determine if laboratory monitoring is necessary • Assess if changes to medications are needed based on labs
		Assess vital signs	• Review vital signs based on medication list • Assess if changes to medications are needed based on vital signs
		Review inputs and outputs	• Determine appropriateness of intravenous maintenance fluids • Identify impact of hidden fluids (volume, type of fluid, need for continuation) • Evaluate outputs (chest tube output, ostomy output, urine output, and stools) • Assess if changes to medications are needed based on inputs and outputs
P	Pain, sedation, neuromuscular blockage, delirium, withdrawal	Pain/sedation (analgosedation)	• Assess pain and sedation scores • Determine need for adjustment in analgosedation based on pain/sedation scores, laboratory and vital sign changes, and other pertinent patient factors
		Neuromuscular blockade	• Determine if pain and sedation are adequately managed • Asses for train of four monitoring (TOF) for depth of paralysis • Ensure patient on appropriate scheduled eye care to prevent corneal abrasions
		Delirium	• Assess delirium scores • Utilize BRAIN MAPs to determine contributing factors for delirium
		Withdrawal	• Assess iatrogenic withdrawal or neonatal withdrawal scores • Identify use of PRN opioids/benzodiazepines to determine need for initiation or adjustment of therapy
T	Time of anti-infective agents	Evaluate cultures and susceptibilities	• Identify if cultures obtained • Follow-up on cultures for reporting of susceptibilities
		Assess for escalation or de-escalation opportunities	• Track number of anti-infective days • Determine if appropriate to de-escalate or initiate anti-infectives based on culture and susceptibilities or clinical response • Ensure stop dates for anti-infectives are added

(Table cont. on page 700)

be developed if at risk.[6] Specific electrolytes to monitor for refeeding syndrome include potassium, magnesium, and phosphorus.

D – Dosing, Dosage Form, and Drug Interactions. The "D" in IN-DEPTH has 3 subcomponents. The first component is to assess the dosing regimen appropriateness. There are several factors to consider with evaluating dosing regimens in pediatric patients. The main 2 factors to check when assessing medication regimen appropriateness in a pediatric patient are age and weight. A vast majority of medications are dosed by age, weight, or a combination of those 2 factors. For neonates and young infants who are growing rapidly, the dose may need to be weight adjusted weekly or every 2 weeks to ensure that weight-based dosing remains in therapeutic range. Another common example would be ensuring weight-based dosing does not exceed maximum adult dosing

Table. The Components of the IN-DEPTH Tool *(cont.)*

Letter	Definition	Subcomponent	Description
H	Hospital prophylaxis	Assess immunization status	• Review CDC recommendations and determine if immunizations are up to date or needed during admission • Determine if adjustment in CDC recommended immunization schedule is needed based on medications received and/or disease states • Assess need for RSV prophylaxis
		Ensure appropriate stress ulcer prophylaxis	• Determine appropriateness of stress ulcer prophylaxis • Ensure de-prescribing occurs upon transitions of care (if needed)
		Venous thromboembolism prophylaxis	• Assess need for VTE prophylaxis • Ensure de-prescribing occurs upon transitions of care (if needed)
		Anti-infective prophylaxis	• Determine need for antibiotic prophylaxis • Ensure anti-infective prophylaxis is discontinued if broad spectrum anti-infectives are initiated for treatment of infection
		Bowel regimen	• Determine need for bowel regimen • Screen for medications that could be associated with constipation or diarrhea

CDC, Centers for Disease Control and Prevention; GT, gastrostomy tube; IV, intravenous; NG, nasogastric; OG, orogastric, RSV, respiratory syncytial virus; TPT, transpyloric tube; VTE, venous thromboembolism

with children weighing ≥40 kg.[7] An additional consideration is that some medications like antiarrhythmics (e.g., flecainide, sotalol), hydrocortisone, and chemotherapy (e.g., vincristine) are dosed based on body surface area. Finally for this subcomponent, medications that have need for hepatic and/or renal dosing adjustments should be identified and assessed. Assessing renal function in pediatric patients differs from adults due to rapid changes in glomerular function and muscle composition. Thus, specific equations are needed when calculating estimated glomerular filtration rate (eGFR) in pediatric patients.[8] There are 2 equations, Schwartz and Bedside Schwartz, which should be utilized based on the age of the patient. The Bedside Schwartz can be used in patients between the ages of 1 to 18 years old. However, it is important to note that it has not been validated in children <1 year of age. Despite this, some institutions may utilize the Bedside Schwartz equation in infants <1 year of age to maintain consistent applications for providers and pharmacists across the continuum of care. Trainees and new practitioners should refer to the preference of their facility as to the preferred method of renal assessment in infants <1 year of age. The final consideration for evaluating the appropriateness of a dosage regimen is to ensure the planned duration of therapy is appropriate for non-maintenance medications. For example, trainees and new practitioners would want to ensure that patients with asthma exacerbations who require systemic corticosteroids have an appropriate stop date for the medication order based on their clinical condition. Another class that duration of therapy is important is anti-infective therapy; this will be discussed in more detail in the "T" section below.

A second subcomponent would be the consideration of dosage forms. Trainees and new practitioners should ensure that all infants and children who are prescribed an oral suspension/solution should have a measurable dose. Though different definitions of measurable doses have been utilized, a measurable dose would be 0.01 mL/dose for <1 mL oral syringe, 0.1 mL/dose for a 1- to 3-mL oral syringe, and 0.2 mL/dose for >3- to 10-mL oral syringe.[9] There are also age and weights that can trigger additional dosing regimen considerations. Although variable and patient-specific, it has been shown that 91% of children between the ages of 6 to 11 years of age can be trained to swallow a tablet or capsule.[10] Therefore, in patients ≥6 years of age, an assessment should be made to determine if an oral tablet or capsule could be utilized in place of oral suspension/solution. This could specifically be beneficial when the medication taste is undesirable, or a significant volume of oral liquid is required for the dose.

The third subcomponent to the "D" in IN-DEPTH is to screen for drug interactions, and these include drug-dug, drug-disease, and drug-food interactions.

Drug-drug interactions are perhaps the most straightforward of the 3. Drugs on the medication list should be screened against each other for known interactions or contraindications. If needed, a drug interaction screening tool can be utilized. Drug-disease interactions should be reviewed to identify medications that should be avoided because they could affect response to therapy (e.g., beta blockers in a patient with asthma) or could exacerbate signs or symptoms of a disease (e.g., acetaminophen in a patient with elevated hepatic enzymes). Although not specifically a drug-disease interaction, an additional factor to consider in this section for pediatric patients is the appropriateness of use of an agent based on age of the patient (e.g., valproic acid in children <2 years). The most concise and comprehensive reference of medications to avoid or use with caution in neonates, infants and children is the Key Potentially Inappropriate Drugs in Pediatrics (KIDs) list.[11] Drug-food interactions could include medications whose efficacy is affected by consistency in the foods consumed (e.g., warfarin and vitamin K) or medications that bind to multivalent cations (e.g., tetracyclines or fluoroquinolones). The consideration for agents that interact with multivalent cations may be most important to screen in pediatric patients that are on a human milk or formula-based diet due to high calcium content of milk-based products. Another example of a type of drug-food interaction would be agents that are administered on an empty stomach (e.g., levothyroxine). This may be more difficult to achieve in neonates due to their frequent feeding schedule (i.e., every 3–4 hours), but the suggestion can be made to administer between feedings and at the same time daily.

E – Electrolytes, Labs, Vital Signs, and Ins & Outs. There are 3 subcomponents to the "E" in IN-DEPTH. The first component is to review electrolytes and other laboratory findings. Pertinent laboratory findings should be identified and reviewed based on the medication list. For example, if a patient is receiving diuretics, it would be prudent to monitor serum sodium, potassium, and chloride concentrations. It is helpful to develop a list of medications that are associated with significant alterations in serum electrolytes (e.g., amphotericin can cause hypomagnesemia and hypokalemia, and oxcarbazepine and vasopressin can cause hyponatremia). Other laboratory values may need to be trended over time based on the medications being administered. For example, if the patient is receiving antimicrobials, then periodic monitoring of white blood cell count, C-reactive protein, or procalcitonin may be needed. In addition, therapeutic drug monitoring may be required for some medications including vancomycin, aminoglycosides, voriconazole, or phenobarbital. Laboratory values may be different based on patient age. For example, the normal range for serum bicarbonate in infants is lower than older pediatric patients due to inability for infants to reabsorb bicarbonate in the proximal tubule in the kidney.[12] In addition, the serum phosphorus range for neonates and infants is generally higher than older pediatric patients as neonates and infants need higher phosphorus concentrations for bone development.[9] The laboratory values outside the normal ranges based on age may or may not be flagged in the electronic medical record. Some health-system's electronic medical records (EMR) have age-specific normal ranges reported for certain labs. However, some health-system's EMRs do not provide these age-specific normal ranges, requiring health care professionals to interpret results based on the age of the patient. In addition to this, trainees and new practitioners should also evaluate trends in laboratory values over time.

The second subcomponent is consideration of vital signs. However, the vital signs in pediatric patients differ compared to adolescents or adults; as a result, other references should be utilized when making therapy management decisions based on vital signs.[8] Some vital signs that may be important to consider in relation to medication therapy could include avoiding enteral administration of medications or nutrition if tachypneic, review of as needed ibuprofen or acetaminophen use when monitoring temperature, or consideration of agents that could increase (e.g., corticosteroids) or decrease (e.g., opioids) blood pressure or increase (e.g., albuterol) or decrease (e.g., opioids) heart rate.

The last subcomponent of the "E" is to review input and output of fluid. The inputs to consider include maintenance or bolus fluids, fluid from IV medication administration, and nutrition. At this step the appropriateness of IV maintenance fluids should be determined using any validated method such as the Holiday-Segar method.[12] The impact of hidden fluids such as volume needed to administer intermittent medications, flushes of lines, or carrier fluids should also be identified to determine if adjustment in maintenance fluid rate is needed. The outputs to consider include urine, stool, chest tube, and ostomy output. If these outputs are substantial, then a decision may be made to initiate replacement fluids for continued losses. The type of replacement fluid is dependent upon the source of output. For example, chest tube output is rich in protein, so replacement with albumin may be considered. Or, if the patient has severe emesis, a chloride-rich fluid may be selected versus if they have severe diarrhea, a bicarbonate rich fluid may be selected. In addition to assessing if replacement fluids are needed, it is also important to evaluate if any medication is contributing to increased inputs or decreased outputs.

P – Pain, Sedation, Neuromuscular Blockage, Delirium, Withdrawal. There are 4 subcomponents to the "P" in IN-DEPTH, the first of which is analgosedation. The first subcomponent is pain and sedation. They go hand in hand and should be assessed in tandem using their respective scoring tools. The 2022 Society

of Critical Care Medicine's Clinical Practice Guidelines on the prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility (PANDEM) provide recommendations for the assessment and management of pain, sedation, neuromuscular blockade, delirium, and iatrogenic withdrawal syndrome (IWS). They suggested validated assessment tools for assessment of pain that vary based on the age of the patient and the ability to communicate.[13] In addition, the PANDEM guidelines provide recommendations on validated sedation scores for nursing assessment. Trainees and new practitioners should work with their preceptors or mentors to identify the scoring tools utilized and familiarize themselves with the scoring range, as there is variation on the sedation scoring tools. To assess if a patient is receiving adequate analgesia and sedation, the pain and sedation scores, the number of as needed administrations of analgesic and sedative agents, and vital signs should be reviewed for the previous 24-hour period.[13] Based on this assessment, an increase or decrease in dose of sedative and analgesic medications can be recommended to optimize this area of therapy for the patient.

The second subcomponent is neuromuscular blockade. Once pain and sedation are optimized, the PANDEM guidelines recommend that train of four (TOF) monitoring can be assessed for patients on neuromuscular blockade therapy to ensure the most appropriate level of paralysis.[13] It is also recommended to consider drug holidays to determine when neuromuscular blockade agents might be able to be discontinued.[12] Finally, it is imperative to ensure the patient is on appropriately scheduled eye care to prevent corneal abrasions.[13]

The third subcomponent is delirium. The PANDEM guidelines also provide recommendations on validated assessment tools for delirium. Several tools exist, and again it is recommended that learners clarify which type of tool is utilized at the institution. The PANDEM guidelines recommend use of the BRAIN MAPs tool to identify contributing factors that can cause or exacerbate delirium.[13] Items included on the BRAIN MAPs analysis are drugs that could affect mentation (such as anticholinergics), sleep-wake cycle disturbances (especially in patients that have established sleep patterns at home), and under or over treated analgosedation.[13]

The final subcomponent for this section is IWS. The PANDEM guidelines provide recommendations for validated tools for assessment of IWS.[13] Several tools exist, and again it is recommended that learners clarify which type of tool is utilized at the institution. Most patients with IWS are often initiated on enteral opioids, benzodiazepines, and/or clonidine to prevent manifestations of withdrawal from opioids, benzodiazepines, and dexmedetomidine, respectively. The doses of the enteral agents can be gradually decreased using a protocolized approach. The IWS scoring can be used to determine if the doses of the enteral agents should be increased, decreased, or remain the same.

T – Time of Anti-infective Agents. The "T" in the acronym has 2 subcomponents, which includes appropriateness of antimicrobial therapy and duration of treatment. The first subcomponent of this section is to evaluate appropriateness of empiric antimicrobial selection and determination if narrowing of therapy is needed based on cultures and susceptibilities. The initial empiric antimicrobial selection can be assessed based on knowledge of the most common organisms associated with a specific infection. Recommendations for narrowing empiric therapy to tailored therapy can be made by monitoring cultures and susceptibilities, and identifying an antibiotic choice based on pathogen identified, location of infection, and appropriateness of agent based on age of patient. An example of selection of an agent based on location of infection would be a first-generation cephalosporin would be appropriate for a susceptible urinary tract infection but would not be appropriate for meningitis due to issues with adequate penetration in the meninges. In addition, an example of selection of an agent based on age of the patient might be avoidance of ceftriaxone for a neonate because of the risk of hyperbilirubinemia and kernicterus.

The second subcomponent is assessment of duration of antimicrobials. This necessitates the need to track the number of days an antimicrobial has been received and determine the planned duration of treatment based on the infection and organism. Ensuring stop dates are included on the medication order, when possible, is also a critical step to ensure that antimicrobials are discontinued in a timely manner and to prevent unnecessary continuation and risk of adverse effects.

H – Hospital Prophylaxis. The last section, "H", of the IN-DEPTH acronym is for hospital prophylaxis. This section contains 5 subcomponents including assessment of need for immunizations, stress ulcer prophylaxis, venous thromboembolism prophylaxis, anti-infective prophylaxis, and need for implementation of a bowel regimen. The first subcomponent is to assess the immunization status of the patient to identify any missed immunizations and assess for contraindications or precautions to immunization administering. The 2025 American Academy of Pediatrics (AAP) Immunization Schedule includes recommendations for immunizations based on age of the child.[14] In addition, catch-up immunization schedules are provided. Reviewing the AAP recommendations for each patient would be appropriate to determine if immunizations are needed during the admission. Adjustments might be suggested based on medications received or disease states at the time of a due immunization. For example, if a patient received intravenous

immunoglobulin (IVIG) during the hospitalization then some live vaccines will need to be deferred for up to 11 months after the IVIG.[15] Although not a vaccine, respiratory syncytial virus (RSV) prophylaxis is included in the 2025 AAP Immunization Schedule.[14] Assessment of need of RSV prophylaxis should be performed near the time of discharge for patients <8 months of age in their first RSV season or <20 months of age if they have risk factors.[14]

The remaining subcomponents of this section will not apply to every pediatric patient, as some are age, therapy, or disease state dependent. For example, assessing the need for venous thromboembolism prophylaxis may be needed for patients with moderate to high risk of venous thromboembolism. For these patients it is important to ensure de-prescribing on transitions of care if able. An example of a therapy dependent prophylaxis would be the need for initiation of a bowel regimen. If agents associated with constipation (e.g., opioids) are initiated, then a scheduled bowel regimen should be considered, and reporting of stools should be assessed daily. An example of prophylaxis that would be dependent on therapy and/or disease state would be stress ulcer prophylaxis. For example, if the patient is initiated on high-dose steroids and/or requires intubation, stress ulcer prophylaxis may be needed. It is important to regularly assess if continuation of stress ulcer prophylaxis is needed based on discontinuation of risk factors, initiation of enteral feeds, or upon transitions of care. Last, determining the need for anti-infective prophylaxis is strictly dependent on disease state. For example, if a patient is chronically immunosuppressed, then antibiotic, antifungal, and/or antiviral prophylaxis may be appropriate and utilized depending on patient-specific factors and their underlying disease state.

Discussion

The IN-DEPTH mnemonic is a novel structured tool for pharmacy trainees and new practitioners to help identify areas in treatment that can be optimized in critically ill pediatric patient populations such as the PICU, NICU, and pediatric CICU. The mnemonic can help alleviate some stress and anxiety from trainees or new practitioners that are not as familiar with critical or pediatric care. We believe this tool will be useful for Doctor of Pharmacy students, pharmacy residents and practitioners who are new to the pediatric critical care arena. It is a structured guide to point out crucial areas of pediatric critical care that should be addressed with every patient encounter. It is also a great resource for preceptors to provide learners when starting on rotation. It will help the learners be able to analyze the patient and develop recommendations that align with the goals of pediatric critical care patient management. We believe studies aiming to validate the IN-DEPTH mnemonic would be beneficial for future use in practice. If validated and demonstrated to be beneficial for learners and practitioners new to pediatric critical care in their ability to identify areas for treatment optimization, more widespread use of the tool could be encouraged in training settings.

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References

1. Prescott WA Jr, Dahl EM, Hutchinson DJ. Education in pediatrics in US colleges and schools of pharmacy. *Am J Pharm Educ*. 2014;78(3):51.
2. Branan TN, Darley A, Anthony Hawkins W. How critical is it? Integrating critical care into the pharmacy didactic curriculum. *Am J Health Syst Pharm*. 2024;81(18):871–875.
3. Mabasa VH, Malyuk DL, Weatherby EM, Chan A. A standardized, structured approach to identifying drug-related problems in the intensive care unit: FASTHUG-MAIDENS. *Can J Hosp Pharm*. 2011;64(5):366–369.
4. Dehbi S, Benabdelouahab, El Hernoussi Z, et al. Give your pediatric intensive care unit patient at least one fast hug in bed each day. *J Pediatr Crit Care*. 2025;12(2):57–63.
5. Cober MP, Gura KM. Enteral and parenteral nutrition considerations in pediatric patients. *Am J Health Syst Pharm*. 2019;76(19):1492–1510.
6. Da Silva JSV, Seres DS, Sabino K, et al. ASPEN consensus recommendations for refeeding syndrome. *Nutr Clin Pract*. 2020;35(2):178–195.
7. Matson KL, Horton ER, Capino AC; Advocacy Committee for the Pediatric Pharmacy Advocacy Group. Medication dosage in overweight and obese children. *J Pediatr Pharmacol Ther*. 2017;22(1):81–83.
8. Eiland LS, Meyers RS. Caring for and assessing pediatric patients: Aspects to consider as a pharmacy practitioner. *Am J Health Syst Pharm*. 2019;76(19):1463–1471.
9. Zahn SO, Tobison JH, Place AJ, et al. Impact of a process change on prevalence of prescribed unmeasurable liquid doses in a neonatal intensive care unit. *J Pediatr Pharmacol Ther*. 2020;25(2):96–103.

10. Meltzer EO, Welch MJ, Ostrom NK. Pill swallowing ability and training in children 6 to 11 years of age. *Clin Pediatr (Phila)*. 2006;45(8):725–733.
11. McPherson C, Meyers RS, Thackray J, et al. Pediatric Pharmacy Association 2025 KIDs list of key potentially inappropriate drugs in pediatrics. *J Pediatr Pharmacol Ther*. 2025;30(4):422–439.
12. Meyers R. Management of pediatric parenteral fluids. *J Pediatr Pharmacol Ther*. 2024;29(4):346–353.
13. Smith HA, Besunder JB, Betters KA, et al. 2022 Society of Critical Care Medicine clinical practice guidelines on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. *Pediatr Crit Care Med*. 2022;23:74–110.
14. American Academy of Pediatrics. 2025 Immunization Schedule. Accessed August 21, 2025. https://downloads.aap.org/AAP/PDF/AAP-Immunization-Schedule.pdf?_gl=1*1pnc0pi*_ga*OTY0MTM4MTQ0LjE3NTI2MDY3NTk.*_ga_FD9D3XZVQQ*czE3NTU4MDE2MDMkbzMkZzEkdDE3NTU4MDE3NTUkajYwJGwwJGgw
15. Kroger A, Bahta L, Long S, Sanchez P. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Accessed August 21, 2025. https://www.cdc.gov/vaccines/hcp/imz-best-practices/?CDC_AAref_Val=https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html

JPPT | Invited Commentary

Naloxone Disparities in Adolescents: Access Laws Are Not Enough

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ABBREVIATIONS NALs, Naloxone Access Laws

KEYWORDS adolescent; health services accessibility; naloxone; opioids; overdoses

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In addressing overdose morbidity and mortality in the United States, one population seems to be left out of the spotlight: adolescents. Overlooking this group is of great detriment from a public health standpoint, given that the increase in overall overdose mortality seen in adolescents has been greater than the population at large: between 2019 and 2020, adolescent overdose mortality increased by 94%, as opposed to 29.5% in the overall population.[1] Between 2020 and 2021, overdose mortality in adolescents increased by 20%, and in the overall population by 11.5%.[1] Following trends of the greater population, adolescents also saw an increase in overdose mortality due to fentanyl beginning in 2019 and continuing through to 2021, when 77.1% of adolescent overdose deaths were positively identified as involving opioids.[1,2] Between 2019 and 2021, median monthly overdose deaths among adolescents increased by 109%, and deaths involving fentanyl almost doubled in jurisdictions with available data, from 22 to 62 (182%).[2] In 2021, 73% of overdose deaths in the general population involved illicitly manufactured fentanyl, while 84% of deaths in adolescents involved illicitly manufactured fentanyls, indicating that not only has the overdose mortality due to fentanyl been rising in adolescents, but also it has done so at a higher rate than in the general population.[2]

Naloxone is an opioid antagonist that is effective for rapid reversal of an opioid overdose. Programs dedicated to overdose education and naloxone distribution have been associated with decreased rates of fatal opioid-related overdoses.[3] Prompt administration of naloxone is critical in preventing overdose morbidity and mortality, but data suggest that naloxone is administered in less than a third of fatal adolescent drug overdoses.[2] While fatal and nonfatal overdoses among adolescents have risen in recent years, the circumstances in which these overdoses are occurring present a specific set of challenges for clinicians and public health officials to address, particularly as it relates to the access to and use of naloxone. To increase the prescription, distribution, and administration of naloxone, individual states and the District of Columbia have passed a variety of Naloxone Access Laws (NALs), which have seen some success: 14% lower incidence of opioid-overdose deaths among men, 23% lower incidence among the black non-Hispanic population, and 16% lower incidence among individuals 35 to 44 years of age.[4] However, in individuals aged 15 to 24 years, implementation of NALs did not result in a statistically significant decrease in the incidence of opioid overdose deaths.[4,5] This suggests that additional efforts outside of NALs are needed to promote adolescent naloxone access and use.

One factor that may limit naloxone's effectiveness in curbing overdose deaths in adolescents may be related to how adolescents misuse substances. Fifty percent of adolescents being assessed for substance use disorder treatment reported using substances alone, with prescription drug misuse occurring most frequently alone (51%), and alcohol use occurring alone least frequently (26%).[6] This would render the very presence of naloxone ineffective because there would be no one to administer the medication. Additionally, even if bystanders are present, there is evidence that many are unaware that an overdose is taking place, highlighting a need for bystander education, particularly in adolescents.[2,7]

Interestingly, despite the rising numbers of adolescent overdoses, only a small percentage of that group has a history of opioid use disorder (35%) or previous overdose (14.1%).[2] This lack of experience may lead to adolescents underestimating the risk of using opioids, in addition to lacking the physical tolerance seen in regular users.[2,8] The lack of history of opioid use and overdose could also prevent traditional harm reduction initiatives that typically target high-risk individuals from engaging with this population effectively. Adolescents may also engage with harm reduction initiatives at a lower rate out of fear of parental discovery. Additionally, the prevalence of mental health conditions among adolescents who die from a drug-related overdose is high (41%), potentially reflecting an unmet need

for mental health services that is contributing to the overdose mortality rate in this population.[2]

Another concerning trend is that counterfeit pills containing fentanyl are increasingly being found at the scene of overdoses for both adolescents and adults,[2,7] suggesting that these individuals were not seeking to use fentanyl but were unintentionally exposed. This may hamper naloxone administration because there may not be a clear history of exposure to opioids. Another aspect of naloxone access initiatives is co-prescribing of naloxone with opioid prescriptions; however, most adolescents do not obtain opioids via their own prescription (55.7% obtained them from friends or relatives),[8] making this of limited utility.

In March 2023, the US Food and Drug Administration approved Narcan (naloxone HCl) for over-the-counter sales, with the hope of reducing barriers to access. Unfortunately, adolescents may not fully realize these benefits owing to continued stigma regarding adolescent drug use. One study found that approximately half of pharmacy employees incorrectly stated that there was a minimum age requirement for dispensing naloxone,[9] possibly preventing adolescents from taking advantage of measures intended to make naloxone more accessible. In addition to being misinformed about age requirements, some of the pharmacies in the study did not have naloxone in stock.[9] There may also be financial barriers in accessing naloxone via purchase, because over-the-counter formulations may not be covered by insurance (in which case, costs can average at $62.94).[10] If it is covered by insurance, concerns may also exist that parents could be alerted if the product is billed to insurance or if there is a prescription record. Even if they can obtain it, adolescents may be hesitant to keep naloxone on hand owing to fears of parental discovery. These barriers can be overcome by programs that provide naloxone in hand to adolescents at little to no cost, without electronic health record documentation or insurance billing.

Most adolescents see a pediatrician for their primary care, but one study found that pediatricians prescribed only around 5% of the total naloxone dispensed, and that naloxone-dispensing rates to youth remain far below dispensing rates to adults.[11] Even following an emergency department visit for an overdose, naloxone-prescribing rates for all ages are low.[12,13] This represents a critical missed opportunity for physicians to intervene and help prevent future overdose mortality.

Additionally, perhaps owing to stigma or reluctance to disclose usage, there is still a lack of screening and education for adolescents on opioid use. Possible measures to reduce mortality must include the education of adolescents on topics such as recognizing signs of substance use, the high prevalence of counterfeit pills, how to effectively respond to an overdose, and education on safer use practices if they chose to continue to use substances. Emphasis needs to be placed on education around naloxone use, as well as how to gain access to it, with the educational content being specifically catered toward adolescents and their parents to facilitate communication. Such education can be incorporated into pediatrician visits, following an acute overdose, and into school curriculums, as well as other outreach programs.

The number of fatal and nonfatal adolescent opioid overdoses have increased over time. Despite an effective antidote in the form of naloxone, increasing access to the vital drug has lagged in the adolescent population. Increased attention needs to be directed toward this disparity, but additional interventions are needed because expanded access to naloxone may not be enough. Educational efforts grounded in adolescent-specific circumstances should aim to increase awareness of the risks of opioid overdose and promote naloxone use. Finally, attention to the worsening mental health crisis is needed given the high prevalence of mental health disorders among individuals who die from drug overdoses and limited access to treatment for adolescents with opioid use disorder. Unless concerted efforts are made not only to educate adolescents on the dangers of drug misuse, but also to put naloxone directly in their hands, the upward trend in adolescent mortality will likely continue unchecked.

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References

1. Friedman J, Godvin M, Shover CL, et al. Trends in drug overdose deaths among US adolescents, January 2010 to June 2021. *JAMA*. 2022;327(14):1398.
2. Tanz LJ, Dinwiddie AT, Mattson CL, et al. Drug overdose deaths among persons aged 10–19 years—United States,

July 2019–December 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(50):1576–1582.
3. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013;346(7894):f174.
4. McClellan C, Lambdin BH, Ali MM, et al. Opioid-overdose laws association with opioid use and overdose mortality. *Addict Behav*. 2018;86:90–95.
5. Toce MS, Michelson KA, Hadland SE, et al. Naloxone access laws and opioid-related overdose deaths in youths. *JAMA Pediatr* [published online ahead of print October 14, 2024]. 10.1001/jamapediatrics.2024.3701
6. Connolly S, Govoni TD, Jiang X, et al. Characteristics of alcohol, marijuana, and other drug use among persons aged 13–18 years being assessed for substance use disorder treatment—United States, 2014–2022. *MMWR Morb Mortal Wkly Rep*. 2024;73(5):93–98.
7. O'Donnell J, Tanz LJ, Gladden RM, et al. Trends in and characteristics of drug overdose deaths involving illicitly manufactured fentanyls—United States, 2019–2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(50):1740–1746.
8. Hudgins JD, Porter JJ, Monuteaux MC, Bourgeois FT. Prescription opioid use and misuse among adolescents and young adults in the United States: a national survey study. *PLoS Med*. 2019;16(11):e1002922.
9. Jimenez DE, Singer MR, Adesman A. Availability of naloxone in pharmacies and knowledge of pharmacy staff regarding dispensing naloxone to younger adolescents. *J Adolesc Health*. 2019;65(5):698–701.
10. Marley GT, Annis IE, Egan KL, et al. Naloxone availability and cost after transition to an over-the-counter product. *JAMA Health Forum*. 2024;5(7):e241920.
11. Terranella A, Guy G, Mikosz C. Naloxone dispensing to youth ages 10–19: 2017–2022. *Pediatrics*. 2024; 154(4):e2023065137.
12. Ramdin C, Chandran K, Nelson L, Mazer-Amirshahi M. Trends in naloxone prescribed at emergency department discharge: a national analysis (2012–2019). *Am J Emerg Med*. 2023;65:162–167.
13. Chua KP, Dahlem CHY, Nguyen TD, et al. Naloxone and buprenorphine prescribing following US emergency department visits for suspected opioid overdose: August 2019 to April 2021. *Ann Emerg Med*. 2022; 79(3):225–236.

JPPT | Invited Commentary

Topical Anesthesia During Minor Surgical and Needle-Related Procedures in Infants and Children

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ABBREVIATIONS EMLA, eutectic mixture of local anesthetics; FDA, US Food and Drug Administration

KEYWORDS local anesthetic agents; lidocaine; prilocaine; cutaneous analgesia; surgical incision

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Introduction

Topical and local anesthetic agents remain key components of providing analgesia in infants and children for minor surgical and needle-related procedures including intravenous cannulation of procedural sedation. As the science of pediatric pain medicine has advanced, the immediate deleterious physiologic effects, as well as the potential for the long-term impact of inadequately treated painful invasive procedures, have been demonstrated.[1,2] Although frequently used in the awake child for topical analgesia prior to peripheral venous cannulation, these agents may also be used to provide superficial analgesia for more invasive needle-related procedures such as lumbar puncture or bone marrow aspiration. In these latter settings, topical analgesia may limit the requirements for procedural sedation and potentially decrease the incidence of adverse hemodynamic and respiratory effects.

History of Local Anesthetic Agents

The history of the use of local anesthetic agents for medicinal and other purposes dates back thousands of years to the first local anesthetic, cocaine, derived from the plant *Erythroxylon coca*, which is indigenous to the valleys of South America. Although its first use in Western medicine for eye surgery in 1884 is attributed to Dr Carl Koller, a Viennese ophthalmologist, its first documented use as a local anesthetic in surgery actually occurred in approximately 800 AD when cocaine-filled saliva formed by the chewing of coca leaves was dripped onto the skull to provide topical anesthesia for trephination.[3] In Western society, cocaine was originally isolated by Albert Niemann in 1859, who reported its local anesthetic effect (numbing) on the tongue. The work of Dr Koller revolutionized surgery in the field of ophthalmology by allowing for painless eye surgery without the need for general anesthesia. Although the use of cocaine as a local anesthetic spread rapidly, its limited safety margin with significant risk of toxicity and addictive potential led to the search for safer alternatives and its eventual abandonment as a topical anesthetic agent. In 1905, a German chemist, Alfred Einhorn, synthesized a new local anesthetic agent, procaine. He subsequently trademarked the name *Novocain*, which is derived from the Latin words “nov” meaning new and “caine,” a common chemical nomenclature for alkaloids used as anesthetics. Novocain’s relative safety and effectiveness made it a widely used local anesthetic for several decades in the medical and dental fields. It became the standard of care for local anesthetic agents until the development of lidocaine in 1948. In the last 20 years, a number of new topical creams and devices have become commercially available that can provide reliable cutaneous analgesia without the use of a needle and with increasingly shorter onset times.

The first topical anesthetic cream to gain significant use in clinical practice was EMLA (eutectic mixture of local anesthetics) originally introduced into the clinical market by Astra Pharmaceutical Production AB, Södertälje, Sweden, which received approval by the US Food and Drug Administration (FDA) in December 1992. The term *eutectic* is a chemical descriptor that signifies a combination of 2 or more substances that has a lower melting point than each individual substance. In the case of EMLA, the mixture of the 2 local anesthetic agents, lidocaine and prilocaine, has a lower melting point than either anesthetic alone. Because of this property, the EMLA compound remains in liquid form at room temperature, which enhances penetration of the skin, thereby facilitating the onset of its local anesthetic properties. Following its introduction into clinical practice, the potential applications of topical anesthetic creams like EMLA expanded to most minor procedures that involved cutting the skin or piercing

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it with a needle, including intravenous cannulation, phlebotomy, removal of superficial skin lesions, lumbar puncture, and vaccinations. Over the years, the options for topical anesthesia have expanded with the intent of improving efficacy, shortening onset times, and increasing the depth of penetration into the layers of the skin.

Local Anesthetic Agents: General Chemical and Physical Properties

A brief review of the pharmacology of local anesthetic agents may be helpful to provide insight into their use topically and the potential, albeit rare, adverse effects of these agents. The 2 chemically distinct classes of local anesthetic agents include amino esters and amino amides. When considering current clinical practice, the amino esters include procaine, chloroprocaine, and tetracaine while the amides include lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine, and ropivacaine. These 2 classes of local anesthetic agents differ in their site of metabolism, plasma half-lives, adverse effect profile, and potential for allergic reactions. Amino esters are metabolized in the plasma by cholinesterases, while amino amides are metabolized in the liver. Given their metabolism, the half-life of the amino esters is relatively constant across all age ranges because the plasma cholinesterases are distributed in body water with less variation, based on gestational and chronologic age. Their metabolism is generally rapid and hence even with excessive dosing, local anesthetic system toxicity is rare. Because the amides are dependent on hepatic metabolism, there are significant age and developmental differences in their metabolism.[4,5] Additionally, the potential for allergic reactions may vary between the esters and the amides. Para-aminobenzoic acid is a metabolite of amino ester breakdown and may result in allergic reactions, whereas amino amides have a diminished allergic potential.

Local anesthetic agents differ in intrinsic potency, onset of action, duration of action, and their ability to produce differential sensory and motor blockade. Both classes of local anesthetic agents block sodium channels in the nerve membrane, thereby interfering with depolarization and propagation of nociceptive input. The non-ionized portion of the local anesthetic agent penetrates the lipid membrane, while the ionized portion reversibly blocks the inner aspect of the sodium channel. Penetration of the lipid membrane of the nerve and therefore lipid solubility is the primary determinant of potency. Agents with a higher potency (bupivacaine, tetracaine, and ropivacaine) are more lipid soluble.[6] The onset of action of a local anesthetic agent is determined primarily by the pKa, which is generally a reflection of the strength of an acid.[7,8] The pKa of local anesthetic agents is generally close to the physiologic range, varying from 7.6 to 9.1. The closer the pKa is to the physiologic pH of 7.4, the more rapid the onset of action because there will be a greater percentage of local anesthetic agent in the non-ionized form at physiologic pH, thereby promoting penetration of the nerve membrane. Lidocaine has a pKa of 7.7, which means that 35% of the drug is non-ionized at a pH of 7.4, resulting in a relatively rapid onset of blockade. In contrast, tetracaine has a pKa of 8.6 and therefore only 5% is in the non-ionized form at a tissue pH of 7.4, resulting in a slower onset of blockade.

Duration of action is determined primarily by the degree of protein binding.[9] Local anesthetic agents bind to protein receptors in the sodium channels. A higher degree or avidity of protein binding produces a longer-lasting blockade of sodium channels and a longer duration of action. Bupivacaine, tetracaine, and ropivacaine are all extensively protein-bound and hence are long-acting local anesthetic agents. Local vasodilation can also affect duration of action by removing the local anesthetic agent more quickly from the site of action.[10] The local vasodilatory effects noted with lidocaine result in a shorter duration of action and also lay the clinical groundwork for the common practice of adding epinephrine, usually in a concentration of 5 µg/mL or 1:200,000, to commercial preparations of lidocaine to prolong its duration of action. The strength or extent of the block provided by any local anesthetic can be increased by increasing the concentration or the volume of the local anesthetic.[11] However, higher plasma concentrations of the local anesthetic agent will also be achieved, thereby increasing the risks of local anesthetic system toxicity.

Topical Anesthetic Agents for Needle-Related Procedures

The stratum corneum of the skin provides an effective barrier to aqueous local anesthetic agents and until the early 1990s, cutaneous analgesia for intravenous catheter placement could only be achieved by injecting the local anesthetic agent directly into the skin or subcutaneous space. In 1980, emergency department physicians began using topical anesthesia for laceration repair with the placement of an anesthetic solution containing tetracaine, epinephrine, and cocaine into a wound.[12] Subsequently, investigators began actively investigating ways to facilitate the penetration of local anesthetic agents across the skin.[12]

Novel delivery forms for topical anesthesia have been developed in the last 30 to 40 years to allow for the provision of cutaneous analgesia without injection into the skin. These have included either changing the physical properties of the local anesthetic preparations to make them more lipophilic (e.g., eutectic mixtures or liposomal preparations) or the development of relatively noninvasive and non-painful techniques to disrupt the epidermis to make it easier for the local anesthetic to penetrate the stratum corneum (e.g., iontophoresis and jet-propulsion injectors). Although the initial topical preparations included a mixture of lidocaine and prilocaine, subsequent preparations have in-

cluded tetracaine, lidocaine, or the two in combination. In general the lidocaine-prilocaine cream provides effective topical analgesia in 60 minutes, while preparations with tetracaine have a shorter onset time of approximately 30 minutes. The reduction in onset time may make the use of these agents more practical in busy clinical settings.

Eutectic Mixture of Lidocaine and Prilocaine. EMLA cream, the first topical anesthetic commercially available for use on intact skin, was introduced into clinical practice in the United States by AstraZeneca in 1992. EMLA is a mixture of the local anesthetic agents prilocaine and lidocaine, which when combined in equal amounts form a liquid at room temperature. During the 1990s EMLA became the most extensively used and studied topical anesthetic cream, with several clinical trials demonstrating its efficacy in reducing the pain of superficial cutaneous procedures including venipuncture and placement of an intravenous cannula. A meta-analysis of 7 controlled trials in children and adults demonstrated that EMLA cream reduced the pain of venipuncture and venous cannulation in most patients (85%).[13] Additional clinical trials demonstrated its efficacy in reducing pain for other needle-stick procedures such as lumbar puncture, heel stick, immunization, and circumcision. Potential drawbacks that may hamper its widespread acceptance and use include the longer onset time (at least 60 minutes); limitation of its depth of penetration; the potential to cause cutaneous vasoconstriction, which can make venous cannulation more difficult; and the recognized side effect, which is specific to prilocaine; the development of methemoglobinemia (see below). Although 60 minutes is the minimum recommended application time by the manufacturer, longer application times (more than 90 minutes) may be associated with better quality of analgesia. Even with longer application times (3–4 hours), depth of penetration is no more than 6 mm, thereby limiting its utility of more invasive procedures without additional subcutaneous infiltration.[14]

A rare yet dangerous adverse effect of one of the local anesthetic agents in EMLA is the formation of methemoglobinemia from a metabolite of prilocaine. The metabolite oxidizes the iron moiety of the hemoglobin molecule from the normal reduced (2^+) or ferrous state to the 3^+ or ferric state, known as methemoglobinemia. Methemoglobin is unable to carry oxygen effectively and depending on the native hemoglobin concentration, methemoglobin concentrations in excess of 10% to 20% can cause systemic symptoms related to tissue hypoxia. Normally, the body can covert small amounts of methemoglobin back to hemoglobin through the NADH-methemoglobin reductase enzyme system. Development of methemoglobin is generally more rapid and problematic in neonates and infants because fetal hemoglobin is more sensitive to oxidative stresses, facilitating the conversion of ferrous to ferric iron, and there is reduced enzyme function given hepatic immaturity. In clinical practice, reports of methemoglobinemia related to the prilocaine in EMLA cream have been exceedingly rare, occurring primarily in neonates or in susceptible individuals with application on large surface areas, on denuded skin, on mucous membranes, for a prolonged period of time, and covering with an occlusive dressing.

Amethocaine (Tetracaine) Gel. Amethocaine gel (Ametop, initial manufacturer was Smith & Nephew, Andover, Massachusetts, USA) is a topical aqueous gel preparation of 4% amethocaine (tetracaine) that is widely available in Europe and Canada. Because the company has not sought approval by the FDA, it is not available for clinical use in the United States. Tetracaine gel preparations may offer potential advantages over EMLA cream, including a more rapid onset of analgesia within 30 to 45 minutes; vasodilation at the application site, which has been proposed to facilitate vascular access, although outcome studies are not available; a longer duration of anesthesia (approximately 4–6 hours) due to a depot effect in the stratum corneum; and a decreased risk of methemoglobinemia.[15] Although amethocaine gel is not available in the United States, other topical preparations with tetracaine in a gel form are available either alone or with other local anesthetic agents such as lidocaine. Additionally, a tetracaine-lidocaine mixture is commercially available as the Synera patch (initial manufacturer was ZARS, Pharma, Salt Lake City, Utah, USA - see below).

Liposomal Lidocaine. Liposomes are microscopic multilamellar vesicles containing several lipid (phospholipids and cholesterol) bilayers dispersed in an aqueous medium. The liposomal structure enhances penetration of the epidermis and protects against rapid degradation of the local anesthetic agent, prolonging the duration of analgesia. Although tetracaine was the first local anesthetic to be encapsulated into a liposome to facilitate penetration through the stratum corneum, a commercial preparation of liposomal tetracaine has not yet been marketed. However, a liposomal preparation of 4% lidocaine was developed and subsequently marketed as an over-the-counter topical anesthetic agent (ELA-Max 4%, initially manufactured by Ferndale Laboratories, Ferndale, Michigan, USA). Incorporation of lidocaine into a liposomal vehicle speeds analgesic onset to approximately 30 to 45 minutes and negates the need for an occlusive dressing, although most health care providers generally cover the cream with a dressing to keep it in place. Because of the excellent safety profile of the product, it has received approval for over-the-counter use by the FAD. Several prospective randomized trials in children and adults have demonstrated no clinical difference in efficacy between liposomal lidocaine 4% applied for 30 minutes and EMLA 5% after a 60-minute

application.[16–18] Adverse events have generally been limited to local cutaneous reactions such as pallor, redness, and mild pruritus at the application site. Even when applied in neonates (application amount of 1 g), measured plasma lidocaine levels have remained low at <300 ng/mL.[19]

Heated Lidocaine-Tetracaine Patch. The Synera patch or S-Caine Patch was a unique delivery system that used a patented ***c***ontrolled ***h***eat-***a***ssisted ***d***rug ***d***elivery system (CHADD) to accelerate the onset of cutaneous analgesia to 20 minutes. The device consisted of a 2.5" × 3.0" patch containing a eutectic mixture of 70-mg lidocaine and 70-mg tetracaine in a ratio of 1:1 by weight, a bio-adhesive layer, and a heating element that was activated by oxidation on exposure to ambient air, generating heat at 39°C to 41°C.[20–22] Cutaneous heating accelerated the solubility, diffusion, and analgesic onset time of the 2 local anesthetic agents. Despite its apparent efficacy in clinical trials, production of the Synera patch, was been discontinued and it is no longer available in the United States.

Summary

The placement of an intravenous cannula remains a source of considerable anxiety and pain, especially for young children. The search for the optimal technique and agents to provide topical dermal anesthesia has been ongoing for the last 40 to 50 years. The current FDA-approved agents can be used to provide effective topical dermal analgesia for various superficial needle procedures, including intravenous catheter placement and venipuncture, with only minor clinical differences in onset time, and with tetracaine gels generally providing a more rapid onset than combinations of lidocaine and prilocaine (EMLA cream or patch). When used properly, these agents have a wide margin of safety with a limited adverse effect profile. Regardless of the agents used and the route of administration, the practitioner must have a thorough understanding of the local anesthetics in the preparation, appropriate dosing recommendations, and potential toxicity of these agents' dosing ranges.

Article Information

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References

1. Taddio A, Katz J. The effects of early pain experience in neonates on pain responses in infancy and childhood. *Paediatr Drugs*. 2005;7(4):245–257.
2. Weisman SJ, Bernstein B, Schechter NL. Consequences of inadequate analgesia during painful procedures in children. *Arch Pediatr Adolesc Med*. 1998;152(2):147–149.
3. Altman AJ, Albert DM, Fournier GA. Cocaine's use in ophthalmology: our 100-year heritage. *Surv Ophthalmol*. 1985;29(4):300–306.
4. Gunter JB. Benefit and risks of local anesthetics in infants and children. *Paediatr Drugs*. 2002;4(10):649–672.
5. Kuhnert BR, Kuhnert PM, Prochaska AL, Gross TL. Plasma levels of 2-chloroprocaine in obstetric patients and their neonates after epidural anesthesia. *Anesthesiology*. 1980;53(1):21–25.
6. Wildsmith JA, Brown DT, Paul D, et al. Structure-activity relationships in differential nerve block at high and low frequency stimulation. *Br J Anaesth*. 1989;63(4):444–452.
7. Covino BG. Pharmacology of local anaesthetic agents. *Br J Anaesth*. 1986;58(7):701–716.
8. Wildsmith JA, Gissen AJ, Takman B, et al. Differential nerve blockade: esters vs amides and the influence of pKa. *Br J Anaesth*. 1987;59(3):379–384.
9. Butterworth JF, Strichartz GR. Molecular mechanisms of local anesthesia: a review. *Anesthesiology*. 1990;72(4):711–734.
10. Johns RA, DiFazio CA, Longnecker DE. Lidocaine constricts or dilates rat arterioles in a dose-dependent manner. *Anesthesiology*. 1985;62(2):141–144.
11. Scott DB, McClure JH, Giasi RM, et al. Effects of concentration of local anesthetic drugs in extradural block. *Br J Anaesth*. 1980;52(10):1033–1037.
12. Pryor G, Kilpatrick W, Opp D. Local anesthesia in minor lacerations: topical TAC vs. lidocaine infiltration. *Ann Emerg Med*. 1980;9(11):568–571.
13. Fetzer SJ. Reducing venipuncture and intravenous insertion pain with eutectic mixture of local anesthetic: a meta-analysis. *Nurs Res*. 2002;51(2):119–124.
14. Wahlgren CF, Quiding H. Depth of cutaneous analgesia after application of a eutectic mixture of the local anesthetics lidocaine and prilocaine (EMLA cream). *J Am Acad Dermatol*. 2000;42(4):584–588.
15. O'Brien L, Taddio A, Lyszkiewicz DA, Koren G. A critical review of the topical local anesthetic amethocaine (Ametop) for pediatric pain. *Paediatr Drugs*. 2005;7(1):41–54.
16. Eichenfield LF, Funk A, Fallon-Friedlander S, Cunningham BB. A clinical study to evaluate the efficacy of ELA-Max (4% liposomal lidocaine) as compared with eutectic mixture of local anesthetics cream for pain reduction of venipuncture in children. *Pediatrics*. 2002;109(6):1093–1099.

17. Taddio A, Soin HK, Schuh S, et al. Liposomal lidocaine to improve procedural success rates and reduce procedural pain among children: a randomized controlled trial. *Can Med Assoc J*. 2005;172(13):1691–1695.
18. Koh JL, Harrison D, Myers R, et al. A randomized, double-blind comparison study of EMLA and ELA-Max for topical anesthesia in children undergoing intravenous insertion. *Paediatr Anaesth*. 2004;14(12):977–982.
19. Taddio A, Shah V, Stephens D, et al. Effect of liposomal lidocaine and sucrose alone and in combination for venipuncture pain in newborns. *Pediatrics*. 2011;127(4): e940–e944.
20. Shoemaker TS, Zhang J, Love G, et al. Evaluating skin anesthesia after administration of a local anesthetic system consisting of an S-Caine patch and a controlled heat-aided drug delivery (CHADD) patch in volunteers. *Clin J Pain*. 2000;16(3):200–204.
21. Sethna NF, Verghese ST, Hannallah RS, et al. A randomized controlled trial to evaluate S-Caine patch for reducing pain associated with vascular access in children. *Anesthesiology*. 2005;102(2):403–408.
22. Curry SE, Finkel JC. Use of the Synera patch for local anesthesia before vascular access procedures: a randomized, double-blind, placebo controlled study. *Pain Med*. 2007;8(6):497–502.