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TABLE OF CONTENTS

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JPPT | Review

Nontraditional Antiseizure Medications to Consider When Traditional Options Have Failed: Medications for Refractory Seizures and Epilepsies

Adrian Turner, PharmD and M. Scott Perry, MD

In the field of epilepsy, the advent of precision medicine and the repurposing of medications for new applications have fortuitously allowed more accurate diagnosing and individually targeted therapeutics. Despite these advances, there remain patients who do not respond sufficiently—or at all—to traditionally prescribed treatments. Clinicians often need to be creative, using clinical experience and rigorous research to intuit the next step when most, if not all, anti-seizure treatments have not produced sufficient results. Herein we describe 5 medications with emerging reports of efficacy for seizure control identified by coauthor clinical experience and prescribers in clinical practice for drug information purposes (e.g., ketamine, memantine, quinidine, riluzole, trazodone). Additionally, we summarize pertinent pharmacokinetics, adverse effects, and known and potential interactions with neurologically focused medications to further guide clinical application. Ketamine and memantine appear to be promising options to apply to patients presently, while quinidine, riluzole, and trazodone have data that could contribute to future applications in specific patient populations.

ABBREVIATIONS ADNFLE, autosomal-dominant nocturnal frontal lobe epilepsy; ASM, antiseizure medication; DEE, developmental and epileptic encephalopathy; DS, Dravet Syndrome; EEG, electroencephalogram; EIMFS, epilepsy with migrating focal seizures; FDA, US Food and Drug Administration; GABA, gamma-aminobutyric acid; ICU, intensive care unit; IM, intramuscular; IN, intranasal; IV, intravenous; LGS, Lennox Gastaut Syndrome; NMDA, N-methyl-D-aspartate; RSE, refractory status epilepticus; SE, status epilepticus;

KEYWORDS epilepsy; ketamine; memantine; quinidine; riluzole; seizure; trazodone

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Introduction and Background

The practice of medicine is ever-changing. In the field of epilepsy, the advent of precision medicine and the repurposing of medications for new applications have fortuitously allowed more accurate diagnosing and individually targeted therapeutics. Despite these advances, there remain patients who do not respond sufficiently—or at all—to traditionally prescribed treatments. Twenty to forty percent of newly diagnosed patients with epilepsy will not achieve seizure remission for many years.[1–3] Patients with medication-resistant seizures are at further risk with mortality rates 4 to 7 times higher compared with pharmacoresponsive patients.[4–6] Clinicians often need to be creative, using clinical experience and rigorous research to intuit the next step when most, if not all, anti-seizure treatments have not produced sufficient results. Expanding on a previously published review of nontraditional anti-seizure medication treatments,[7] herein we describe 5 medications with emerging reports of efficacy for seizure control identified by coauthor clinical experience and prescribers in clinical practice for drug information purposes (e.g., ketamine, memantine, riluzole, quinidine, trazodone). Literature searches were performed via PubMed database by using search terms "[medication name]," "seizure," "epilepsy," "status epilepticus," and/or known or potential associated genetic mutations. Additionally, we summarize pertinent pharmacokinetics, adverse effects, and known and potential interactions with neurologically focused medications to further guide clinical application.

Ketamine. Ketamine exerts its action via noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonism, resulting in the blockade of glutamate—the major excitatory neurotransmitter in the central nervous system. [see Table 1] The blockade of glutamate ultimately results in analgesia, modulation of central sensitization, and reduction of polysynaptic spinal reflexes.[8,9] Ketamine's US Food and Drug Administration (FDA) approved indications are limited to anesthetic purposes (sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation;

Table 1. Ketamine Dosing, Pharmacokinetic, and Clinically Relevant Interaction Summary[8,9]

Labeled/Reported Dosing	IM	5–13 mg/kg (Indications: induction of anesthesia; procedural sedation/analgesia)
	IN	0.5–6 mg/kg/dose (Indications: acute pain; preanesthetic sedation; procedural sedation/analgesia)
	IV	Loading dose: 0.5–2 mg/kg Maintenance: 0.3–15 mg/kg/hr (Indications: induction of anesthesia; procedural sedation/analgesia; sedation/analgesia in critically ill patients; status epilepticus)
	PO	5–8 mg/kg/dose (Indications: preanesthetic sedation; procedural sedation/analgesia)
	PR	8–10 mg/kg/dose (Indications: preanesthetic sedation; procedural sedation/analgesia)
Pharmacokinetics	Onset	~30 sec (IV); 3–15 min (IM); 5–10 min (IN); 9.5–30 min (PO)
	Peak	5–30 min (IM); 10–20 min (IN); ~30 min (PO); ~45 min (PR)
	Bioavailability	93% (IM); 20%–30% (PO); 35%–50% (IN); 25% (PR)
	Distribution	2.1–3.1 L/kg
	Protein binding	27%
	Metabolism	Hepatic; active metabolite norketamine 33% as potent as parent compound (higher norketamine concentrations with PO due to extensive 1st pass metabolism)
	Half-life	4–6 hr; ~7 hr (CrCl < 30 mL/min); 9.7 hr (ESRD)
	Excretion	Urine (91%); feces (3%)
Interactions	Increased CNS depression	Barbiturates; benzodiazepines; cannabinoid containing products; dexmedetomidine; ethosuximide; felbamate; fenfluramine; gabapentin; lacosamide; lamotrigine; levetiracetam; methsuximide; perampanel; propofol; stiripentol; tiagabine; topiramate; vigabatrin; VPA; zonisamide
	Decreased ketamine serum concentration	CYP2B6 inducers (moderate, strong); CYP3A4 inducers (moderate, strong)
	Increased ketamine serum concentration	CYP3A4 inhibitors (strong)
Commercially Available Formulations	Solution, injection	10 mg/mL; 50 mg/mL; 100 mg/mL

CrCl, creatinine clearance; ESRD, end-stage renal disease; IM, intramuscular; IN, intranasal; IR, immediate release; IV, intravenous; PO, oral; VPA, valproic acid and derivatives

induction of anesthesia before the administration of other general anesthetic agents; and as a supplement to other anesthetic agents).[8,9] However, ketamine's usefulness in the treatment of posttraumatic stress disorder, depression, migraines, pain, and seizures has emerged.[10–17] For seizures, it is reasonable to deduce some anti-seizure activity may stem from NMDA receptor antagonism. In fact, ketamine may be especially useful in prolonged seizures where seizures become more difficult to treat, in part due to loss of sensitivity to gamma-aminobutyric acid (GABA) agonists[18,19] but do not appear to have the same sensitivity loss to NMDA antagonists.[19–22]

Gaspard et al[23] reported experience with intravenous (IV) ketamine in the treatment of refractory status epilepticus (RSE) via a retrospective, multicenter study in 2013. Sixty episodes in patients with RSE were included for analysis (age 7 months to 74 years); 12 (20%) were less than 18 years old. The authors defined response as *likely response* being permanent control of status epilepticus (SE) within 24 hours of ketamine initiation and *possible response* being permanent

control of SE within 24 hours when ketamine was not the last medication added. Furthermore, permanent control of SE was defined as no SE recurrence during the same intensive care unit stay. Sixty-three percent (n = 38/60) had a seizure semiology of focal nonconvulsive SE, 23% (n = 14/60) were classified as generalized convulsive seizures, and the remaining seizure types varied. Only 9 patients (15%) had a prior history of epilepsy. Overall ketamine regimens included a median loading dose of 1.5 mg/kg (maximum of 5 mg/kg) followed by a median continuous infusion rate of 2.75 mg/kg/hr (maximum rate of 10 mg/kg/hr). Seven episodes were categorized as *likely response*; of *likely response* patients with available data, 6 of 6 (100%) received a loading dose of ketamine and had a maximum median rate of 7 mg/kg/hr (0.9–10 mg/kg/hr). Twelve episodes were categorized as *possible response*; of *possible response* patients with available data, 5 of 8 (63%) received a ketamine loading dose and had a maximum median rate of 1.8 mg/kg/hr (0.6–7 mg/kg/hr). Based on a stepwise, multivariable logistic regression analysis, the authors noted younger age and positive response to ketamine were associated with lower mortality. It was also noted that improved response was observed with "early" ketamine initiation (e.g., third- or fourth-line agent in contrast to agent introduced > 8 days into a course or as a seventh-line agent or later).[23]

In one of the largest studies examining ketamine in the management of pediatric and neonatal RSE, Jacobwitz et al[24] reported positive outcomes. Sixty-nine patients in the intensive care unit (median age = 0.7 [0.15–7.2] years) underwent continuous electroencephalogram (EEG) and were treated with ketamine. At baseline, 17 of 69 patients (25%) had preexisting epilepsy; the majority were classified as focal (9 of 17 [53%]), while 2 of 17 (12%) were classified as generalized. The remaining 6 of 17 (35%) were classified as having both focal and generalized seizure types. Sixty-five patients (94%) received a ketamine bolus (specific dosing not defined); continuous ketamine infusions ranged from 1 to 7 mg/kg/hr. After ketamine initiation, seizure termination on continuous EEG was seen in 32 of 69 patients (46%), seizure reduction in 19 of 69 patients (28%), and no change in 18 of 69 patients (26%). Of the 51 of 69 patients (74%) with complete or some reduction in seizures, 37 (73%) saw effects within 6 hours of ketamine initiation. Of note, seizure termination was more likely to be seen when ketamine was administered as the first anesthetic antiseizure medication (ASM) compared with ketamine administered after midazolam (23/38, 61% vs 9/31, 29% [$p < 0.01$]).[24] While one of the largest studies in this population, generalizability is limited as it was performed at a single institution. Interpretations for neonates may also be limited due to the small neonatal sample size. Additionally, clinician variation in clinical data interpretation may be present as multiple practitioners were involved in the interpretation, classification, and documentation.

In a case series of 3 pediatric patients with RSE and super-refractory SE, DeVine et al[25] reported some success with adjunctive continuous ketamine infusions. All 3 patients (aged 29–79 days) were refractory to an average of 6 ASMs at optimized doses before ketamine initiation. Ketamine infusions were initiated at 1 mg/kg/hr and titrated up, with 1 patient requiring a maximum of 6 mg/kg/hr. After ketamine initiation, patients were maintained on an average of 3 ASMs; additionally, 1 patient was able to taper a benzodiazepine continuous infusion to a lower rate. However, 1 patient, in whom ketamine was initiated on day 7, did not have a response to ketamine after 5 days and was tapered off over 24 hours. The second patient initiated ketamine on hospital day 52 (24 hours after the patient's first seizure), and seizures ceased within 1 hour of ketamine initiation. Over the course of admission and readmissions, ketamine was tapered, and seizures recurred. Once ketamine resumed, most clinical seizures resolved, and some subclinical seizures remained. In the last patient, ketamine was initiated on day 7 of admission after the patient was placed on continuous renal replacement therapy due to propylene glycol toxicity from pentobarbital. Unfortunately, no significant changes were seen on the EEG by day 8, and the family opted for limitation of life-sustaining therapy. The patient passed away shortly thereafter. The authors stated it was unclear if seizures were controlled on continuous ketamine in this patient.[25]

In a 2022 single-center, retrospective review, Machado et al[26] presented data that could further delineate effective SE seizure termination with ketamine. Twenty-four adult patients with RSE were included; all patients' video EEGs were examined for any changes after ketamine administration. Patients were classified as responders (complete seizure cessation of electrographic seizures and no recurrence of SE during admission) and nonresponders (cessation of electrographic seizures with recurrence of SE during the same admission or no cessation of SE). Ketamine doses were not significantly different between responders and nonresponders; patients were administered a loading dose (101–105 mg) and started on a ketamine infusion (0.69–6 mg/kg/hr). Ultimately, 12 of 24 patients (50%) were classified as responders. All 12 responding patients' EEGs showed significantly more beta activity superimposed to the background 1 hour after ketamine was initiated compared with only 4 of 12 (33.3%) in the nonresponder group ($p = 0.001$). Further statistically significant differences were seen between the responder and nonresponder groups' EEG backgrounds at the ketamine peak dose. Theta with superimposed beta activity was seen in 11 of 12 (91.6%) responders and only 4 (33.3%) nonresponders ($p = 0.003$); sustained beta activity was statistically significantly observed in 11 of

12 (91.6% responders) and 1 of 12 (8.3%) nonresponders (p = 0.005). In contrast to Jacobwitz et al[24] and Gaspard et al,[23] time to ketamine initiation was not found to be significantly different between responders and nonresponders.[26] Like Jacobwitz et al,[24] however, varying clinicians documented, interpreted, and analyzed a myriad of data points—thus limiting consistency and increasing the potential for bias.[26] Machado et al[26] did not report any side effects in their subjects throughout the duration of the study. The authors concluded background superimposed beta activity induced by ketamine could be an early, reliable EEG finding indicating the success of SE termination.[26]

Perlmutter et al[27] reported promising results in a 6-patient case series using IV and IM ketamine as a prehospital, second-line ASM for pediatric seizures refractory to benzodiazepines. All 6 patients (aged 18 months to 10 years) received ketamine after multiple doses of benzodiazepines (diazepam PR/IV, midazolam IN/IM/IV) and/or levetiracetam IV; 5 patients (83%) received ketamine IV at doses ranging from 1.6 to 2.5 mg/kg and 1 patient (17%) received IM ketamine at a dose of 4.1 mg/kg. All 6 patients were noted to have seizure resolution after ketamine, and only 1 patient experienced further seizures after presentation to the emergency department. Only 1 patient was noted to have any side effects; this ventilator-dependent patient was noted to have a decreased oxygen saturation of 70% after ketamine administration. Baseline oxygen saturation was not recorded. It is unclear if the desaturation was related to the patient's underlying respiratory condition, prolonged seizures, or ketamine administration. Perlmutter et al[27] acknowledged the small sample size and retrospective review of emergency medical services records as limitations but concluded that, despite these limitations, ketamine might appear to be a safe and useful medication in the prehospital setting for seizures unresponsive to benzodiazepines.[27] This report is unique in that it provides evidence of safe and efficacious applications in a prehospital setting as most literature examines ketamine administration in-hospital and as a later-line option. While this case review alone is not compelling enough to warrant protocol changes, it could perhaps spur the design and implementation of more robust trials. This could further elucidate optimal ketamine implementation in pre- and in-hospital seizure emergencies.

Pin et al[28] described their experience with ketamine in a patient with neonatal seizures. The authors additionally systematically reviewed 7 other cases of ketamine application in neonatal seizures. In the single case report from their institution, a term male with an uneventful gestational period and birth presented with apneic spells and bilateral clonic jerks at 18 hours of life. An EEG subsequently revealed multifocal seizures, and magnetic resonance imaging showed abnormal diffusion restriction in fronto-temporal-parietal cortical/subcortical regions and thalamus bilaterally. The patient's seizures worsened and soon developed into RSE (unresponsive to phenobarbital, levetiracetam, phenytoin, midazolam, lidocaine, and pyridoxine). Thiopental reduced clinical seizures, but electrical seizures persisted. Ketamine 10 mcg/kg/min was initiated and titrated up to 100 mcg/kg/min. Electroclinical seizures ceased, and all other ASMs and sedative medications were able to be tapered to discontinuation. Unfortunately, imaging showed diffuse white matter edema and bilateral necrotic lesions; the patient had severe neurologic impairment, extensive brain damage, and the absence of spontaneous respiratory activity and ultimately passed at day 23 of life. In the subsequent review of 7 other cases, 6 of 7 patients had seizure cessation, and 1 had seizure reduction in the acute phase with the addition of ketamine (1.5–100 mcg/kg/hr). Most patients received phenobarbital as the first line, followed by phenytoin, midazolam, levetiracetam, lacosamide, and/or propofol; ketamine was the third or later line ASM in 6 of 7 patients. Two patients passed after withdrawal of care due to poor prognosis. At follow-up (3–17 months), 3 of the remaining 5 patients achieved complete seizure cessation; only 1 patient had poor control of seizures. Pin et al[28] concluded ketamine could likely be used safely as a third-line ASM in neonatal status epilepticus—especially given the alternative mechanism compared to the traditional GABAnergic ASM. While these results and analyses seem promising, caution must be observed as a singular case report may not provide strong data for clinical action. It does, however, yield promise in the potential for larger-scale future studies in neonates.[28]

Ketamine is generally well tolerated when used for SE. Gaspard et al[23] reported a discontinuation rate of 7% (n = 4). One patient developed a propofol-related infusion syndrome-like reaction (4 mg/kg/hour for 4 days). Supraventricular tachycardia (n = 2) and an idiopathic adverse reaction (n = 1) led to ketamine discontinuation as well.[23] Sabharwal et al[29] reported hypothermia incidences in 41 of 79 patients (52%) treated with ketamine; higher ketamine infusion rates and longer durations appeared to be statistically significant (p = 0.001 and p = 0.048, respectively) in those who did and did not experience hypothermia. Jacobwitz et al[24] reported adverse effects requiring intervention in 3 of 69 patients (4%). One patient experienced delirium requiring quetiapine administration; 2 patients experienced hypertension requiring intervention and ketamine infusion wean.[24] Pin et al[28] did not report any side effects in the 8 case reports of ketamine use in neonatal SE.

The retrospective nature of many of these studies presents commonly observed barriers to interpretation—lack of control for comparison, recall bias, potential for missing data, and so on. It should be considered that the severity of the episode may influence the

response or lack of response to ketamine. Alternatively, it cannot be completely ruled out there may be spontaneous resolution of SE or that positive response may be a result of cumulative or delayed effects of concomitant medications.

Ketamine presents a unique opportunity to add to the treatment options for refractory and super refractory status epilepticus in pediatric and neonatal patients. Most seizure rescue medications target inhibitory pathways via GABA and GABA receptors. Ketamine provides an alternative mechanism through the downregulation of excitatory neurologic pathways via NMDA antagonism. Additionally, ketamine could have potential for alternative routes of administration in which other seizure rescue medications are limited. The intranasal route for benzodiazepines for seizure rescue is quite established.[30,31] Intranasal ketamine administration for various indications such as migraine, pain, and depression are reported in the literature.[10,13,14,32] However, only anecdotal reports of intranasal ketamine for seizure rescue exist, indicating an area for future exploration and research that could potentially benefit patients. Ketamine appears to have a relatively mild side effect emergence when used for seizure cessation; side effects may be attenuated by minimizing dose and exposure time if possible. The American College of Emergency Physicians does present potential hesitation for use in infants younger than 3 months of age; the organization considers ketamine use in this population an absolute contraindication due to the higher risk of airway complications.[8] However, in emergent situations where seizure control is of utmost importance, patient airways are often established, and the use of ketamine for a short period of time could prove to have more benefits than risks. Position within the treatment cascade is not yet established, given reports of improved outcomes with early initiation and other studies that show no significant difference in initiation latency. More robust controlled trials are needed, but data are promising and could be considered in patients with particularly refractory seizures unresponsive to at least 2 traditional rescue ASMs.

Memantine. Memantine is presently FDA approved for the treatment of moderate to severe Alzheimer's dementia.[33,34] [see Table 2]Off-label uses include depression, schizophrenia, obsessive-compulsive disorder, substance misuse, pervasive developmental disorders, bipolar disorder, and binge eating (although some data may be lacking).[35] In pediatric patients, memantine is frequently used in the treatment of attention-deficit/hyperactivity disorder and autism spectrum disorder.[35–37] The NMDA receptor antagonist, however, has shown promise in certain types of epilepsy. NMDA receptors are ligand-gated cation channels that mediate a calcium-permeable component within the excitatory pathway.[38] Through NMDA antagonism, pathologic glutamate serum concentrations can be dampened, thus downregulating excitatory neuronal pathways and, possibly, reducing seizures and seizure potential. Additionally, memantine is thought to have some potential anti-inflammatory effects—a particularly interesting characteristic in the treatment of epileptic encephalopathies, as neuroinflammation is thought to play a role in epileptogenesis.[36,39] In some cases, specific genetic mutations associated with the NMDA receptor and identified in cases of epilepsy (e.g., *GRIN1*, *GRIN2a*, *GRIN2b*) may be particularly susceptible to the positive effects of memantine on seizure control.[38]

Table 2. Memantine Dosing, Pharmacokinetic, and Clinically Relevant Interaction Summary[33,34]

Labeled/Reported Dosing	PO	IR: 5–20 mg/day divided 1–2× daily ER: 7–28 mg daily (Indications: Alzheimer's disease, dementia)
Pharmacokinetics	Peak	3–7 hr (IR); 9–12 hr (ER)
	Absorption	Well-absorbed; not affected by food
	Distribution	9–11 L/kg
	Protein binding	45%
	Metabolism	Partially hepatic
	Half-life	~60–80 hr
	Excretion	Urine (74%; ~48% as unchanged drug)
Interactions	Enhanced memantine adverse/toxic effect	NMDA receptor antagonists; trimethoprim (increased risk of myoclonus)
	Increased memantine serum concentration	Alkalinizing agents; carbonic anhydrase inhibitors
Commercially Available US Formulations	Capsule ER 24 hr, oral	7 mg, 14 mg, 21 mg, 28 mg
	Solution, oral	2 mg/mL
	Tablet, oral	5 mg, 10 mg

ER, extended release; PO, oral; IR, immediate release; NMDA, N-methyl-D-aspartate

In 2023, Schiller et al[39] performed a single-center, randomized, double-blind, placebo-controlled crossover clinical trial examining memantine therapy in pediatric patients with developmental and epileptic encephalopathy (DEE)—severe epilepsy with childhood onset characterized by refractory seizures, developmental regression, and EEG abnormalities. Patients with DEE frequently have genetic abnormalities or inflammation after a brain injury; additionally, behavioral disturbances often accompany cognitive deficits, presenting unique and often challenging quality of life considerations for the patients and caregivers. Patients aged 6 to 18 and over 20 kg were included. Patients were randomized to receive memantine followed by placebo or vice versa. Memantine doses were increased in a stepwise manner (5 mg daily × 1 week; 5 mg twice daily × 1 week; 5 mg + 10 mg × 4 weeks); a 2-week washout period was applied between memantine/placebo treatment changes, and a final evaluation was performed at week 16. Investigators assessed treatment response via caregiver seizure diary and EEG obtained after each treatment phase compared with baseline as interval worsening, no significant change, or interval improvement. The primary outcome was responder rate (defined as having 2 of the following: > 50% reduction in seizure frequency, EEG improvement, caregiver impression of improvement, or clear improvement on neuropsychological testing). Ultimately, 27 patients enrolled. Epilepsy syndromes of enrolled patients included DEE of unknown etiology (n = 12), Dravet Syndrome (DS, n = 5), DEE with spike-and-wave activation in sleep (n = 3), and Lennox Gastaut Syndrome (LGS, n = 3); other syndromes reported with an n of 1 were infantile epileptic spasms syndrome, epilepsia partialis continua with regression, epilepsy with myoclonic-atonic seizures, and febrile infection–related epilepsy syndrome. Primary etiologies included *SCN1a* pathogenic variant (n = 6 [22%]) or known or suspected prenatal/perinatal brain injury (n = 5 [19%]); other etiologies with an n of 1 included *GRIN1* pathogenic variant, *GRIN2B* likely pathogenic variant, *DYNC1H1* pathogenic variant, biallelic *POLG* pathogenic variants, *CLCN4* likely pathogenic variant, and brain malformation. A further 10 patients were classified as having an unknown etiology. The memantine group had a statistically significant higher responder rate compared with placebo (9 [33%] vs 2 [7%], $p < 0.04$). Additionally, of those patients on whom EEGs could be obtained (patients were excluded from EEG monitoring if there was a known history of continuous spike wave in sleep), the memantine group had statistically significant EEG improvement and seizure improvement compared with placebo (8 [30%] vs 2 [4%], $p < 0.04$ and 8 [30%] vs 2 [4%], $p < 0.04$, respectively). While perceived behavioral improvements per caregiver impressions were not statistically significant between treatment groups, there was a numerical clinical improvement noted (10 [37%] vs 7 [26%]). Unfortunately, subgroups of epilepsy syndromes and genetic etiologies were too small to perform subgroup analyses. No serious adverse effects were reported. Ultimately, Schiller et al[39] concluded memantine could be a potentially efficacious medication in children with DEE.

Memantine application within the spectrum of epilepsy could potentially be further individualized. Several reports of improved efficacy in the presence of specific genetic mutations have been reported. Bouhadoun et al[36] retrospectively reviewed experiences with 8 pediatric patients aged 2 to 16 years, who were receiving memantine for a neurologic diagnosis.[36] Of these 8 patients, 4 had a diagnosis of epilepsy (2 with DEE; 1 with drug-resistant focal epilepsy and suspected autoimmune encephalitis; 1 with focal epilepsy). Of these 4 patients, all had genetic testing results revealing the following mutations: *GRIN2A* VUS [c.2888 T>C, p.Leu963Pro], Biallelic *PLCB1* pathogenic variants, likely pathogenic *ATP1A2* variant, and variant of uncertain significance in *ATP6*. Only 1 patient's seizures were well controlled at baseline; otherwise, seizure frequency ranged from 3 to 5 seizures per month, with up to 2 to 6 seizure clusters per day. Initial memantine dose in epilepsy patients ranged from 0.1 to 0.17 mg/kg/day (max 5 mg/day); doses were titrated up to a maximum range of 0.2 to 1 mg/kg/day (max 20 mg/day). In 1 patient with DEE, seizure frequency significantly decreased from 3 to 4 seizures per day to approximately 4 seizures per year, while in the other patients, no clear benefit was observed. Of note, the 1 patient with significant response to memantine was the patient with the *GRIN2A* mutation. *GRIN2A* is the gene that encodes the 2A subunit of the NMDA receptor; the authors hypothesized that the clinical benefit in seizure reduction could have been due to the targeted effect on an overactive mutant receptor.[36] Small sample size limits generalizability and limits statistical conclusions due to insufficient power for analyses. However, these findings provide a potential jumping-off point for larger, more robust studies to examine memantine and *GRIN2* mutations.

Similarly, other smaller case studies have reported success with memantine in *GRIN*-related mutations. Mir et al[40] reported success in a pediatric patient with West Syndrome, likely secondary to a *GRIN2A* mutation. The 3-year-old male patient's genetic testing revealed a heterozygous *GRIN2A* variant [c.1083G>A(p.Leu361=]. Of previously trialed ASMs, lacosamide and the ketogenic diet had some benefits, but he continued to have epileptic spasms. He was initiated on memantine 0.15 mg/kg/day and titrated up to 1 mg/kg/day. After memantine initiation, the patient achieved seizure cessation for nearly 10 months. The only recurrence was due to a febrile illness, and the patient returned to a seizure-free state thereafter.[40]

Li et al[38] described their experience with the application of memantine in 2 patients with *GRIN2D*

mutations (c.1999G>A (P.Val667Ile)) in the setting of refractory epilepsy. For the first patient, a 6.5-year-old female, memantine was initiated at 2 mg daily for 1 week and titrated up by 2 mg weekly to a goal dose of 20 mg daily (0.85 mg/kg/day). As no improvement of clinical or subclinical seizures on EEG was noted and memantine was subsequently discontinued; however, after memantine discontinuation, complex focal seizures became more frequent and memantine was restarted and escalated to 20 mg/day (1.3 mg/kg/day). While memantine was well tolerated, the patient did not see any further improvement. Of note, after many medication changes and admissions, oral ketamine and magnesium appeared to resolve subclinical seizures, and the patient remained clinically seizure free. The second patient, a 2.5-year-old female, was initiated on 0.5 mg/kg/day of memantine. At baseline, the patient reported 29 seizures over the 5 days before memantine initiation (5.8 seizures/day). After memantine initiation, during the 5 days preceding discharge, the patient's seizure burden had reduced by 59% (2.4 seizures/day). Moreover, at a 3-week follow-up, the patient had complete seizure freedom, and developmental improvement was noted (e.g., improved visual fixation, motor development progress).[38]

Overall, memantine appeared to be well tolerated among the previous reports. Common side effects noted on medication labeling include confusion, dizziness, headache, agitation, hallucinations, abdominal pain, and urinary retention.[33] Schiller et al[39] described 1 patient with reported "deterioration of behavior" after starting memantine, which led clinicians to discontinue memantine. However, this behavior was felt to be within the patient's baseline behavior fluctuation, and no improvement in behavior fluctuations was seen after memantine discontinuation.[39] Bouhadoun et al[36] reported 1 patient experiencing nocturnal incontinence and another experiencing decreased appetite (neither of which were patients with epilepsy).

Memantine, especially applied in cases of identified genetic mutations, could be especially helpful in the treatment of drug-resistant epilepsies. However, more robust studies are needed to further bolster seemingly safe and effective reports. While current data are promising, responses can be quite variable—even with similar genetic mutations. Factors such as age, mutation-specific impacts, or treatment timing could potentially affect results; thus, more data are needed to truly determine memantine's true role in precision medicine. Many factors (e.g., epileptic syndrome diagnosis, seizure type, genetic mutations, age, etc.) may affect patient response and need and should be weighed seriously when considering memantine in the treatment of drug-resistant epilepsies. Memantine, regardless, appears to show promise in many instances and could be considered in patients with *GRIN* mutation–related epilepsies and patients with DEE when traditional ASMs do not appear to produce an adequate response.

Quinidine. Quinidine is an older medication traditionally used in treating malaria and cardiac arrhythmias. [see Table 3] Specifically, the Class Ia antiarrhythmic has an FDA indication for the treatment of atrial fibrillation/flutter conversion, reduction of frequency of relapse into atrial fibrillation/flutter, and suppression of ventricular arrhythmias.[41,42] It exerts antiarrhythmic activity by depressing rapid, inward depolarizing sodium currents in cardiac muscle and Purkinje fibers ultimately slowing phase-0 depolarization and reducing amplitude without affecting resting potential.[41–43] Use largely ceased when its proarrhythmic potential due to QT prolongation and gastrointestinal intolerance became more widely observed.[44] Recent studies and meta-analyses of quinidine for antiarrhythmic therapy demonstrated increased mortality—especially in those with structural heart disease.[41,42] Of note, the 2 salt formations available (quinidine gluconate and quinidine sulfate) are not interchangeable. Additionally, the IV formulation is discontinued in the United States. In the treatment of malaria, quinidine appears to act primarily as an intra-erythrocytic schizonticide (an agent selectively destructive of the multinucleated form stage of a sporozoan parasite) and is gametocidal to *Plasmodium vivax* and *Plasmodium malariae* (not to *Plasmodium falciparum).*[41,42,45]

Recently, quinidine has been investigated as a treatment for epilepsies secondary to *KCNT1* variants. *KCNT1* encodes a potassium sodium–activated channel subfamily T member 1, and mutations in the gene typically result in channel gain-of-function, the magnitude of which correlates with the clinical severity of epilepsy. This gene has been implicated in several epilepsy syndromes, including autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE) and epilepsy of infancy with migrating focal seizures (EIMFS). *KCNT1*-related epilepsy, notably, typically responds poorly to conventional ASM treatment and can significantly negatively affect the patient's (and caregiver) quality of life.[46,47]

An observational, multi-institutional study of 43 *KCNT1*-related epilepsy patients was performed by Fitzgerald et al[48] in 2019. The team sought to compare the response to traditional treatments as well as quinidine in the cohort of *KCNT1* patients (which, remarkably, is one of the world's largest databases of *KCNT1* epilepsy patients). Clinical phenotypes of enrolled subjects included EIMFS (n = 28), early-onset epileptic encephalopathy (EOEE) (n = 9), and ADNFLE (n = 6). To ensure the response to quinidine was not transient, seizure reduction was considered sustained if a percent reduction in seizures lasted for at least 3 months. Quinidine was utilized in 20 patients with daily doses ranging from 30 to over 90 mg/kg/day. Quinidine was not utilized in any of the patients with ADNFLE but was utilized in 17 EIMFS (61%) and 3 early-onset epileptic

Table 3. Quinidine Dosing, Pharmacokinetic, and Clinically Relevant Interaction Summary[41,42]

Labeled/Reported Dosing	IV (gluconate)	Loading: 10 mg/kg over 60–120 min Maintenance: 0.02 mg/kg/min (Indication: malaria [severe/life-threatening])
	PO (sulfate)	15–60 mg/kg/day divided every 6 hr (Indication: tachyarrhythmia [SVT, AFib, AF, VT])
Pharmacokinetics	Peak	2 hr (sulfate); 3–5 hr (gluconate)
	Bioavailability	45%–100% (sulfate); 70%–80% (gluconate)
	Distribution	2–3 L/kg (adults)
	Protein binding	50%–70% (neonates, infants); 80%–88% (older pediatric, adults)
	Metabolism	Hepatic (50%–90%)
	Half-life	3–4 hr (pediatrics); 6–8 hr (adults)
	Excretion	Urine (5%–20% unchanged)
Interactions	Decreased quinidine serum concentration	CYP3A4 inducers (moderate, strong)
	Increased quinidine serum concentration	CYP3A4 Inhibitors (moderate, strong); grapefruit juice
	Increased concomitant medication serum concentration	Carbamazepine; everolimus; fenfluramine; midazolam; sirolimus (X)
	Increased risk of cardiac side effects (bradycardia, QTc prolongation)	Citalopram (X); lacosamide; propofol; quetiapine (X)
Commercially Available Formulations	Tablet ER, oral (gluconate)	324 mg
	Tablet, oral (sulfate)	200 mg, 300 mg

AF, atrial flutter; AFib, atrial fibrillation; ER, extended release; IM, intramuscular; IN, intranasal; IR, immediate release; IV, intravenous; PO, oral; SVT, supraventricular tachycardia; VT, ventricular tachycardia; X, contraindicated

encephalopathy (33%) patients. Sustained seizure freedom was observed in only 1 patient (5%); a more than 50% reduction was observed in 4 patients (20%)—all of whom had a *KCNT1* epilepsy phenotype of EIMFS. Worsened seizures were reported in 3 subjects (15%). Also of note, no statistically significant difference in seizure frequency was noted between patients receiving quinidine versus those not receiving quinidine. Those patients who responded to quinidine appeared to be older. The authors additionally evaluated variant-specific responses. The *KCNT1* variant G288S demonstrated both responsiveness and nonresponsiveness to quinidine. Patients with the *R474H* variant saw no quinidine response. Additionally, patients with *R929Q*, *R950Q*, and *R961S* variants demonstrated transient seizure freedom for at least 1 month. These 3 variants are notably immediately distal to the NADP domain within the RCK2 domain on the *KCNT1* protein. This region, the authors note, is "hypothesized to be important in coupling sensitivity to intracellular sodium levels with channel gating." Though results are not as promising as other reports in nontraditional ASMs, authors highlight an important population and that future studies may be targeted at efficacy in patients with *KCNT1* variants *G288S*, *R929Q*, *R950Q*, and *R961S*. It may be difficult, however, because of the small patient population of known patients with *KCNT1* epilepsy.[48]

Mullen et al[49] performed a single-center, randomized, blinded, placebo-controlled crossover trial of oral quinidine in patients with ADNFLE secondary to *KCNT1* mutation.[49] The difference in video EEG-measured seizure frequency between quinidine and placebo was noted as the primary outcome; secondary endpoints included a 50% response rate, tolerability, and paroxysmal arousal rate. Six patients were enrolled and randomized; 4 were adults (ages 28–54), while 2 were pediatric subjects (ages 15 and 17 years). Subjects received either drug or placebo for 2 blocks of 4 days with a 2-day washout period between blocks; a 2-day post-completion inpatient stay was applied to ensure patient safety. Four patients ultimately completed the trial as 2 patients (patient 1 and patient 2) were withdrawn due to dose cardiac toxicity. Patients 1 and 2 were initiated on a dose of 900 and 600 mg/day, respectively. The serum concentrations of these 2 patients were below the normal antiarrhythmic therapeutic range (0.61 and 0.51 mcg/mL, respectively). Subsequent subjects were initiated at a dose of 300 mg/day. The remaining 4 patients did not experience adverse events. Of the 4 patients completing the study, 3 were observed to have

increased focal seizures, and 2 had increased paroxysmal arousals. Seizure frequency was not significantly different between placebo and quinidine groups (p = 0.15). Though the sample size is small, Mullen et al[49] demonstrated quinidine is likely not just inefficacious but can worsen seizures in patients with ADNFLE secondary to a *KCNT1* mutation.

Mikati et al[50] reported 2 patients with EIMFS caused by *KCNT1* mutations. Patient 1, an 11-year-old female, had a heterozygous de novo *KCNT1* mutation (NM_020822.1:c.2386T>C; p.[Tyr796His], *Y796H*) which was previously reported in a family with ADNFLE. The *Y796H* variant resulted in a significantly greater magnitude of peak current in channels compared with the wild type during in vitro testing. When quinidine was applied in vitro, there was significant inhibition of the *Y796H* channel, ultimately reducing currents. Patient 1 was thus admitted on 3 separate occasions for quinidine dose initiation/titration; quinidine was initiated and titrated over 3 days to 11, 40, and 54 mg/kg/day divided into 3 doses. On the last admission, the mean serum quinidine concentrations did not appear to increase, and QT prolongation was noted; the dose was subsequently reduced from 54 to 34 mg/kg/day. The patient did not have a statistically significant reduction in seizure frequency from baseline, though minimal reduction was reported from baseline (3.1 seizures/day) to a quinidine dose of 34 mg/kg/day (2.8 seizures/day). EEGs did not show any significant changes throughout any admission, but investigators reported minimally improved alertness and interaction.[50]

The second case was a 3-year-old male with a de novo *KCNT1* mutation (NM_020822.2:c.1887G>C; p.[Lys629Asn], *K629N*).[50] In vitro functional testing showed the *K629N* variant was also a GOF and increased channel magnitude (greater than that of the *Y796H* variant). Of note, quinidine application was less effective in channel current reduction in the *K629N* mutation compared with the wild type or *Y796H*. At quinidine initiation, the EEG showed interictal multifocal spikes, ictal electrodecremental fast beta rhythms, and multifocal subclinical electrographic seizures. Additionally, multiple daily seizures were present, magnetic resonance imaging showed diffuse atrophy, and the patient had failed 8 ASMs and the ketogenic diet. Three admissions for treatment titration occurred. On the first admission, quinidine was initiated at 12 mg/kg/day divided 3 times per day and was titrated up to 22.6 mg/kg/day in 3 divided doses over 4 days. During the second admission, quinidine was titrated further over 4 days to a dose of 34.4 mg/kg/day in 3 divided doses. Mean quinidine serum concentrations reached 0.3 and 0.77 mcg/mL after the second and third titrations, respectively. The patient experienced an 80% reduction in seizure frequency (mean baseline daily seizure frequency = 4.15 seizures/day vs quinidine treatment 34 mg/kg/day = 0.83 seizures/day). Investigators also noted patient 2 was more alert and more interactive and did not have QT interval changes.[50]

Bearden et al[51] reported another 3-year-old female with EIMFS and a *KCNT1* mutation (c.1283G>A; p.Arg428Gln) treated with quinidine. The patient previously trialed phenobarbital, levetiracetam, phenytoin, topiramate, valproic acid, lamotrigine, clorazepate, gabapentin, clobazam, and ketogenic diet without significant seizure reduction. A baseline seizure frequency of 5 seizures per day and developmental arrest/regression were noted. Upon admission, the ASM regimen consisted of topiramate, levetiracetam, clobazam, gabapentin, and ketogenic diet before quinidine was added up to 100 mg every 6 hours (33 mg/kg/day). After 1 week at the target dose, the patient became seizure free and remained seizure free for the next 6 weeks. Additionally, development appeared to improve and was characterized by improved head control, an increase in spontaneous movement, alertness, and initiation of single-word speech. After 6 weeks, seizures returned at a rate of 0 to 2 seizures/day; quinidine was increased to 42 mg/kg/day, and seizures again resolved. This resolution continued for nearly a year except for slight seizure emergence during times of illness. Quinidine serum concentrations remained within a typical therapeutic range for arrhythmia treatment (1.5–4 mcg/mL). No adverse effects were observed.[51]

Abdelnour et al[52] described 3 cases of quinidine treatment in patients with *KCNT1*-related epilepsy. The authors defined response as a greater than 50% reduction in seizure frequency. Of note, older patients (9 and 13 years old) did not respond to quinidine doses of 60 and 36 mg/kg/day divided 3 times daily and had focal seizures and asymmetric tonic seizures, respectively. However, a 3-month-old patient EIMFS went from 3.2 seizures/hour at baseline to 1 seizure/hour on quinidine 40 mg/kg/day divided 3 times daily. Abdelnour et al[52] concluded that, after analysis of the current literature, response to quinidine might be age dependent and patients younger than 4 years may be more likely to respond to quinidine.

In contrast, Chong et al[53] described a lack of efficacy using quinidine treatment in a 6-year-old male with a gain of function *KCNT1* mutation (*R428Q*) and without a diagnosis of EIMFS. Before quinidine initiation, baseline seizure frequency was 106 ± 13.3 seizures/month. Quinidine was initiated and adjusted to maintain serum quinidine concentration troughs of 1.5 to 3 mcg/mL (maximum dose reached: 73 mg/kg/day). Unfortunately, the authors noted no improvement in seizure frequency after quinidine therapy.[53]

A successful case report of quinidine treatment in a 12-year-old male with LGS with a *KCNT1* mutation (c.625C>T) was described by Jia et al[54] in 2019. The patient had no history of perinatal asphyxia, head injury, or encephalitis and an unremarkable family

history of seizures. In fact, the patient was seizure free until the age of 10 years. The patient was refractory to valproate, levetiracetam, clonazepam, topiramate, and lamotrigine and experienced multiple seizure types, including tonic, atypical absence, myoclonic, and generalized tonic-clonic refractory to valproic acid, levetiracetam, clonazepam, topiramate, and lamotrigine. Given the refractory nature of the patient's seizures and the identification of the *KCNT1* mutation, a trial of quinidine was approved by the institution's ethics committees, guardians, and physicians. In the month before quinidine initiation, 16 tonic, 12 atypical absence, 10 myoclonic, and 1 generalized tonic-clonic seizure(s) were documented. Quinidine was initiated at 5 mg/kg/day in 3 divided doses and was titrated over 4 months up to 13.75 mg/kg/day in 3 divided doses; the patient was maintained at this dose for another 4 months. At the end of the assessment period, tonic seizures were reduced to 4 seizures per month (75% reduction); other seizure-type frequencies remained the same. No side effects were noted, and the QTc interval remained normal throughout therapy.[54]

Quinidine side effects on labeling range from diarrhea (24%), to fever, rash (6%), arrhythmia, abnormal electrocardiogram, dizziness (3%), and cerebral ischemia (2%).[41,42] Fitzgerald et al[48] similarly reported sedation (11%), arrhythmia (5%), elevated liver function tests (5%), and rash (5%). However, the most common side effect with quinidine therapy in the reviewed manuscripts appears to be QTc prolongation—Fitzgerald et al[48] reporting a 47% rate.[50,52] Prolongation may require dose reduction. Specifically, FDA labeling recommends a reduction if the QRS complex widens to 130% of the pretreatment duration; the QTc interval widens to 130% of pretreatment duration and is more than 500 ms; the P waves disappear; or if the patient develops significant tachycardia, symptomatic bradycardia, or hypotension. Monitoring is recommended for 2 to 3 days once the appropriate dose has been attained.[41,42] Otherwise, in the reviewed reports, quinidine appeared to be well tolerated.[50,52]

Quinidine may have some value repurposed to treat *KCNT1*-related epilepsies. There are conflicting reports in regard to age and potential response to quinidine; in the largest observational review, authors concluded older pediatric patients responded more favorably to quinidine than their younger counterparts (median age 4 years vs 11 months, respectively). Patients with a diagnosis of EIMFS appear to respond more favorably compared with other *KCNT1*-related epilepsies based on current available data. Even at higher doses, serum concentrations did not seem to rise above normal antiarrhythmic ranges of 2 to 5 mcg/mL. Rather, the therapy-limiting factor appears to be QTc prolongation, suggesting regular cardiac monitoring would be wise if considering initiation. Unfortunately, most conclusions to date are tenuous as they are gleaned from case studies, case series, or small retrospective reviews. While intriguing, it is arguably still contentious to consider the clinical application of quinidine unless all other reasonable ASMs have been trialed—and even then, great caution and consideration must be taken. While more data are needed to define dosing and substantiate efficacy claims, in patients with *KCNT1*-related epilepsy who have exhausted all traditional ASM options, quinidine could be considered with great thought and caution while closely monitoring for increased seizure frequency with initiation and titration.

Riluzole. A member of the benzothiazole class, riluzole is presently indicated for the treatment of amyotrophic lateral sclerosis; however, riluzole also appears to have some neuroprotective properties in other neurologic diseases (e.g., traumatic brain injury, Parkinson's Disease, Alzheimer's Disease).[55,56] [see Table 4] The exact mechanism of action in the treatment of amyotrophic lateral sclerosis is not fully elucidated; however, riluzole is known to be a glutamate inhibitor; specifically, riluzole exerts action pre- and post-synapse via inhibition on glutamate release and inactivation of voltage-dependent sodium channels.[55–59] Some reports suggest riluzole may inhibit potassium and calcium channel activity and/or protein kinase C.[60] Riluzole may additionally exert an ability to interfere with intracellular events after the binding of neurotransmitters at excitatory amino acid receptors as well as strengthening GABAergic neurotransmission.[55–57] All of these modalities considered, the basis of seizure control may be partially attributed to the balance of excitatory and inhibitory action potentials. The downregulation of excitatory potential could be achieved, in part, with the inhibition of glutamate and glutamatergic receptors and regulation of action potential, and the upregulation of inhibitory potential may be achieved by attenuating the ability to respond to GABA (all aforementioned mechanisms suggested in the efficacy of riluzole in neurologic diseases).

Citraro et al[56] performed EEG analysis on riluzole's effect in Sprague-Dawley rats with limbic seizures (induced by AMPA, kainite, and NMDA receptor agonists) and on Wistar Albino Glaxo/Rijswijk rats with a well-validated genetic model of absence epilepsies. Riluzole was administered before seizure induction. Riluzole appeared to be effective in both models (limbic and absence seizures); furthermore, Citraro et al[56] observed that riluzole acted mainly on the NMDA glutamate receptor. Efficacy appeared to be more sustained with incremental dose increases (0.5 mg/kg < 1 mg/kg < 5 mg/kg < 7.5 mg/kg) with a maximum reduction at 90 minutes.[56]

Tidball et al[61] used generated cell culture lines from 3 patients with sodium voltage-gated channel alpha subunit 8 (*SCN8A*) epileptic encephalopathy to examine the effect of riluzole. *SCN8a* variants present as a spectrum of phenotypes, with a severe DEE

Table 4. Riluzole Dosing, Pharmacokinetic, and Clinically Relevant Interaction Summary[55,57]

Labeled/Reported Dosing	PO	50 mg BID (Indication: amyotrophic lateral sclerosis)
Pharmacokinetics	Peak	0.8 hr
	Absorption	AUC and peak blood concentrations decreased by high-fat meals
	Bioavailability	~60%
	Distribution	~3.4 L/kg
	Protein binding	96%
	Metabolism	Hepatic (CYP1A2, UGT-HP4)
	Half-life	12 hr
	Excretion	Urine (90%); feces (5%)
Interactions	Decreased riluzole serum concentration	CYP1A2 inducers (moderate)
	Increased riluzole serum concentration	CYP1A2 inhibitors (strong)
Commercially Available Formulations	Film, oral	50 mg
	Suspension, oral	5 mg/mL
	Tablet, oral	50 mg

BID, twice daily; PO, oral

most commonly characterized by refractory seizures, cognitive and motor impairment, and an increased risk of sudden unexpected death in epilepsy. SCN8A DEE phenotypes may largely be associated with gain-of-function variants resulting in severe epilepsy; loss-of-function variants may also produce generalized epilepsy and absence seizures.[62–64] These variants affect sodium channel activity; gain-of-function variants appear to increase sodium channel activity resulting in neuronal hyperexcitability and a higher neuronal firing rate—thus increasing the risk for seizure and seizures themselves.[65] Loss-of-function appears to reduce sodium channel firing, resulting in ataxia and/or myoclonus; in these instances, sodium channel blockers could potentially worsen seizures.[66,67] In the in vitro cellular models described in Tidball et al[61], phenytoin and riluzole were applied. Both phenytoin and riluzole reduced aberrant firing, but riluzole appeared to be more effective in reducing burst spikes and mean firing rates compared with phenytoin. Given these results, riluzole was initiated in 2 of 3 patients whose cells were examined, as well as an additional patient—all 3 subjects were suggested to have an *SCN8a* gain-of-function mutation.[61]

Patient 1, a 16-year-old female with myoclonic and gelastic seizure types, experienced approximately 50% seizure reduction with riluzole added onto phenytoin, clobazam, and topiramate (initial riluzole dose 25 mg/day; titrated up to 50 mg twice a day over 4 weeks).[61] Patient 1 had 164 recorded seizures (8.2 seizures/wk) at baseline and during the first 20 weeks of treatment experienced seizure reduction to 83 seizures (4.2 seizures/wk). Patient 3, a 7-year-old female with myoclonic jerks, experienced an undefined seizure reduction when riluzole was added to levetiracetam treatment (initial riluzole dose: 50 mg; titrated up to 75 mg/day). At 1 month, the patient was free of myoclonic jerks and had a notably improved EEG background. However, because of sleepiness, riluzole was reduced to 50 mg/day; an increase in seizures was noted. Patient 4 (the additional patient) experienced an initial reduction in seizures but returned to the pretreatment baseline after 4 months. Unfortunately, all 3 patients ultimately discontinued riluzole treatment because of side effects (excessive sleepiness, urinary tract infection) or loss of efficacy.[61]

Riluzole labeling specified hepatotoxicity as a potential dose- or therapy-limiting side effect that can appear within the first 3 months of use; therapy is not recommended if the baseline liver function tests are 5 times the upper limit of normal or more.[55,57] Severe neutropenia (ANC < 500/mm^3) has also been reported within the first 2 months of treatment. Other common side effects noted on riluzole labeling include dizziness, somnolence, asthenia, decreased lung function, hypertension, emesis, and urinary tract infection.[55,57] Of note, higher riluzole serum concentrations are linked with a higher risk of adverse effects. Further, patients of Japanese descent are more likely to have higher serum concentrations of riluzole, thus predisposing this particular population to a higher risk of adverse effects.[55,57] Therapy limiting side effects in human epilepsy patients, though small in number, appear to be sleepiness and urinary tract infection.[61]

The data for riluzole application in the treatment of epilepsy are limited and lacking, though potentially promising in certain populations pending more robust human studies. Riluzole, specifically, may yield positive results when patients with refractory epilepsy associated with an *SCN8A* mutation have exhausted all feasible options. Even still, side effects could hinder prolonged treatment durations. Larger retrospective and prospective studies are needed to explore dosing, efficacy, and side effects in the human population. Prescribing riluzole may present its own hurdles. Insurance companies are unlikely to cover riluzole for an indication of seizure treatment; this may subsequently cause undue financial strain on the family and/or affect the patient's ability to remain adherent to a seizure treatment regimen with riluzole. Riluzole, while possibly providing some antiepileptic activity, should be only considered with great caution, given potential access issues and limited information in humans for the treatment of seizures.

Trazodone. Initially approved for the treatment of major depressive disorder in 1981, trazodone has subsequently expanded therapeutic indications over the decades, including depression, migraine, agitation, and insomnia.[68,69] [see Table 5] Of note, sleep disorders appear to be especially prevalent in patients with DS due to a myriad of factors, including, but not limited to, nighttime seizures, medication side effects, enuresis, and dysregulated sleep patterns.[70,71] Licheni et al[71] reported sleep disturbances in 75% (n = 43/57) of studied patients with DS; Van Nuland et al[70] reported sleep was disrupted in 76% (n = 58/76) of DS patients due to non-seizure etiologies and in 53% (n = 40/76) of DS patients due to seizure etiologies.

The 5HT2a receptor antagonist inhibits serotonin reuptake, causes adrenoreceptor sub-sensitivity, induces significant 5-HT presynaptic adrenoreceptor changes, and significantly blocks histamine (H1) and alpha1-adrenergic receptors.[68,69] While depression, migraine, agitation, and insomnia are frequent indications for trazodone use, some recent animal studies suggest trazodone may have some antiseizure effect.[68,69] At first, this may seem unorthodox. The recently reintroduced

Table 5. Trazodone Dosing, Pharmacokinetic, and Clinically Relevant Interaction Summary[68,69]

Labeled/Reported Dosing	PO	0.75–2 mg/kg/day divided 1–3× daily (maximum 200 mg/dose) (Indications: insomnia/sleep disturbances; major depressive disorder; migraine prophylaxis)
Pharmacokinetics	Onset	1–2 wk (depression)
	Peak	30–100 min; delayed with food
	Absorption	Well-absorbed; increased with food
	Bioavailability	100%
	Protein binding	89%–95%
	Metabolism	Hepatic; active metabolite (mCPP)
	Half-life	5–9 hr (prolonged in obesity)
	Excretion	Urine (~74%, < 1% unchanged); feces (~21%)
Interactions	Increased CNS depression	Barbiturates; benzodiazepines; brivaracetam; cannabinoid-containing products; dexmedetomidine; felbamate; gabapentin; ketamine; lacosamide; lamotrigine; levetiracetam; methsuximide; perampanel; propofol; stiripentol; tiagabine; topiramate; vigabatrin; VPA; zonisamide
	Decreased trazodone serum concentration	Carbamazepine; cenobamate; CYP3A4 inducers (moderate, strong); Fos/phenytoin; phenobarbital
	Increased trazodone serum concentration	CYP3A4 inhibitors (moderate, strong)
	Increased concomitant medication serum concentration	Carbamazepine; Fos/phenytoin
	Increased serotonergic effects	Fenfluramine
Commercially Available Formulations	Tablet, oral	50 mg, 100 mg, 150 mg, 300 mg

CNS, central nervous system; IM, intramuscular; IN, intranasal; IR, immediate release; mCPP, meta-chlorophenylpiperazine; PO, oral; VPA, valproic acid and derivatives

fenfluramine is a seemingly effective antiseizure medication in the treatment of DS and LGS and has potential serotonergic implications.[72–74] Fenfluramine and its metabolite, norfenfluramine, increase extracellular serotonin via serotonin transporter protein interaction and exhibits serotonin 5HT2 receptor agonist activity. Total seizure control may not necessarily be directly attributed to fenfluramine's serotonergic activity, but the pathway is notable and may offer an alternative effective mechanism for seizure control.[72–80] Of note, some studies in patients with temporal lobe epilepsy have shown reduced 5-HT1A receptor binding and that the decreased expression of hippocampal or neocortex 5-HT1a receptors may result in neuronal hyperexcitability and, therefore, seizure activity.[81–84] For these reasons, trazodone has been considered and examined in several preclinical animal studies. Sourbron et al[75] found selective 5-HT1D, 1E, 2A, 2C, and 7 agonists significantly decreased epileptiform activity in zebrafish larvae with homozygous *SCNa1* mutations.[75] Furthermore, local field potential measurements in zebrafish larvae forebrains confirmed antiepileptiform activity of 5-HT1D, 2C, and 2A agonists—especially the latter.[75–77] Griffin et al[85] identified 3 novel analogs of clemizole that exert meaningful epileptiform activity via 5-HT receptors (especially 5-HT2) in DS zebrafish models.

Aygun applied intraperitoneal (IP) trazodone to Wistar rats with penicillin-induced epileptiform activity and Wistar Albino Glaxo/Rijswijk rats (which represent a genetic absence model) at doses of 5, 10, and 30 mg/kg.[86] While 5 mg/kg doses did not affect frequency or amplitude, the 10 and 30 mg/kg doses significantly reduced the frequency of penicillin-induced focal seizure models. Mean epileptiform activity for 5, 10, and 30 mg/kg trazodone doses were reported as 41.57 ± 4.67, 27.87 ± 2.4, and 22.95 ± 2.94 spikes/min, respectively. Conversely, all doses produced an increase in spike-wave discharge frequency and duration in the genetic absence model rats.[86] Translatability of intraperitoneal administration to clinical practice is not feasible for regular administration in humans. Further dose findings with oral trazodone would be more beneficial for consideration in human studies.

Syntaxin-binding protein-1 *(STXBP1)* mutations—missense, nonsense, frameshifts, and deletions—are linked to neurodevelopmental disorders and drug-resistant epilepsies such as Ohtahara syndrome, DS, LGS, West syndrome, and atypical Rett syndrome.[87] Seizures associated with this mutation also include early-onset infantile spasms, focal, tonic-clonic, and absence seizures. Moog et al[87] examined trazodone applied in zebrafish larvae models with homozygous *STXBP1* mutations generated using CRISPR-Cas9 gene editing. A 1-mM trazodone bath was applied to the larvae while continuous local field potential recordings were obtained (baseline: 0–15 min; 45 min after medication exposure = 45–60 min) to monitor for events defined as long-duration (> second), large amplitude (> 0.5 mV) Type II ictal-like multi- or poly-spike events.[87] These were specifically monitored because of previous correlations with whole-body convulsive seizure behaviors. Events were significantly reduced by 83% with the application of trazodone.[87]

In zebrafish *SCN1*lab homozygous mutants, nighttime hyperactivity, decreased time spent in the center of an open arena, and decreased responsiveness to sudden darkness can be used to measure seizure-like activity associated with *SCN1a* mutations.[88] In another preclinical study, Grone et al[88] applied 10-mM solutions of various medications, including trazodone. While other medications proved to have some effect on the reduction of nighttime hyperactivity and increased time spent at the center of the arena, trazodone did not have any effect on either of these data points.[88]

Of note, Borowic et al[89] examined trazodone's antiepileptic activity and effect on the cerebrospinal fluid concentration of other ASMs in mouse models. A single dose of up to 40 mg/kg of trazodone did not affect the electroconvulsive threshold. However, chronic administration of trazodone 40 mg/kg increased the electroconvulsive threshold. Additionally, acute and chronic administration of trazodone increased valproic acid cerebrospinal fluid concentrations and reduced phenytoin concentrations. Chronic administration decreased cerebrospinal fluid concentrations of carbamazepine and phenobarbital.[89]

Human studies in the application of trazodone for epilepsy are notably absent. Trazodone has been shown as relatively safe for use in insomnia, migraine prophylaxis, and major depressive disorder; however, there still is a risk of increased or worsened seizures in patients with epilepsy. More preclinical data are needed to determine possibly safe dosing and safe epilepsy populations before trials in humans can be initiated. However, in the setting of refractory *SCN1a*-related epilepsies, the idea of adding options to the treatment arsenal is promising—especially if trazodone can serve dual purposes for the treatment of insomnia and reduction in seizures. While theoretical for now, future applications of trazodone in these refractory *SCN1a* epilepsies could provide more efficacious results for these patients.

Conclusion

Refractory and super-refractory seizures and epilepsies present significant hurdles for clinicians and patients. When traditional ASMs applied at optimized doses do not produce sufficient seizure reduction to provide improved quality of life, it may feel as though we, as health care practitioners, have failed. Advantageously, some nontraditional ASMs have data to support their use in these instances. [see Table 6]

Of the medications assessed in the present review, ketamine has the strongest data for application in a

Table 6. Dosing, Seizure Efficacy, and Clinical Summary of Nontraditional Antiseizure Medications

Medication	Population	Seizure/ Syndrome Types Studied*	Genetic Mutations with Potential Applications	Antiseizure Dose Range/ Reported Regimen	Efficacy Range Reported†	Relative Strength of Data‡
Ketamine[16–29]	A, N, P	**RSE; SRSE;** generalized; focal; multifocal; mixed type; **neonatal seizure**	n/a	*Loading dose*: 1–5 mg/kg IV • 4.1 mg/kg IM (n = 1) *Continuous rate*: 0.6–10 mg/kg/hr IV	*Responder*: ~32%–100%	++
Memantine[36–40]	P	**DEE**; **West Syndrome**; focal; absence; myoclonic	*GRIN1A; GRIN1B; GRIN2B; GRIN2D*	0.1–1.3 mg/kg/day PO divided 1–2× daily (maximum 20 mg)	*Responder*: 25%–100% • 59%–~100% seizure frequency reduction in responders	+
Quinidine[49–54]	P	ADNFLE; **EIMFS**; **focal; tonic**	*KCNT1*	5 to >90 mg/kg/day PO divided 3–4× daily; 300–900 mg/day	*Responder*: 25%–100% • 75% worsened with ADNFLE • 50%–100% seizure frequency reduction in responders	+/–
Riluzole[56,60,61]	Animal (rats); pluripotent stem cells (human) P	Absence; limbic; **myoclonic**; gelastic	*SCN8a*	0.5–7.5 mg/kg/dose; 25–75 mg, 1–2×daily	*Responder*: 33%–100% • 50%–100% seizure frequency reduction (n = 2)	-
Trazodone[85–89]	Animal (rats, zebrafish)	**DS**; LGS; **focal**; generalized	*SCN1a; STXBP1*	5–40 mg/kg; 1–10 mM bath	*Responder*: 0%–83%	––

A, adult; ADNFLE, autosomal-dominant nocturnal frontal lobe epilepsy; DEE, developmental and epileptic encephalopathy; DS, Dravet Syndrome; EIMFS, epilepsy with migrating focal seizures; LGS, Lennox Gastaut Syndrome; N, neonate; P, pediatric; RSE, refractory status epilepticus; SRSE, super refractory status epilepticus

* **bold** = most efficacy reported
† % response and/or % reduction
‡ ++, most reassuring data; +, some reassuring data; +/-, mixed data; -, minimal or no reassuring data; –, minimal or no reassuring data in humans

clinical setting—specifically in patients with RSE, super-refractory SE, and neonatal seizures. Despite some contradictory findings of ketamine initiation timing within the treatment cascade, one of the largest reviews found ketamine initiation before anesthetic midazolam dosing yielded better patient outcomes and seizure cessation. If patients have failed several benzodiazepine doses, it could be reasonable to consider the incorporation of the alternative mechanism of NMDA-receptor antagonism provided by ketamine into the treatment cascade before or in conjunction with anesthetic midazolam.

Memantine has promising but comparatively weaker evidence. Memantine appears to be generally well tolerated; memantine could be considered as an adjunctive ASM in patients with DEE or West Syndrome—especially in the presence of a *GRIN*-related mutation. Quinidine has even less convincing data compared with memantine and ketamine. While some studies show

promise in *KCNT1*-related EIMFS, worsened seizures were still noted in this population and patients with *KCNT1*-related ADNFLE. Given side effect risk (e.g., QTc prolongation), caution must be taken when considering adjunctive quinidine. Data currently suggest using quinidine in patients with a *KCNT1* mutation, and EIMFS may be most effective; even then, simultaneous diligent cardiac and neurological monitoring for QTc prolongation and seizure frequency, respectively, would be appropriate.

Finally, riluzole and trazodone are unlikely to be reasonable candidates to consider in a clinical setting at this time. Both have compelling data in animals (for riluzole, in human stem cells), but this does not translate into safe human usage. For riluzole, it appears to be most effective for the reduction of myoclonic seizure models, especially in the setting of an *SCN8a* mutation. Trazodone may be effective in DS and focal seizure models, especially in the setting of an *SCN1a* or *STXBP1* mutation. Thus, practitioners interested in using these medications for their patients in the future should closely follow any proposed clinical trials in humans to further bolster presently available data with both riluzole and trazodone. As of the publishing of this manuscript, no studies are presently active within ClinicalTrials.gov concerning either riluzole or trazodone for the treatment of epilepsies or seizures in humans.

The 5 reviewed medications all provide unique opportunities. Some, such as ketamine and memantine, have potential applications in patients today. Of those with less convincing available data, the unique ASM mechanisms of action, potential for use in targeted patient populations, and comparatively reasonable side effect profiles could aid in the design and implementation of larger studies, which may provide more well-defined recommendations for clinical application and implications.

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References

1. Mohanraj R, Brodie MJ. Early predictors of outcome in newly diagnosed epilepsy. *Seizure*. 2013;22(5):333–344.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342(5):314–319.
3. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. *JAMA Neurol*. 2018;75(3):279–286.
4. Löscher W, Klein P. The pharmacology and clinical efficacy of antiseizure medications: from bromide salts to cenobamate and beyond. *CNS Drugs*. 2021;35(9):935–963.
5. Schmidt D, Löscher W. Drug resistance in epilepsy: putative neurobiologic and clinical mechanisms. *Epilepsia*. 2005;46(6):858–877.
6. Epilepsy and seizures. National Institutes of Health. Accessed August 15, 2023. https://www.ninds.nih.gov/health-information/disorders/epilepsy-and-seizures
7. Turner AL, Perry MS. Outside the box: medications worth considering when traditional antiepileptic drugs have failed. *Seizure*. 2017;50:173–185.
8. Ketamine. Lexicomp Online®. Accessed April 15, 2024. https://online.lexi.com/
9. Ketamine hydrochloride [package insert]. Lake Forest, IL: Hospira, Inc.; 2022.
10. Schwartz J, Murrough JW, Iosifescu DV. Ketamine for treatment-resistant depression: recent developments and clinical applications. *Evid Based Ment Health*. 2016;19(2):35–38.
11. Feder A, Parides MK, Murrough JW, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. 2014;71(6):681–688.
12. Hartberg J, Garrett-Walcott S, De Gioannis A. Impact of oral ketamine augmentation on hospital admissions in treatment-resistant depression and PTSD: a retrospective study. *Psychopharmacology* (Berl). 2018;235(2):393–398.
13. Afridi SK, Giffin NJ, Kaube H, Goadsby PJ. A randomized controlled trial of intranasal ketamine in migraine with prolonged aura. *Neurology*. 2013;80(7):642–647.
14. Benish T, Villalobos D, Love S, et al. The THINK (Treatment of Headache with Intranasal Ketamine) Trial: a randomized controlled trial comparing intranasal ketamine with intravenous metoclopramide. *J Emerg Med*. 2019;56(3):248–257.e1.
15. Schoevers RA, Chaves TV, Balukova SM, et al. Oral ketamine for the treatment of pain and treatment-resistant depression. *Br J Psychiatry*. 2016;208(2):108–113.
16. Höfler J, Trinka E. Intravenous ketamine in status epilepticus. *Epilepsia*. 2018;59 Suppl 2:198–206.
17. Alkhachroum A, Der-Nigoghossian CA, Mathews E, et al. Ketamine to treat super-refractory status epilepticus. *Neurology*. 2020;95(16):e2286–e2294.
18. Niquet J, Lumley L, Baldwin R, et al. Rational polytherapy in the treatment of cholinergic seizures. *Neurobiol Dis*. 2020;133:104537.
19. Goodkin HP, Kapur J. The impact of diazepam's discovery on the treatment and understanding of status epilepticus. *Epilepsia*. 2009;50(9):2011–2018.

20. Mazarati AM, Wasterlain CG. N-methyl-D-asparate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. *Neurosci Lett*. 1999;265(3):187–190.
21. Niquet J, Lumley L, Baldwin R, et al. Early polytherapy for benzodiazepine-refractory status epilepticus. *Epilepsy Behav*. 2019;101(Pt B):106367.
22. Wasterlain CG, Naylor DE, Liu H, et al. Trafficking of NMDA receptors during status epilepticus: therapeutic implications. *Epilepsia*. 2013;54 Suppl 6(0 6):78–80.
23. Gaspard N, Foreman B, Judd LM, et al. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. *Epilepsia*. 2013;54(8):1498–1503.
24. Jacobwitz M, Mulvihill C, Kaufman MC, et al. Ketamine for management of neonatal and pediatric refractory status epilepticus. *Neurology*. 2022;99(12):e1227–e1238.
25. DeVine MN, Gordon SE, Press CA. Use of continuous ketamine infusion as an adjunctive agent in young infants with refractory and super refractory status epilepticus: a case series. *J Pediatr Pharmacol Ther*. 2023;28(2): 161–166.
26. Machado RA, Patel J, Elsayed MS. The role of ketamine-induced beta activity in the treatment of refractory status epilepticus. Is the EEG useful to determine responder's rate? A retrospective study. *Epilepsy Behav*. 2022;127:108512.
27. Perlmutter M, Price M, Kothari K, et al. Prehospital treatment of benzodiazepine-resistant pediatric status epileticus with parenteral ketamine: a case series. *Prehosp Emerg Care*. 2023;27(7):920–926.
28. Pin JN, Leonardi L, Nosadini M, et al. Efficacy and safety of ketamine for neonatal refractory status epilepticus: case report and systematic review. *Front Pediatr*. 2023;11:1189478.
29. Sabharwal V, Poongkunran M, Talahma M, et al. Secondary hypothermia in patients with super-refractory status epilepticus managed with propofol and ketamine. *Epilepsy Behav*. 2020;105:106960.
30. Nayzilam® (midazolam) nasal spray [package insert]. Smyrna, GA: UCB, Inc.; 2022.
31. Valtoco® (diazepam nasal spray) [package insert]. San Diego, CA: Neurelis, Inc.; 2022.
32. Seak YS, Nor J, Tuan Kamauzaman TH, et al. Efficacy and safety of intranasal ketamine for acute pain management in the emergency setting: a systematic review and meta-analysis. *J Clin Med*. 2021;10(17):3978.
33. Memantine. Lexicomp Online®. Accessed April 15, 2024. https://online.lexi.com/
34. Namenda® (memantine HCl) [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2013.
35. Zdanys K, Tampi RR. A systematic review of off-label uses of memantine for psychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(6):1362–1374.
36. Bouhadoun S, Poulin C, Berrahmoune S, Myers KA. A retrospective analysis of memantine use in a pediatric neurology clinic. *Brain Dev*. 2021;43(10):997–1003.
37. Findling RL, McNamara NK, Stansbrey RJ, et al. A pilot evaluation of the safety, tolerability, pharmacokinetics, and effectiveness of memantine in pediatric patients with attention-deficit/hyperactivity disorder combined type. *J Child Adolesc Psychopharmacol*. 2007;17(1):19–33.
38. Li D, Yuan H, Ortiz-Gonzalez XR, et al. GRIN2D recurrent de novo dominant mutation causes a severe epileptic encephalopathy treatable with NMDA receptor channel blockers. *Am J Hum Genet*. 2016;99(4):802–816.
39. Schiller K, Berrahmoune S, Dassi C, et al. Randomized placebo-controlled crossover trial of memantine in children with epileptic encephalopathy. *Brain*. 2023;146(3):873–879.
40. Mir A, Qahtani M, Bashir S. GRIN2A -related severe epileptic encephalopathy treated with memantine: an example of precision medicine. *J Pediatr Genet*. 2020;9(4):252–257.
41. Quinidine. Lexicomp Online®. Accessed April 15, 2024. https://online.lexi.com/
42. Quinidine gluconate [package insert]. Philadelphia, PA: Mutual Pharmaceutical Company, Inc.; 2009.
43. Jain A, Sisodia J. *Quinidine*. Treasure Island, FL: StatPearls Publishing; 2023.
44. Li DL, Cox ZL, Richardson TD, et al. Quinidine in the management of recurrent ventricular arrhythmias: a reappraisal. *JACC Clin Electrophysiol*. 2021;7(10):1254–1263.
45. Achan J, Talisuna AO, Erhart A, et al. Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. *Malar J*. 2011;10:144.
46. Gertler T, Bearden D, Bhattacharjee A, Carvill G. KCNT1-related epilepsy. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews*. Seattle, WA: University of Washington, Seattle; 2018:1993–2024.
47. KCNT1 potassium sodium-activated channel subfamily T member 1 [*Homo sapiens* (human)]. NIH National Library of Medicine – Gene. Accessed April 15, 2024. https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=57582
48. Fitzgerald MP, Fiannacca M, Smith DM, et al. Treatment responsiveness in KCNT1-related epilepsy. *Neurotherapeutics*. 2019;16(3):848–857.
49. Mullen SA, Carney PW, Roten A, et al. Precision therapy for epilepsy due to *KCNT1* mutations: a randomized trial of oral quinidine. *Neurology*. 2018;90(1):e67–e72.
50. Mikati MA, Jiang YH, Carboni M, et al. Quinidine in the treatment of KCNT1-positive epilepsies. *Ann Neurol*. 2015;78(6):995–999.
51. Bearden D, Strong A, Ehnot J, et al. Targeted treatment of migrating partial seizures of infancy with quinidine. *Ann Neurol*. 2014;76(3):457–461.
52. Abdelnour E, Gallentine W, McDonald M, et al. Does age affect response to quinidine in patients with KCNT1 mutations? Report of three new cases and review of the literature. *Seizure*. 2018;55:1–3.
53. Chong PF, Nakamura R, Saitsu H, et al. Ineffective quinidine therapy in early onset epileptic encephalopathy with KCNT1 mutation. *Ann Neurol*. 2016;79(3):502–503.
54. Jia Y, Lin Y, Li J, et al. Quinidine therapy for Lennox-Gastaut Syndrome with *KCNT1* mutation. A case report and literature review. *Front Neurol*. 2019;10:64.
55. Rilutek® (riluzole) [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S., Inc.; 2008.
56. Citraro R, Bosco F, Di Gennaro G, et al. An in vivo electroencephalographic analysis of the effect of riluzole against limbic and absence seizure and comparison with glutamate antagonists. *Pharmaceutics*. 2023;15(7):2006.

57. Riluzole. Lexicomp Online®. Accessed April 15, 2024. https://online.lexi.com/
58. He Y, Benz A, Fu T, et al. Neuroprotective agent riluzole potentiates postsynaptic GABA(A) receptor function. *Neuropharmacology*. 2002;42(2):199–209.
59. Jahn K, Schlesinger F, Jin LJ, et al. Molecular mechanisms of interaction between the neuroprotective substance riluzole and GABA(A)-receptors. *Naunyn Schmiedebergs Arch Pharmacol*. 2008;378(1):53–63.
60. Kyllo T, Singh V, Shim H, et al. Riluzole and novel naphthalenyl substituted aminothiazole derivatives prevent acute neural excitotoxic injury in a rat model of temporal lobe epilepsy. *Neuropharmacology*. 2023;224:109349.
61. Tidball AM, Lopez-Santiago LF, Yuan Y, et al. Variant-specific changes in persistent or resurgent sodium current in SCN8A-related epilepsy patient-derived neurons. *Brain*. 2020;143(10):3025–3040.
62. Johannesen KM, Liu Y, Koko M, et al. Genotype-phenotype correlations in SCN8A-related disorders reveal prognostic and therapeutic implications. *Brain*. 2022;145(9):2991–3009.
63. Liu Y, Schubert J, Sonnenberg L, et al. Neuronal mechanisms of mutations in SCN8A causing epilepsy or intellectual disability. *Brain*. 2019;142(2):376–390.
64. Meisler MH, Hill SF, Yu W. Sodium channelopathies in neurodevelopmental disorders. *Nat Rev Neurosci*. 2021;22(3):152–166.
65. Liu Y, Koko M, Lerche H. A SCN8A variant associated with severe early onset epilepsy and developmental delay: Loss- or gain-of-function? *Epilepsy Res*. 2021;178:106824.
66. Hammer MF, Xia M, Schreiber JM. *SCN8A*-related epilepsy and/or neurodevelopmental disorders. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews*. Seattle, WA: University of Washington; 2016:1993–2024.
67. Wagnon JL, Mencacci NE, Barker BS, et al. Partial loss-of-function of sodium channel SCN8A in familial isolated myoclonus. *Hum Mutat*. 2018;39(7):965–969.
68. Trazodone hydrochloride [package insert]. Sellersville, PA: Teva Pharmaceuticals USA.; 2014.
69. Trazodone. Lexicomp Online®. Accessed April15, 2024. https://online.lexi.com/
70. Van Nuland A, Ivanenko A, Meskis MA, et al. Sleep in Dravet syndrome: a parent-driven survey. *Seizure*. 2021;85:102–110.
71. Licheni SH, Mcmahon JM, Schneider AL, Davey MJ, et al. Sleep problems in Dravet Syndrome: a modifiable comorbidity. *Dev Med Child Neurol*. 2018;60(2):192–198.
72. Fintepla® (fenfluramine) [package insert]. Smyrna, GA: UCB, Inc.; 2023.
73. Fenfluramine. Lexicomp Online®. Accessed April 15, 2024. https://online.lexi.com/
74. Frampton JE. Fenfluramine: a review in Dravet and Lennox-Gastaut Syndromes. *Drugs*. 2023;83(10):923–934.
75. Sourbron J, Smolders I, de Witte P, Lagae L. Pharmacological analysis of the anti-epileptic mechanisms of fenfluramine in *scn1a* mutant zebrafish. *Front Pharmacol*. 2017;8:191.
76. Sourbron J, Schneider H, Kecskés A, et al. Serotonergic modulation as effective treatment for Dravet Syndrome in a zebrafish mutant model. *ACS Chem Neurosci*. 2016;7(5):588–598.
77. Tupal S, Faingold CL. Serotonin 5-HT_4 receptors play a critical role in the action of fenfluramine to block seizure-induced sudden death in a mouse model of SUDEP. *Epilepsy Res*. 2021;177:106777.
78. Li J, Nelis M, Sourbron J, et al. Efficacy of fenfluramine and norfenfluramine enantiomers and various antiepileptic drugs in a zebrafish model of Dravet Syndrome. *Neurochem Res*. 2021;46(9):2249–2261.
79. Martin P, de Witte PAM, Maurice T, et al. Fenfluramine acts as a positive modulator of sigma-1 receptors. *Epilepsy Behav*. 2020;105:106989.
80. Prakash S, Rathore C, Rana K, Patel H. Antiepileptic drugs and serotonin syndrome- a systematic review of case series and case reports. *Seizure*. 2021;91:117–131.
81. Rocha L, Lorigados-Pedre L, Orozco-Suárez S, et al. Autoradiography reveals selective changes in serotonin binding in neocortex of patients with temporal lobe epilepsy. *Prog Neuropsycopharmacol Biol Psychiatry*. 2007;31(6):1208–12018.
82. Savic I, Lindström P, Gulyás B, et al. Limbic reductions of 5-HT1A receptor binding in human temporal lobe epilepsy. *Neurology*. 2004;62(8):1343–1351.
83. Theodore WH, Hasler G, Giovacchini G, et al. Reduced hippocampal 5HT1A PET receptor binding and depression in temporal lobe epilepsy. *Epilepsia*. 2007;48(8)1526–1530.
84. Marinho AMDN, Lobão-Soares B, Targino HAS, et al. Decreased hippocampal serotonin 5HT1A expression in mesial temporal lobe of epilepsy patients. *Epilepsy Behav*. 2022;129:108574.
85. Griffin AL, Jaishankar P, Grandjean JM, et al. Zebrafish studies identify serotonin receptors mediating antiepileptic activity in Dravet syndrome. *Brain Commun*. 2019;1(1):fcz008.
86. Aygun H. Trazodone increases seizures in a genetic WAG/Rij rat model of absence epilepsy while decreasing them in penicillin-evoked focal and seizure model. *Epilepsy Behav*. 2020;103(Pt A):106847.
87. Moog M, Baraban SC. Clemizole and trazodone are effective antiseizure treatments in a zebrafish model of STXBP1 disorder. *Epilepsia Open*. 2022;7(3):504–511.
88. Grone BP, Qu Tiange, Baraban SC. Behavioral comorbidities and drug treatments in a zebrafish scn1lab model of DS. *ENeuro*. 2017;4(4):ENEURO.0066-17.2017.
89. Borowic KK, Gurdziel E, Czuczwar SJ. Trazodone reduces anticonvulsant action of certain classical antiepileptics in the mouse maximal electroshock model. *Pharmacol Rep*. 2012;64(5):1136–1145.

A Review of Neonatal Selective Serotonin Reuptake Inhibitor Withdrawal Syndrome

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The purpose of this review is to define "neonatal selective serotonin reuptake inhibitor (SSRI) withdrawal syndrome" (NSWS) from a developmental perspective and outline its management strategies as described in the current body of literature, with a focus on pharmaceutical interventions. A literature search was conducted with PubMed, OVID Medline, Google Scholar, Embase, and Web of Science. Search terms included *neonatal* and *SSRI* combined with the Boolean operator "AND" coordinated with the terms *withdrawal*, *poor neonatal adaptation*, and *neonatal abstinence syndrome*. Non-pharmacologic interventions include appropriate hydration, nutrition, and providing a quiet and soothing environment for the infant. Most treatment algorithms for neonatal withdrawal syndromes involve *in utero* exposure to opioids and other psychotropics, and it is rare to find one that outlines specific guidelines for the management of NSWS. Symptomatic pharmacologic management should be individualized to the patient. Potential measures can include the administration of clonidine for tachycardia, hypertension, diaphoresis, and restlessness; phenobarbital for seizures; or chlorpromazine for agitation and irritability. There is generally no role for the use of morphine or methadone in the treatment of NSWS without combined exposure to opioids *in utero*. Without studies specifically designed to understand NSWS and guidelines on treatment, there is a lack of clarity regarding the management of neonates with this syndrome. There are limited data differentiating NSWS from neonatal opioid withdrawal despite these disease states being caused by different pharmaceutical agents. There needs to be clear and comprehensive guidelines inclusive of newer studies and comparative treatment efficacies to promote evidence-based practices surrounding NSWS.

ABBREVIATIONS APGAR, Appearance, Pulse, Grimace, Activity, and Respiration; BDNF, brain-derived neuropathic factor; CNS, central nervous system; FNAST, Finnegan Neonatal Abstinence Scoring Tool; GI, gastrointestinal; HPA, hypothalamic-pituitary-adrenal; NAS, neonatal abstinence syndrome; NICU, neonatal intensive care unit; NOWS, neonatal opioid withdrawal syndrome; NSWS, neonatal SSRI withdrawal syndrome; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; 5HT, serotonin

KEYWORDS neonatal abstinence syndrome; poor neonatal adaptation; selective serotonin reuptake inhibitors; SSRI withdrawal; substance withdrawal syndrome

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Introduction

As many as 11.9% of women experience perinatal depression.[1,2] Depression is associated with psychological alterations and psychosocial sequelae that can negatively affect pregnancy outcomes independently of drug exposure, such as inadequate maternal weight gain, underutilization of health care resources, smoking, substance use, preeclampsia, and suicide.[3] The mainstay treatments for perinatal depression include cognitive-behavioral therapy and antidepressants such as selective serotonin reuptake inhibitors (SSRIs) including fluoxetine, paroxetine, sertraline, citalopram, and escitalopram.[4]

The National Birth Defects Prevention Registry estimates that approximately 100,000 infants born in the United States each year are exposed to SSRIs during fetal development, and about 70% of women taking SSRIs at conception continue them throughout pregnancy.[1] While both perinatal depression and SSRI exposure can affect reproductive outcomes, SSRI treatment may present a more favorable risk-benefit balance than the risks of perinatal depression-related sequelae.[2] However, prolonged fetal exposure to SSRIs is associated with physical and psychological signs of withdrawal in up to 30% of newborns.[1,5]

Controversy persists regarding the appropriate terminology for SSRI withdrawal. As a result, multiple terms have been used in the peer-reviewed literature to describe this condition, including neonatal abstinence syndrome (NAS), neonatal SSRI discontinuation syndrome, neonatal serotonergic discontinuation

syndrome, neonatal serotonergic withdrawal syndrome (NSWS), poor neonatal adaptation syndrome, neonatal antidepressant discontinuation syndrome, and neonatal antidepressant exposure syndrome.[6–12] The use of multiple and inconsistent terms has led to confusion and a lack of standardization in the literature. Systematic reviews by Fava and colleagues,[13] Harvey and Slabbert,[14] and Wang and Cosci[15] emphasize that, based on the pharmacologic mechanism(s) underlying this condition (reviewed below), SSRI withdrawal rather than discontinuation is the proper terminology.[13–15] This article will use the terms *neonatal abstinence syndrome* (NAS) to refer to withdrawal from *in utero* drug exposure leading to clinical symptoms, *neonatal opioid withdrawal syndrome* (NOWS) to refer to neonatal withdrawal from opioid exposure, and *neonatal SSRI withdrawal syndrome* (NSWS) to refer to neonatal withdrawal from SSRI exposure.

This narrative review aims to define NSWS, discuss its pathophysiology, and outline management strategies described in the current literature, focusing on pharmacologic interventions.

Materials and Methods

A literature search was conducted with PubMed, OVID Medline, Google Scholar, Embase, and Web of Science for articles published between 1995 and 2022. Search terms included *neonatal* and *SSRI* combined with the Boolean operator "AND," coordinated with the terms *withdrawal*, *poor neonatal adaptation*, and *neonatal abstinence syndrome* combined with the Boolean operator "OR." The explode feature and MeSH terms were used within PubMed and Medline. Articles on NOWS, articles that did not research the neonatal population, and articles not written or translated in English were excluded. Titles and abstracts were reviewed by at least 2 authors for inclusion in the narrative review, and full texts were obtained for relevant articles. Guidance was provided by faculty practitioners with formal training in drug information, medication-use safety and policy, neonatology, and pediatrics. A total of 120 articles were identified. Following the review process, 47 articles were excluded, and 73 articles were included in the final article.

Pathophysiology of NSWS

The underlying pathophysiology of SSRI withdrawal remains incompletely understood, and much of the current evidence is derived from preclinical rodent models. SSRI withdrawal likely results from the sudden lack of available serotonin (5HT) in the synapses of 5HT neurons in the brain, spinal cord, and gut, following adaptive changes in 5HT receptor sensitivity with chronic SSRI exposure.[10] The SSRIs increase intrasynaptic 5HT in serotonergic neurons by binding to the high-affinity presynaptic 5HT transporter that is responsible for 5HT reuptake.[11,12] The affinity of 5HT transporter for 5HT is decreased, resulting in an immediate increase in synaptic 5HT exposure, and the rapid appearance of typical SSRI adverse effects. In contrast, the antidepressant benefit of SSRIs typically requires 4 to 6 weeks of chronic dosing.[11–14]

The term *neuronal plasticity* describes adaptive changes in both synaptic number and function, and may help explain the delay in clinical benefits observed when starting SSRI therapy.[14,16] Neuroplasticity appears to be mediated by the activity of the hypothalamic-pituitary-adrenal (HPA) axis, the production of neurotrophic factors such as brain-derived neuropathic factor (BDNF), and glutamate, the primary excitatory neurotransmitter in the brain.[16–19] Activation of the HPA axis causes an increase in cortisol secretion, contributing to neuronal atrophy in the prefrontal cortex and hippocampus, and behavioral stress reduces the function of BDNF.[17] Chronic SSRI administration increases BDNF expression, enhancing synaptic formation and hippocampal neurogenesis.[17] Abrupt SSRI discontinuation causes a sudden, temporary intrasynaptic deficiency of 5HT, inducing a stress response.[10,14] Postsynaptic 5HT2C receptors are strongly implicated in regulating behavioral stress responses. Still, evidence also suggests the involvement of HPA axis activation, N-methyl-d-aspartate receptor signaling, and alterations in dopaminergic, adrenergic, and cholinergic transmission.[14,20]

Notably, the adaptive effects of chronic SSRI exposure on cortisol concentrations have been observed in neonates undergoing SSRI withdrawal.[21,22] Pawluski and colleagues[21] measured serum cortisol and corticosteroid-binding globulin concentrations in prenatal SSRI exposed (n = 25) and non-exposed (n = 40) neonates born by vaginal or cesarean delivery. Serum cortisol concentrations were significantly higher following vaginal delivery than by cesarean delivery, regardless of SSRI exposure ($p \leq 0.003$), but in the subgroup born by vaginal delivery, serum corticosteroid-binding globulin concentrations were significantly higher in the neonates that had been exposed to prenatal SSRIs ($p \leq 0.009$). No differences were observed in neonates delivered by cesarean delivery, regardless of SSRI exposure.[21] Kieviet et al[22] studied hair cortisol concentrations in 25 neonates exposed to prenatal SSRIs who developed withdrawal, 40 exposed neonates who did not develop withdrawal, and 105 neonates without prenatal exposure. The association of SSRI withdrawal and elevated hair cortisol concentrations was only evident in female neonates, with higher concentrations in those with withdrawal than those without withdrawal ($p = 0.04$).[22]

Clinical Presentation and Diagnosis

NSWS can present as a constellation of autonomic nervous system, central nervous system (CNS), and gastrointestinal (GI) symptoms that vary in severity based on gestational age, comorbidities, the SSRI characteristics (e.g., dose, protein-binding capacity,

half-life, presence of active metabolites, and other pharmacokinetic parameters), and additional maternal risk factors such as duration of SSRI use and polydrug use during pregnancy.[6–8] The onset of symptoms varies based on the pharmacokinetics of the SSRI used. The onset of symptoms typically occurs shortly after birth or within the first few days of life. Neonates who do not have symptoms within the first 48 hours are extremely unlikely to become symptomatic. A shorter drug half-life and longer time since last maternal serotonin norepinephrine reuptake inhibitor (SNRI) or SSRI ingestion are associated with an earlier onset of symptoms in the neonate. Symptoms of NSWS resolve hours to days after birth.[7] In contrast, neonates with NOWS present with symptoms within 72 hours of birth or as late as 5 to 10 days after birth and can last 1 week to 6 months.

Klinger and Merlob[7] divide the presenting signs and symptoms of NSWS into 4 domains, with an initial period of CNS depression, followed by CNS hyperactivity, GI disturbances, and respiratory symptoms (Table). The CNS depression phase commonly includes hypotonicity and poor sucking reflex, while the period of CNS hyperactivity often includes hypertonicity, restlessness, tremor, high-pitched or continuous crying, and disturbed patterns of sleep. Occasional autonomic nervous system signs and symptoms include temperature instability, diaphoresis, nasal congestion, and skin mottling. Common GI signs and symptoms include vomiting or regurgitation, poor feeding, and an uncoordinated sucking reflex, while respiratory difficulties commonly include tachypnea.[7] Notably, *in utero* SSRI exposure has been shown to increase the risk of premature delivery and neonatal intensive care unit (NICU) admission.[23] Yang and colleagues[23] studied 214 pregnant women: 41 receiving an SNRI or SSRI, 79 with a mood disorder not treated with an antidepressant, and 79 control subjects. Compared with control subjects, newborns of mothers taking SNRIs or SSRIs were more likely to be premature (24.5% vs 8.9%; mean birth weight, 3304.3 ± 704.4 vs 3546.3 ± 567.8 g), have a 5-minute APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score lower than 8 (6.2% vs 0%), and require NICU admission (33.3% vs 10.3%).

Approximately 2% of women taking an SSRI during their second- or third-trimester pregnancy are also using an opioid, 17% a sedative or hypnotic, and approximately 9% a benzodiazepine.[8] Concomitant use of such drugs with SSRIs has been shown to increase the severity score of NSWS and the need for NICU admission during management.[24–27] Symptoms commonly observed with both NSWS and NOWS include high-pitched cry, tremor, poor feeding, and loose stool. Restless sleep, increased muscle tone, hyperactive Moro reflex, exaggerated sucking, disturbances (fever, sweating, frequent yawning or sneezing, and nasal stuffiness or flaring), and tachypnea are more commonly observed with NOWS, although they can present in a newborn with NSWS.[5,28] One key symptom that is more often seen in NSWS than in NOWS is persistent pulmonary hypertension.[7] Another consideration in differentiating possible NSWS from other etiologies such as serotonin syndrome or acute neonatal encephalopathy is the mother's medication history. A thorough medication reconciliation should be one of the first steps in assessing neonates with symptoms similar to NSWS, to distinguish symptoms from other disease states and medication withdrawals.[10]

Table. Presenting Signs and Symptoms of Neonatal Selective Serotonin Reuptake Inhibitor Withdrawal Syndrome[7]

System	Common	Occasional	Rare
CNS depression	Hypotonicity Poor sucking	Lethargy Weak crying	Aphonia
CNS hyperactivity	Restlessness Tremor Hypertonicity High-pitched crying Disturbed sleep patterns	Hyperreflexia Exaggerated Moro reflex Seizures	Frequent yawning or sneezing
ANS		Temperature instability Diaphoresis Nasal congestion Skin mottling	
GI	Vomiting Poor feeding Regurgitation Uncoordinated sucking	Diarrhea Dehydration	
Respiratory	Tachypnea	Dyspnea	

ANS, autonomic nervous system; CNS, central nervous system; GI, gastrointestinal

The Finnegan Neonatal Abstinence Scoring Tool (FNAST) was developed to diagnose withdrawal in infants prenatally exposed to opioids, but has also been used to assess and track the progression of neonatal symptoms in SSRI-exposed infants.[6,7] The Finnegan scoring system comprises 4 categories (CNS, Respiratory, GI, and Other symptoms), and classifies a score of 8 or above as severe, 4 to 7 as mild, and 0 to 3 as normal. Forsberg et al[6] modified the Finnegan scoring system to monitor 205 neonates exposed to SSRIs *in utero*, and the modified Finnegan scoring system is now the most commonly used monitoring tool in the United States.[5–7] This modified scoring system breaks down symptoms by organ class: CNS (21 points), Respiratory (6 points), GI (9 points), and Other (4 points). If the Finnegan score is ≥8, the neonate requires pharmacologic treatment. However, there are several limitations to using the Finnegan scoring system in the setting of NSWS. The clinical evidence to validate the cutoff score of 8 to necessitate pharmacologic intervention is lacking. The Finnegan score is often used to guide the management of NSWS simply because a validated instrument specific to NSWS is lacking, but results should be interpreted with caution.

Developmental Review

In regard to the impact NSWS has on development, there has been a reported slight delay (within normal limits) in the achievement of motor milestones in children exposed to SSRIs during gestation, but no differences were observed between the exposed and control groups at 19 months.[29] Limited data are available that follow up exposed neonates through puberty, which is a critical neurodevelopmental stage.[2]

Exposed fetuses tend to have a shorter gestation length than unexposed fetuses, reduced fetal head growth, lower birth weight, pulmonary hypertension, other malformations at birth, and increased risk for social behavioral abnormalities.[30,31] Because these are known effects of SSRIs, it has been associated with delays in developmental milestones early in a newborn's life.[32]

Some studies have concluded that the differences in development are caused by other factors underlying treatment than the SSRI medication itself.[30] To account for different lifestyle environments, one study focused on 45 pairs of siblings with ages ranging from 3 to approximately 7 years, where 1 sibling (mostly second-born) was exposed to SSRIs while their sibling was not. To assess each pair's intelligence and behavior, the Wechsler Preschool and Primary Scale of Intelligence–Third Edition, Child Behavior Checklist, and Conners Parent Rating Scale–Revised were used. It was found that the intelligence quotients and rates of problematic behaviors were not significantly different. Thus, SSRIs were found not to be neurotoxic.[33]

The literature is not without limitations; many SSRI neonatal developmental studies include a small number of participants, children younger than 3 years, clinical disorders, and participants from clinics vs the general population.[30]

Acute Management of Neonatal SSRI Withdrawal Syndrome

The management of NSWS is not well defined in the literature and largely overlaps with the management of NOWS. All neonates with *in utero* exposure to SSRIs should be observed for at least 48 hours, and a FNAST score should be measured every 8 hours to guide therapy.[7,34] Based on limited literature, if the score is ≥8 and the newborn presents with severe symptoms, they should be monitored in a NICU and treated until their NSWS signs and symptoms normalize to a score of ≤3.[5,7] Although literature references the use of the FNAST score to guide therapy, there are varying clinical practices owing to the lack of a standard of care for the management of NSWS. Therefore, treatment should be individualized to the patient and targeted to manage the presenting symptoms. Current treatment strategies for symptomatic management include both non-pharmacologic and pharmacologic interventions.

Supportive Measures. The primary goal of supportive care measures is to ensure the newborn remains comfortable through the withdrawal episodes. Mainstays of care during observation include appropriate hydration, nutrition, and providing a quiet and soothing environment.[35] The mother can also swaddle the newborn and increase skin-to-skin contact, which can help improve the infant's breathing and temperature regulation.[36] In addition, breastfeeding in particular, has been theorized to decrease the duration and severity of withdrawal symptoms owing to the presence of SSRIs and their metabolites in breast milk, leading to continued exposure; however, this has not been studied in major trials and is an area for further research.[7,36,37] The American College of Obstetricians and Gynecologists strongly recommends against the discontinuation of SSRIs for mental health treatment if the sole concern is the pregnancy or lactation status of the mother, because drug transmission is more limited through lactation than through fetal exposure. Additionally, more severe consequences can result from the abrupt discontinuation of SSRIs.[38]

Pharmacologic Interventions. Generally, pharmacologic management should be considered when the FNAST score is ≥8 on 3 consecutive score measurements performed at intervals of 8 hours.[7,34] In most cases of NOWS, treatment revolves around controlled re-exposure and tapering of the causative agent.[7,39] However, there are no established data on the effects of using an SSRI taper schedule in neonates with NSWS. The following medications discussed in this section are used based on an individualized approach

to treat the withdrawal symptoms associated with NSWS rather than to treat the pathology associated with the withdrawal.

Clonidine. Clonidine has been studied as an adjunctive or monotherapy agent for the treatment of NSWS.[38] Clonidine is an alpha-2-adrenergic receptor agonist and is proposed to reduce withdrawal symptoms through a negative feedback mechanism by inhibiting the CNS sympathetic activity. This results in a net reduction in autonomic activity, thus reducing the withdrawal symptoms of tachycardia, hypertension, diaphoresis, restlessness, and diarrhea.[37] In case reports, clonidine has been used successfully as a first-line monotherapy agent over conventional agents in neonates exposed only to SSRIs *in utero*.[40,41] The suggested initial dose is 1 mcg/kg, with a maximum dose of 4 mcg/kg administered orally every 3 to 4 hours (in contrast to the frequency for NAS, namely every 3 to 6 hours).[40,42] This dosing regimen may vary, but is largely agreed upon in both SSRI and opioid-based NAS treatment studies. Clonidine is not commercially available in a liquid formulation but can be extemporaneously compounded as either a 0.01-mg/mL or 0.02-mg/mL oral suspension or solution from 0.1-, 0.2-, or 0.3-mg tablets. Notably, a 0.1-mg/mL (100 mcg/mL) concentration can be prepared, but this is too concentrated for neonatal dosing and can inadvertently lead to medication errors and patient harm. It is important to note that symptomatic bradycardia was seen in a case report after administering clonidine at a dose of 4 mcg/kg every 3 hours, highlighting the need for careful monitoring of heart rate during initiation.[43,44] Symptoms pertaining to alterations in feeding, weight gain or loss, or blood pressure were not seen with significant changes throughout the course of reviewed studies. While benefits were observed, most evidence for this indication comes from case reports, which limits the generalizability of this recommendation.[42] However, clonidine remains the most well-supported pharmacologic agent in the management of NSWS.

Other Pharmacologic Agents. Other medications have been considered adjunctive agents to control symptoms associated with NSWS, but their use is limited by the lack of data in NSWS. Chlorpromazine has been used to decrease autonomic overactivity and promote sedation, making it beneficial in attenuating CNS symptoms associated with SSRI withdrawal.[45–48] Common side effects associated with chlorpromazine that may affect the newborn include sedation, anticholinergic effects, and QTc prolongation.[47] As a result, blood pressure, heart rate, and heart rhythm must be closely monitored. Owing to the adverse events associated with chlorpromazine and its need for extensive monitoring, it has fallen out of favor as a treatment option for NOWS. Evidence suggests that patients treated with chlorpromazine as a sedative for NOWS have higher rates of treatment failure, leading to its unfavorable use, but the same cannot be determined for NSWS owing to insufficient literature.[48,49]

Symptomatic pharmacologic management of NSWS may also include the administration of phenobarbital to control seizures, irritation, or convulsions. Phenobarbital is a barbiturate used as first-line therapy for neonatal seizures, given its high efficacy, low cost, and favorable adverse effect profile.[47] The recommended phenobarbital dosing strategy varies considerably.[45,50,51] However, significant adverse effects associated with phenobarbital include CNS and respiratory depression, as well as irritability, hyperactivity, and long-term adverse neurodevelopmental outcomes particularly in children. While respiratory depression may be avoided with therapeutic drug monitoring, phenobarbital's other adverse effects cannot, which resulted in its falling out of favor for treating NSWS.[47,52–55] Other antiepileptic medications have been studied for efficacy in controlling neonatal seizures, such as levetiracetam, but further research is needed to explore these alternative antiseizure agents in the setting of NSWS.[56] Evidently, data support the clinical utility of phenobarbital in managing seizures associated with NSWS, but the risks must be carefully evaluated prior to its use.

Treatment for Mixed Neonatal Opioid and SSRI Exposure. In the case of neonatal withdrawal from polypharmacy exposure to opioids and SSRIs, morphine and methadone can be used to promote analgesia and sedation. Morphine is a short-acting natural opioid, compared with methadone, which is a longer-acting synthetic opioid.[57] Some studies show that neonates with NAS, inclusive of those with NSWS, are treated with morphine or methadone owing to *in utero* opioid exposure or polysubstance exposure to opioids and SSRIs. However, no studies currently exist providing clinical evidence of the use of morphine or methadone in the standalone setting of NSWS.[37,57–63] Relevant side effects of methadone and morphine that limit their use are GI disturbances, poor feeding, CNS depression, respiratory depression, and general signs of rebound.[21,62,64,65] Other opioid subsidiaries, including paregoric elixir and tincture of opium, were historically the drugs of choice but have since fallen out of favor owing to concerns for patient safety and the lack of standardization for their formulation composition.[57,62,66] There is a lack of concrete evidence for opioid use in NSWS without opioid co-exposure, and by weighing the risks and benefits of opioids, these treatment options should be reserved for NSWS symptomatic management only if the mother's medication history reveals that the neonate had a polysubstance *in utero* exposure to opioids and SSRIs. While phenobarbital is of key consideration for treating symptomatic seizures, it is also important to note its role in a mixed presentation. The use of phenobarbital has been traditionally preferred for non-opiate–related NAS, targeting symptoms of CNS irritability.[50] Owing to the adverse

overdepressant effects, such as decreased sucking reflex, and its ethanol-ethanol–containing commercially available formulations, resulting in potential adverse effects toward neurodevelopmental outcomes in infants, it has since fallen out of favor as a first-line agent.[50,67]

Clinical Trials and Research

As of the writing of this article, only 24 studies exploring NAS are registered in ClinicalTrials.gov. After excluding studies exploring NAS due to opioid use disorder, 1 study focused on the pharmacologic management of NAS in the context of SSRI exposure *in utero*. Challenges in studying this patient population include difficulty in recruitment during the COVID-19 pandemic, difficulty obtaining parental consent, and lack of a consensus on nomenclature. As SSRI use in mothers is becoming more prevalent, there is a substantial need for further research on developmental changes related to SSRI use, in addition to more effective treatment options for NSWS.

Conclusions

Despite the available literature on NSWS, much remains unclear regarding treatment strategies, awareness of this condition, and high-quality evidence and guidelines. With the rise in social media–led awareness of and initiatives on mental health—hoping to reduce the stigma surrounding this disorder—more women are finding guidance and empowerment through online support groups and forums to seek professional help for their perinatal depression.[68] With the increased prevalence of psychiatric diagnoses among women of childbearing age, we may observe rising trends in both SSRI use as well as NSWS. Specifically during the COVID-19 pandemic, rates of depression diagnoses among pregnant women were higher than among postpartum women, even though rates for both of these population groups increased over time.[69] Importantly, with greater willingness to accept treatments for depression during pregnancy, there has been a rise in antidepressant use among women from 10.6% to 13.8% over a decade.[70] Diving deeper, retrospective data show that between 1996 and 2005, antidepressant use increased from 2.0% to 7.6%, with SSRIs in particular from 1.5% to 6.2%.[71] Because SSRIs are first-line pharmacologic agents used for the management of depression in pregnant women, these agents are greatly used, leading to an increasing prevalence of risk for NSWS.[72]

Much remains unknown about the burden of NSWS, its natural course, and effective therapies. Part of the uncertainty lies in the confusing terminology used for neonatal withdrawal syndromes. Currently, the all-encompassing term of NAS includes the use of various substances that may precipitate neonatal withdrawal. Expenditure in NAS is known to be costly, with the average cost per infant estimated at $22,552. Compounded with the financial burden, more vulnerable populations who rely on Medicaid or are without insurance are reported to have the highest incidence.[73] NSWS can be assumed to contribute to this cost, but the exact details have not been previously explored. Furthermore, the rise of polypharmacy approaches to depression therapy may complicate diagnosis and management. Pregnant women with depression may initiate SSRI therapy on a background of other medications for additional comorbidities, thus blurring the relationship between SSRI use and neonatal development.[39] Additional factors to be considered include the lack of long-term studies that reliably follow up patients for delayed outcomes affected by changing environments and dysfunctional caregivers.[37] Considering these points, there is a need for clear and comprehensive guidelines inclusive of more recent studies and comparative treatment efficacies to promote evidence-based practices surrounding NSWS.

Furthermore, there is immense overlap in the literature for terminology related to withdrawal associated with SSRIs, opioids, and other psychotropics despite these agents being used for distinct disease states. A simplified standard disease state name would facilitate delineating the different withdrawal settings and assist with various treatment options. Therefore, there is a need to agree on a specific name for withdrawal syndrome specific to SSRIs, such as the proposed *neonatal SSRI withdrawal syndrome* (NSWS). The distinction in naming could provide a clearer target for treatment research moving forward. Current research tends to group SSRI and SNRI use in pregnant women, further greying the specificity to SSRIs. In the same path, studies could be easily compared with a new modality for a diagnostic tool specific to this syndrome. Without studies specifically targeting populations with NSWS, there is limited literature for practitioners to provide care for affected neonates. They may also struggle to provide adequate context to affected patients regarding the potential risk of SSRI use during pregnancy.

The methodologic limitations of published studies introduce heterogeneity and uncertainty in the proposed NSWS pathophysiology and treatment models. The scope of this review was limited to SSRIs and did not include other agents such as SNRIs or atypical antidepressants that may be implicated in NAS. The objective in this limitation was to avoid generalized conclusions on the efficacy of SSRI and SNRI treatment when the studies used had a mixed tendency to group the 2 together or study only SSRIs. Given the involvement of vulnerable populations, most pathophysiologic models of SSRI withdrawal syndromes are rooted in animal models, which may not translate fully to human patients. Furthermore, the observational nature of most human NSWS studies introduces information bias in possible misclassification of antidepressant exposure, thus biasing estimates of NSWS sequela—recall of SSRI

use may be increased in response to serious neonatal adverse effects. Finally, bioethical concerns complicate the prospective or interventional analysis of NSWS natural history; however, prospective analysis of treatment modalities may be reasonable given the lack of a single standard of care for treatment.

The path to better understanding NSWS requires clearer terminology, a mechanistic understanding of pathophysiology, and a more rigorously explored treatment algorithm. Currently, adaptive changes in 5HT receptors, cortisol concentrations, and synaptic function within the neonate are proposed as pathophysiologic changes contributing to NSWS. The current diagnosis and treatment determination is based on a modified FNAST scoring system, and treatment targets supportive measures using phenobarbital, clonidine, and, alternatively, chlorpromazine. Additional research for SSRI-individualized regimens is required to better understand the mechanistic patterns of withdrawal, and subsequently individualized treatment patterns to SSRI-related cases, from the generalized patterns currently recommended for NAS.

Article Information

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References

1. Huybrechts KF, Palmsten K, Mogun H, et al. National trends in antidepressant medication treatment among publicly insured pregnant women. *Gen Hosp Psychiatry*. 2013;35(3):265–271.
2. Woody CA, Ferrari AJ, Siskind DJ, et al. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. *J Affect Disord*. 2017;219:86–92.
3. Bonari L, Pinto N, Ahn E, et al. Perinatal risks of untreated depression during pregnancy. *Can J Psychiatry*. 2004;49(11):726–735.
4. Wichman CL, Stern TA. Diagnosing and treating depression during pregnancy. *Prim Care Companion CNS Disord*. 2015;17(2). https://www.psychiatrist.com/pcc/diagnosing-treating-depression-during-pregnancy/
5. Levinson-Castiel R, Merlob P, Linder N, et al. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. *Arch Pediatr Adolesc Med*. 2006;160(2):173–176.
6. Forsberg L, Navér L, Gustafsson LL, et al. Neonatal adaptation in infants prenatally exposed to antidepressants—clinical monitoring using Neonatal Abstinence Score. *PLoS One*. 2014;9(11):e111327.
7. Klinger G, Merlob P. Selective serotonin reuptake inhibitor induced neonatal abstinence syndrome. *Isr J Psychiatry Relat Sci*. 2008;45(2):107–113.
8. Anbalagan S, Mendez MD. Neonatal abstinence syndrome. In: *StatPearls*. StatPearls Publishing; 2023. Accessed July 24, 2023. http://www.ncbi.nlm.nih.gov/books/NBK551498/
9. Herbst F, Gortner L. Paroxetine withdrawal syndrome as differential diagnosis of acute neonatal encephalopathy? *Z Geburtshilfe Neonatol*. 2003;207(6):232–234.
10. Schatzberg AF, Haddad P, Kaplan EM, et al. Possible biological mechanisms of the serotonin reuptake inhibitor discontinuation syndrome: Discontinuation Consensus Panel. *J Clin Psychiatry*. 1997;58(suppl 7):23–27.
11. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors: serotonin receptors and pathways mediate therapeutic effects and side effects. *J Affect Disord*. 1998;51(3):215–235.
12. O'Donnell JM, Bies RR, Williams AJ. Drug therapy of depression and anxiety disorders. In: Brunton LL, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 14th ed. McGraw Hill; 2023. Accessed May 22, 2023. https://accessmedicine.mhmedical.com/book.aspx?bookid=3191&sectionid=269307357
13. Fava GA, Gatti A, Belaise C, et al. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. *Psychother Psychosom*. 2015;84(2):72–81.
14. Harvey BH, Slabbert FN. New insights on the antidepressant discontinuation syndrome. *Hum Psychopharmacol*. 2014;29(6):503–516.
15. Wang J, Cosci F. Neonatal withdrawal syndrome following late in utero exposure to selective serotonin reuptake inhibitors: a systematic review and meta-analysis of observational studies. *Psychother Psychosom*. 2021;90(5):299–307.

16. Amidfar M, Woelfer M, Réus GZ, et al. The role of NMDA receptor in neurobiology and treatment of major depressive disorder: evidence from translational research. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;94:109668.
17. Duman RS, Aghajanian GK, Sanacora G, et al. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med*. 2016;22(3):238–249.
18. Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. *Nat Rev Neurosci*. 2010;11(10):682–696.
19. Du MY, Wu QZ, Yue Q, et al. Voxelwise meta-analysis of gray matter reduction in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;36(1):11–16.
20. Martin CBP, Hamon M, Lanfumey L, et al. Controversies on the role of 5-HT(2C) receptors in the mechanisms of action of antidepressant drugs. *Neurosci Biobehav Rev*. 2014;42:208–223.
21. Pawluski JL, Brain UM, Underhill CM, et al. Prenatal SSRI exposure alters neonatal corticosteroid binding globulin, infant cortisol levels, and emerging HPA function. *Psychoneuroendocrinology*. 2012;37(7):1019–1028.
22. Kieviet N, de Groot S, Noppe G, et al. Is poor neonatal adaptation after exposure to antidepressant medication related to fetal cortisol levels: an explorative study. *Early Hum Dev*. 2016;98:37–43.
23. Yang A, Ciolino JD, Pinheiro E, et al. Neonatal discontinuation syndrome in serotonergic antidepressant-exposed neonates. *J Clin Psychiatry*. 2017;78(5):605–611.
24. Källén B, Reis M. Neonatal complications after maternal concomitant use of SSRI and other central nervous system active drugs during the second or third trimester of pregnancy. *J Clin Psychopharmacol*. 2012;32(5):608–614.
25. Laine K, Heikkinen T, Ekblad U, et al. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Arch Gen Psychiatry*. 2003;60(7):720–726.
26. Sanz EJ, De-las-Cuevas C, Kiuru A, et al. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *Lancet*. 2005;365(9458):482–487.
27. Bhatt-Mehta V, Richards J, Sturza J, et al. Impact of in-utero exposure to selective serotonin reuptake inhibitors and opioids on neonatal opioid withdrawal syndrome. *J Addict Med*. 2019;13(3):227–234.
28. Heyward A, Minich N, Hoffman AC, et al. Characteristics and outcomes of neonatal opioid withdrawal syndrome in preterm infants: a retrospective cohort study in the current era. *J Perinatol*. 2023;43(7):909–915.
29. Pedersen LH, Henriksen TB, Olsen J. Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. *Pediatrics*. 2010;125(3):e600–e608.
30. Viktorin A, Uher R, Kolevzon A, et al. Association of antidepressant medication use during pregnancy with intellectual disability in offspring. *JAMA Psychiatry*. 2017;74(10):1031–1038.
31. Klinger G, Frankenthal D, Merlob P, et al. Long-term outcome following selective serotonin reuptake inhibitor induced neonatal abstinence syndrome. *J Perinatol*. 2011;31(9):615–620.
32. Hanley GE, Brain U, Oberlander TF. Infant developmental outcomes following prenatal exposure to antidepressants, and maternal depressed mood and positive affect. *Early Hum Dev*. 2013;89(8):519–524.
33. Nulman I, Koren G, Rovet J, et al. Neurodevelopment of children prenatally exposed to selective reuptake inhibitor antidepressants: Toronto sibling study. *J Clin Psychiatry*. 2015;76(7):e842–e847.
34. Sie SD, Wennink JMB, van Driel JJ, et al. Maternal use of SSRIs, SNRIs and NaSSAs: practical recommendations during pregnancy and lactation. *Arch Dis Child Fetal Neonatal Ed*. 2012;97(6):F472–F476.
35. Koren G, Finkelstein Y, Matsui D, et al. Diagnosis and management of poor neonatal adaptation syndrome in newborns exposed in utero to selective seretonin/norepinephrine reuptake inhibitors. *J Obstet Gynaecol Can*. 2009;31(4):348–350.
36. Kieviet N, Dolman KM, Honig A. The use of psychotropic medication during pregnancy: how about the newborn? *Neuropsychiatr Dis Treat*. 2013;9:1257–1266.
37. Hudak ML, Tan RC, Committee on Drugs, et al. Neonatal drug withdrawal. *Pediatrics*. 2012;129(2):e540–e560.
38. Miller ES, Metz T, Moore-Simas TA, et al. Treatment and management of mental health conditions during pregnancy and postpartum. *Obstet Gynecol*. 2023;141:1262–1288.
39. Warner CH, Bobo W, Warner C, et al. Antidepressant discontinuation syndrome. *Am Fam Physician*. 2006;74(3):449–456.
40. Burdine J, Luedtke S. Serotonin toxicity versus withdrawal: clonidine one size fits all? *J Pediatr Pharmacol Ther*. 2021;26(5):502–517.
41. Rivera-Hernandez P, Quin J, Slater-Myer L. Clonidine to treat neonatal withdrawal due to in-utero venlafaxine exposure. *Pediatrics*. 2018;142(1_MeetingAbstract):223.
42. O'Mara K, Gal P, Davanzo C. Treatment of neonatal withdrawal with clonidine after long-term, high-dose maternal use of tramadol. *Ann Pharmacother*. 2010;44(7–8):1342–1344.
43. Artigas V. Management of neonatal abstinence syndrome in the newborn nursery. *Nurs Womens Health*. 2014;18(6):509–514.
44. Clonidine (catapres hydrocloride) [prescribing information]. Maple Grove, MN: Upsher-Smith Laboratories; 1974. Revised March 2018.
45. Nordeng H, Lindemann R, Perminov KV, et al. Neonatal withdrawal syndrome after in utero exposure to selective serotonin reuptake inhibitors. *Acta Paediatr*. 2001;90(3):288–291.
46. Mazurier E, Cambonie G, Barbotte E, et al. Comparison of chlorpromazine versus morphine hydrochloride for treatment of neonatal abstinence syndrome. *Acta Paediatr*. 2008;97(10):1358–1361.
47. O'Donnell JM, Bies RR, Williams AJ. Hypnotics and sedatives. In: Brunton LL, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 14th ed. McGraw Hill; 2023. Accessed May 22, 2023. https://accessmedicine.mhmedical.com/content.aspx?sectionid=269719266&bookid=3191#269719380
48. Zankl A, Martin J, Davey JG, et al. Sedatives for opioid withdrawal in newborn infants. *Cochrane Database Syst Rev*. 2021;2021(5):CD002053.
49. Zimmermann U, Rudin C, Duò A, et al. Treatment of opioid withdrawal in neonates with morphine, phenobarbital, or

chlorpromazine: a randomized double-blind trial. *Eur J Pediatr*. 2020;179(1):141–149.
50. Burgos A, Burke B. Neonatal abstinence syndrome. *NeoReviews*. 2009;10:222–229.
51. Degiacomo J, Luedtke S. Neonatal toxicity from escitalopram use in utero: a case report. *J Pediatr Pharmacol Ther*. 2016;21(6):522–526.
52. El-Dib M, Soul JS. The use of phenobarbital and other anti-seizure drugs in newborns. *Semin Fetal Neonatal Med*. 2017;22(5):321–327.
53. Šíma M, Michaličková D, Slanař O. What is the best predictor of phenobarbital pharmacokinetics to use for initial dosing in neonates? *Pharmaceutics*. 2021;13(3):301.
54. Pauwels S, Allegaert K. Therapeutic drug monitoring in neonates. *Arch Dis Child*. 2016;101(4):377–381.
55. Maitre NL, Smolinsky C, Slaughter JC, et al. Adverse neurodevelopmental outcomes after exposure to phenobarbital and levetiracetam for the treatment of neonatal seizures. *J Perinatol*. 2013;33(11):841–846.
56. Sharpe C, Reiner GE, Davis SL, et al. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. *Pediatrics*. 2020;145(6):e20193182.
57. Davis JM, Shenberger J, Terrin N, et al. Comparison of safety and efficacy of methadone vs morphine for treatment of neonatal abstinence syndrome: a randomized clinical trial. *JAMA Pediatr*. 2018;172(8):741–748.
58. Langenfeld S, Birkenfeld L, Herkenrath P, et al. Therapy of the neonatal abstinence syndrome with tincture of opium or morphine drops. *Drug Alcohol Depend*. 2005;77(1):31–36.
59. Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*. 2014;134(2):e547–e561.
60. Brown MS, Hayes MJ, Thornton LM. Methadone versus morphine for treatment of neonatal abstinence syndrome: a prospective randomized clinical trial. *J Perinatol*. 2015;35(4):278–283.
61. Jones HE, Johnson RE, Jasinski DR, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Depend*. 2005;79(1):1–10.
62. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010;363(24):2320–2331.
63. Siu A, Robinson CA. Neonatal abstinence syndrome: essentials for the practitioner. *J Pediatr Pharmacol Ther*. 2014;19(3):147–155.
64. Hall ES, Meinzen-Derr J, Wexelblatt SL. Cohort analysis of a pharmacokinetic-modeled methadone weaning optimization for neonatal abstinence syndrome. *J Pediatr*. 2015;167(6):1221–1225.e1.
65. Bhatt-Mehta V, Ng CM, Schumacher RE. Effectiveness of a clinical pathway with methadone treatment protocol for treatment of neonatal abstinence syndrome following in utero drug exposure to substances of abuse*. *Pediatr Crit Care Med*. 2014;15(2):162–169.
66. Sauberan J, Rossi S, Kim JH. Stability of dilute oral morphine solution for neonatal abstinence syndrome. *J Addict Med.* 2013;7(2):113–115.
67. Brusseau C, Burnette T, Heidel RE. Clonidine versus phenobarbital as adjunctive therapy for neonatal abstinence syndrome. *J Perinatol*. 2020;40:1050–1055.
68. Moore D, Ayers S, Drey N. A thematic analysis of stigma and disclosure for perinatal depression on an online forum. *JMIR Ment Health*. 2016;3(2):e18.
69. Adrianto N, Caesarlia J, Pajala FB. Depression in pregnant and postpartum women during COVID-19 pandemic: systematic review and meta-analysis. *Obstet Gynecol Sci*. 2022;65(4):287–302.
70. Products - Data Briefs - Number 377. Published September 8, 2020. Accessed May 11, 2023. https://www.cdc.gov/nchs/products/databriefs/db377.htm
71. Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. *Am J Obstet Gynecol*. 2008;198(2):194.e1-5.
72. Armstrong C. ACOG guidelines on psychiatric medication use during pregnancy and lactation. *Am Fam Physician*. 2008;78(6):772–778.
73. Strahan AE, Guy GP, Bohm M, et al. Neonatal abstinence syndrome incidence and health care costs in the United States, 2016. *JAMA Pediatr*. 2020;174(2):200–202.

JPPT | Survey Study

Inhaled Tobramycin Usage in Critically Ill Pediatric Patients Without Cystic Fibrosis: A Pediatric Pharmacy-Association, Practice-Based Research Network Survey Study

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OBJECTIVE The purpose of this study was to characterize reported usage, dosage regimens, and monitoring practices of inhaled tobramycin in health systems with neonatal intensive care units (NICUs), pediatric intensive care units (PICUs), and cardiovascular intensive care units (CICUs) from the members of the Pediatric Pharmacy Association (PPA). The primary objective was to identify the number of respondents who use an inhaled tobramycin protocol. The secondary objectives included the main indications, dosage regimens, monitoring parameters used, and administration details for inhaled tobramycin.

METHODS A cross-sectional questionnaire was distributed to PPA members from March 28–May 22, 2023. Descriptive statistics were employed.

RESULTS The questionnaire was completed by respondents at 79 institutions; respondents at 61 institutions used inhaled tobramycin in PICUs (n = 45; 73.8%), NICUs (n = 36; 59.0%), and CICUs (n = 14; 23.0%). Most respondents (n = 73; 92.4%) in the 61 institutions that use inhaled tobramycin did not have an established protocol. The most common tobramycin product used was a tobramycin nebulization solution, and the most common indication was ventilator-associated tracheitis. Respondents noted the most common dosage regimen was 40 to 80 mg every 8 to 12 hours or 150 mg every 12 hours, regardless of patient age. Most respondents were unaware of the nebulizer used and the location of the nebulizer within the ventilator circuit. Additionally, the respondents noted that their intensive care units do not routinely check tobramycin serum concentrations.

CONCLUSION Most respondents did not have a standardized inhaled tobramycin protocol. There are variations in the dosage regimen, administration, and monitoring practices in critically ill children receiving inhaled tobramycin. Pediatric clinical pharmacists should work with interprofessional teams, including respiratory therapists and providers, to standardize the use of inhaled antibiotics.

ABBREVIATIONS AKI, acute kidney injury; CF, cystic fibrosis; CICU, cardiac intensive care unit; ICU, intensive care unit; IDSA: Infectious Diseases Society of America; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; PBRN, Pharmacy Practice-Based Research Network; PPA, Pediatric Pharmacy Association; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheitis

KEYWORDS pediatrics; inhaled tobramycin; acute kidney injury; mechanical ventilator; pharmacokinetics; nebulizers

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Introduction

In critically ill children with respiratory infections, such as ventilator-associated pneumonia (VAP) or ventilator-associated tracheitis (VAT), inhaled antibiotics are a potential treatment option. The 2016 Infectious Diseases Society of America (IDSA) guidelines for adults with VAP and hospital-acquired pneumonia recommend using inhaled colistin or aminoglycosides in addition to systemic antibiotics for patients with multidrug-resistant organisms.[1] However, there are no consensus recommendations on the use of inhaled antibiotics in critically ill children for VAP or VAT. In addition, there is a paucity of data on the efficacy and safety of inhaled antibiotics in critically ill adults and children.[2]

Several case reports and studies have evaluated the use of inhaled tobramycin in critically ill adults and

children.[3–11] Most of the case reports have described reports of critically ill patients with detectable tobramycin troughs and acute kidney injury (AKI).[3–6] Geller and colleagues[12] conducted a pharmacokinetic study in 258 patients with cystic fibrosis (CF) in the ambulatory care setting receiving inhaled tobramycin 300 mg twice daily by a PARI LC PLUS (Pari Respiratory, Midlothian, VA) nebulizer. They found that patients had a mean peak concentration of 1.2 mcg/mL, 1 hour after dosing and undetectable trough concentrations. However, 5 studies have evaluated the incidence of detectable serum concentrations in adults and children, with the majority being critically ill and without CF; these investigators found between 8.3% and 68.2% of patients had detectable serum concentrations, and up to 24.3% of patients developed AKI.[7–11] Several studies identified risk factors for detectable tobramycin serum concentrations, including mechanical ventilation, increased age, and AKI or chronic kidney disease at the time of inhaled tobramycin initiation.[9–11] However, the results of these studies are limited in that different tobramycin products, dosage regimens, nebulizer devices, and mechanical ventilator set-ups were used between studies.

There are many unknowns regarding inhaled tobramycin use in critically ill children regarding dosage regimen, type of nebulizers used, and placement of the nebulizer within the ventilator system. These factors are crucial as they potentially contribute to the variability in patient outcomes, such as detectable serum drug concentrations and the incidence of AKI. The purpose of this study was to characterize reported usage, dosage regimens, and monitoring practices of inhaled tobramycin in health systems with neonatal intensive care units (NICUs), pediatric intensive care units (PICUs), and pediatric cardiovascular intensive care units (CICUs). By identifying inconsistencies in current practices, this research aims to gather essential data that could support the development of standardized protocols, ultimately enhancing the safety and efficacy of inhaled tobramycin treatments in this vulnerable population.

Materials and Methods

Study Design and Survey Administration. This was a descriptive survey study of pediatric clinical pharmacists. The survey included 74 questions, including health-system demographics, policies of inhaled antibiotics for non-CF patients in the NICU, PICU, and CICU, inhaled tobramycin administration details, tobramycin product and dosage regimen, and monitoring considerations. Questions were asked separately for each unit type, consisting of multiple choice, mark all that apply, and text entry. Although the questionnaire included 74 questions, the length depended upon the number of units chosen. A summary of these questions is found in the Supplemental Appendix.

The electronic questionnaire was developed and distributed through Qualtrics (Provo, Utah) and sent through email using the Pediatric Pharmacy Association's (PPA) Pharmacy Practice-Based Research Network (PBRN) from March 28–May 22, 2023, with 2 reminder emails sent during the time frame. PPA members could forward the questionnaire link to nonmembers at their institution for increased participation. Based on the information provided by the PPA Interim Executive Director, the questionnaire was sent to approximately 957 pharmacist members representing 310 health systems, which included 268 NICUs (86.5%), 178 PICUs (57.4%), and 70 CICUs (22.6%). Clinicians were asked to provide the first 2 letters of the hospital street and the last 3 digits of the hospital zip code to ensure that duplicate responses did not occur. Participation in the survey was voluntary and anonymous. Incomplete surveys were excluded from the analysis.

Study Objectives and Data Analysis. Demographic data collected included geographical location (i.e., Northeast, Midwest, Southeast, Southwest, West) of the institution, number of pediatric beds, which intensive care unit(s) (ICU) in the institution used inhaled tobramycin in patients without CF, and whether the unit has a protocol for the use of inhaled antibiotics in critically ill patients without CF. Regarding each unit, the number of beds, along with components of the protocol (if applicable), were collected. The type of respiratory support, mode of delivery, type of nebulizer used, and the location of the nebulizer within the mechanical ventilator circuit (if applicable) were collected. In addition, the tobramycin product used, indications for use, dosage regimen, duration, and monitoring considerations were collected.

The primary objective was to identify the number of respondents who use inhaled tobramycin in critically ill pediatric patients without CF in the NICU, PICU, and CICU. The secondary objectives included the main indications, dosage regimens, and monitoring parameters used. An additional secondary objective was to identify administration details for inhaled tobramycin, including the type of respiratory support, mode of delivery, type of nebulizer used, and the location of the nebulizer within the mechanical ventilator circuit.

All investigators developed and reviewed the questionnaire to ensure its face validity. In addition, informal feedback was obtained from 2 pediatric pharmacists who serve on the PPA PBRN. Descriptive statistics, including frequencies and percentages, were used to summarize the survey responses using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

During the study period, 159 respondents accessed the questionnaire. Of these entries, 80 were excluded for the following reasons: opened link but did not complete required questions (n = 76) and duplicate submission of information from the same institution (n = 4). Seventy-nine responses from 79 unique health systems

were included for analysis. An overall response rate of 25.5% was calculated from the 310 health systems represented by PPA members.

Demographics of Respondents Using Inhaled Tobramycin in NICU/PICU/CICU. Sixty-one (77.2%) of 79 respondents indicated that they use inhaled tobramycin for critically ill children without CF in 1 or more ICU. Table 1 provides an overview of the health system and demographics of the 61 institutions using inhaled tobramycin in their ICUs. Most respondents were from the United States in either the Southeast (n = 15/61; 24.6%) or West (n = 14/61; 23.0%). In addition, most respondents (n = 25/61; 41.0%) had 200 or more pediatric beds in their health system. The number of respondents that used inhaled tobramycin in their ICUs varied, including 37 respondents (60.7%) with 1 ICU type, 14 (23.0%) with 2 types of ICUs, and 10 (16.4%) with 3 types of ICUs. The ICU with the most usage of inhaled tobramycin was the PICU (n = 45, 73.8%), followed by the NICU (n = 36; 59.0%) and CICU (n = 14; 23.0%). There was variability in the number of beds in the NICUs, PICUs, and CICUs.

Inhaled Tobramycin Protocol Components. Most respondents (n = 73, 92.4%) indicated that their institution did not have an inhaled tobramycin protocol. There was variability in the ICU type that had a protocol. Table 2 summarizes the protocol and administration details for inhaled tobramycin by ICU type. The majority of PICUs (n = 25/45; 56.6%) and NICUs (n = 16/36; 44.5%) use 1 of the commercially available inhaled tobramycin products for nebulization solution that has an FDA-labeled indication for eradication of *Pseudomonas aeruginosa* in CF patients (TOBI; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Bethkis, Cornerstone Therapeutics Inc., Woodstock, IN).[13,14] Some respondents noted that their ICUs use an intravenous tobramycin product either with or without preservatives for administration via nebulization, including the majority of CICUs (n = 10; 71.4%). Respondents were asked for indications for inhaled tobramycin, including for non-CF bronchiectasis, chronic colonization suppression, VAP, or VAT. There was variability in indication according to ICU type, with the highest indication among all ICUs for VAT (69.4%–77.8%).

Table 2 also summarizes the administration details of inhaled tobramycin according to ICU type. Most respondents (78.6%–88.9%, depending on the unit type) noted that inhaled tobramycin is administered in mechanically ventilated patients in their ICUs, with a smaller percentage of respondents (55.6%–66.7%) indicating that patients with high-frequency mechanical ventilation (e.g., high-frequency jet ventilator or high-frequency oscillatory ventilation) received inhaled tobramycin. For patients who are mechanically ventilated, most respondents noted that the endotracheal (90.0%–100%) or tracheostomy tube (66.7%–82.5%) were the main modes of delivery of inhaled tobramycin. Most respondents indicated that they were unaware of the nebulizer used and the location of administration within the mechanical ventilator circuit used to deliver inhaled tobramycin. The number of institutions using a vibrating mesh nebulizer ranged from 11.1% to 21.4%, depending upon ICU type. There were various responses from respondents who were aware of the delivery location in the ventilator circuit.

Table 1. Baseline Demographics of Health-Systems for Respondents Using Inhaled Tobramycin in Critically Ill Children Without Cystic Fibrosis

Variables	*N* (%)
Location of institutions:	
Northeast United States	10 (16.4)
Midwest United States	11 (18.0)
Southeast United States	15 (24.6)
Southwest United States	10 (16.4)
West United States	14 (23.0)
Outside of the United States	1 (1.6)
Number of pediatric hospital beds in the health system:	
50–99	17 (27.9)
100–149	10 (16.4)
150–199	9 (14.8)
≥ 200	25 (41.0)
Types of ICUs:	
NICU	36 (59.0)
PICU	45 (73.8)
CICU	14 (23.0)
Number of beds in NICU (n = 36):	
0–25	1 (2.8)
26–50	11 (30.6)
51–75	13 (36.1)
≥ 75	11 (30.6)
Number of beds in PICU (n = 45):	
0–25	27 (60.0)
26–50	14 (31.1)
51–75	3 (6.7)
≥ 75	1 (2.2)
Number of beds in CICU (n = 14):	
0–25	12 (85.7)
26–50	2 (14.3)
51–75	–
≥ 75	

CICU, cardiac intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit

Tobramycin Dosage Regimen and Monitoring. Respondents were asked to indicate the dosage regimen and duration for all 4 indications (i.e., non-CF bronchiectasis, suppression of chronic colonization, VAP, or VAT). Because VAT was the most common indication noted among ICU units, the subsequent analysis was focused on VAT. There was variability in the dosage and duration of VAT (Table 3). For the NICU and CICU, the most common dosage regimens were 40 to 80 mg every 8 to 12 hours (NICU [n = 18; 72.0%]; CICU [n = 5; 38.5%]) or 150 mg every 12 hours (NICU [n = 4; 16.0%];

Table 2. Inhaled Tobramycin Protocol and Administration Considerations Among ICUs

Variables	PICU (n = 45)	NICU (n = 36)	CICU (n = 14)
		N (%)	
Inhaled Antibiotic Policy Information and Product Used			
Has policy for inhaled antibiotics in critically ill children without CF	6 (13.3)	3 (8.3)	2 (14.3)
Components included in policy:	n = 6	n = 3	n = 2
Indications for use	3 (50.0)	2 (66.7)	1 (50.0)
Administration details	4 (66.7)	2 (66.7)	1 (50.0)
Dosage regimen	4 (66.7)	3 (100.0)	2 (100.0)
Monitoring considerations	4 (66.7)	2 (66.7)	1 (50.0)
Tobramycin product most frequently used:			
Solution for injection (10 mg/mL preservative-free)	10 (22.2)	10 (27.8)	3 (21.4)
Solution for injection (10 or 40 mg/mL)	10 (22.2)	10 (27.8)	7 (50.0)
Solution for inhalation (TOBI)	23 (52.2)	15 (41.7)	4 (28.6)
Solution for inhalation (Bethkis)	2 (4.4)	1 (2.8)	–
Indication for inhaled tobramycin:			
Non-CF bronchiectasis	18 (40.0)	6 (16.7)	3 (21.4)
Suppression of chronic colonization	33 (73.3)	20 (55.6)	8 (57.1)
VAP	28 (62.2)	17 (47.2)	8 (57.1)
VAT	35 (77.8)	25 (69.4)	13 (92.9)
Respiratory Support and Mode of Delivery With Mechanical Ventilation Used with Inhaled Tobramycin			
Respiratory support:			
Mechanical ventilation	40 (88.9)	30 (83.3)	11 (78.6)
High-frequency mechanical ventilation	25 (55.6)	24 (66.7)	8 (57.1)
Noninvasive mechanical ventilation	31 (68.9)	24 (66.7)	10 (71.1)
Mode of delivery with mechanical ventilator:			
Endotracheal tube	36 (90.0)	30 (100.0)	11 (100.0)
Tracheostomy tube	33 (82.5)	20 (66.7)	9 (81.8)
Mouthpiece	6 (15.0)	4 (13.3)	1 (9.1)
Nebulizer and Location of Nebulizer With Mechanical Ventilator			
Type of nebulizer used with mechanical ventilator:			
Jet or compression	9 (20.0)	4 (11.1)	2 (14.3)
Ultrasonic	5 (11.1)	5 (13.9)	1 (7.1)
Vibrating mesh	5 (11.1)	5 (13.9)	3 (21.4)
Unknown	26 (57.8)	21 (58.3)	8 (57.1)
Location of nebulizer with mechanical ventilator circuit:	n = 40	n = 30	n = 11
Distal (i.e., on the inlet of the humidifier)	6 (15.0)	4 (13.3)	–
Proximal (i.e., between patient wye connector within inspiratory limb of ventilator circuit)	2 (5.0)	4 (13.3)	1 (9.1)
Between the wye connector and the endotracheal tube	1 (2.5)	–	1 (9.1)
Unknown	31 (77.5)	22 (73.3)	9 (81.8)

CF, cystic fibrosis; CICU, cardiac intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheitis

CICU [n = 4; 30.8%]). The most common dosage regimen for VAT in the PICU was 300 mg every 12 to 24 hours (n = 13; 37.2%). Some respondents indicated that their ICUs adjust their dosage for patients with AKI (PICU [n = 8; 17.8%], NICU [n = 6; 16.7%], CICU [n = 6; 42.9%]). The most common duration noted for VAT among the ICUs was between 7 and 10 (45.7%–56.0%) and 11 and 14 days (17.1%–30.8%) (Table 3). However, a few respondents indicated that providers in their ICUs would use inhaled tobramycin every 14 or 28 days on and 14 or 28 days off instead of a defined duration.

Table 4 provides a summary of monitoring considerations with inhaled tobramycin among ICUs. There was a wide variability of renal function monitoring with serum creatinine while on inhaled tobramycin, with some monitoring daily and others not performing routine monitoring. A few respondents (8.9%–21.4%, depending on ICU type) indicated their ICUs monitor tobramycin

Table 3. Summary of Inhaled Tobramycin Dosing and Duration with VAT Among ICUs

Variables	PICU (n = 45)	NICU (n = 36)	CICU (n = 14)
		N (%)	
Number of ICUs using inhaled tobramycin for VAT	35 (77.8)	25 (69.4)	13 (92.9)
Dose:			
40–80 mg every 8–12 hours	11 (31.4)	18 (72.0)	5 (38.5)
150 mg every 12 hours	6 (17.1)	4 (16.0)	4 (30.8)
300 mg every 12–24 hours	13 (37.2)	1 (4.0)	2 (15.4)
Age and weight-dependent	2 (5.7)	1 (4.0)	2 (15.4)
Dosing not specified	3 (8.6)	1 (4.0)	–
Duration:			
1–6 days	7 (20.0)	1 (4.0)	1 (7.7)
7–10 days	16 (45.7)	14 (56.0)	7 (53.8)
11–14 days	6 (17.1)	8 (32.0)	4 (30.8)
15–21 days	1 (2.9)	–	–
14 days on and 14 days off	–	–	1 (7.7)
28 days on and 28 days off	2 (5.7)	1 (4.0)	–
Duration not specified	3 (8.6)	1 (4.0)	–

CICU, cardiac intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; VAT, ventilator-associated tracheitis

Table 4. Inhaled Tobramycin Monitoring Data by Unit

Variable	PICU (n = 45)	NICU (n = 36)	CICU (n = 14)
		N (%)	
Frequency of serum creatinine monitoring for patients on inhaled tobramycin:			
Daily	9 (20.0)	5 (13.9)	4 (28.6)
Every other day	2 (4.4)	1 (2.8)	–
Twice a day	5 (11.1)	8 (22.2)	2 (14.3)
Once weekly	6 (13.3)	9 (25.0)	1 (7.1)
Not routinely performed	18 (40.0)	11 (30.6)	7 (50.0)
No response provided	5 (11.1)	2 (5.6)	–
Monitor tobramycin concentrations routinely	4 (8.9)	6 (16.7)	3 (21.4)
Timing of initial tobramycin concentration:	n = 4	n = 6	n = 3
Before 2–4 dose	2 (50.0)	4 (66.6)	1 (33.3)
Only in patients with acute kidney injury	2 50.0)	1 (16.7)	–
Varies based on provider discretion	–	1 (16.7)	–
Timing of subsequent concentrations:	n = 4	n = 6	n = 3
Weekly	1 (25.0)	1 (16.7)	1 (33.3)
No subsequent concentrations unless concerns for acute kidney injury	2 (50.0)	3 (50.0)	1 (33.3)
Varies based on provider discretion	1 (25.0)	2 (33.3)	1 (33.3)
Serum concentration tobramycin dose decreased or discontinued:	n = 4	n = 6	n = 3
No threshold established	1 (25.0)	1 (16.7)	–
≤ 0.5 mcg/mL	1 (25.0)	2 (33.3)	1 (33.3)
≥ 1 mcg/mL	1 (25.0)	2 (33.3)	1 (33.3)
< 2 mcg/mL	1 (25.0)	1 (16.7)	1 (33.3)

CF, cystic fibrosis; CICU, cardiac intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit

serum concentrations while receiving inhaled tobramycin. Of those respondents who monitored tobramycin serum concentrations, some indicated it was before the second to fourth inhaled tobramycin dose, while others indicated it was only in patients with AKI at baseline. In addition, there was a variety of responses for subsequent tobramycin serum concentration monitoring, with some performing weekly monitoring and others

based on provider discretion. For those who perform tobramycin serum concentration monitoring, there was a variety of responses with some indicating their goal concentration in which they reduced or discontinued the tobramycin was ≥ 0.5 to 2 mcg/mL and others who had no established threshold.

Discussion

To our knowledge, this is the first survey exploring the use of inhaled antibiotics in children without CF in pediatric-specific health systems. While the 2016 IDSA guidelines for hospital-associated pneumonia or VAP recommend inhaled antibiotics for multidrug-resistant organisms, there remains a paucity of studies evaluating inhaled tobramycin in critically ill children.[1] In pediatric patients, most of the data surrounding the use of inhaled tobramycin is in patients with CF. As previously noted, tobramycin is available in 2 commercially available solutions for inhaled use, TOBI (300 mg/4 mL) and Bethkis (300 mg/5 mL), and both agents have an FDA-approved labeled indication for eradication of *P. aeruginosa* for CF children 6 years of age and older.[15] Additionally, the Cystic Fibrosis Foundation has also recommended its use in children older than 6 months to 5 years of age.[16] Several case reports or studies have explored the use of inhaled tobramycin for off-label indications in adults and children without CF.[3–8,11,17–19] However, not all of these studies have explored the use of inhaled tobramycin in critically ill patients who are mechanically ventilated, particularly because there is concern regarding the disposition of inhaled tobramycin in the ventilator circuit. We noted that most respondents (n = 61; 77.2%) use inhaled tobramycin in critically ill children without CF for off-label indications, including non-CF bronchiectasis, chronic colonization suppression, VAT, and/or VAP. Despite the small sample, these findings may provide the pediatric pharmacy community with insight into the tobramycin product most commonly used, the nebulizer used for its administration, and monitoring considerations (serum concentrations and lung function) for inhaled tobramycin. The findings in the present study will be used to develop additional studies aimed at outlining the parameters that are critical to ensure the efficacy and safety of inhaled antibiotics in critically ill children and, in the future, to propose a standard protocol to guide the treatment of patients in the NICU with inhaled antibiotics

Most respondents (92.4%) indicated that their institution did not have a standardized protocol for inhaled tobramycin in their ICUs. As previously noted, several studies evaluating inhaled tobramycin have noted between 8.3% and 68.2% of critically ill adults and children with detectable tobramycin serum concentrations.[7–11] It is possible that standardization of the tobramycin product used, dose, the nebulizer used, and administration details within the ventilator circuit may limit systemic toxicities, including AKI with inhaled tobramycin. Most of the published studies evaluating the use of inhaled tobramycin in critically ill patients do not elucidate all these details.[7–10]

Variability was observed in the inhaled tobramycin product administered in the ICUs, with most PICU and NICU respondents using commercially available solutions, such as TOBI or Bethkis, while others administered intravenous tobramycin solution via nebulizer. Previous studies evaluating inhaled tobramycin in critically ill children and adults have used the TOBI product[7,10,11] or the 40 mg/mL intravenous tobramycin formulation.[8,9] The tobramycin product selected may have some impact on absorption and adverse events with inhaled administration. The airway epithelium has a pH of around 5 to 6, and both TOBI and Bethkis are pyrogen-free and sterile solutions that are buffered to match the pH of airway epithelium.[13,14,20] In contrast, intravenous tobramycin has a pH ranging from 3 to 6.5.[21] It is possible that the increased acidity of the intravenous tobramycin solution may cause damage to the airway epithelium and lead to increased or decreased absorption compared with the buffered tobramycin solutions. We also noted several institutions that used the 10 or 40 mg/mL intravenous tobramycin solutions that contain preservatives (Table 2). Experts caution against the use of solutions that contain preservatives as they may cause airway irritation and increase the risk of bronchospasm.[20]

Respondents were asked several questions regarding the nebulizer, mode of delivery of inhaled tobramycin, and placement within the ventilator circuit. Overall, the most common modes of delivery were the endotracheal tube followed by the tracheostomy tube. In the 3 studies evaluating inhaled tobramycin in 96 critically ill children, most patients received tobramycin via a tracheostomy tube (n = 74; 77.1%) compared with endotracheal tubes (n = 21; 21.9%).[7,8,11] This is likely because most of these patients may have received inhaled tobramycin for VAT. Most respondents indicated using inhaled tobramycin in patients receiving noninvasive ventilation, but fewer respondents reported use for patients requiring high-frequency mechanical ventilation. This may reflect the fact that there are limited data about the disposition of inhaled antibiotics in high-frequency mechanical ventilation and additional safety considerations when administering these medications.[1,20] In our study, most respondents were unaware of the nebulizer used and the location of the nebulizer within the ventilator circuit. For mechanically ventilated patients, experts recommend the use of vibrating mesh nebulizers as the preferred nebulizer as they are more efficient than jet, compression, or ultrasonic nebulizers.[1,20] Additionally, it is recommended that the nebulizers are connected approximately 15 to 40 cm proximal to the mechanical ventilator (i.e., between the wye connector within the inspiratory limb of

the ventilator circuit) to enhance medication delivery.[1] The fact that so many respondents were unaware of the nebulizer used and the location of the nebulizer within the ventilator circuit may reflect that their institution has not established a preferred nebulizer or ventilator set up or perhaps a lack of pharmacist involvement. Given the concerns for either diminished or enhanced delivery of inhaled medications, we recommend that clinical pharmacists work with their providers and respiratory therapy colleagues to ensure appropriate administration techniques to increase efficacy while limiting adverse effects.

Respondents noted a variety of dosage regimens and durations of inhaled tobramycin based on the indication for use. Owing to the considerable variability, our analysis focused on VAT because it was the most common indication noted by respondents. The most common dosage regimens for VAT were 40 to 80 mg every 8 to 12 hours or 150 mg every 12 hours. Previous studies have published a variety of dosage regimens used for non-CF critically ill children ranging from 40 to 300 mg/dose at intervals of every 8 to 12 hours.[7,8] For patients older than 6 months with CF, the recommended dose is 300 mg every 12 hours for 28 days in an on-and-off cycle.[13–15] However, there is a paucity of pharmacokinetic data in children younger than 6 months of age.[11,12,16] So, it is possible that respondents with NICUs and CICUs may use lower doses due to the lack of pharmacokinetic and safety data.

One study evaluating the incidence of detectable concentrations in critically ill children receiving TOBI 300 mg every 12 hours found 68.2% with detectable concentrations less than 0.5 mcg/mL.[11] In contrast, Hughes and colleagues[8] evaluated the concentrations of 12 critically ill children receiving inhaled tobramycin 80 mg every 8 hours using the 40 mg/mL intravenous tobramycin formulation and found 1 (8.3%) child with detectable serum concentrations, which they defined as < 0.6 mcg/mL. Given the limited sample size and the use of an intravenous tobramycin formulation not buffered to match the pH of the respiratory epithelium, determining an optimal dose for inhaled tobramycin remains challenging. This highlights a significant gap in our understanding and underscores the need for future studies to undertake comprehensive pharmacokinetic analyses of the tobramycin regimen.

The limited routine monitoring for detectable tobramycin serum concentrations reported by respondents is troubling, especially considering previous research that found between 8.3% and 68.2% of critically ill adults and children exhibited detectable serum concentrations of the drug.[7–11] Several of these studies have attempted to determine risk factors for detectable concentrations, but there remains a paucity of data on which patients may have the greatest risk. Compounding these concerns is the notable variability in how frequently ICUs monitor renal function despite evidence suggesting that up to 24% of patients with detectable serum concentrations may develop AKI.[7–11] Based on the findings in our study, we recommend pediatric clinical pharmacists work with interprofessional team members to ensure monitoring components are included in developing policies or protocols for inhaled tobramycin.

This study has several limitations that must be addressed. First, it has a limited response rate of only one-quarter of pediatric institutions represented by members of the PPA. Despite this, the study did include respondents from across the United States who practice at institutions with a variety of bed sizes. Second, the questionnaire used in this study was not validated. As a result, some respondents may have been confused when answering questions. We did address face validity by obtaining feedback from 2 practicing pediatric pharmacists affiliated with the PPA PBRN. Third, though we asked respondents several questions about the administration of tobramycin through several types of nebulizers, we did not have a question about age restrictions for these nebulizer devices. Several of the nebulizers may have FDA-labeled indications for young infants and neonates.

Conclusions

This study noted that most respondents used inhaled tobramycin in their ICUs, but most did not have a standardized protocol for use in critically ill children without CF. There was substantial variability in the nebulizers used, position with the ventilator circuit, dosage regimen, and monitoring considerations among the ICUs of respondents. This study highlights opportunities for pediatric clinical pharmacists to work with interprofessional teams, including respiratory therapists and providers, to standardize the use of inhaled antibiotics like tobramycin. Additionally, these findings may provide a foundation for future prospective, multicenter studies investigating the use of inhaled tobramycin for critically ill children for a variety of indications, including VAT and VAP.

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including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the 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.

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References

1. Kalil A, Metersky M, Klompas M, et al. Management of adults with hospital-acquired and ventilator associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63(5):e61–e111.
2. Desgrouas M, Ehrmann S. Inhaled antibiotics during mechanical ventilation—why it is will work. *Ann Transl Med*. 2021;9(7):598.
3. Abdulhamid I, Wise TL, Andrews S, et al. Elevated serum tobramycin concentrations after treatment with tobramycin inhalation in a preterm infant. *Pharmacother*. 2008;28(7):939–944.
4. Bentur Y, Hummel D, Roifman CM, et al. Interpretation of excessive levels of inhaled tobramycin. *Ther Drug Monit*. 1989;11(1):109–110.
5. de Velde F, Emonts M, Verbruggen S, et al. High tobramycin serum concentrations after tobramycin inhalation in a child with renal failure. *J Antimicrob Chemother.* 2014;69(11):3163–3164.
6. Trone Deni J, Hall EA. Therapeutic drug monitoring of inhaled tobramycin in a post-hematopoietic cell transplant patient with bronchiolitis obliterans and end-stage renal disease. *J Pediatr Pharmacol Ther*. 2020;25(5):451–454.
7. Miller JL, Lepa TM, Ranallo C, et al. Detectable concentrations of inhaled tobramycin in critically-ill children without cystic fibrosis: Should routine monitoring be recommended? *Pediatr Crit Care Med*. 2017;18(12):e615–e620.
8. Hughes KM, Cristea AI, Tillman EM. Tobramycin serum concentrations in tracheostomy-dependent children receiving inhaled tobramycin. *Pediatr Allergy Immunol Pulmonol*. 2020;33(2):92–95.
9. Droege CA, Ernst NE, Foertsch MJ, et al. Assessment of detectable serum tobramycin concentrations in patients receiving inhaled tobramycin for ventilator-associated pneumonia. *Respir Care*. 2022;67(1):16–23.
10. Schultheis JM, Durham ME, Kram SJ, et al. Incidence and associated risk factors for systemic drug levels with inhaled aminoglycoside therapy. *J Antimicrob Chemother*. 2023;78(2):450–456.
11. Johnson PN, Chang E, Cormack E, et al. Detectable concentrations with inhaled tobramycin in critically ill infants and children following implementation of a standardized protocol [published online ahead of print September 28, 2024]. *Ann Pharmcother*. 10.1177/10600280241282433
12. Geller DE, Pitlick WH, Nardella PA, et al. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. *Chest*. 2002;122(1):219–226.
13. TOBI (tobramycin inhalation powder) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018.
14. Bethkis (tobramycin inhalation solution) [package insert]. Woodstock, IL: Catalent Pharma Solutions LLC; 2012.
15. Takemoto CK, Hodding JH, eds. *Pediatric and Neonatal Dosage Handbook*. 31st ed. Hudson, OH: Lexicomp, Inc; 2024.
16. 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.
17. Plioplys AV, Kasnicka I. Nebulized tobramycin: prevention of pneumonias in patients with severe cerebral palsy. *J Pediatr Rehabil Med*. 2011(2);4:155–158.
18. Varricchio A, Tricarico D, De Lucia A, et al. Inhaled tobramycin in children with acute bacterial rhinopharyngitis. *Int J Immunopathol Pharmacol.* 2006;19(1):131–140.
19. Gipsman A, Prero M, Toltzis P, Craven D. Inhaled antibiotics in children with tracheostomy tubes: a descriptive study. *Pediatr Pulmonol*. 2023(4);58:1028–1033.
20. Ehrmann S, Chastre J, Diot P, Lu Q. Nebulized antibiotics in mechanically ventilated patients: a challenge for translational research from technology to clinical care. *Ann Intensive Care*. 2017;7(1):78.
21. Tobramycin [package insert]. Deerfield, IL: Baxter Healthcare Corporation; 2023.

JPPT | Randomized Double-Blind Controlled Study

Comparison of Sequential versus Concurrent Albumin and Furosemide in Pediatric Nephrotic Syndrome Patients: A Blinded Randomized Controlled Clinical Trial

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OBJECTIVE Comparing the effectiveness of sequential and concurrent administration of albumin and furosemide in reducing edema in children with nephrotic syndrome.

METHOD A double blinded randomized controlled clinical trial was conducted in patients diagnosed with nephrotic syndrome between 2 and 15 years of age. The patients were randomly divided into 2 groups of 32 subjects. One group received an admixture of albumin and furosemide, and the other received furosemide immediately after the albumin infusion. The weight loss and urinary sodium concentration results were analyzed in each group.

RESULTS The comparison of the 2 groups demonstrated that the group that received albumin and furosemide sequentially had statistically significant weight loss. There was no significant difference in the amount of urinary sodium, as determined by random spot urine analysis in 9 subjects in each group, and no study drug-associated adverse effects were observed in any patient.

CONCLUSIONS there was a significant difference between weight loss in the 2 groups that received albumin and furosemide simultaneously or sequentially and according to this study, the sequential method of furosemide administration after albumin infusion is the preferred method to reduce edema in pediatric patients with nephrotic syndrome.

ABBREVIATIONS BUN, blood urine nitrogen; GFR, glomerular filtration rate

KEYWORDS albumin; edema; furosemide; loop diuretic; nephrotic syndrome; pediatric

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Introduction

Nephrotic syndrome is characterized by edema, hypoalbuminemia, and proteinuria.[1] The condition is classified into primary and secondary causes, with primary causes being idiopathic or genetic diseases, and secondary causes including infections, medications, immunological diseases, and malignancies.[2,3] In pediatrics, nephrotic syndrome is primarily idiopathic, with Minimal Change Disease (MCD) being the most common subtype. The syndrome may also arise secondary to conditions such as systemic lupus erythematosus or infections like hepatitis and HIV. Hypoalbuminemia contributes to edema by reducing vascular oncotic pressure, allowing fluid to escape into the interstitial space.[4,5]

Edema, a hallmark of nephrotic syndrome in children, can present as periorbital edema, often mistaken for allergies, and may progress to leg edema, abdominal swelling, or significant weight gain if left untreated. Severe edema can lead to complications like pulmonary edema or pleural effusion, and can also negatively impact the quality of life.[6] Studies have shown that children with nephrotic syndrome-associated edema experience increased anxiety, pain, and fatigue, highlighting the importance of effective management.[7]

The primary treatment for nephrotic syndrome includes salt restriction and diuretics.[8] However, when these are insufficient to control edema, albumin infusion is considered.[9] Albumin increases vascular oncotic pressure and facilitates the transfer of fluid from interstitial tissues to the intravascular compartment, which can help reduce edema.[10] Combining albumin with loop diuretics, such as furosemide, has been explored to improve drug efficacy,[9,11,12] especially in hypoalbuminemic patients where the response to diuretics alone is diminished due to decreased drug secretion in the nephron.[13]

This study aims to investigate the optimal method of administering albumin and furosemide to improve edema reduction in pediatric patients with nephrotic

syndrome. While both simultaneous and sequential albumin-furosemide approaches have been used, studies focusing on the most effective administration method in children remain limited.

Material and Methods

Study Population and Study Design. This prospective, parallel, randomized, double-blind interventional clinical trial was conducted in pediatric patients admitted at a single freestanding children's hospital between August 2021 and August 2022 Inclusion criteria for this study were as follows: children ages 2 to 15 years old, admission to hospital for treatment of edema, diagnosis of nephrotic syndrome, and candidate for treatment with intravenous albumin and furosemide. In our treatment protocol, the first line of treatment in steroid-resistant patients is repeated treatment with albumin, diuretics, and fluid restriction, and if the patients do not respond, they are treated with drugs such as tacrolimus, cyclosporine, and mycophenolate. None of our patients were treated with these drugs. Exclusion criteria include renal failure, defined as GFR < 30 mL/min calculated by an onsite patient recruiter using the Schwartz bedside method (2009)[14]; hepatic failure, defined as child-Pugh class B and C; patients who received diuretics within 30 days prior to participation; patients who lose weight in a manner other than urine (such as diarrhea and vomiting due to gastroenteritis); patients who received albumin and furosemide more than 1 dose during the first 24 hours of the study; patients undergoing renal dialysis or anuria for 24 hours after the intervention; and patients receiving rituximab before the intervention.

A power analysis was performed to determine the number of patients for enrollment: difference between 2 independent means with alpha 0.05 and beta 0.8 and in 2 groups of 64 people. The selected 128 patients were divided into 2 random groups (n = 64). Randomization was carried out in 32 quadruple blocks using the block randomization method. One group received a mixture of albumin and furosemide simultaneously, and the other group received albumin and furosemide, respectively (after the albumin infusion was finished). Albumin 20% infused intravenously 0.5 to 1 g/kg/dose over 30 to 60 minutes and furosemide (20 mg/2 mL) administered with dose of 1 mg/kg/dose intravenously over 30 minutes. The double dummy method was used for blinding the study; each patient was assigned a unique nonsequential code and 2 identical syringes marked with codes and numbers 1 and 2. In 1 group, syringe 1 contains 4 mL of sterile normal saline; syringe 2 contains 40 mg of furosemide in 4 mL, and vice versa in the other group. According to the protocol, syringe 1 is injected into an albumin 20% vial, and syringe 2 is injected intravenously at the end of the infusion at a dose of 0.1 mL per kg based on the volume of prepared syringes. After 50% sampling, the codes are opened, and an interim analysis is performed in the middle of the study. If it is significant ($p < 0.05$), the end of the study is announced. By the end of the study, the code-breaking process is performed in 2 stages. In the first stage, the results are divided into 2 groups and analyzed, and in the second stage, it is determined which intervention was conducted in which group.

Data and Specimen Collection. Body weight was measured before and after drug administration for all patients in the same manner in both groups. All patients were weighed using the same scale for both pre- and post-administration measurements, and the scale was calibrated weekly by the hospital's medical engineering department to ensure accuracy. Vital signs, demographic information, and routine patient clinical tests, including serum sodium and potassium, BUN, and serum creatinine, are recorded before and after the intervention were obtained from our clinical laboratory. Urine sodium was randomly sampled at 6-hour intervals during the 24 hours following study medication infusion. Urine was collected in 4 separate 6-hour time blocks throughout the 24-hour period. Total sodium excretion was calculated by measuring the sodium concentration in each sample and multiplying it by the corresponding urine volume. The cumulative total sodium excreted over the 24-hour period was then calculated by summing the sodium content from all 4 intervals. Moreover, the duration of hospitalization and the patient's outcome was recorded. Patients underwent a standard clinic visit with their physician on day 28 following discharge. Additionally, patients received weekly calls from trained pharmacists for interviews. A trained pharmacist evaluated for possible adverse drug reactions during and after administration. Any adverse reaction related to medications and method of administration such as any nausea and vomiting, blue lips, dizziness, pulse rate, body temperature, chest pain, hypersensitivity, pale skin, flushing sweating, swelling in the legs and ankles, blood pressure and rate of breathing was recorded to assess the safety of the administration methods. A project manager coordinated the budget, human resources, and study time.

Statistical Analysis. All statistical analyses were performed using SPSS statistical software (version 26). After data collection, quantitative data were described using mean and SD. Also, independent-test and T-test statistical analysis were used to compare the sequential versus combined groups. The significance level (p value) was considered less than 0.05. The linear regression method was used to investigate the effect of intervening factors.

Results

In our study, initially 128 patients were selected, and block randomization was performed on 128 subjects. After 50% sampling, the codes were opened, and due

to the significance of the results, the end of the study was announced. Finally, out of 85 patients, 68 patients were included in our study.

The Supplemental Figure shows inclusion and exclusion of patients in the intervention. The participants in this study were divided into simultaneous administration and sequentially administration groups, with 58.1% males and 41.9% females.

Table 1 indicates the demographic information of the patients and our study findings.

A T-test of 2 independent samples with equal variance was performed to investigate the intervention conducted on patients' weight difference percentage [(W2-W1)/W1] and urine sodium. according to the analytical results, there was a significant relationship between the injection time of furosemide relative to albumin and weight loss (reduction of edema) in children with nephrotic syndrome (p = 0.0151). A t-test comparing urinary sodium excretion after the intervention revealed no significant relationship between the timing of furosemide and albumin administration and the amount of urinary sodium excreted (p = 0.337). Thus, the timing of administration did not influence the effectiveness of sodium excretion in children with nephrotic syndrome.

The relationship between serum albumin concentration and serum creatinine concentration was investigated. A correlation test revealed a weak positive correlation between the initial concentrations of serum albumin and serum creatinine (correlation coefficient = 0.273, p = 0.057).

Additionally, sex was found to significantly affect both serum albumin and serum creatinine concentrations. Males had lower serum albumin (2.20 g/dL) and serum creatinine (0.53 mg/dL) concentrations compared with females, who had higher values (serum albumin = 2.44 g/dL, serum creatinine = 0.80 mg/dL). Due to the significant relationship between sex, serum albumin, and serum creatinine, these variables were not included in the same statistical model to avoid confounding.

In terms of weight difference percentage before and after the intervention, no significant impact was observed from the initial concentration of serum creatinine (p = 0.463) or serum albumin concentration (p = 0.783). Similarly, sex did not significantly affect the weight difference before and after the intervention, with a p value of 0.497 for gender's effect on weight change.

The vital signs of the patients in this study were monitored during the drug infusion. None of the patients had side effects or infusion reactions. The pharmacist who evaluated the side effects was blinded. The pharmacist operated under the supervision of the

Table 1. Demographic Information and Patient Data

Parameters	Simultaneous Group				Sequential Group				p value	
	Mean Pre-intervention	Mean Post-intervention	SD Pre-intervention	SD Post-intervention	Mean Pre-intervention	Mean Post-intervention	SD Pre-intervention	SD Post-intervention	Sig. (2-tailed) Pre-intervention	Sig. (2-tailed) Post-intervention
Age, yr	4.56	NA	3.83	NA	5.98	NA	3.36	NA	0.28	NA
Body weights, kg	20.25	19.95	15.03	14.85	22.63	22.63	10.46	10.19	0.46	0.56
Serum albumin, g/dL	2.20	NA	0.34	NA	2.40	NA	0.28	NA	0.112	NA
Initial serum creatinine, mg/dL	0.60	NA	0.32	NA	0.71	NA	0.55	NA	0.569	NA
Initial BUN, mg/dL	19.64	NA	9.25	NA	20.54	NA	12.53	NA	0.835	NA
Initial serum sodium, mEq/L	132.42	NA	3.57	NA	133.73	NA	3.19	NA	0.367	NA
Urine sodium, mEq/L	36.00	57.625	21.16	42.42	10.10	77.9	2.96	43.75	0.165	0.337

BUN, blood urea nitrogen; NA, not applicable

attending pharmacist. If any issues had arisen during the process (though none did), the blinded pharmacist was required to report them to the attending pharmacist. Also, patients' vital signs were checked every 6 hours for 48 hours after receiving the medicine, and none of the patients had any side effects caused by the medications.

Discussion

This study showed that sequential administration of albumin and furosemide improves the efficacy of this combination by investigating the optimal method of administering albumin and furosemide to children with nephrotic syndrome presenting with edema and hypoalbuminemia. Albumin and furosemide can be prescribed in 2 different ways when patients meet the clinical need for receiving these drugs. One method is the simultaneous administration of albumin and furosemide, mixed before injection. Another method is to administer furosemide after the completion of the albumin infusion. This study helps to determine the optimal method to reduce edema and increase the efficacy of furosemide in patients with nephrotic syndrome. Despite the high frequency of the use of albumin and furosemide in children with nephrotic syndrome, the therapeutic experience of the best method to reduce edema in pediatrics is limited.[15]

This study examined the effect of sex, serum creatinine, and serum albumin concentration on the patient's body weight reduction before and after the intervention. Moreover, in this study, to eliminate a possible influence of albumin infusion duration on weight loss, as discussed in some articles, albumin infusion was done over 1 hour after a complete examination of vital signs by hospital staff and the project manager. Furthermore, there are relatively few studies that have investigated the effects of age and sex on the serum albumin concentration in these patients. Among the studies that have been conducted, the findings are inconsistent. One study reported no difference in serum albumin concentration between sex and age.[16] The data of Manolio et al,[17] which were studied in the age range of 18 to 30 years, did not show any correlation between concentration of albumin and age or sex. All these studies were done in adults, and there was no detailed study on this factor in pediatrics. In our study, a significant relationship was observed between sex and serum albumin, and sex with serum creatinine, and to remove interfering factors, the relationship of each of these factors on weight was examined separately.

Some hypotheses exist for pathophysiological mechanisms of edema in nephrotic syndrome, including volume depletion and overfill. Considering that the cause of edema and the pathophysiology of nephrotic syndrome in children and adults may be different,[18,19] the effectiveness of the administration methods of these drugs (albumin and furosemide) in these 2 groups may also be different. As a result, separate investigations should be conducted for children and adults. Unlike adults, children often have more severe hypoalbuminemia and edema, requiring hospitalization and IV administration of albumin.[20] There are various reasons why albumin is commonly used in children, including decreased serum oncotic pressure due to hypoalbuminemia, resistance to diuretics, and reduced diuretic effectiveness when administered to patients with nephrotic syndrome,[1,21–23] and reluctance to treat patients with diuretics alone due to concerns about dehydration and an increase in the risk of thromboembolism.[17,22,24]

In 2012, Phakdeekitcharoen and Boonyawat[25] compared the effects of furosemide and the combination of albumin and furosemide in 24 adults (66.4 ± 12.8 patient years) with chronic kidney disease and hypoalbuminemia. The administrated dose for furosemide was less than 40 mg. Clinical endpoints measured 6 and 24 hours after administration included urine volume, sodium, potassium, blood pressure, calculated GFR, and the albumin serum concentration. According to the results of their study, albumin combined with furosemide compared with furosemide alone produced a beneficial effect on diuresis and natriuresis in the short term (6 hours). Additionally, the researchers stated that their results support the hypothesis that albumin may assist in delivering furosemide to the site of action and increase renal blood flow in hypoalbuminemia patients.[25]

Some clinical trials have been published on using albumin and furosemide to treat edema in patients with nephrotic syndrome in adults and children to determine whether such a combination is beneficial in these patients.[26] Due to differences in selection criteria, trial design, and clinical endpoints, no definitive recommendation has been made regarding using albumin and furosemide.[27] It seems beneficial to consider the creation of the experiment according to the doses and the administration methods for these 2 drugs. Both albumin and furosemide administration methods have been studied; receiving albumin and furosemide simultaneously or albumin infusion before furosemide. The timing of albumin administration is related to the time of furosemide administration. Albumin shows maximum intravascular volume-increasing effects within 30 to 60 minutes after administration. Based on the work of Na et al,[28] albumin administration before furosemide can facilitate diuresis more effectively than furosemide alone and should be considered as a treatment option in diuretic-resistant patients.[8,28] Furthermore the peak effect of intravenous administration of furosemide is approximately 30 minutes[29] and the peak effectiveness of these 2 drugs can overlap with each other.

According to an article published in 2003 by Elwell et al, which reviewed several studies from 1996 to 2002,[26] furosemide and albumin are sometimes combined simultaneously or separately, depending on

Table 2. T-test Interventions Performed on the Weight Difference Percentage of Patients*

Interventional Groups	Number	Mean	SE	SD	CI (conf. 95%)	Approximate Interval
Simultaneous group	32	0.009333	0.009202	0.035638	−0.0104	0.029069
Sequential group	32	0.048625	0.01193	0.047721	0.023196	0.074054
The 2 groups in total	64	0.029613	0.008289	0.04615	0.012685	0.046541
The difference between the 2 groups		−0.03929	0.01521		−0.0704	−0.00818

* p = 0.0151; degree of freedom = 29; t = −2.5833

the administration technique. The optimal method of administering these 2 drugs is controversy, and after rigorous search, 3 reports were found that furosemide and albumin were mixed before administration.[1,30,31] Interestingly, an investigation compared the efficacy of premixed furosemide and albumin with infusions of these 2 drugs separately but simultaneously into the contralateral forearms of similar subjects. They found no significant difference between these methods.[31] Although mixing the 2 drugs may have no clinical advantage over simultaneous infusion, furosemide stability in a premixed furosemide/albumin mixture has been demonstrated. The combination of 60 mg of furosemide with 50 mL of 25% human albumin solution is chemically stable and free of microbial contamination when protected from light and stored at room temperature for up to 48 hours.[32] The studies described here did not report any side effects associated with this combination. However, these studies were underpowered and were not designed to assess the incidence of rare or unusual adverse reactions.

According to the studies and the results presented, the need for a controlled clinical trial with appropriate samples was felt. To check whether other factors such as sex, concentration of creatinine before the intervention, and concentration of albumin before the intervention affected this response, the effect of each of these factors on weight loss was also analyzed. According to our results of the relationship, these 3 confounding factors could not be investigated in the same model. Therefore, the relationship between these factors and weight loss before and after the intervention was analyzed separately. According to our results, sex, serum creatinine concentration, and the initial serum albumin concentration did not affect the weight loss before and after the intervention or the relationship between the intervention and weight loss (Table 2).

Weight loss is considered a measure of the reduction of edema in patients; therefore, we investigated the difference in weight before and 24 hours after the intervention for both groups receiving albumin simultaneously with furosemide and the group receiving furosemide following albumin infusions. It was demonstrated that children receiving albumin and furosemide sequentially experienced more weight loss and, therefore, more significant edema reduction.

Also, the amount of urinary sodium, which indicates the effectiveness of furosemide in patients, was examined in 18 of these patients (9 patients in each group), and the results demonstrated no significant difference in the amount of urinary sodium in the 2 groups. This negative finding could very well reflect the small sample size, the use of a spot urine sample combined with the random timing of obtaining the spot sample post study drug administration.

No adverse reactions were reported during the study period. This may be related to the short duration of the intervention, and the patients included in the study were indicated to receive albumin and furosemide.

Limitations

Urine spot sodium testing has limitations as an indicator of total sodium output. It can be influenced by factors such as hydration status, urine concentration, and timing of collection. In pediatric patients, particularly younger children, obtaining a reliable sample may be challenging, and variability in urine output can further affect accuracy. Thus, spot urine sodium should be interpreted with caution, especially in pediatric populations.

Conclusion

There was a significant difference between weight loss in the 2 groups that received albumin and furosemide simultaneously or sequentially. Because weight reduction is the most basic clinical parameter in assessing the edema reduction in pediatrics, we employed this metric to assess it in these patients. According to this study it seems that sequential administration of furosemide after infusion of albumin is more effective and sequential injection of these 2 drugs can be the preferred method to reduce edema in pediatric patients with nephrotic syndrome.

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References

1. Ellis D. Pathophysiology, evaluation, and management of edema in childhood nephrotic syndrome. *Frontiers Pediatr*. 2016;3:111.
2. Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet*. 2003;362:629–638.
3. Robert M, Kligmn JWSGI, Nathan J, et al. *Nelson Textbook of Pediatrics*. Amsterdam: Elsevier; 2020.
4. Pasini A, Aceto G, Ammenti A, et al. Best practice guidelines for idiopathic nephrotic syndrome: recommendations versus reality. *Pediatr Nephrol*. 2015;30(1):91–101.
5. Niaudet P. Clinical manifestation, diagnosis, and evaluation of nephrotic syndrome in children. 2013. Accessed May 9, 2025. http://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-evaluation-of-nephrotic-syndrome-in-children
6. Kallash M, Mahan JD. Mechanisms and management of edema in pediatric nephrotic syndrome. *Pediatr Nephrol*. 2021;36(7):1719–1730.
7. Gipson DS, Selewski DT, Massengill SF, et al. Gaining the PROMIS perspective from children with nephrotic syndrome: a Midwest pediatric nephrology consortium study. *Health Qual Life Outcomes*. 2013;11:30.
8. Duffy M, Jain S, Harrell N, et al. Albumin and furosemide combination for management of edema in nephrotic syndrome: a review of clinical studies. *Cells*. 2015;4(4):622–630.
9. Garba AO, Nephrotic Syndrome (Chapter 23), in Benavides S, Nahata MC eds. in *Pediatric Pharmacotherapy*. Second edition. ed. Lenexa, Kansas: American College of Clinical Pharmacy; 2020:335-339.
10. Kaku Y, Ohtuska Y, Komastu Y, et al. Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: general therapy. *Clin Exp Nephrol*. 2015;19:34–53.
11. Hampson KJ, Gay ML, Band ME. Pediatric nephrotic syndrome: pharmacologic and nutrition management. *Nutr Clin Pract*. 2021;36(2):331–343.
12. Elwell RJ, Spencer AP, Barnes JF, et al. Stability of furosemide in human albumin solution. *Ann Pharmacother*. 2002;36(3):423–426.
13. Ponto LL, Schoenwald RD. Furosemide (frusemide). A pharmacokinetic/pharmacodynamic review (Part II). *Clin Pharmacokinet*. 1990;18(6):460–471.
14. Schwartz GJ, Mun A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20(3):629–637.
15. Weiss RA, Schoeneman M, Greifer I. Treatment of severe nephrotic edema with albumin and furosemide. *N Y State J Med*. 1984;84(8):384–386.
16. Sachs E, Bernstein LH. Protein markers of nutrition status as related to sex and age. *Clin Chem*. 1986;32(2):339–341.
17. Manolio TA, Burke GL, Savage PJ, et al. Sex- and race-related differences in liver-associated serum chemistry tests in young adults in the CARDIA study. *Clin Chem*. 1992;38(9):1853–1859.
18. Vande Walle J, Donckerwolcke R, Boer P, et al. Blood volume, colloid osmotic pressure and F-cell ratio in children with the nephrotic syndrome. *Kidney Int*. 1996;49(5):1471–1477.
19. Vande Walle JG, Donckerwolcke RA, van Isselt JW, et al. Volume regulation in children with early relapse of minimal-change nephrosis with or without hypovolaemic symptoms. *Lancet*. 1995;346(8968):148–152.
20. Kapur G, Valentini RP, Imam AA, Mattoo TK. Treatment of severe edema in children with nephrotic syndrome with diuretics alone: a prospective study. *Clin J Am Soc Nephrol*. 2009;4(5):907–913.
21. Kirchner KA, Voelker JR, Brater DC. Intratubular albumin blunts the response to furosemide- a mechanism for diuretic resistance in the nephrotic syndrome. *J Pharmacol Exp Ther*. 1990;252(3):1097–1101.
22. Fliser D, Zurbrüggen I, Mutschler E, et al. Coadministration of albumin and furosemide in patients with the nephrotic syndrome. *Kidney Int*. 1999;55(2):629–634.
23. Sjöström PA, Odlind BG, Beermann BA, Karlberg BE. Pharmacokinetics and effects of frusemide in patients with the nephrotic syndrome. *Eur J Clin Pharmacol*. 1989;37(2):173–180.
24. Haws RM, Baum M. Efficacy of albumin and diuretic therapy in children with nephrotic syndrome. *Pediatrics*. 1993;91(6):1142–1146.
25. Phakdeekitcharoen B, Boonyawat K. The added-up albumin enhances the diuretic effect of furosemide in patients with hypoalbuminemic chronic kidney disease: a randomized controlled study. *BMC Nephrol*. 2012;13:92.

26. Elwell RJ, Spencer AP, Eisele G. Combined furosemide and human albumin treatment for diuretic-resistant edema. *Ann Pharmacother*. 2003;37(5):695–700.
27. Kitsios GD, Mascari P, Ettunsi R, Gray AW. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. *J Crit Care*. 2014;29(2):253–259.
28. Na KY, Han JS, Kim YS, et al. Does albumin preinfusion potentiate diuretic action of furosemide in patients with nephrotic syndrome? *J Korean Med Sci*. 2001;16(4): 448–454.
29. Carone L, Oxberry SG, Twycross R, et al. Furosemide. *J Pain Symptom Management*. 2016;52(1):144–150.
30. Mattana J, Patel A, Ilunga C, Singhal PC. Furosemide-albumin complexes in refractory nephrotic syndrome and chronic renal failure. *Nephron*. 1996;73(1):122–123.
31. Chalasani N, Gorski JC, Horlander JC, et al. Effects of albumin/furosemide mixtures on responses to furosemide in hypoalbuminemic patients. *J Am Soc Nephrol*. 2001;12(5):1010–1016.
32. Lee TH, Kuo G, Chang CH, et al. Diuretic effect of co-administration of furosemide and albumin in comparison to furosemide therapy alone: an updated systematic review and meta-analysis. *PLoS One*. 2021;16(12):e0260312.

JPPT | Single Center Retrospective Study

Implementation of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nasal Polymerase Chain Reaction (PCR) Screening in Pediatric Patients for De-escalation of Antibiotics

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OBJECTIVE Recent literature supports the use of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal polymerase chain reaction (PCR) screening to guide de-escalation of anti-MRSA antibiotics. The objective of this study was to expand on the limited pediatric data, encouraging the use of MRSA nasal PCRs as a tool to guide de-escalation of anti-MRSA antibiotics.

METHODS This single center, pre- and post-interventional, retrospective cohort study compared antibiotic regimens in pediatric patients treated empirically with anti-MRSA antibiotics, with and without MRSA nasal PCRs. Use of MRSA nasal PCRs in the pediatric hospital was encouraged following an antimicrobial stewardship provider-led continuing education presentation. The primary outcome was duration of therapy of anti-MRSA antibiotics in days. Secondary outcomes included positive predictive values (PPVs) and negative predictive values (NPVs) for all infections, pneumonia, and skin and soft tissue infections.

RESULTS A total of 319 patients were included in the study, 252 in the pre-intervention group and 67 in the post-intervention group. The duration of anti-MRSA antibiotic therapy in the pre-intervention group was 6.6 days compared with the post-intervention group at 2.0 days (p value = 0.027). Using data from 38 patients with concordant culture results for the infectious diagnosis, overall NPV was calculated as 92.1%. Skin and soft tissue infections and pneumonia were found to have NPVs of 90.1% (22 patients) and 100% (5 patients), respectively.

CONCLUSION Implementation of MRSA nasal PCRs in pediatric patients significantly reduced the duration of anti-MRSA antibiotic therapy, promoting their utility for antimicrobial stewardship.

ABBREVIATIONS IDSA, Infectious Diseases Society of America; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value; SSTIs, skin and soft tissue infections; VAP, ventilator-associated pneumonia

KEYWORDS anti-MRSA; diagnostic; MRSA nasal PCRs; pediatric; retrospective

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Introduction

The current adult Infectious Disease Society of America (IDSA) and the American Thoracic Society guidelines for community-, hospital-, and ventilator-acquired pneumonia mention use of nasal screening for de-escalation of anti–methicillin-resistant *Staphylococcus aureus* (anti-MRSA) antibiotics.[1,2] These guidelines state that depending on relative patient risks and prevalence of MRSA, a negative MRSA nasal polymerase chain reaction (PCR) result suggests pneumonia is likely not due to MRSA and anti-MRSA antibiotics can be discontinued. It is anticipated that additional data, including other disease states, will be forthcoming about the utility of the MRSA nasal PCRs.

MRSA nasal PCRs have a 96.5% negative predictive value (NPV) for treatment of community-acquired pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia.[3] In Mergenhagen et al,[4] de-escalation of anti-MRSA antibiotics in adults was achieved by using MRSA nasal PCRs in several different types of infections including bloodstream, intra-abdominal, respiratory, wound, and urinary. In this study the NPVs were 96.1% for bloodstream and respiratory infections, 98.6% for intra-abdominal, 93.1% for wound, and 99.2% for urinary infections. Because most studies looking at MRSA nasal PCRs took place in adult patients, the question of whether or not these

data are generalizable to the pediatric population remains. In 1 single center retrospective analysis of 95 pediatric patients, MRSA nasal PCRs showed an NPV of 95.5% in multiple types of infections.[5] The objective of this study was to expand on the limited pediatric literature, encouraging the use of MRSA nasal PCRs in pediatric patients as a tool to guide de-escalation of anti-MRSA antibiotics.

Materials and Methods

Study Design. This single center, pre- and post-interventional, retrospective cohort study evaluated pediatric patients who were initiated on anti-MRSA antibiotics for any infection at Prisma Health Children's Hospital – Upstate between March 1, 2022, and August 31, 2022 (pre intervention) and March 1, 2023, to August 31, 2023 (post intervention). As part of Prisma Health- Upstate's pediatric antimicrobial stewardship team, our lead pediatric infectious diseases physician provided a continuing education presentation to pediatric inpatient faculty. The presentation promoted the use of MRSA nasal PCRs, was presented on February 6, 2023, and was used as the intervention of the study. She discussed the benefits and place of therapy for MRSA nasal PCRs, based on existing adult and pediatric primary literature.

Patients in the pre-intervention group were found by using medication administration reports for the included anti-MRSA agents. Patients in the pre-intervention group were not excluded if they received an MRSA nasal PCR. In the post-intervention group, patients were found by using the MRSA nasal PCR usage report for the selected dates, then filtered to patients younger than 18 years. They were included if they were younger than 18 years, admitted for inpatient treatment, and received at least 1 dose of, or were treated with 1 of the following anti-MRSA agents: clindamycin, daptomycin, linezolid, or vancomycin. Excluded patients included those in the neonatal intensive care unit owing to existing hospital protocols screening for MRSA surveillance. Patients receiving the anti-MRSA agents ceftaroline, sulfamethoxazole/trimethoprim, and doxycycline were excluded because these medications, with the exception of ceftaroline, were generally used for disease processes other than MRSA infections, such as *Pneumocystis jirovecii* prophylaxis or tick-borne infections. With ceftaroline being a restricted antimicrobial, it was excluded because it was unlikely for patients to undergo de-escalation. Patients were identified by using administration reports for included anti-MRSA agents, along with a MRSA nasal PCR collection report. No restriction was placed on timing of MRSA nasal PCR collection.

Outcomes. The primary outcome of this study was to compare the median number of days patients received anti-MRSA agents before and after implementation of MRSA nasal PCRs. Secondary outcomes included duration of intravenous (IV) antibiotic therapy, hospital length of stay, number of patients who required surgical interventions for infections, types of infections, comparison of empiric anti-MRSA antibiotics, comparison of oral antibiotic prescribed (if applicable), number of patients with cultures, evaluation of culture results, positive predictive values (PPVs) and NPVs of MRSA nasal PCRs, and specificity and sensitivity of MRSA nasal PCRs.

Statistical Analysis. Continuous variables were assessed with the Wilcoxon rank sum test. Categorical data were assessed with the Fisher exact test. Results are reported as median values (IQR, 25–75). All statistical analyses were analyzed by using SAS statistical software. p values <0.05 were considered statistically significant.

Results

Study Population. A total of 454 patients were screened. There were 252 included patients in the pre-intervention group and 67 in the post-intervention group. Excluded patients included 32 patients discharged from the emergency department, 6 patients admitted to the neonatal intensive care unit, and 54 patients who did not receive an anti-MRSA antibiotic.

Patient demographics are summarized in Table 1. Similarities between the pre-intervention group and the post-intervention groups were observed in terms of sex, age, and hospital length of stay. Differences in the empiric anti-MRSA agent were seen between the 2 groups, with the pre-intervention group using clindamycin more (122 patients [48.41%] vs 13 patients [19.4%]) than the post-intervention group. The post-intervention group did use more vancomycin (123 patients [48.81%] vs 51 patients [76.12%]). More pneumonia infections were found in the post-intervention group (20 patients [7.94%] vs 17 patients [25.37%]). Other infections included bone and joint infections and were seen at a higher rate in the post-intervention group (85 [33.73%] vs 43 [64.18%] patients). Head, eyes, ears, nose, and throat infections were seen at a higher rate in the pre-intervention group (57 patients [22.62%]) vs zero seen in post-intervention group.

Primary Outcome. The primary outcome was total duration of MRSA coverage. The total duration was shorter in the post-intervention group than the pre-intervention group (6.6 days [IQR, 1.5–10.3] vs 2.0 days [IQR, 1.0–8.5]; p = 0.027).

Secondary Outcomes. An NPV for all infections was calculated to be 92.10% and included 38 patients in total. Breaking this down further, 22 of the patients had a skin and soft tissue infection (SSTI) with correlating cultures giving an NPV of 90.1%. An NPV for pneumonia was also calculated at 100.0% and included 5 patients in total. A PPV of 50% was calculated for all infections and included 6 patients (Table 2).

Table 1. Patient Baseline Characteristics

	Pre Intervention (n = 252)	Post Intervention (n = 67)	p value
Male sex, n (%)	131 (52.61)	38 (56.72)	0.550
Hem/Onc, n (%)	39 (15.48)	9 (13.43)	—
Age, n (%)			0.178
<12 mo	22 (8.73)	12 (17.91)	
1–5 yr	99 (39.29)	22 (32.84)	
6–12 yr	68 (29.98)	18 (26.87)	
>12 yr	63 (25.00)	15 (22.39)	
Length of hospital stay, median (IQR), days	3 (2–6)	4 (2–8)	0.081
Type of infections, n (%)			
PNA	20 (7.94)	17 (25.37)	<0.001
SSTI	108 (42.86)	35 (52.24)	0.170
Bacteremia	31 (12.30)	1 (1.49)	0.004
Sepsis	10 (3.97)	2 (2.99)	0.707
CNS infections	18 (7.14)	0 (0.00)	0.024
HEENT	57 (22.62)	0 (0.00)	<0.001
Other	85 (33.73)	43 (64.18)	<0.001
Empiric IV MRSA covering agent, n (%)			
Clindamycin	122 (48.41)	13 (19.40)	<0.001
Daptomycin	4 (1.59)	0 (0.00)	
Linezolid	3 (1.19)	3 (4.48)	
Vancomycin	123 (48.81)	51 (76.12)	

CNS, central nervous system; HEENT, head, eyes, ears, nose, and throat; Hem/Onc, hematology/oncology; IV, intravenous; MRSA, methicillin-resistant Staphylococcus aureus*; PNA, pneumonia; SSTI, skin and soft tissue infection.*

Table 2. Secondary Outcomes

	Pre Intervention (n = 252)	Post Intervention (n = 67)	p value
Length of IV anti-MRSA coverage, median (IQR), days	1.29 (0.66–2.00)	1.00 (0.75–2.00)	0.993
Total duration antibiotic coverage, median (IQR), days	10.00 (6.66–14.00)	10.54 (7.08–17.00)	0.148
Cultures,* n (%)	220 (87.30)	63 (94.03)	0.122
Culture results, MRSA, n (%)	31 (14.09)	5 (7.94)	0.003
Surgical intervention,† n (%)	100 (42.19)	30 (37.97)	0.5092
Narrowed therapy without MRSA results, n (%)	35 (13.94)	—	
Narrowed therapy following MRSA PCRs,‡ n (%)	1 (7.69)	32 (47.76)	0.007

IV, intravenous; MRSA, methicillin-resistant Staphylococcus aureus*; PCRs, polymerase chain reactions*

* Any of the following: blood, wound or abscess, respiratory, urine, cerebral spinal fluid.
† Any surgical intervention aimed at gaining primary source control including but not limited to tooth extractions, video-assisted thoracoscopic surgery, incision and drainage of wound or abscess.
‡ Patient received MRSA nasal PCR, and anti-MRSA therapy was discontinued.

Discussion

The most recent IDSA hospital-acquired pneumonia/ventilator-acquired pneumonia guidelines recommend the use of MRSA nasal PCRs for de-escalation of antibiotic therapy and increased antimicrobial stewardship.[2] The amount of data regarding the utility of this diagnostic test for other indications, including sepsis, SSTI, to name a few, is increasing. The data in previous

trials support the use of the MRSA nasal PCRs, owing to its high NPV of >90%, for most infections.[4,6] This study found a similar NPV for all infections and expanded these data to pinpoint the NPV for pneumonia and SSTIs in pediatric patients. Both pneumonia and SSTIs maintained an NPV of >90% individually.

With the information published, our pediatric providers began using the MRSA nasal PCRs in their daily practice, without an official change to hospital protocols. Our retrospective study found that using MRSA nasal PCR screening decreased the number of days patients received anti-MRSA therapy. The increased antimicrobial de-escalation has the potential to decrease the risk for adverse events associated with anti-MRSA agents and may increase cost savings, based on associated drug monitoring costs, although these endpoints were not evaluated.

The implementation of MRSA nasal PCR testing decreased the number of anti-MRSA antibiotic days, correlating to an increased provider willingness to de-escalate antibiotics when compared with the period before its use. Despite this, providers opted to de-escalate therapy in only about 50% of cases in the post-intervention group. Although specific reasons for providers' reluctance to de-escalate therapy were not captured, this presents an opportunity for future pharmacy-provider education and antimicrobial stewardship involvement. The findings from this study still may lead to a change in protocol, as the adult hospital associated with our campus has a pharmacy-driven protocol for ordering the MRSA nasal PCRs following a vancomycin consult to pharmacy for dosing. In the current adult protocol, the only infections included are those with significant data supporting MRSA nasal PCRs and consist of sepsis, pneumonia, and SSTIs. The results of this study provide rationale for the expansion of this protocol to pediatric patients.

Our study has limitations. First, the small pre- and post-intervention sample size. Owing to the timeline of our intervention, the data collection period was compressed, resulting in the small sample size. Second, the intervention was a one-time, virtual presentation. This led to decreased attendance and limited personal connection and questions. The material was available in slide format for those unable to attend the live presentation, but this still led to limited discussion and is not as effective as other interventional strategies. There were no policy changes implemented owing to the presentation, so the use of the MRSA nasal PCRs relied on changes to individual provider practice. Third, the inclusion of the hematology/oncology population in this study may have skewed the de-escalation results because providers may be less likely to de-escalate therapy in significantly immunocompromised patients. Additionally, trimethoprim-sulfamethoxazole was excluded from the list of anti-MRSA agents owing to its routine use in the oncology population for *Pneumocystis jirovecii* pneumonia prophylaxis. Fourth, determining whether the reason for de-escalation was due to the MRSA nasal PCR or determining the reason for not de-escalating therapy was not able to be collected owing to the retrospective nature of this study and the limitations associated with electronic medical record review in this setting. This information would be beneficial to determine how to educate providers moving forward. Fifth, there was a nationwide IV clindamycin shortage during the post-intervention period, which led to usage discrepancies between the 2 groups. There was also a significant difference in the types of infections treated between the pre- and post-intervention groups, potentially resulting in different de-escalation practices. Lastly, the lack of diagnostic cultures collected resulted in fewer patients being available for inclusion in the NPV calculations.

Conclusions

Use of the MRSA nasal PCRs decreased the number of anti-MRSA agent days in the pediatric population at our center. The calculated NPVs and PPVs of MRSA nasal PCRs for all infections was comparable to those seen in current adult and pediatric literature. MRSA nasal PCRs are a valuable tool for antimicrobial stewardship by providing guidance to support discontinuation of unnecessary antibiotics and preventing resistance. In conclusion, this study demonstrates the utility of MRSA nasal PCRs to guide antibiotic de-escalation in the pediatric population.

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

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References

1. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45–e67.
2. Kalil AC, Metersky ML, Klompus M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63(5):e61–e111.
3. Parenta DM, Cunha CB, Mylonakis E, Timbrook TT. The clinical utility of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screening to rule out MRSA pneumonia: a diagnostic meta-analysis with antimicrobial stewardship implications. *Clin Infect Dis*. 2018;67(1):1–7.
4. Mergenhagen KA, Starr KE, Wattengel BA, et al. Determining the utility of methicillin-resistant *Staphylococcus aureus* nasal screening antimicrobial stewardship. *Clin infect Dis*. 2020;71(5):1142.
5. Sands A, Mulvey N, Iacono D, et al. Utility of methicillin-resistant *Staphylococcus aureus* nares screening in hospitalized children with acute infectious disease syndromes. *Antibiotics*. 2021;10(12):1434.
6. Bono K, Caceda JA, Zhai M, et al. Evaluating methicillin-resistant *Staphylococcus aureus* polymerase chain reaction nasal screening as a tool for antimicrobial stewardship. *J Surg Res*. 2023;283:1047–1052.

JPPT | Simulation Trial

Dosing Recommendations for Ampicillin and Ceftriaxone in the Treatment of Pediatric Community-Acquired Pneumonia Using Monte Carlo- and Physiologic-Based Pharmacokinetic Simulations

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OBJECTIVE Since 2011, Ampicillin (AMP) has been recommended as the parenteral antibiotic of choice for pediatric community-acquired pneumonia (CAP), but ceftriaxone (CRO) is recommended for unvaccinated children and those with complicated CAP. Using penicillin and CRO susceptibility data for pneumococcus, we evaluated the adequacy of currently recommended doses of AMP and CRO.

METHODS With nonlinear mixed-effects modeling v7.3, Monte Carlo simulations (MCS, N = 10,000) for AMP and CRO were conducted for 6 virtual patients aged 3 months, 1, 2, 5, 10, and 15 years. PK-Sim v9.0 was used to develop physiologic-based pharmacokinetic (PBPK) models for AMP (N = 4000) and CRO (N = 3000). The probability of target attainment (PTA) was determined for both serum and lung (epithelial lining fluid [ELF]) exposure to achieve free drug concentrations above the minimum inhibitory concentration (%*f*T>MIC) for pneumococci at 30% to 50% of the dosing interval.

RESULTS We performed simulations based on susceptibility data from 21 pneumococci isolated from children with CAP and found all 21 (100%) to be susceptible to AMP and CRO using Clinical & Laboratory Standard Institute/US Food and Drug Administration breakpoints, where susceptible, intermediate, and resistant strains of *Streptococcus pneumoniae* were ≤1, 2, and ≥4 mg/L for CRO and ≤2, 4, and ≥8 mg/L for AMP (extrapolated from penicillin), respectively (where intermediate and resistant were considered nonsusceptible); and 18 (85.7%) were susceptible to AMP, and 19 (90.5%) to CRO using the European Committee on Antimicrobial Susceptibility Testing/European Medicines Agency breakpoints, where susceptible and nonsusceptible strains were as follows: 0.5 and 2 mg/L for CRO and 0.5 and 1 mg/L for AMP. Both the serum and ELF, antibiotic regimens achieved >99% PTA at 30% to 50% *f*T>MIC using MCS and PBPK.

CONCLUSION In the pneumococcal conjugate era, standard doses of AMP and CRO appear to provide the appropriate serum and ELF exposure for clinical and microbiologic success for >98% of children with pediatric CAP. The required dose to achieve the desired outcomes may change if beta-lactam resistance in pneumococcus increases.

ABBREVIATIONS AMP, ampicillin; CAP, community-acquired pneumonia; CLSI, Clinical & Laboratory Standard Institute; CRO, ceftriaxone; ELF, epithelial lining fluid; EUCAST, European Committee on Antimicrobial Susceptibility Testing; IDSA, Infectious Diseases Society of America; MCS, Monte Carlo simulation; MIC, minimum inhibitory concentration; NONMEM, nonlinear mixed-effects modeling; PBPK, physiologic-based pharmacokinetic; PCV, pneumococcal conjugate vaccines; PIDS, Pediatric Infectious Diseases Society; PMPSSG, Pediatric Multicenter Pneumococcal Surveillance Study Group; PTA, probability of target attainment; %*f*t>MIC, percent fraction of time above the MIC

KEYWORDS beta-lactams; children; Monte Carlo simulation; pharmacodynamic; physiologic-based pharmacokinetic simulation; pneumococcal vaccine; *Streptococcus pneumoniae*

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Introduction

Community-acquired pneumonia (CAP), occurring in 155 million children annually, continues to be a leading cause of childhood death worldwide.[1] Even in a developed country, such as the United States, CAP is a leading cause of hospitalization in children and cost the health care system approximately $1 billion in 2009.[2] The most common pathogen implicated in childhood CAP is *Streptococcus pneumoniae,* which is responsible for up to 44% of cases.[1] With extensive clinical use of ampicillin (AMP) for almost 50 years, providing clinical and microbiologic efficacy with a favorable adverse event profile, 2011 guidelines from the Pediatric Infectious Diseases Society (PIDS) and Infectious Diseases Society of America (IDSA) recommended AMP as the first-line treatment for pediatric CAP, with penicillin G as an equivalent option. For complicated CAP or those with a high risk of penicillin resistance, ceftriaxone (CRO) was recommended. Oral switch therapy was recommended for recovering children using high-dose amoxicillin therapy because it was believed necessary for penicillin-nonsusceptible strains that were prevalent before the widespread use of pneumococcal conjugate vaccines (PCVs).[1] The time-dependent pharmacodynamic property of beta-lactams in pneumococcal infections is optimized when free drug concentrations are above the minimum inhibitory concentration (%*f*T>MIC) for at least 30% to 50% of the dosing interval.[3,4]

PCVs have been approved by the US Food and Drug Administration for the prevention of CAP for children in the US, the PCV 7-valent in 2000 and PCV 13-valent in 2010. The use of PCV-13 has significantly decreased the incidence of documented CAP, particularly cases requiring hospitalization and those that are considered complicated.[5,6] In addition, the resistance to beta-lactam antibiotics for pneumococcal strains isolated from community-acquired infections has significantly decreased with the widespread use of PCV-13 immunization.[7] PCV-20 vaccine with protection against serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F was licensed by the US Food and Drug Administration in April 2023.[8,9]

Table 1. Demographic Data of Simulated Subjects

N	Age, yr	Weight, kg	Serum Creatinine, mg/dL
1	0.25	6	0.24
2	1	9.55	0.28
3	2	12.7	0.3
4	5	18	0.38
5	10	32	0.53
6	15	52	0.59

Currently, the attainment of optimal pharmacodynamic parameters in the era of PCV vaccination, with increasing antibiotic susceptibility, using guideline-recommended beta-lactam dosing regimens has not been evaluated. To this end, we aimed to evaluate, by modeling, the probability of target attainment (PTA) of 2 different beta-lactam antibiotics recommended by the pediatric CAP guidelines in achieving optimal %*f*T>MIC within the serum and epithelial lining fluid (ELF) against *S. pneumoniae.*

Methods

Monte Carlo simulations (MCS) were conducted using nonlinear mixed-effects modeling (NONMEM) v7.3 via Pirana using 6 virtual subjects (ages 3 months,1, 2, 5, 10, and 15 years; Table 1). Individual subject weight was obtained by averaging the male and female weights at the 50th percentile from the Centers for Disease Control and Prevention Clinical Growth Chart for the respective age.[10] Normal age-based serum creatinine values were obtained from published literature.[11]

Simulations (N = 10,000) were conducted to determine the PTA after the administration of 2 guideline-recommended beta-lactam regimens (AMP 150 mg/kg/day every 6 hours, CRO 50 mg/kg/day every 24 hours).[2] The target PTA of 90% was selected for these simulations and based on free, nonprotein-bound concentrations in the plasma and in ELF at concentrations above the MIC ranging from 30% to 50% of the dosing interval at steady state (which represented the onset of bacteriostatic activity for most beta-lactams).[12] Antibiotic concentrations were derived using pharmacokinetic parameters from published literature (Table 2).[13–18]

Simulations were also conducted using PK-Sim to develop physiologic-based pharmacokinetic (PBPK) models, evaluating 4 virtual subjects (1, 2, 5, and 10 years; Table 1). Individual subject demographics provided by Bayer for PK-Sim were based on the 1997 National Health and Nutrition Examination Survey of White Americans. Weight was obtained by averaging the male and female weights at the 50th percentile from the Centers for Disease Control and Prevention Clinical Growth Chart for the respective age.[10] Glomerular filtration rate was obtained by PK-Sim from published clinical pharmacokinetic

Table 2. Antibiotic Pharmacokinetic Parameters

PK Parameter	Ampicillin	Ceftriaxone
Clearance, L/hr/kg	0.293 (SD 0.084)[14]	0.0384 (SD 0.0072)[15]
Volume of distribution, L/kg	0.3 (SD 0.08)[14]	0.26[15]
Protein binding, %	20[17]	80.48,[18] 95[17]
Epithelial Lining Fluid:Plasma Ratio	0.53[13]	1[16]

data, and an age-based formula was used to estimate glomerular filtration rate.[19] Physico-chemistry properties of both antibiotics were required for PK-Sim simulations and obtained from published literature and databases. These included, but were not limited to, molecular weight, lipophilicity, plasma albumin binding fraction, pKa values, and solubility. When determining the ELF concentrations, the ELF-to-plasma ratio was obtained from published literature.[20] A concentration versus time curve graph was digitized from the Nahata 1999[14] paper to produce an observed data set to assess the validity of the AMP model (Figure 1a). For CRO, however, an observed data set to compare our simulated model with was not readily available and, therefore, was created using the intermittent short-infusion equation and PK parameters provided in the Nahata 1986[15] paper to also estimate fraction unbound using the regression equation from Fukumoto 2009[18] (Figure 1b).

Intermittent short-infusion

$$MD = \frac{Cpssmax\ (Cl)\cdot(tin)\cdot(1 - e^{-k\tau})}{(1 - e^{-ktin})\ e^{-ktmax}}$$

$$tmax = 0 \text{ and starts from the end of infusion}$$

$$LD = (C_{max,ss})(V)$$

Simulations (N = 4000 and 3000 for AMP and CRO, respectively) were conducted using PK-Sim v9.0 to determine the PTA of 2 guideline-recommended beta-lactam regimens (AMP 150 mg/kg/day every 6 hours, CRO 50 mg/kg/day every 24 hours).[2] The target PTA and MIC used were the same as previously described for the MCS modeling. Antibiotic concentrations were derived using pharmacokinetic parameters from published literature (Table 2).[13–18]

The following CLSI breakpoints were used for nonmeningitis infections: susceptible, intermediate, and resistant strains of *S. pneumoniae* were ≤1, 2, and ≥4 mg/L for CRO and ≤2, 4, and ≥8 mg/L for AMP (extrapolated from penicillin), respectively (where intermediate and resistant were considered nonsusceptible).[21] Additionally, EUCAST breakpoints used for susceptible and nonsusceptible strains were as follows: 0.5 and 2 mg/L for CRO and 0.5 and 1 mg/L for AMP.[22] The MIC data used in our study were based on 2018 surveillance from a program spanning almost 3 decades by the US Pediatric Multicenter Pneumococcal Surveillance Study Group (PMPSSG) focusing on isolates of *S. pneumoniae* from lower respiratory tract infections after PCV-13 vaccination from 2007–2018.[23,24] Each virtual patient was stochastically assigned an MIC based on the frequency distribution of PMPSSG susceptibility data from 2018.

Results

The CRO regimen achieved 100% PTA in the serum for 30% to 50% *f*T>MIC at both CLSI and EUCAST susceptible breakpoints and 2018 PMPSSG susceptibility data (Figure 3a and b and Tables 3 and 4, respectively) for both simulation methods (NONMEM and PK Sim). AMP regimen achieved >99% PTA in the serum for 30% to 50% *f*T>MIC at both CLSI and EUCAST susceptible breakpoints and 100% PTA in the serum for 30% to 50% represented in the assigned MIC based on 2018 PMPSSG susceptibility data (Figure 3a and b and Tables 3 and 4, respectively) for both simulation methods. CRO achieved 100% PTA in the serum even at both its CLSI "resistant" and EUCAST "nonsusceptible" breakpoints (i.e., 4 and 2 mg/L, respectively; Figure 3).

Serum and Epithelial Lining Fluid Data. Compared with serum, the PTA in the ELF was lower for AMP. As expected, given ELF penetration of 100% (Table 2), CRO achieved 100% PTA for 30% to 50% *f*T>MIC in both serum and ELF, even at the CLSI and EUCAST nonsusceptible breakpoints. At 30% to 40% *f*T>MIC in the ELF, 100% PTA was achieved at both CLSI and EUCAST susceptible MIC values, and at 30% *f*T>MIC, 100% PTA was achieved at the nonsusceptible breakpoint for AMP in the MCS. Whereas in the PK-Sim simulation, for the goal of achieving 30% *f*T>MIC in the ELF, 100% PTA was achieved at susceptible MIC values.

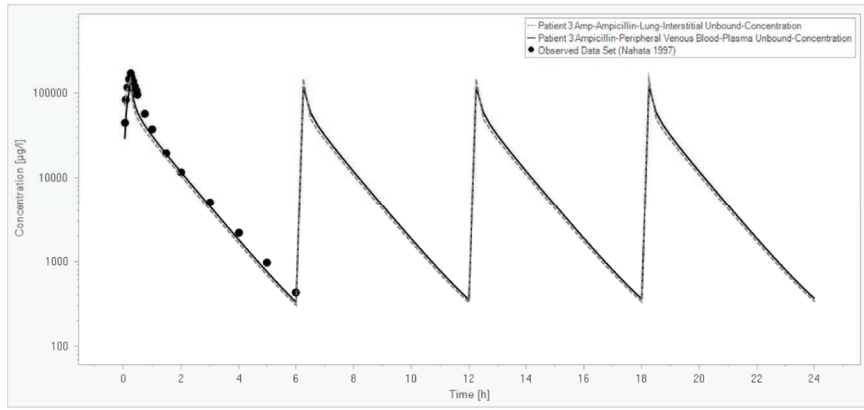
AMP and CRO both displayed good PTA profiles. Overall, the PTA was higher when using a more easily achieved lower %*f*T>MIC in both serum and ELF (30% vs 50%). In the serum, 100% PTA was achieved for AMP administered every 6 hours at 30%, 40%, and 50% *f*T>MIC when MIC was 8, 4, and 1 mg/L, respectively, for the MCS antibiotic concentrations (Figure 3a). One hundred percent PTA in serum was achieved for AMP administered every 6 hours at 30%, 40%, and 50% *f*T>MIC when MIC was 4, 1, and 0.5 mg/L, respectively, for the PK-Sim antibiotic concentrations (Figure 3b). The ELF data demonstrated 100% PTA achievement for AMP administered every 6 hours at 30%, 40%, and 50% *f*T>MIC when MIC was 4, 2, and 1 mg/L, respectively, for the MCS antibiotic concentrations (Figure 3a). One hundred percent PTA in ELF was achieved for AMP administered every 6 hours at 30%, 40%, and 50% *f*T>MIC when MIC was 4, 1, and 0.5 mg/L, respectively, for the PK-Sim antibiotic concentrations (Figure 3b). Given that the susceptible breakpoint for CRO is 1 (CLSI) and 0.5 (EUCAST) mg/L, 100% PTA was retained in both serum and ELF when MIC was ≤4 mg/L even at 50% *f*T>MIC for both simulation methods (Figure 3a and b).

Susceptibility Data. Compared with the pre–PCV-13 from 1993–2001, the susceptibility of *S. pneumoniae* to penicillin and CRO improved post–PCV-13 vaccination from 2007–2018 (Figure 2).[23,24] If this susceptibility trend continues to hold true, the currently recommended PCV-20 will further improve susceptibility to penicillin and CRO. The data on susceptibility impact by PCV-20 have not been published.

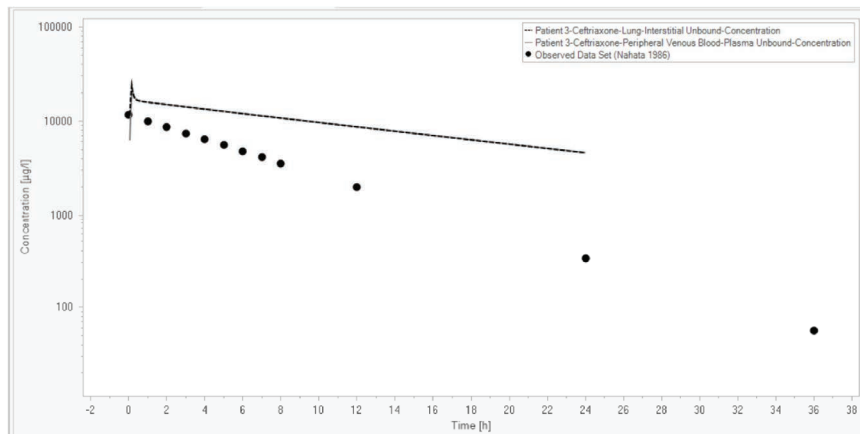
When using the PMPSSG susceptibility data obtained during the PCV-13 period, for AMP, 100% PTA was seen

Figure 1. PK-Sim Models (Concentration [mcg] vs Time [h]). **(a)** Ampicillin. **(b)** Ceftriaxone.

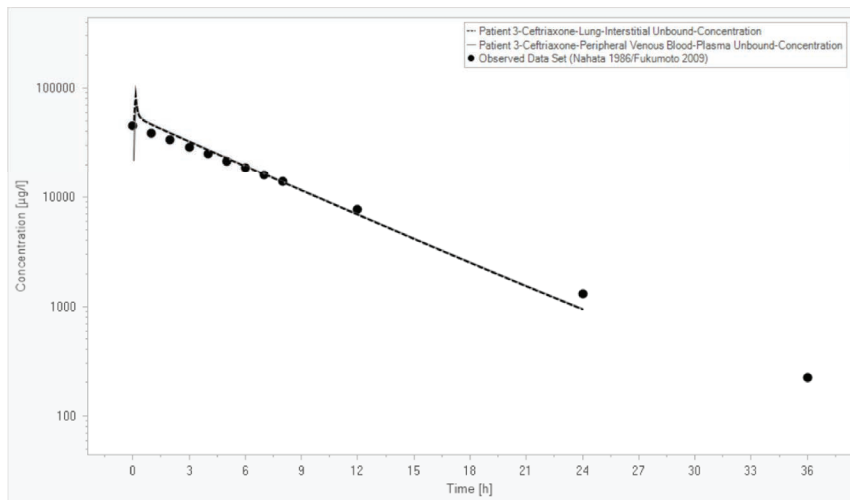
(a)



(b) Using protein fraction unbound (fu) = 0.05

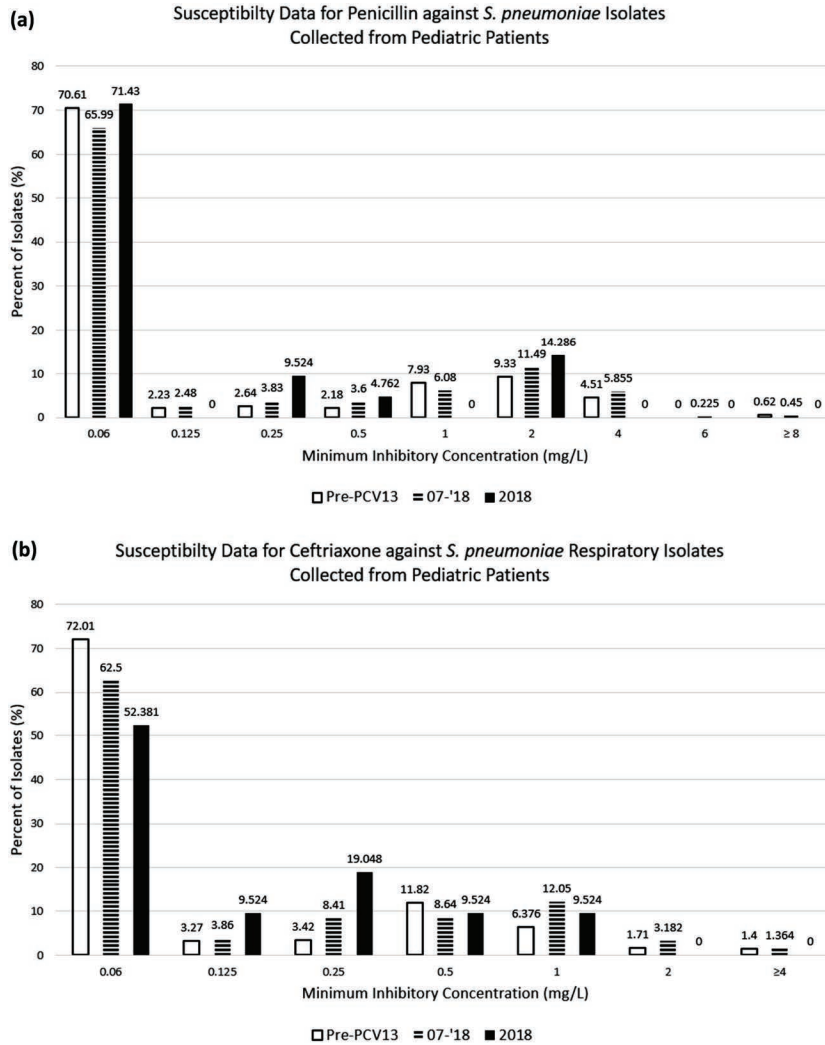


Using protein fraction unbound (fu) = 0.1952



at 30% to 50% *f*T>MIC when each patient was stochastically assigned an MIC based on the 2018 PMPSSG susceptibility data for both the MCS and PK-Sim serum antibiotic concentrations (Tables 3 and 4). For CRO, 100% PTA was seen at 30% to 50% *f*T>MIC when each patient was stochastically assigned an MIC based on the 2018

Figure 2. Susceptibility data for penicillin **(a)** and ceftriaxone **(b)** against *S. pneumoniae* respiratory isolates collected from pediatric patients from the Pre-PCV-13 Period (1993–2001) and post-PCV-13 period (2007–2018) minimum inhibitory concentration (MIC) vs percent of isolates.



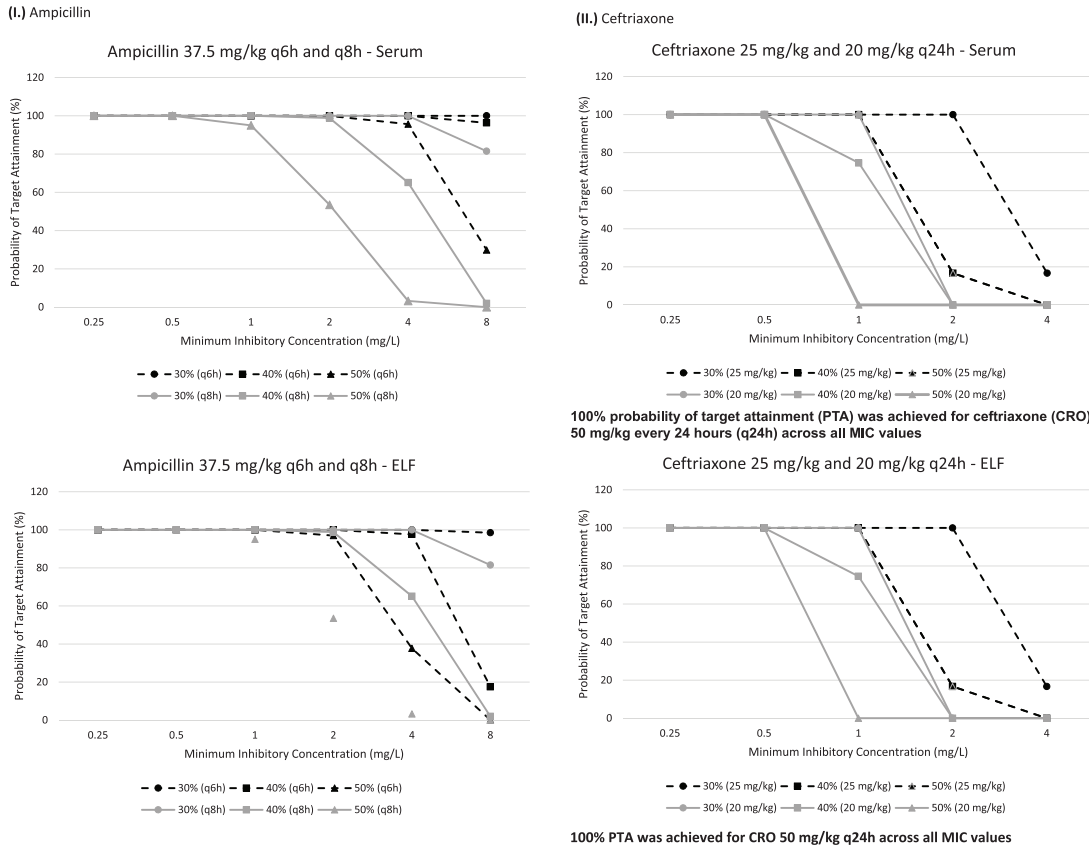
PMPSSG susceptibility data for both the simulation's serum and ELF antibiotic concentrations (Table 3a and b).

In addition to similar PTA profiles produced by both the MCS and PBPK simulations (Tables 3 and 4), the PK-Sim models were visually comparable to observed data. Both the digitized concentration versus time graph and the observed data set derived from the intermittent short-infusion equation (for AMP and CRO, respectively) matched the simulated curve, providing validity upon visualization (Figure 1a and b).

Discussion

While a wide range of antibiotics can easily be evaluated *in vitro* for antibacterial effect against *S. pneumoniae*, selecting the best antibiotic and dose effective for pneumonia is based on achieving sufficient antibiotic exposure at the site of infection. The rate of eradication of the pathogen at the site of infection varies between antibiotic classes with respect to the antibiotic concentration and the time the antibiotic is present at the site of infection. Pharmacodynamics is the term used to describe the concept of the different observed bacterial eradication rates as a function of dosing and, therefore, exposure. Some antibiotics kill the pathogens more rapidly at higher exposures, often in direct proportion to increasing antibiotic concentrations (e.g., aminoglycosides). Other antibiotics just require a specific amount of time at the site of infection in

Figure 3a. (NONMEM) Probability of target attainment of beta-lactams against *S. pneumoniae* using Clinical & Laboratory Standard Institute (CLSI)* and European Committee on Antimicrobial Susceptibility Testing (EUCAST)† breakpoints in the serum and epithelial lining fluid (ELF).



x-axis represents the percent fraction of time above the minimum inhibitory concentration.

* For susceptible and non-susceptible (intermediate and resistant isolates), minimum inhibitory concentration (MIC) = 2, 4, and 8 mg/L, respectively, for ampicillin.
* For susceptible and non-susceptible (intermediate and resistant isolates), MIC = 1, 2, and 4 mg/L, respectively, for ceftriaxone.
† For susceptible and non-susceptible, MIC = 0.5 and 1, respectively, for ampicillin.
† For susceptible and non-susceptible, MIC = 0.5 and 2, respectively, for ceftriaxone.

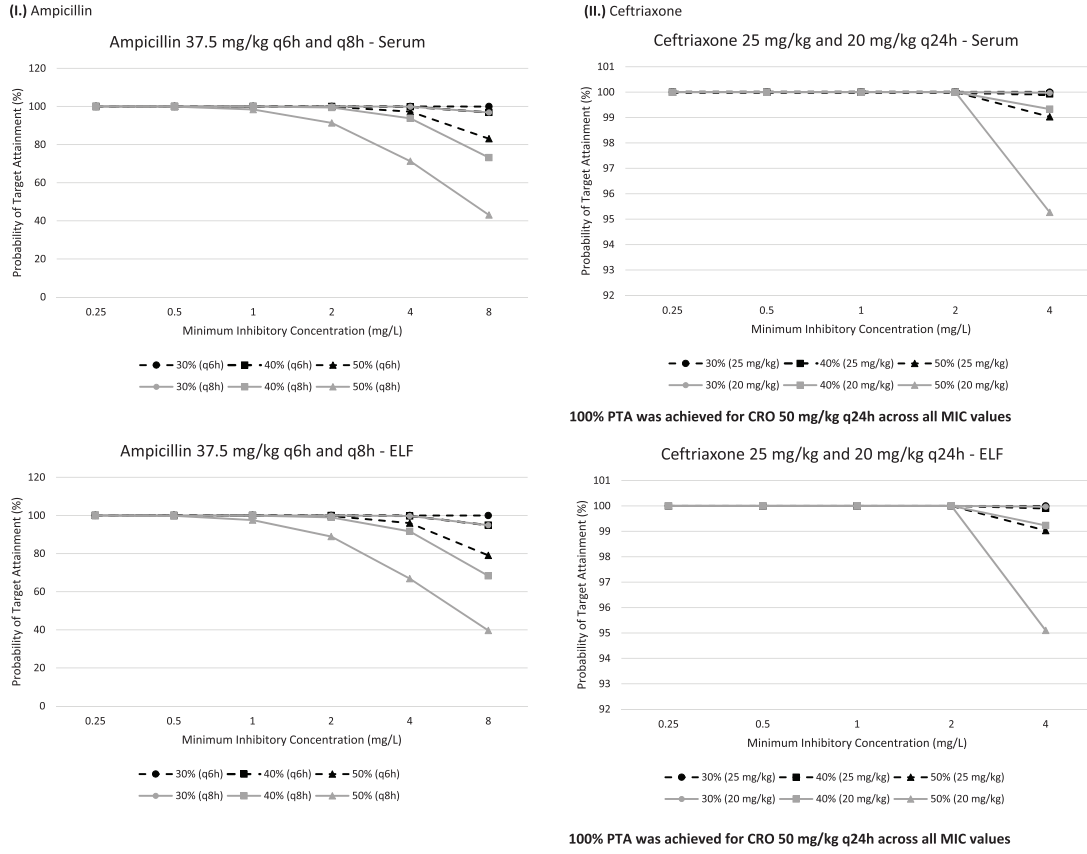
concentrations of free, unbound antibiotic above the MIC to kill the pathogen (e.g., beta-lactams), described as %*f*T>MIC. In this scenario, higher concentrations do not enhance rapid killing, nor does prolonged exposure beyond that required for inhibition.

The best empiric antibiotic dose is the one that is sufficient to cure the specific infection in most children. Achieving the antibiotic exposure associated with a cure in 90% to 95% of those infected is a standard target for otherwise healthy patients with non-central nervous system infections. In special circumstances, such as a neutropenic host, where failure may lead to death, 98% to 99% would be a more appropriate target to achieve. Higher doses may be appropriate and well tolerated for some classes of antibiotics (beta-lactams); however, for others (aminoglycosides), higher doses should be avoided as they can be associated with increased side effects.

Using available data for susceptibility of pneumococcus to beta-lactams and population pharmacokinetics of AMP and CRO during the creation of the PIDS/IDSA Pediatric CAP Guidelines, efforts were made to incorporate pharmacodynamic dosing concepts into the actual recommendations, rather than merely citing literature on doses previously used in clinical trials.[2] A full explanation of the rationale behind pharmacodynamic dosing was not presented in the guidelines. We now present a more complete explanation of the way in which pharmacodynamics, MCS, and PK-Sim PBPK modeling can be used to determine the most appropriate dose to recommend to health care providers based on the current susceptibilities of clinical isolates collected from pediatric patients.

We report the first MCS of the pharmacodynamics of PIDS/IDSA guideline-recommended beta-lactam

Figure 3b. (PK-Sim) PTA of beta-lactams against *S. pneumoniae* using CLSI* and EUCAST† breakpoints in the serum and ELF.



x-axis represents the %fT>MIC.

* For susceptible and nonsusceptible (intermediate and resistant isolates), MIC = 2, 4, and 8 mg/L, respectively, for ampicillin.
* For susceptible and nonsusceptible (intermediate and resistant isolates), MIC = 1, 2, and 4 mg/L, respectively, for ceftriaxone.
† For susceptible and nonsusceptible, MIC = 0.5 and 1, respectively, for ampicillin.
† For susceptible and nonsusceptible, MIC = 0.5 and 2, respectively, for ceftriaxone.

regimens for pediatric CAP in the serum and ELF before and after the era of conjugate pneumococcal vaccination with PCV-13. Using the PMPSSG penicillin and CRO susceptibility data for *S. pneumoniae* strains before and after the advent of PCV-13, we observed that a vast majority of strains had MIC values well below even the EUCAST breakpoints for susceptibility both before and after widespread use of PCV-13 (77.6% [N = 500 of 644] and 75.9% [N = 337 of 444] for penicillin; 90.5% [N = 582 of 643] and 83.4% [N = 367 of 440] for CRO, respectively), a trend that we believe will continue in the era of PCV-20 vaccine.[23,24]

Our data demonstrated that guideline-recommended regimens for both AMP and CRO for pediatric CAP are pharmacodynamically effective against recent *S. pneumoniae* strains because they achieved desirable pharmacodynamic parameters, including the concentrations via MCS and PK-Sim that displayed good PTA profiles in both serum and ELF. These findings support the first-line use of beta-lactams for the treatment of community-acquired pediatric CAP.[25–27] Furthermore, adherence to guideline recommendations has not been associated with adverse events, and the use of narrow-spectrum antibiotics (i.e., penicillins), as compared with vancomycin and broad-spectrum antibiotics previously used for penicillin-resistant pneumococci, resulted in shorter hospital stay.[2,28–30]

Of note, in our study, we evaluated standard doses on the lower end of the dosing range from guideline recommendations from 2011 and additional doses below the recommendations. As these doses have shown sufficient pharmacodynamic attainment in our analyses, higher doses are not likely to be necessary for the treatment of routine pediatric CAP, given the current susceptibility profiles of pneumococcus. In fact, most *S. pneumoniae* clinical isolates modeled in our study displayed MICs well below the CLSI and EUCAST susceptible breakpoints for penicillin, AMP, and CRO

Table 3. Probability of Target Attainment from NONMEM of Beta-Lactam Regimens Against *Streptococcus pneumoniae* with Antibiotic Concentrations Using 2018 MIC PMPSSG Susceptibility Data With Random Assignment of Minimum Inhibitory Concentration for Patients in the Serum and Epithelial Lining Fluid

%*f*T>MIC	Concentration Site	Probability Target Attainment (%)*		
		Ampicillin 37.5 mg/kg every 6h	Ampicillin 37.5 mg/kg every 8h	Ceftriaxone 20 mg/kg every 24h†
30	Serum	100	100	100
	ELF	100	100	100
40	Serum	100	99.85	97.6
	ELF	100	95.67	97.61
50	Serum	100	92.72	90.36
	ELF	99.6	85.97	90.36

%ft>MIC, percent fraction of time above the minimum inhibitory concentration; ELF, epithelial lining fluid; MIC, minimum inhibitory concentration; NONMEM, nonlinear mixed-effects modeling; PMPSSG, Pediatric Multicenter Pneumococcal Surveillance Study Group

* Patients 1–6

† 100% probability of target attainment was achieved for ceftriaxone 25 mg/kg and 50 mg/kg q24h

Table 4. Probability of Target Attainment from PK-Sim of Beta-Lactam Regimens Against *Streptococcus pneumoniae* with Antibiotic Concentrations Using 2018 MIC PMPSSG Susceptibility Data With Random Assignment of Minimum Inhibitory Concentration for Patients in the Serum and Epithelial Lining Fluid

%*f*T>MIC	Concentration Site	Probability Target Attainment, %		
		AMP 37.5 mg/kg every 6h*	AMP 37.5 mg/kg every 8h*	CRO 20 mg/kg every 24h†‡§
30	Serum	100	100	100
	ELF	100	100	100
40	Serum	100	99.95	100
	ELF	100	99.85	100
50	Serum	100	98.98	100
	ELF	100	98.73	100

%ft>MIC, percent fraction of time above the minimum inhibitory concentration; AMP, ampicillin, CRO, ceftriaxone, ELF, epithelial lining fluid; MIC, minimum inhibitory concentration; PMPSSG, Pediatric Multicenter Pneumococcal Surveillance Study Group

* Patients 2–5 only

† Patients 2–4 only

‡ Using protein fraction unbound (fu) = 0.05 and 0.1952

§ 100% probability of target attainment was achieved for CRO 25 mg/kg and 50 mg/kg q24h

both before and after the pneumococcal conjugate vaccine use was widespread.

There are several limitations to our analysis. The pharmacokinetic parameters used in our simulations often originated from older, small studies with varying methodologies. In addition, some parameters were extrapolated from adult data because no pediatric data were available. This analysis was only preliminary, and prospective, controlled studies need to be conducted to confirm findings. Analyzing these regimens in the context of more resistant *S. pneumoniae* strains and in subjects, real or simulated, with altered pharmacokinetics (i.e., critically ill and renally impaired or those with augmented renal clearance) may also be warranted. Additionally, the use of breakpoints, which are an interpretation of the MIC, may underestimate the ability of a beta-lactam antibiotic to successfully treat an infection, as higher doses of AMP and CRO may achieve the required target exposure for pneumococci with higher MICs, even for strains labeled as nonsusceptible.

PBPK modeling is an area that holds the potential to further validate dosing recommendations in populations with scarce clinical data. PK-Sim is a whole-body PBPK modeling tool that can be used to predict human drug concentrations based on the physiologic properties of a drug and preclinical data in patients of various ethnicities, ages, and disease states. One of the major advantages of PK-Sim is that enzyme synthesis and degradation can be modeled to predict concentrations of parent drugs and metabolites at any given time.

These models allow the integration of data that are not traditionally used in PK modeling, which include drug properties, physiological changes, and biological parameters that can differ between populations of individuals. Generated PBPK models for both AMP and CRO yielded similar PTA to those generated by the MCS with >98% PTA at 30%, 40%, and 50% *f*T>MIC in both serum and ELF. We originally developed models for penicillin G and amoxicillin, but these were not included because of a lack of observed pediatric data to validate the use of the model.

However, PK-Sim comes with its own limitations. The program itself requires ample clinical trial data to validate PBPK models that are able to simulate concentrations adequately. For this reason, models for penicillin G and amoxicillin were omitted. Current published literature with the mention of PK-Sim in the methodology mentions the scaling of adult PBPK models to develop a pediatric model, possibly due to a lack of clinical trial data. In this study, physiologic drug properties and pharmacokinetic parameters were collected from various databases as well as published literature, which were then input into PK-Sim for simulation. As this is a preliminary analysis, a dedicated study collecting the physiologic properties of the drug, pharmacokinetic parameters of the intended study population, and observed concentration data are needed to confirm simulated concentrations and help rationalize the difference in PTAs observed. Alternatively, an adult PBPK model could be used to develop a pediatric model, which could then be further assessed for validity by comparing simulated concentrations to observed concentrations from the available scientific literature on the drug of choice.

Conclusion

Using MCS, pharmacodynamic-based dosing of beta-lactams achieves appropriate antibiotic concentrations in the serum and ELF for the treatment of CAP caused by *S. pneumoniae*. Simulated antibiotic concentrations using PK-Sim further confirm these results for both AMP and CRO, highlighting the potential of PBPK modeling in aiding decisions for dose-finding studies or guideline recommendations for various populations.

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References

1. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53(7):e25–e76.
2. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;372(9):835–845.
3. Turnidge JD. The pharmacodynamics of beta-lactams. *Clin Infect Dis*. 1998;27(1):10–22.
4. Kuti J. Optimizing antimicrobial pharmacodynamics: a guide for your stewardship program. *Rev Med Clin Condes*. 2016;5(27):615–624.
5. Levy C, Biscardi S, Dommergues MA, et al. Impact of PCV13 on community-acquired pneumonia by C-reactive protein and procalcitonin levels in children. *Vaccine*. 2017;35(37):5058–5064.
6. Olarte L, Barson WJ, Barson RM, et al. Pneumococcal pneumonia requiring hospitalization in US children in the 13-valent pneumococcal conjugate vaccine era. *Clin Infect Dis*. 2017;64(12):1699–1704.
7. Tomczyk S, Lynfield R, Schaffner W, et al. Prevention of antibiotic-nonsusceptible invasive pneumococcal disease with the 13-valent pneumococcal conjugate vaccine. *Clin Infect Dis*.2016;62(9):1119–1125.
8. Simon MW, Bataille R, Caldwell NS, et al. Safety and immunogenicity of a multivalent pneumococcal conjugate vaccine given with 13-valent pneumococcal conjugate vaccine in healthy infants: a phase 2 randomized trial. *Hum Vaccin Immunother*. 2023;19(2): 2245727.

9. Lytle D, Grajales Beltran AG, Perdrizet J, et al. Cost-effectiveness analysis of PCV20 to prevent pneumococcal disease in the Canadian pediatric population. *Hum Vaccin Immunother*. 2023;19(2):2257426.
10. Centers for Disease Control. Clinical growth charts. Accessed August 20 2017. www.cdc.gov/growthcharts/clinical_charts.htm.
11. Pottel H, Mottaghy FM, Zaman Z, Martens F. On the relationship between glomerular filtration rate and serum creatinine in children. *Pediatr Nephrol*. 2010;25(5):927–934.
12. Crandon JL, Nicolau DP. Pharmacodynamic approaches to optimizing beta-lactam therapy. *Crit Care Clin*. 2011;27(1):77–93.
13. Valcke YJ, Rosseel MT, Pauwels RA, et al. Penetration of ampicillin and sulbactam in the lower airways during respiratory infections. *Antimicrob Agents Chemother*. 1990;34(6):958–962.
14. Nahata MC, Vashi VI, Swanson RN, et al. Pharmacokinetics of ampicillin and sulbactam in pediatric patients. *Antimicrob Agents Chemother*. 1999;43(5):1225–1229.
15. Nahata MC, Durrell DE, Barson WJ. Ceftriaxone kinetics and cerebrospinal fluid penetration in infants and children with meningitis. *Chemotherapy*. 1986;32(2):89–94.
16. MacVane SH, So W, Nicolau DP, Kuti JL. In vitro activity of human-simulated epithelial lining fluid exposures of ceftaroline, ceftriaxone, and vancomycin against methicillin-susceptible and -resistant Staphylococcus aureus. *Antimicrob Agents Chemother*. 2014;58(12):7520–7526.
17. Pediatric & Neonatal Lexi-Drugs and Lexi-interact. Lexicomp. Hudson, OH: Wolters Kluwer Health, Inc. Accessed March 15, 2024. http://online.lexi.com
18. Fukumoto K, Aida S, Oishi T, Ueno K. Pharmacokinetics of ceftriaxione, a third-generation cephalosporin, in pediatric patients. *Biol Pharm Bull*. 2009;32(7):1139–1141.
19. Schlender JF, Meyer M, Thelen K, et al. Development of a whole-body physiologically based pharmacokinetic approach to assess the pharmacokinetics of drugs in elderly individuals. *Clin Pharmacokinet*. 2016;55(12):1573–1589.
20. Rodvold KA, Hope WW, Boyd SE. Considerations for effect site pharmacokinetics to estimate drug exposure: concentrations of antibiotics in the lung. *Curr Opin Pharmacol*. 2017;36:114–123.
21. CLSI. eCLIPSE Ultimate Access. Accessed March 15, 2024. http://em100.edaptivedocs.net/Login.aspx
22. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 12.0. 2022. Accessed March 15, 2024, http://www.eucast.org.
23. Kaplan SL, Mason EO, Jr., Wald E, et al. Six year multicenter surveillance of invasive pneumococcal infections in children. *Pediatr Infect Dis J*. 2002;21(2):141–147.
24. Kaplan SL, Barson WJ, Lin PL, et al. Invasive pneumococcal disease in children's hospitals: 2014-2017. *Pediatrics*. 2019;144(3).
25. Ambroggio L, Taylor JA, Tabb LP, et al. Comparative effectiveness of empiric beta-lactam monotherapy and beta-lactam-macrolide combination therapy in children hospitalized with community-acquired pneumonia. *J Pediatr*. 2012;161(6):1097–1103.
26. Ribeiro CF, Ferrari GF, Fioretto JR. Antibiotic treatment schemes for very severe community-acquired pneumonia in children: a randomized clinical study. *Rev Panam Salud Publica.*2011;29(6):444–450.
27. Williams DJ, Edwards KM, Self WH, et al. Effectiveness of beta-Lactam monotherapy vs macrolide combination therapy for children hospitalized with pneumonia. *JAMA Pediatr*. 2017;171(12):1184–1191.
28. Thomson J, Ambroggio L, Murtagh Kurowski E, et al. Hospital outcomes associated with guideline-recommended antibiotic therapy for pediatric pneumonia. *J Hosp Med*. 2015;10(1):13–18.
29. Iroh Tam PY, Hanisch BR, O'Connell M. The impact of adherence to pediatric community-acquired pneumonia guidelines on clinical outcomes. *Clin Pediatr (Phila)*. 2015;54(10):1006–1008.
30. Batard E, Javaudin F, Kervagoret E, et al. Are third-generation cephalosporins associated with a better prognosis than amoxicillin-clavulanate in patients hospitalized in the medical ward for community-onset pneumonia? *Clin Microbiol Infect*. 2018;24(11):1171–1176.

JPPT | Compatibility Study

Chemical Compatibility of N-Acetylcysteine After the Simultaneous Intravenous Administration of Ondansetron

Stacy Brown, PhD; Benjamin Kennard, PharmD, MS; and Jim Thigpen, PharmD

OBJECTIVE This study evaluated the chemical compatibility of N-acetylcysteine (NAC) and ondansetron to simplify the treatment of acute nausea and vomiting during intravenous (IV) NAC administration. NAC is commonly used to treat acetaminophen overdose, but its 21-hour IV infusion is often interrupted for ondansetron administration, which can pose risks.

METHODS High-performance liquid chromatography with ultraviolet detection was used to quantify NAC. To simulate IV administration, a closed-circuit pump with multiple independent lines, was plumbed with Y-sites to circulate NAC at concentrations matching 30- and 100-kg loading doses and 4-mg ondansetron was pushed into the flow paths. Control lines without ondansetron were also maintained. Samples were collected at 10, 20, and 30 minutes postondansetron introduction. NAC concentrations in single-drug and combination lines were compared using an unpaired *t*-test with Welch's correction ($p = 0.05$).

RESULTS The mean concentrations for the 100-kg dose were 55.23 and 55.28 mg/mL for control and with ondansetron, respectively. The 30-kg cohort included 36.38 mg/mL for control and 36.49 mg/mL with ondansetron. The results of the unpaired *t*-test for either weight illustrated that no statistical significance was achieved. Furthermore, the *t*-values of 0.2013 for 100 kg and 0.8556 for 30 kg support a less likely chance of significant difference.

CONCLUSION Based on this experiment, ondansetron can be introduced into an NAC infusion via IV push *in vitro* without affecting the NAC concentration in the solution. The likelihood of IV compatibility for NAC and ondansetron could permit no infusion interruptions, reducing unnecessary risk of acetaminophen toxicity.

ABBREVIATIONS: HPLC, high-performance liquid chromatography; IV, intravenous; LC, liquid chromatography; LD, loading does; MS, mass spectrometry; NAC, N-acetyl cysteine; NS, normal saline; UV, ultraviolet

KEYWORDS acetaminophen; NAC; N-acetylcysteine; ondansetron; compatibility

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Introduction

Acetaminophen is associated with more than 50,000 annual emergency room visits and approximately 500 deaths, mostly attributed to unintentional overdose.[1] Acetaminophen overdose poses a significant risk of hepatotoxicity, especially in children and adolescents. N-acetylcysteine (NAC) is the most effective therapy for acetaminophen poisoning. However, oral and intravenous (IV) administration of NAC are often complicated by nausea and vomiting, with a reported occurrence of 23% and 9%, respectively, necessitating the use of antiemetics.[2] Ondansetron, a 5-HT3 receptor antagonist, is an antiemetic often employed to treat acute nausea and vomiting in the setting of NAC use. While NAC can be used both orally and IV, IV administration has been associated with fewer side effects, shorter treatment duration, and lower cost.[3] Protocols for NAC administration involve 20- to 21-hour-long infusions. Any interruption of the infusion for incompatible or unknown compatibility medications involves delays in the treatment due to flushing, medication administration, flushing, and restart of the NAC. Errors could be made at any point during this interruption, including a failure to restart the NAC infusion. The risks associated with unknown compatibility or infusion interruption are minimized by determining the compatibility of ondansetron with NAC. The need to mitigate nausea and vomiting applies to up to 60% of patients and is often most urgent within the initial hours of NAC therapy. It also coincides with when acetaminophen serum concentrations are also at their peak.[4,5] Administration of ondansetron is shown to increase overall tolerance of NAC treatment to a positive clinical endpoint.[6,7] As such, we investigated the IV compatibility of NAC when combined with ondansetron to reduce the steps in treating acute nausea and vomiting. Some hospitals have already demonstrated the utility of a simpler "one-bag"

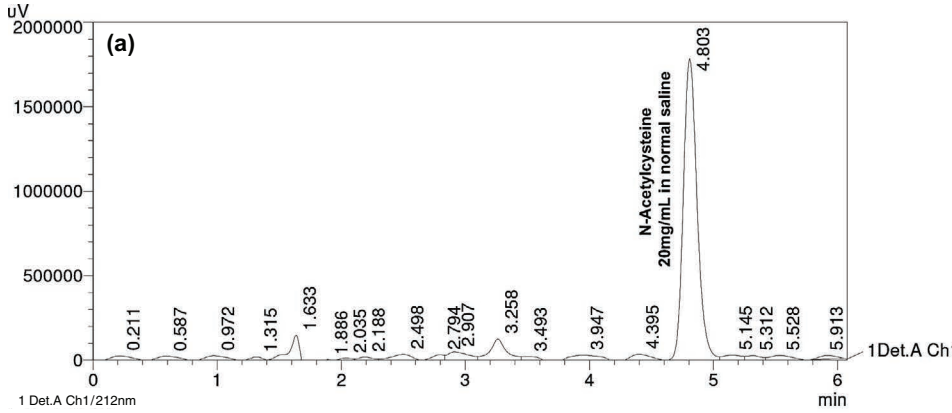
method for administering NAC, which could include ondansetron if chemical compatibility is confirmed.[8]

Methods

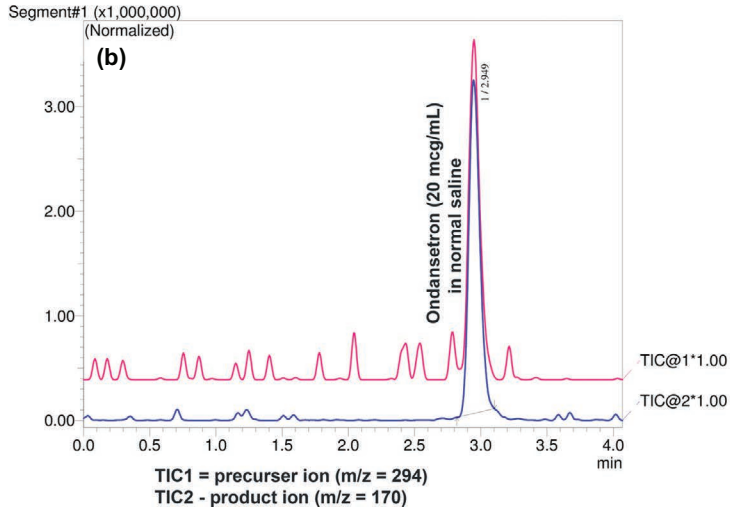
Equipment and Chromatographic Conditions. A Shimadzu high-performance liquid chromatography (HPLC) system, equipped with an autosampler, column oven, in-line degasser, and ultraviolet (UV) detection set at 212 nm was used for all chromatographic measurements (Shimadzu Scientific, Kyoto, Japan). NAC calibration solutions (1–60 mg/mL) were prepared in HPLC-grade water. The NAC standard was acquired from Alfa Aesar (Haverhill, MA, USA). The chromatographic separation used isocratic conditions with 90% water with 0.1% trifluoroacetic acid (A) and 10% acetonitrile (B) at a flow rate of 0.5000 mL/min (Honeywell Burdick & Jackson, Morris Township, NJ, USA). The analytical column was a Waters XBridge C18 column (4.6 × 150 mm; 3.5 µm), maintained at 50°C (Waters Corporation, Milford, MA, USA). All injected samples were filtered using a 0.22-µm syringe filter before injection (Signa Aldrich, St. Louis, MO, USA). All sample injection volumes were 1 µL, and the autosampler was purged with 2-propanol between injections (Fisher Scientific, Waltham, MA, USA).

The HPLC method for quantification of NAC in normal saline (NS) was fashioned after Gowda et al,[9] who used an isocratic mixture of 0.1% trifluoroacetic acid in water and acetonitrile (96/4) on a reversed-phase column. The concentration of aqueous was adjusted in our method to ensure the retention time of NAC differed from that of ondansetron. While ondansetron was not quantified using HPLC-UV, as the concentration in the experimental samples was too low, its retention time was verified by

Figure 1. (a) Example HPLC-UV chromatogram (212 nm) of N-acetylcysteine in normal saline (20 mg/mL)* (b) Example ion chromatogram (+ESI-LC-MS/MS) of ondansetron in normal saline (20 mcg/mL)



*Det, detector; HPLC-UV, high-performance liquid chromatography with ultraviolet detection; UV, Ultraviolet



ESI, electrospray ionization; LC, liquid chromatography; MS, mass spectrometry; m/z, mass-to-charge ratio; TIC, total ion chromatogram

a positive electrospray ionization liquid chromatography with tandem mass spectrometry experiment. An example of a UV chromatogram of NAC in NS and an electrospray ionization liquid chromatography with a tandem mass spectrometry ion chromatogram of ondansetron are shown in Figure 1.

Table 1. Interday Precision and Accuracy for HPLC-UV Assay Used in the for Quantification of N-Acetylcysteine in Normal Saline

Concentration Spiked, mg/mL	Concentration Measured,* mg/mL ± SD	% Error (n = 20)	% RSD (n = 20)
30	29.77 ± 0.65	0.75	2.19
20	21.37 ± 0.42	6.86	1.97
15	15.97 ± 0.38	6.46	2.40
10	10.37 ± 0.40	3.73	3.88
5	4.92 ± 0.37	1.62	7.55

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

* n = 5 replicate measurements per concentration per day, collected over 4 separate days.

Method Validation. The HPLC-UV method for NAC was validated in the range of 1 to 30 mg/mL over 4 nonconsecutive days. The precision, as represented by the percent relative standard deviation and accuracy, as represented by the percent error, were assessed for each calibration point on 4 separate nonconsecutive days by 2 different analysts. On each day of validation, a calibration curve was prepared with the following points: 1, 5, 10, 20, and 30 mg/mL NAC, and an additional 5 quality control samples were prepared at each concentration. The results of the interday and intraday precision and accuracy are summarized in Tables 1 and 2, respectively. The designation of spiked concentration refers to the intended concentration in the preparation of the calibration standards. System suitability parameters were monitored throughout the validation, including tailing factor, resolution, and theoretical plates. System suitability indicated symmetrical peaks that were well resolved

Table 2. Intraday Precision and Accuracy for HPLC-UV Assay Used in the for Quantification of N-Acetylcysteine in Normal Saline

Validation Day	Parameter	Spiked Concentration, mg/mL				
		30	20	15	10	5
1	Concentration measured, mg/mL (n = 5)	30.00	21.84	16.27	10.67	5.19
	SD	0.22	0.06	0.05	0.03	0.44
	% Error	0.01	9.19	8.47	6.69	3.71
	% RSD	0.73	0.28	0.32	0.24	8.45
2	Concentration measured, mg/mL (n = 5)	30.03	21.31	16.12	10.75	5.00
	SD	1.16	0.61	0.04	0.17	0.02
	% Error	0.10	6.53	7.45	7.55	0.00
	% RSD	3.88	2.85	0.24	1.54	0.39
3	Concentration measured, mg/mL (n = 5)	29.81	21.29	16.10	10.25	5.00
	SD	0.23	0.21	0.16	0.22	0.27
	% Error	0.62	6.46	7.34	2.45	0.00
	% RSD	0.77	0.99	1.02	2.12	5.40
4	Concentration measured, mg/mL (n = 5)	29.25	21.05	15.39	9.82	4.49
	SD	0.28	0.10	0.29	0.05	0.23
	% Error	2.50	5.25	2.57	1.78	10.19
	% RSD	0.94	0.46	1.86	0.48	5.20

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

from other components in the chromatogram, with theoretical plates averaging 5036, average resolution of 1.92, and tailing factor of 1.34. Method selectivity was verified by injecting blank 0.9% sodium chloride from Baxter (LOT P419764, EXP Dec 2022; Deerfield, IL, USA) and ondansetron (Baxter, Deerfield, IL, USA; Lots A0E1015A [11/23] and O61096 [6/24]) diluted in NS at the experimental concentrations.

Chemical Compatibility Experiment. For this experiment, NAC from Sagent (Schaumburg, IL. USA; LOTS 7606333 [2/23], 7606476 [4/23], A000040574 [6/23], and 7606953 [10/23]) was diluted in NS to replicate loading dose (LD) concentrations for a 30- and 100-kg patient.[10,11] For the 30-kg patient LD, this involved diluting 22.5 mL of the NAC drug product into 100-mL NS for an approximate final NAC concentration of 36.7 mg/mL. For the 100-kg patient LD, 75 mL of NAC was diluted into 200-mL NS for an approximate final NAC concentration of 54.5 mg/mL. Two iterations of each LD solution were prepared, and each was introduced to a 250-mL Erlenmeyer flask. Each flask was connected on independent channels to a multichannel pump (MCP 3000 Digital Multichannel Pump, Model #13-310-662, Fisher Scientific, Waltham, MA, USA) using medical-grade tubing (Component Supply Company, Tygon ND100-65 Med/Surgical Tubing, 1/16" ID, 1/8" OD, 1/32" wall, Sparta, TN, USA). The pump was set to continuously recirculate the preparations through 4 independent channels at the lowest pump flow rate setting. The tubing was plumbed to accommodate a y-site junction. After allowing the NAC solutions to circulate through the pump for 10 minutes, 2 mL of ondansetron drug was administered via IV push into the y-site for 1 channel of the 30-kg LD and 1 channel of the 100-kg LD. For the other 30- and 100-kg LD flasks, 2-mL NS was introduced via IV push to maintain consistent volume with the experimental samples (ondansetron flasks). Three samples (1-mL each) were removed from each flask at 10, 20, and 30 minutes of circulation and filtered into autosampler vials. These times indicate the duration of contact between the 2 drugs in the IV solutions. These samples were subject to immediate HPLC analysis using the aforementioned method, with 1 injection per sample. Peak areas from the samples were compared to freshly prepared calibration standards of NAC in water, and NAC concentrations in the samples were calculated. The average calculated concentrations from the NAC + ondansetron samples were compared with the NAC (no ondansetron) samples for each loading dose using an unpaired, 2-tailed students *t*-test with a p value of 0.05 (Graph Pad Prism, v 9.03, La Jolla, CA, USA).

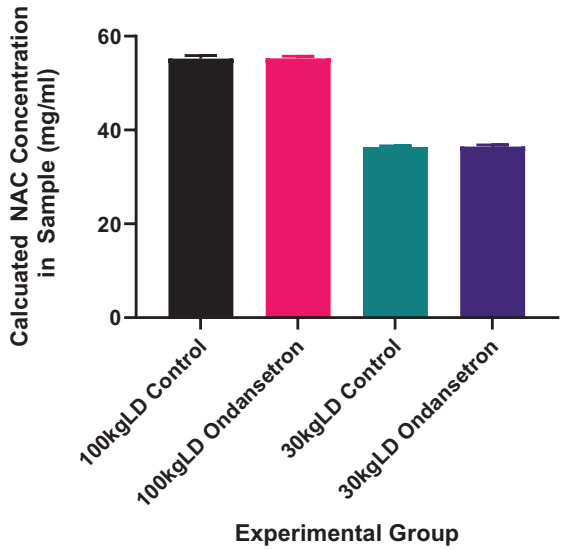


Figure 2. Graphical representation of calculated concentrations of N-acetylcysteine infusion solutions with and without the introduction of ondansetron. No statistically significant difference was detected between the groups using an unpaired student's *t*-test ($p < 0.05$)

Results

Chemical Compatibility. For the 30-kg patient LD, the NAC concentrations in the samples with ondansetron added were 36.49 ± 0.32 mg/mL, while those without ondansetron (controls) contained 36.38 ± 0.23 mg/mL NAC. For the 100-kg patient LD, the NAC concentrations in the samples with ondansetron added were 55.28 ± 0.44 mg/mL, while those without ondansetron (controls) contained 55.23 ± 0.63 mg/mL NAC. These data are graphically represented in Figure 2. Of note, these were in line with the approximate concentration of NAC expected in the preparation of NAC solutions in NS, 36.7 and 54.5 mg/mL, respectively. When the control and experimental groups were compared using an unpaired, 2-tailed student's *t*-test, no statistically significant differences were found (30-kg LD group, $p = 0.4062$; 100-kg LD group, $p = 0.8432$). Additionally, the retention time of the NAC peak remained unchanged.

Discussion

Based on this chemical compatibility experiment, the introduction of IV push or infusion of up to 30 minutes of ondansetron via a y-site into an IV infusion of NAC at loading doses appropriate for a 30- and 100-kg patient does not affect the NAC concentration in a statistically significant way. While those of the 30- and 100-kg patients represent a high and low concentration, in terms of loading dose, for NAC, additional experiments at concentrations appropriate for second and third doses of NAC could investigate if this compatibility is compromised at lower NAC solution concentrations. As such, our data indicate

that the administration of IV push or infusion of up to 30 minutes of ondansetron (4 mg) via a y-site into an NAC infusion of loading dose concentration does not compromise the concentration of NAC delivered to the patient.

Possible limitations of our study include the absence of ondansetron quantification during the compatibility experiment with NAC. Future experiments may consider an assay that can simultaneously quantify both drugs. Additionally, our experimental conditions were limited because an *in vitro* closed-circuit pump may not capture all potential variables in clinical IV administration. Despite these limitations, our data support that ondansetron and NAC can be co-administered without compromising the chemical integrity of NAC, the most critical component of mitigating acetaminophen toxicity.

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References

1. Agrawal S, Khazaeni B. Acetaminophen toxicity. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2024.
2. Bebarta VS, Kao L, Froberg B, et al. A multicenter comparison of the safety of oral versus intravenous acetylcysteine for treatment of acetaminophen overdose. *Clin Toxicol* (Phila). 2010;48(5):424–430.
3. Miller MA, Navarro M, Bird SB, Donovan JL. Antiemetic use in acetaminophen poisoning: how does the route of N-acetylcysteine administration affect utilization? *J Med Toxicol*. 2007;3(4):152–156.
4. Bateman DN, Dear JW, Thanacoody HKR, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. *Lancet*. 2014;383(9918):697–704.
5. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. *Clin Toxicol* (Phila). 2009;47(2):81–88.
6. Clark RF, Chen R, Williams SR, et al. The use of ondansetron in the treatment of nausea and vomiting associated with acetaminophen poisoning. *J Toxicol Clin Toxicol*. 1996;34(2):163–167.
7. Tobias JD, Gregory DF, Deshpande JK. Ondansetron to prevent emesis following N-acetylcysteine for acetaminophen intoxication. *Pediatric Emergency Care*. 1992;8(6):345.
8. Mullins ME, Yu M, O'Grady L, et al. Adverse reactions in patients treated with the one-bag method of N-acetylcysteine for acetaminophen ingestion. *Toxicol Commun*. 2020;4(1):49–54.
9. Gowda P, Schaefer A, Schuck T. A simple RP-HPLC method for the stability-indicating determination of N-acetyl-L-cysteine and N,N'-diacetyl-L-cystine in cell culture media. *Cell Gene Ther Insights*. 2020; 6:303–323.
10. Dart RC, Mullins ME, Matoushek T, et al. Management of acetaminophen poisoning in the US and Canada: a consensus statement. *JAMA Netw Open*. 2023;6(8):e2327739.
11. Drugs.com. Acetylcysteine dosage guide + max dose, adjustments. Accessed July 3, 2024. https://www.drugs.com/dosage/acetylcysteine.html

Gluten-Free Options for the Top 100 Pediatric Medications

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OBJECTIVE Celiac disease and gluten sensitivities are on the rise, with a greater prevalence of the condition in children than adults. Resources to ascertain gluten content exist but can be incomplete and focus on medications for adults. The objective of this research is to determine gluten-free status of the top 100 pediatric medications dispensed.

METHODS The top 100 pediatric medications were identified by using Optum Clinformatics Data Mart database. After list creation, manufacturers and National Drug Code (NDC) for each drug were procured and used to contact manufacturers directly for gluten content information.

RESULTS Evaluation of 689 NDCs was completed with 50.2% of medications documented to be gluten-free. Additional categories were confirmed gluten-free but cannot confirm cross-contamination (22.6%), cannot confirm gluten-free (25.7%), and contains gluten (1.5%). Resource tables were developed from findings though information may change, based on manufacturing ingredients and processing.

CONCLUSIONS Pediatric medications differ in gluten content, compared with medications for adults. Incomplete information exists regarding gluten content of medications, especially pediatric resources. Development of a pediatric-specific resource for gluten content of commonly dispensed medications in children and adolescents will hopefully benefit patients with celiac disease.

ABBREVIATIONS FDA, US Food and Drug Administration; HCl, hydrochloride; NDC, National Drug Code; penicillin VK, penicillin V potassium

KEYWORDS celiac disease; children; gluten; pediatric

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Introduction

Celiac disease is an immune-mediated condition characterized by inflammation of the small intestine from ingesting gluten, a protein found in wheat, barley, and rye.[1] Diagnosis of celiac disease and gluten sensitivity in the United States has increased in the past few decades with an average 7.5% increase per year, in addition to cases that have gone undiagnosed.[2] Children have a significantly greater prevalence of celiac disease than adults.[3] Currently, celiac disease has no cure, thus gluten avoidance not only in foods, but also in less commonly noted sources, such as medications, is the only treatment.[3] Previous research and analysis on the gluten status of medications have focused primarily on commonly dispensed adult medications.[4,5] Even with these data available, there is still a large unmet need of public resources for gluten status of medications and greater still among commonly dispensed medications for children. The purpose of this assessment is to summarize gluten-free status of the top 100 medications dispensed to children and adolescents by developing a pediatric-specific resource for health care professionals to use when prescribing medications for pediatric patients with gluten sensitivities.

Materials and Methods

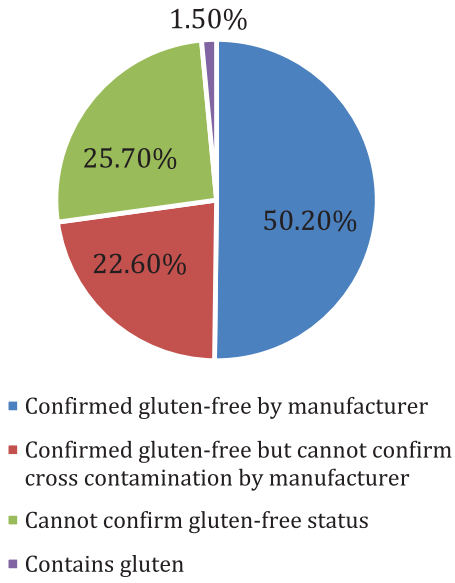
The top 100 dispensed medications to 10,000 patients younger than 18 years were identified from January 1, 2020, to December 31, 2020, using Optum Clinformatics.[6] Exclusion criteria consisted of non-oral medications and any National Drug Code (NDC) that was discontinued or no longer manufactured. Following the creation of the medication list, each drug was individually reviewed in the Lexicomp database[7] under Facts and Comparison's Product List to procure its NDC and manufacturer. Each drug manufacturer was subsequently contacted for gluten-free status, using the NDC/NDCs for all the top 100 medications. Manufacturers were first contacted through email, and if no response, investigators contacted companies via phone call(s). Information collected was organized by name, NDC, and gluten-free status. Gluten-free status was further differentiated into 4 categories: 1) confirmed gluten-free by manufacturer; 2) confirmed gluten-free but cannot

confirm cross-contamination by manufacturer, that is, ingredients were deemed gluten-free, but drug may have encountered gluten anytime during manufacturing process; 3) cannot confirm gluten-free status; and 4) contains gluten.

Results

A total of 689 NDCs was analyzed. The most dispensed medication was amoxicillin 400 mg/5 mL suspension with almost 2 million prescriptions dispensed, accounting for more than 7% of the total dispenses during the study period. Additional top 5 commonly dispensed medications were azithromycin 200 mg/5 mL suspension (4.6% of total prescription dispensed), cefdinir 250 mg/5 mL suspension (3.4%), prednisolone sodium phosphate 15 mg/5 mL solution (2.1%), and amoxicillin/potassium clavulanate 600 mg–42.9 mg/5 mL suspension (2%). Of the 689 NDCs reviewed, 346 (50.2%) were confirmed gluten-free by the manufacturer, 156 (22.6%) were confirmed gluten-free but could not confirm cross-contamination by the manufacturer, 177 (25.7%) could not confirm gluten-free status, and 10 (1.5%) contained gluten (Figure). Overall, 95 medications were identified to have at least 1 confirmed gluten-free option. Five medications were identified to not have a gluten-free option, which included clarithromycin 250 mg/5 mL suspension, levocetirizine dihydrochloride 2.5 mg/5 mL solution, mebendazole 100-mg chewable tablet, mefloquine hydrochloride (HCl) 250-mg tablet, and penicillin V potassium (VK) 250 mg/5 mL oral solution. Commonly used medications and their corresponding NDCs that were confirmed by the manufacturer to contain gluten included azithromycin 250 mg (59762-2198-XX), levocetirizine dihydrochloride 2.5 mg/5 mL solution (45802-0680-XX), lansoprazole 15-mg delayed-release capsule (00536-1236-XX, 00536-1324-XX), methylprednisolone 4-mg tablet (00603-4593-XX, 59746-0001-XX, 59762-4440-XX), prednisone 10-mg tablet (59746-0173-XX), and prednisone 20-mg tablet (59746-0175-XX). All NDCs for the following medications were confirmed gluten-free: acetaminophen-codeine 120 mg–12 mg/5 mL suspension, cefixime 100 mg/5 mL suspension, cefixime 200 mg/5 mL suspension, lisdexamfetamine of all strengths, prednisolone sodium phosphate 5 mg/5 mL and 25 mg/5 mL solution, and prednisolone sodium phosphate 15-mg disintegrating tablet. A resource table was developed to include all pediatric medications reviewed (Table).

Figure. Percentages of gluten content in the top 100 pediatric medications.



Discussion

Per the US Food and Drug Administration (FDA) requirement, for food products to be deemed "gluten-free" or "no gluten" on a label they must contain fewer than 20 parts per million of gluten.[8] However, the FDA only recommends that drug manufacturers use "contains no ingredient made from a gluten-containing grain (wheat, barley, or rye)" as a statement for medicines if true.[9] The statement if made is nonbinding and voluntary. If submitting a new drug application, manufacturers only need to ensure information is available to substantiate recommended labeling. If the drug application is already approved, manufacturers may add recommended labeling at any time if they can substantiate information but must add it to the next annual report. If using an alternative gluten statement or changing the product formulation to make a gluten statement, manufacturers must then submit a prior approval supplement. An example of alternative labeling (ie, "gluten-free") is not endorsed because the FDA has no established criteria for such statements on oral drug products. Furthermore, the FDA has not determined whether a gluten-free statement should refer to absence of intact gluten or should also require absence of gluten peptides.

Currently, the amount of gluten for a unit dose of an oral drug is estimated to be less than 0.5 mg, which is less gluten than in a gluten-free diet (ie, 5–50 mg).[9] Thus, the FDA infers that those patients who have positive response to a gluten-free diet should be at low risk for gluten-related gastrointestinal problems from the estimated gluten in an oral drug product. Patients with celiac disease should be advised to avoid oral medications labeled as containing wheat starch or flour; however, patients with gluten sensitivities may need additional information owing to unintentional intake of gluten from either drug excipients or the manufacturing process.[8,9]

Lack of gluten-free manufacturing policies is a barrier for patients with gluten sensitivities.[8] There are

currently no validated measures to detect or quantify gluten content in oral drug products.[9] Manufacturers may state their products are without gluten though they do not certify or test for gluten-free status.[5] Gluten categories for our pediatric resource were determined from manufacturers' responses in good faith, and cross-contamination was concluded to occur with an oral drug product if gluten may have been encountered at any time in the manufacturing process, though the ingredients were deemed gluten-free. Most patients with celiac disease can tolerate cross-contamination of approximately 10-mg gluten, but some sensitive patients may have an immune response to lower gluten content, leading them to attempt to eliminate or minimize exposure to gluten in drugs and other products.[8–10] Our findings identified 5 medications—clarithromycin 250 mg/5 mL suspension, levocetirizine dihydrochloride 2.5 mg/5 mL solution, mebendazole 100-mg chewable tablet, mefloquine HCl 250-mg tablet, and penicillin VK 250 mg/5 mL oral solution—that are without a gluten-free commonly used dosage form in the top 100 medications. If medications with gluten content are prescribed for patients with gluten sensitivities, the recommendation would be to identify an alternative dosage form (eg, penicillin VK solution to tablet), recommend a therapeutic alternative (eg, mefloquine tablet to doxycycline tablet),[5] or if no other alternative options exist, then the patient may proceed with caution given estimated gluten of 0.5 mg or less for a unit dose of oral drug.[9] Hopefully in the near future, patients will have additional alternatives, as several medications for celiac disease are in the drug development pipeline with therapeutic approaches consisting of breaking down gluten with enzymes, interrupting effects of gluten on the intestines, preventing gluten modification to reduce abnormal immune response, and interrupting the overall immune reaction from gluten.[11]

Limitations to our gluten-content medication list are the lack of over-the-counter drug products, as well as herbal and dietary supplements. Given the FDA ensures over-the-counter drug products for quality, effectiveness, and safety, similar recommendations for gluten-free status would carry through for their labeling. On the contrary, herbals and dietary supplements would not have the same oversight because they are not FDA approved, leaving their gluten content unknown or unsubstantiated.

Conclusion

Inactive ingredients produced from wheat starch or transferred through the manufacturing process can result in gluten content in medications.[4,12] A previous list of medications for adults found 18% of manufacturers specified their medications contain gluten.[4] Additionally, 69% indicated their medications were gluten-free, although only 17% tested their products and could provide documentation. Findings from our assessment differed, because 50% of medications were documented to be gluten-free, with only 1% confirmed as containing gluten. Currently, gluten information in package inserts is voluntary, as the FDA has issued guidance for manufacturers to voluntarily label medications if known to be gluten-free.[9] However, most medication package inserts have limited information regarding gluten, and potential sources of gluten are not always easily recognized by health care professionals.[8] Benefits from this collective pediatric-specific resource will hopefully improve patient care by providing pharmacists and other health care providers appropriate gluten-free prescription options for children with celiac disease and gluten sensitivities, though information should be updated periodically by contacting the manufacturer because gluten content may change.[8]

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References

1. King JA, Jeong J, Underwood FE, et al. Incidence of celiac disease is increasing over time: a systematic review and meta-analysis. *Am J Gastroenterol*. 2020;115(4):507–525.

2. Incidence of celiac disease steadily increasing. *Celiac Disease Foundation. Published February* 20, 2020. Accessed August 1, 2023. https://celiac.org/about-the-foundation/featured-news/2020/02/incidence-of-celiac-disease-steadily-increasing/#:~:text=Celiac%20disease%20incidence%20among%20children,over%20the%20past%20several%20decades.
3. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16(6):823–836.e2.
4. King AR. Gluten content of the top 200 medications: follow-up to the influence of gluten on a patient's medication choices. *Hospital Pharmacy*. 2013;48(9):736–743.
5. Cruz JE, Cocchio C, Lai PT, Hermes-DeSantis E. Gluten content of medications. *Am J Health Syst Pharm*. 2015;72(1):54–60.
6. Clinformatics Data Mart [Database]. Optum (2020). Accessed September 2021.
7. Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc. https://online-lexi-com.uri.idm.oclc.org. Accessed August 1, 2023.
8. Lizano-Díez I, Mariño EL, Modamio P. Gluten in pharmaceutical products: a scoping review. *Syst Rev*. 2021;10(1):218.
9. Gluten in Drug Products and Associated Labeling Recommendations, Draft Guidance for Industry. US Food and Drug Administration. Published December 2017. Accessed August 1, 2023. https://www.fda.gov/media/116958/download.
10. Chartrand LJ, Russo PA, Duhaime AG, Seidman EG. Wheat starch intolerance in patients with celiac disease. *J Am Diet Assoc*. 1997;97(6):612–618.
11. Wieser H, Segura V, Ruiz-Carnicer Á, et al. Food safety and cross-contamination of gluten-free products: a narrative review. *Nutrients*. 2021;13(7):2244.
12. Drug development pipeline. *Beyond Celiac*. Published August 16, 2023. Accessed November 28, 2023. https://www.beyondceliac.org/research/drugdevelopment/drug-development-pipeline/.
13. Data on file for drug gluten content. Parsippany, NJ: Pharmaceutical Associates Inc; 2022.
14. Data on file for drug gluten content. Norcross, GA: Hi-Tech Pharmaceuticals; 2022.
15. Data on file for drug gluten content. Parsippany, NJ: Teva Pharmaceuticals USA Inc; 2022.
16. Data on file for drug gluten content. Staines-upon-Thames, UK: Mallinckrodt Pharmaceuticals; 2022.
17. Data on file for drug gluten content. Chestnut Ridge, NY: Par Pharmaceutical; 2022.
18. Data on file for drug gluten content. East Windsor, NJ: Aurobindo Pharma Limited; 2022.
19. Data on file for drug gluten content. Bridgewater, NJ: Amneal Pharmaceuticals; 2022.
20. Data on file for drug gluten content. East Windsor, NJ: Eywa Pharma; 2022.
21. Data on file for drug gluten content. Canonsburg, PA: Mylan Pharmaceuticals Inc; 2022.
22. Data on file for drug gluten content. Parsippany, NJ: Actavis Pharma Inc; 2022.
23. Data on file for drug gluten content. East Brunswick, NJ: Avet Pharmaceuticals Inc; 2022.
24. Data on file for drug gluten content. East Windsor, NJ: Novitium Pharma; 2022.
25. Data on file for drug gluten content. Berkeley Heights, NJ: Pharmaceuticals USA Inc; 2022.
26. Data on file for drug gluten content. Holzkirchen, Germany: Sandoz; 2022.
27. Data on file for drug gluten content. East Brunswick, NJ: Rising Pharmaceuticals Inc; 2022.
28. Data on file for drug gluten content. East Brunswick, NJ: Citron Pharma; 2022.
29. Data on file for drug gluten content. Memphis, TN: NorthstarRx LLC; 2022.
30. Data on file for drug gluten content. Parsippany, NJ: Workhardt USA LLC; 2022.
31. Data on file for drug gluten content. Somerset, NJ: Micro Labs USA Inc; 2022.
32. Data on file for drug gluten content. Piscataway, NJ: Camber Pharmaceuticals Inc; 2022.
33. Data on file for drug gluten content. Mason, OH: Burel Pharmaceuticals Inc; 2022.
34. Data on file for drug gluten content. Princeton, NJ: Dr Reddy's Laboratories Inc; 2022.
35. Data on file for drug gluten content. Toronto, Canada: Apotex Pharmaceuticals Inc; 2022.
36. Data on file for drug gluten content. Glenmark Pharmaceuticals Inc. Toronto, Canada; 2022.
37. Data on file for drug gluten content. Livonia, MI: Major Pharmaceuticals Inc; 2022.
38. Data on file for drug gluten content. Springfield Gardens, NY: Epic Pharma LLC; 2022.
39. Data on file for drug gluten content. Peapack, NJ: Greenstone LLC; 2022.
40. Data on file for drug gluten content. Hopewell Township, NJ: Zydus Pharmaceuticals USA Inc; 2022.
41. Data on file for drug gluten content. Iselin, NJ: PuraCap Pharmaceuticals; 2022.
42. Data on file for drug gluten content. Hawthorne, NY; Taro Pharmaceuticals USA Inc; 2022.
43. Data on file for drug gluten content. Trevose, PA: Lannett Company Inc; 2022.
44. Data on file for drug gluten content. South Beloit, IL: Tagi Pharma Inc; 2022.
45. Data on file for drug gluten content. Bedminster, NJ: Alembic Pharmaceuticals Inc; 2022.
46. Data on file for drug gluten content. Baltimore, MD: Lupin Limited; 2022.
47. Data on file for drug gluten content. Princeton, NJ: Bionpharma Inc; 2022.
48. Data on file for drug gluten content. Hauppauge, NY: AiPing Pharmaceutical Inc; 2022.
49. Data on file for drug gluten content. Alpharetta, GA: Acella Pharmaceuticals; 2022.
50. Data on file for drug gluten content. East Brunswick; NJ: Strides Pharma Inc; 2022.
51. Data on file for drug gluten content. Herndon, VA: Ascend Therapeutics US LLC; 2022.
52. Data on file for drug gluten content. Central Islip, NY: XLcare Pharmaceuticals Inc; 2022.
53. Data on file for drug gluten content. Allegan, MI: Padagis LLC; 2022.
54. Data on file for drug gluten content. Raleigh, NC: Mayne Pharma US; 2022.
55. Data on file for drug gluten content. Berlin, CT: Breckenridge Pharmaceutical; 2022.

56. Data on file for drug gluten content. Dublin, Ireland: BluePoint Laboratories; 2022.
57. Data on file for drug gluten content. Princeton, NJ: Orchid Pharma Limited; 2022.
58. Data on file for drug gluten content. Princeton, NJ: Sun Pharmaceutical Industries Inc; 2022.
59. Data on file for drug gluten content. Paramus, NJ: TWi Pharmaceuticals USA Inc; 2022.
60. Data on file for drug gluten content. Pulaski, TN: AvKARE Inc; 2022.
61. Data on file for drug gluten content. Oceanside, CA: American Health Packaging; 2022.
62. Data on file for drug gluten content. Largo, FL: Belcher Pharmaceuticals LLC; 2022.
63. Data on file for drug gluten content. Levittown, PA: Torrent Pharma Inc; 2022.
64. Data on file for drug gluten content. Lake Villa, IL: Xttrium Laboratories Inc; 2022.
65. Data on file for drug gluten content. Concord, NC: Sky Pharmaceutical Packaging Industries; 2022.
66. Data on file for drug gluten content. Upper Saddle River, NJ: Dash Pharmaceuticals LLC; 2022.
67. Data on file for drug gluten content. New Castle, DE: Marlex Pharmaceuticals Inc; 2022.
68. Data on file for drug gluten content. East Brunswick, NJ: Unichem Pharmaceuticals USA Inc; 2022.
69. Data on file for drug gluten content. Tampa, FL: TruPharma LLC; 2022.
70. Data on file for drug gluten content. Arlington, TX: Method Pharmaceuticals LLC; 2022.
71. Data on file for drug gluten content. Skokie, IL: Patrin Pharma Inc; 2022.
72. Data on file for drug gluten content. Caldwell, NJ: Quagen Pharmaceuticals; 2022.
73. Data on file for drug gluten content. Newtown, PA: KVK Tech; 2022.
74. Data on file for drug gluten content. Berwyn, PA: Amring Pharmaceuticals; 2022.
75. Data on file for drug gluten content. Morristown, NJ: Alvogen Pharmaceuticals; 2022.
76. Data on file for drug gluten content. Locust Valley, NY: Fera Pharmaceutical LLC; 2022.
77. Data on file for drug gluten content. Monmouth Junction, NJ: Tris Pharma Inc; 2022.
78. Data on file for drug gluten content. Coventry, RI: Rhodes Pharmaceuticals; 2022.
79. Data on file for drug gluten content. Chantilly, VA: Granules Pharmaceuticals Inc; 2022.
80. Data on file for drug gluten content. Baudette, MN: ANI Pharmaceuticals Inc; 2022.
81. Data on file for drug gluten content. Cincinnati, OH: Prasco Laboratories; 2022.
82. Data on file for drug gluten content. Farmingdale, NY: Time-Cap Laboratories Inc; 2022.
83. Data on file for drug gluten content. Hauppauge, NY: ScieGen Pharmaceuticals Inc; 2022.
84. Data on file for drug gluten content. Earth City, MO: Legacy Pharmaceuticals Packaging; 2022.
85. Data on file for drug gluten content. Nashville, TN: Westminster Pharmaceuticals; 2022.
86. Data on file for drug gluten content. Congers, NY: Chartwell Pharmaceuticals LLC; 2022.
87. Data on file for drug gluten content. Miami, FL: Cipla USA Inc; 2022.
88. Data on file for drug gluten content. Fort Lauderdale, FL: Bioramo LLC; 2022.
89. Data on file for drug gluten content. Fairfield, NJ: Leading Pharma LLC; 2022.
90. Data on file for drug gluten content. Durham, NC: Precision BioSciences Inc; 2022.
91. Data on file for drug gluten content. Allentown, PA: Genus Lifesciences; 2022.
92. Data on file for drug gluten content. Largo, FL: VistaPharm; 2022.
93. Data on file for drug gluten content. Mahwah, FL: Lifestar Pharma LLC; 2022.
94. Data on file for drug gluten content. Cambridge, MA: Takeda Pharmaceuticals USA Inc; 2022.
95. Data on file for drug gluten content. Durham, NC: Accord Healthcare; 2022.
96. Data on file for drug gluten content. Somerset, NJ: Solco Healthcare US; 2022.
97. Data on file for drug gluten content. Horsham, PA: Patriot Pharmaceuticals LLC; 2022.
98. Data on file for drug gluten content. Alpharetta, GA: Trigen Laboratories LLC; 2022.
99. Data on file for drug gluten content. St. Louis, MO: Oakrum Pharma LLC; 2022.
100. Data on file for drug gluten content. Bridgewater, NJ: Ajanta Pharma USA Inc; 2022.
101. Data on file for drug gluten content. Princeton, NJ: Macleods Pharma USA Inc; 2022.
102. Data on file for drug gluten content. Sacramento, CA: Nivagen Pharmaceuticals Inc; 2022.
103. Data on file for drug gluten content. New Brunswick, NJ: OHM Laboratories Inc; 2022.
104. Data on file for drug gluten content. Lakewood, NJ: Gericare Pharmaceuticals Inc; 2022.
105. Data on file for drug gluten content. Florham Park, NJ: XiroMed LLC; 2022.
106. Data on file for drug gluten content. Piscataway, NJ: Novadoz Pharmaceuticals LLC; 2022.
107. Data on file for drug gluten content. Boca Raton, FL: LGM Pharma; 2022.
108. Data on file for drug gluten content. Berlin, Germany: Bayer Healthcare Pharmaceuticals LLC; 2022.
109. Data on file for drug gluten content. Rahway, NJ: Sunrise Pharmaceutical Inc; 2022.
110. Data on file for drug gluten content. Wall Township, NJ: Seton Pharmaceuticals LLC; 2022.
111. Data on file for drug gluten content. San Antonio, TX: Mission Pharmacal Co; 2022.
112. Data on file for drug gluten content. Salibury, MD: Cadista Pharmaceuticals Inc; 2022.
113. Data on file for drug gluten content. Coral Springs, FL: ACI Healthcare USA Inc; 2022.
114. Data on file for drug gluten content. Boca Raton, FL: Exelan Pharmaceuticals Inc; 2022.

JPPT | Case Report

Carbamazepine-Induced DRESS Syndrome During Epstein-Barr Virus Reactivation in an Adolescent

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare and potentially life-threatening syndrome. Herein, we present the case of a 14-year-old female who developed a diffuse erythematous rash with fever and facial edema 6 weeks after initiating treatment with carbamazepine and sertraline. Laboratory tests showed an inflammatory reaction, elevated liver enzymes, and mild eosinophilia. Serology tests were negative for viral hepatitis, cytomegalovirus, herpes simplex virus, and parvovirus B19, but positive anti-VCA IgM and anti-EBNA IgG confirmed the presence of Epstein-Barr virus reactivation. Drugs were withdrawn, and the patient was treated with corticosteroid. Carbamazepine was identified as the culprit drug after performing patch tests. Even though DRESS is rare in childhood, we present another case of carbamazepine-induced DRESS in an adolescent associated with EBV activation.

ABBREVIATIONS CBZ, carbamazepine; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; NR, normal range

KEYWORDS drug hypersensitivity syndrome; drug-related side effects and adverse reactions; carbamazepine; herpesvirus 4, human; pediatrics

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Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, referred to as drug-induced hypersensitivity syndrome, is a distinct, potentially life-threatening adverse reaction. It is seen in children and adults most often as a morbilliform cutaneous eruption with fever, lymphadenopathy, hematologic abnormalities, and multiorgan manifestations.[1] The initial event of this reaction is often viral reactivation; the virus in question is typically a member of the herpes family, such as human herpesvirus-6, Epstein-Barr virus (EBV), or cytomegalovirus.[2] DRESS syndrome is more common in adults and rarely seen in children. The most common clinical presentation of pediatric DRESS includes morbilliform rash in more than 99% of cases.[3]

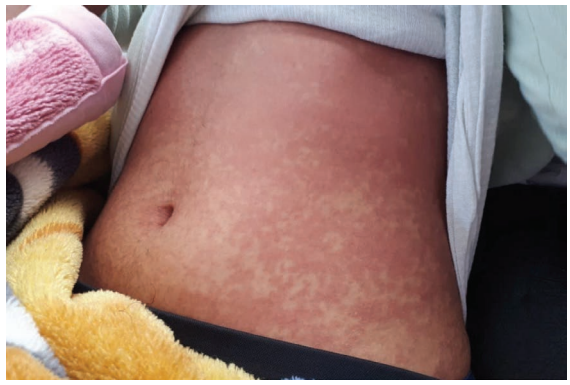
Recognizing this syndrome is important as the mortality rate is around 5.4%.[4] DRESS syndrome must be recognized promptly and the causative drug withdrawn. It has been reported that the earlier the drug withdrawal, the better the prognosis.[5]

Here, we present a case of DRESS syndrome in which the causative agent was carbamazepine (CBZ), which was associated with EBV reactivation, which was confirmed by a positive patch test.

Case Report

A 14-year-old female was admitted to the hospital with fever, facial edema, and a spreading rash, evolving over 3 days. She was seen 6 weeks prior by a child psychiatrist who prescribed a treatment consisting of CBZ 20 mg/kg/day and sertraline 50 mg/day for depressive syndrome. She had no significant past medical history, no prior medication use, and no known allergies. On physical examination, her temperature was 40°C, a diffuse erythematous rash was noted over the trunk (Figure 1), the face, and extremities with evident facial edema, and she weighed 40 kg. CBZ and sertraline were immediately withdrawn and replaced by fluoxetine with an initial dose of 10 mg/day. The patient received pulsed intravenous methylprednisolone 3 mg/kg/day for 3 days and oral prednisone 0.5 mg/kg/day for 3 weeks, followed by a gradual taper. Initial investigations were compatible with an inflammatory reaction and liver dysfunction as follows: C-reactive protein 65 mg/L (normal range [NR]: 0–8 mg/L), alanine aminotransferase 141 U/L (NR: 5–41 U/L), aspartate aminotransferase 114 U/L (NR: 0–50 U/L), and gamma-glutamyltransferase 110 U/L (NR: 9–50 U/L). Initial full blood count showed a white blood cell count of 6.8 × 10^3/µL (NR: 4.3–10 × 10^3/µL) and mild eosinophilia with 11% (NR: 0–5%). Serology tests were negative for viral hepatitis, cytomegalovirus, herpes simplex virus, and parvovirus B19. Recurrent EBV infection was demonstrated by the presence of IgM anti-VCA antibodies and IgG anti-EBNA antibodies in the serum taken 3 days after the resolution of the skin eruptions. A biopsy of the

Figure 1. Diffuse erythematous rash in the trunk.



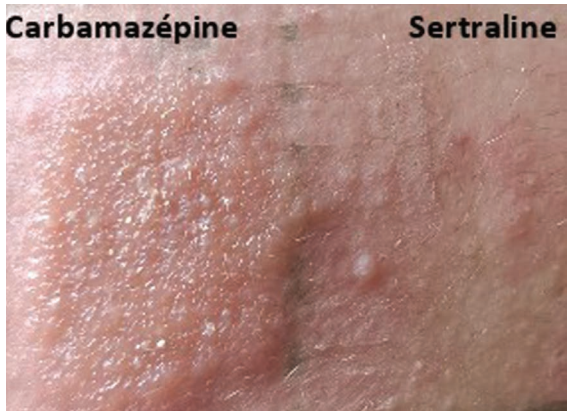
skin lesions revealed a combination of mild spongiosis and some necrotic keratinocytes with infiltration of lymphocytes and eosinophils, suggesting a drug reaction.

Within 4 weeks, the outcome was favorable, with a resolution of symptoms. The abnormal laboratory test results described above had normalized. Over a follow-up period of 4 months, the patient had no further episodes of skin rash nor any symptoms of autoimmune disease.

To identify the inducing agent of the hypersensitivity reaction for this patient, patch tests for CBZ and sertraline were performed 6 months after complete recovery and induced a strongly positive skin reaction to CBZ in 48 hours but was negative to sertraline (Figure 2).

In our case, the clinical, biological, and histological data are in accordance with the DRESS diagnosis criteria. According to the Registry of Severe Cutaneous Adverse Reactions scoring system established by Kardaun et al,[6] our case yielded a score of 6. Thus, the DRESS diagnosis was "definite" (Table 1).

Figure 2. Patch test results: positive to carbamazepine and negative to sertraline.



Discussion

Carbamazepine and sertraline were the suspected culprit drugs in view of a clear temporal relationship between their administration and the onset of the symptoms (6 weeks), as well as the improvement of the clinical and biological disorders some weeks after their withdrawal.

In our case, this adverse drug reaction was reported as "probable" by applying the Naranjo adverse drug reaction probability scale for the suspected drugs[7] (Table 2). However, the role of CBZ in the occurrence of this adverse drug reaction was confirmed by skin tests. Therefore, the diagnosis of CBZ-induced DRESS was established.

CBZ-induced DRESS is well documented in the adult literature, with many case reports.[8,9]

In our review of the literature and according to data from MEDLINE, only 1 case of CBZ-induced DRESS during EBV infection was reported with an 8-year-old male during treatment with CBZ for epilepsy 9 weeks after drug withdrawal and corticosteroid treatment.[10] Contrary to our case, this was a primary EBV infection and not reactivation, and patch tests were not performed.

Only 4 documented pediatric cases of CBZ-induced DRESS have been previously reported.[11–14] Patch tests were not performed in 3 cases, and viral reactivation was not causative.[11–13] One report of an 8-year-old female who developed a DRESS syndrome 5 weeks after starting CBZ did not have viral reactivation, but patch tests were positive for CBZ.[14]

In children, one of the major difficulties in the diagnosis of drug hypersensitivity is the differentiation of maculopapular eruption as an allergic reaction from a viral exanthema, which is very common. Peripheral blood eosinophilia may sometimes be helpful in the differentiation of drug reactions from viral infections. If an allergy is suspected, an allergy workup is recommended. Patch tests are a useful and safe tool for identifying the culprit drug for the DRESS syndrome.[15]

The most common causative agents in pediatric DRESS are antiepileptic drugs (50%), including carbamazepine, phenytoin, and phenobarbital.[3] The aromatic ring in the chemical structure of carbamazepine leads to a higher risk of hyper sensitivity reactions. Age-related differences in drug metabolism may result in increased hypersensitivity to antiepileptic drugs in young children.[15]

Human herpes virus HHV-6, HHV-7, herpes simplex virus, cytomegalovirus, and EBV reactivation have been associated with DRESS syndrome.[16,17] The role of EBV in the pathogenesis of DRESS syndrome is still unclear. It is uncertain whether the commonly encountered viral infections during childhood play a role in or trigger hypersensitivity reactions to antiepileptic drugs in children.[15] Viral infections may change drug metabolism or act as danger signals, leading to an immune response.[18] Descamps et al[19] proposed that EBV amplifies the T-cell

Table 1. Results of the RegiSCAR Scoring System

Items	Scoring for DRESS			Patient Results	Patient Score
	Yes	No	Unknown		
Fever ≥ 38.5°C	0	–1	–1	Yes	0
Enlarged lymph nodes	1	0	0	Yes	0
Eosinophilia ≥ 0.7 × 10^9/L ≥ 1.5 × 10^9/L or ≥ 20%	1 2	0	0	Yes No	1
Atypical lymphocytes	1	0	0	No	0
Skin rash > 50% BSA Rash suggesting DRESS	1 1	0 –1	0 0	Yes Yes	1 1
Skin biopsy suggesting DRESS	0	–1	0	Yes	1
Organ involvement (score 1 for each organ, maximal score: 2)	1 2	0	0	Yes No	1
Rash resolution ≥ 15 days	0	–1	–1	No	0
Excluded other causes (≥ 3 tests of the following tests were negative: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood culture)	1	0	0	Yes	1
Final score*					6

ANA, anti-nuclear antibody; BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus

* Final score < 2: no case, final score 2–3: possible case, final score 4–5: probable case, and final score > 5: definite case.

Table 2. Naranjo Adverse Drug Reaction (ADR) Probability Scale

Question	Yes	No	Do Not Know or Not Done	Score in Our Case
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 given?	+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

Scoring of Naranjo algorithm: >9 = definite ADR; 5–8 = probable; 1–4 = possible ADR; 0 = doubtful ADR

activation induced by drugs and participates in developing visceral manifestations.

The concept that DRESS is no more than a viral disease triggered by a direct effect of drugs on virus reactivation and proliferation has been proposed.[16,20] Immunosuppression from treating DRESS with corticosteroids could contribute to viral reactivations.[21]

Conclusion

Even though DRESS is rare in childhood, we present here another case of carbamazepine-induced DRESS in an adolescent associated with EBV activation and confirmed by a positive patch test. Clinicians should be aware of the severe adverse effects that could be induced by CBZ in pediatric patients.

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

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References

1. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: part I. *Clinical perspectives. J Am Acad Dermatol*. 2013;68(5):693.e1–14.
2. Tawhari I, Tawhari F, Aljuaid M. Lamotrigine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) during primary Epstein-Barr virus (EBV) infection. *BMJ Case Rep*. 2018;bcr2017222416.
3. Metterle L, Hatch L, Seminario-Vidal L. Pediatric drug reaction with eosinophilia and systemic symptoms: a systematic review of the literature. *Pediatr Dermatol*. 2020;37(1):124–129.
4. Manieri E, Dondi A, Neri I, Lanari M. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome in childhood: a narrative review. *Front Med*. 2023;10:1108345.
5. Syn W-K, Naisbitt DJ, Holt AP, et al. Carbamazepine-induced acute liver failure as part of the DRESS syndrome. *Int J Clin Pract*. 2005;59(8):988–991.
6. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol*. 2007;156(3):609–611.
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. Fathallah N, Slim R, Rached S, et al. Carbamazepine-induced DRESS with severe eosinophilia confirmed by positive patch test. *Dermatitis*. 2014;25(5):282–284.
9. Moreta Rodríguez M, García-Pajares F, Almohalla-Álvarez C, et al. DRESS syndrome secondary to carbamazepine. *Rev Esp Enferm Dig*. 2023;115(2):96–97.
10. Scagni P, Morello M, Ramus MV, et al. Drug-induced hypersensivity syndrome associated with Epstein-Barr virus infection: a pediatric case report. *Pediatr Dermatol*. 2009;26(2):229–231.
11. EL omairi N, Abourazzak S, Chaouki S, et al. Drug reaction with eosinophilia and systemic symptom (DRESS) induced by carbamazepine: a case report and literature review. *Pan Afr Med J*. 2014;18:9.
12. Karuppannasamy D, Andavar R, Arumugam J, et al. DRESS syndrome secondary to carbamazepine therapy presenting with bilateral acute anterior uveitis and angle closure glaucoma. *J Ophthalmic Vis Res*. 2019;14(3):382–386.
13. Dursun A, Bayram AK, Tekerek NÜ, et al. A case of DRESS syndrome associated with carbamazepine treatment. *Turk Pediatri Ars*. 2018;53(1):48–50.
14. Buyuktiryaki AB, Bezirganoglu H, Sahiner UM e. Patch testing is an effective method for the diagnosis of carbamazepine-induced drug reaction, eosinophilia and systemic symptoms (DRESS) syndrome in an 8-year-old girl. *Australas J Dermatol*. 2012;53(4):274–277.
15. Atanasković-Marković M, Janković J, Tmušić V, et al. Hypersensitivity reactions to antiepileptic drugs in children. *Pediatr Allergy Immunol*. 2019;30(5):547–552.
16. Roujeau JC, Dupin N. Virus reactivation in drug reaction with eosinophilia and systemic symptoms (Dress) results from a strong drug-specific immune response. *J Allergy Clin Immunol Pract*. 2017;5(3):811–812.
17. Stirton H, Shear NH, Dodiuk-Gad RP. Drug reaction with eosinophilia and systemic symptoms (DReSS)/drug-induced hypersensitivity syndrome (DiHS)-readdressing the DReSS. *Biomedicines*. 2022;10(5):999.
18. Chang JY, Kim S-C. Anticonvulsant hypersensitivity syndrome associated with Epstein-Barr virus reactivation. *Yonsei Med J*. 2007;48(2):317–320.
19. Descamps V, Mahe E, Houhou N, et al. Drug-induced hypersensitivity syndrome associated with Epstein-Barr virus infection. *Br J Dermatol*. 2003;148(5):1032–1034.
20. Picard D, Janela B, Descamps V, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. *Sci Transl Med*. 2010;2(46).
21. Ushigome Y, Kano Y, Ishida T, et al. Short- and long-term outcomes of 34 patients with drug-induced hypersensitivity syndrome in a single institution. *J Am Acad Dermatol*. 2013;68(5):721–728.

JPPT | Case Series

A Case Series of the Use of Intranasal Dexmedetomidine for Procedural Sedation in the Pediatric Emergency Department

Haili Gregory, PharmD; Claire Bethel, MD; Greta Anton, PharmD; Megan Whitaker, RN; and Shiva Zargham, MD

Procedural sedation in children has the propensity to result in costly hospital admissions and prolonged lengths of stay in emergency departments due to the coordination and resources required for completion. The use of intranasal (IN) dexmedetomidine in children for procedural sedation has been growing in popularity and demand in many clinical settings. Dexmedetomidine is a centrally acting alpha-2 agonist with anesthetic and anxiolytic properties, making it a useful option for sedation. Additional benefits of its use in the pediatric emergency department include high tolerability, decreased emotional distress of children, and ease of administration without need for parenteral access. Of the 18 pediatric patients who received IN dexmedetomidine for procedural sedation, 10 patients had successful procedural sedation solely with IN dexmedetomidine use. The success rate with IN dexmedetomidine was 63% for non-painful procedures (magnetic resonance imaging [MRI], computed tomography [CT]) and 57% for painful procedures (eye examinations, laboratory draw/intravenous [IV] placement, fracture reduction, foreign body removal). There were no documented adverse events with IN dexmedetomidine. Of the 18 patients, only 1 patient needed to return for a repeated scan and 2 patients were admitted owing to sedation needs. The use of IN dexmedetomidine in the pediatric emergency department provides a safe and less invasive option for sedation than commonly used sedatives. This leads to a reduced need for admissions dedicated to obtaining procedural sedation.

ABBREVIATIONS CT, computed tomography; ED, emergency department; IN, intranasal; IV, intravenous; MRI, magnetic resonance imaging

KEYWORDS dexmedetomidine; intranasal sedation; pediatric emergency medicine; pediatric sedation; procedural sedation

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Information Box

What specific question(s) does this report address?

We aim to evaluate what dose of dexmedetomidine intranasally is most effective for sedation in the pediatric ED.

What does this report add to our current knowledge?

This report shows that doses closer to 3 mcg/kg most effectively induce adequate sedation for non-painful procedures in the pediatric ED.

Introduction

In the landscape of pediatric emergency care, the pursuit of safe and efficacious sedation strategies is paramount.[1] The use of sedatives in this context not only is aimed at alleviating distress and discomfort but also is essential for accurate diagnosis and timely treatment, with the ultimate goal of ensuring procedural success. Among the array of sedatives available, dexmedetomidine has emerged as a promising candidate owing to its unique pharmacologic profile and route of administration. Dexmedetomidine works centrally as an alpha-2 agonist, inducing sedation by suppressing the release of excitatory neurotransmitters.[2,3] It has also been suggested that dexmedetomidine has analgesic properties, but it is unclear in current literature how applicable this is to patients in the emergency department (ED) setting.[4] Much of the literature surrounding its use has been in the intensive care setting as an agent for sedation in patients who are intubated, or as an adjunctive agent in combination with other drugs such as midazolam, ketamine, or fentanyl for sedation. As it is investigated further, its utility as a single agent in procedural sedation has been demonstrated.[2,4,5] Intranasal (IN) administration of dexmedetomidine

presents as an attractive option for a few reasons including ease of administration, few adverse effects (e.g., hypotension and bradycardia), and avoidance of invasive procedures such as intravenous (IV) access in patients who do not require IV access for longer-term treatments (e.g., sepsis, long-term antibiotics).[2,5–9] By identifying optimal dosing regimens, and elucidating safety considerations, this case series seeks to enhance procedural sedation protocols, and improve the quality of care and outcomes in the pediatric ED.[10]

Methods

In September 2023 the pediatric ED at 1 academic medical center began stocking dexmedetomidine in the automated dispensing cabinets for IN administration for patients who require procedural sedation. The pediatric ED team was educated on this new option for procedural sedation including dosing, administration, and patient-specific considerations to guide selection of optimal sedative agents. We describe here a case series of the first 18 pediatric patients during a 4-month period who received IN dexmedetomidine in this pediatric ED. Retrospective chart review was undertaken to collect data including age of patient, body weight, past medical history, dose of IN dexmedetomidine, procedure requiring sedation, timing of drug administration to procedure start and finish, success rate of single-dose IN dexmedetomidine, adverse events, and admission rates required to complete the procedure.

Results

Of the 18 pediatric patients who received IN dexmedetomidine for procedural sedation, 10 patients had successful procedural sedation solely with IN dexmedetomidine use. The success rate with IN dexmedetomidine was 63% for non-painful procedures (magnetic resonance imaging [MRI], computed tomography [CT]) and 57% for painful procedures (eye examinations, laboratory draw/IV placement, fracture reduction, foreign body removal). The average dosage used for all patients was 2.4 mcg/kg (1–3 mcg/kg), the average dosage for successful completion of procedures solely with IN dexmedetomidine was 2.6 mcg/kg (1–3 mcg/kg), and the average dosage of failed completion with solely IN dexmedetomidine was 2.25 mcg/kg. The average age of successful completion using IN dexmedetomidine was 3.74 years, whereas the average age of failed attempt using IN dexmedetomidine was 6.1 years. There were no documented adverse events for any patients who received IN dexmedetomidine. Of the 18 patients, only 1 patient needed to return for a repeated scan and 2 patients were admitted owing to additional sedation requirements.

Patient A. Patient A is a 5-year-old female weighing 16.7 kg with a history of heart failure and renal transplant who required an MRI of the brain for stroke evaluation. She received dexmedetomidine IN 1 mcg/kg, then the MRI was delayed and did not start until 110 minutes after the dexmedetomidine was administered. The imaging was not able to be obtained and the patient was admitted for further sedation and imaging.

Patient B. Patient B is an 11-year-old male weighing 83.1 kg with a history of autism and asthma who received dexmedetomidine IN 3 mcg/kg for an MRI of his spine. The IN dose was given 38 minutes prior to the beginning of the MRI scan. The patient was unable to remain still for the entirety of the procedure, and adequate imaging was not obtained in the ED. The patient returned to an outpatient appointment for further sedation and imaging.

Patient C. Patient C is a 2-year-old male weighing 11.5 kg who required sedation for a CT scan of the head to assess for head injury after a fall. He received dexmedetomidine IN 1.5 mcg/kg, then 40 minutes later the CT scan began. Adequate imaging was obtained, and the patient was discharged from the ED without additional need for medications.

Patient D. Patient D is a 14-month-old male weighing 11.2 kg who received dexmedetomidine IN 3 mcg/kg for a CT scan of the head owing to concerns for head swelling following a fall. The scan began 22 minutes after the IN dose was given. The patient was unable to remain still for the scan, so was also given midazolam IN 0.5 mg/kg 1 hour later to attempt the scan again. Again, the patient was unable to remain still, so 2 hours following the midazolam IN dose he received midazolam 0.5 mg/kg orally and the modality of imaging was changed to x-ray, which was successful.

Patient E. Patient E is a 3-year-old male weighing 18.3 kg who required sedation for an MRI of the brain to evaluate neurologic changes. He received dexmedetomidine IN 3 mcg/kg, and the scan began 29 minutes after the medication was given. The sedation was successful and lasted the duration of the procedure, leading to the patient being discharged home.

Patient F. Patient F is a 19-month-old female weighing 10.1 kg who received dexmedetomidine IN 3 mcg/kg to obtain an MRI of the brain following trauma to the head. The scan was started 87 minutes after administration of the medication. The patient was unable to remain still, so 72 minutes after dexmedetomidine was given, the patient received midazolam IN 0.5 mg/kg and the MRI was able to be completed successfully, and the patient was discharged.

Patient G. Patient G is a 3-year-old male weighing 14.3 kg who required sedation to obtain a thorough eye examination owing to chemical exposure to the eye. He received dexmedetomidine IN 3 mcg/kg and the examination began 4 minutes later. The examination was successful and showed that the eye would need irrigation, so 83 minutes after the dexmedetomidine was given, IV access was obtained and the patient received ketamine IV 1.4 mg/kg for the additional procedure,

which was completed successfully. The patient was discharged from the ED.

Patient H. Patient H is an 11-year-old female weighing 67.9 kg with a history of autism, intellectual disability, and behavior abnormalities who required dexmedetomidine IN 3 mcg/kg to obtain difficult IV access. An attempt to secure IV access was made 52 minutes after the dexmedetomidine was administered, however it was unsuccessful. The patient then received midazolam IN 0.15 mg/kg (10 mg) and IV access was successfully obtained. The appropriate workup was successful and the patient was discharged from the ED.

Patient I. Patient I is an 8-year-old male weighing 23 kg who required dexmedetomidine IN 3 mcg/kg for a laceration repair following an animal bite. The procedure began 35 minutes following the administration of dexmedetomidine and was completed successfully. The patient was discharged home.

Patient J. Patient J is a 4-year-old female weighing 14.7 kg with a history of spina bifida and hydrocephalus and was experiencing headaches, sleepiness, and nausea with vomiting. She required sedation for an MRI of the head. Dexmedetomidine IN 2 mcg/kg was administered and the scan was started 18 minutes later. The MRI scan lasted 18 minutes and sedation was adequate to complete the procedure successfully; however, from the findings of the imaging, the patient was admitted to the hospital.

Patient K. Patient K is a 2-year-old female weighing 11.6 kg who required an MRI of the brain for intermittent episodes of hypothermia and ataxia she was having at home. She received dexmedetomidine IN 3 mcg/kg and the MRI began 22 minutes later. The procedure lasted 120 minutes and was successful, and the patient was discharged home.

Patient L. Patient L is a 3-year-old male weighing 17.5 kg who required sedation for an eye examination following trauma to the eye. He received dexmedetomidine IN 2.7 mcg/kg and the examination began 20 minutes later. The examination lasted 10 minutes and was successful, and the patient was discharged home.

Patient M. Patient M is a 17-month-old male weighing 10 kg who received dexmedetomidine IN 3 mcg/kg for an MRI to evaluate ocular abnormalities. The MRI began 19 minutes after administration of the dexmedetomidine and all images were successfully obtained. The patient was discharged home.

Patient N. Patient N is a 5-year-old male weighing 18 kg with a history of sickle cell disease and moyamoya disease that required sedation to obtain MRI, magnetic resonance angiography, and magnetic resonance venography to evaluate for a possible stroke. He received dexmedetomidine IN 2.8 mcg/kg 1 minute before the MRI began. The procedure took 82 minutes to complete and was successful. The patient was admitted to the hospital for monitoring owing to the severity of symptoms that prompted presenting to the ED. No further sedation was required.

Patient O. Patient O is a 12-year-old female weighing 46.3 kg with a history of postural orthostatic tachycardia syndrome, chronic migraines, and anxiety who required sedation for an MRI of the brain and spine to evaluate new symptoms of leg weakness. First, she received midazolam IV 0.04 mg/kg; the patient was unable to tolerate the MRI and IV access was lost. Further sedation with dexmedetomidine IN 2 mcg/kg was attempted and the patient was again unable to tolerate the MRI. She was then admitted to the hospital to complete the procedure under full sedation.

Patient P. Patient P is a 7-year-old male weighing 51.7 kg who required sedation for the reduction of a fracture sustained after falling onto an arm. About 30 minutes prior to receiving any sedation, he was given acetaminophen 15 mg/kg orally. He received dexmedetomidine IN 1.9 mcg/kg and 16 minutes later the procedure began. The patient did not tolerate the reduction and was given fentanyl IN 1.4 mcg/kg for pain management, then IV access was established and ketamine IV 1.5 mg/kg was given to complete the reduction. The patient was discharged home following the procedure.

Patient Q. Patient Q is a 2-year-old male weighing 12.1 kg who required sedation for the removal of a foreign body from the foot. Shortly after presentation to the ED, he was given ibuprofen 10 mg/kg orally, then 90 minutes later received dexmedetomidine IN 1 mcg/kg and an attempt to remove the foreign body was made 13 minutes later. This was unsuccessful. Intravenous access was then obtained, and the patient was administered ketamine IV 1.5 mg/kg, which led to successful removal of the foreign body. The patient was discharged home following the procedure.

Patient R. Patient R is a 6-year-old male weighing 56 kg with a history of autism and developmental delay who required sedation for the placement of an IV for hydration and laboratory tests for medical workup. He received dexmedetomidine IN 2 mcg/kg, then 137 minutes later IV access was attempted and successfully obtained. The patient was admitted owing to findings on laboratory tests, but no further sedation was required.

Discussion

Procedural sedation in the pediatric population is an evolving practice area. The use of IN dexmedetomidine outside of intensive care units has been a catalyst for advancing procedural sedation in pediatric patients.[1,2,4] Within the space of procedural sedation, there are several options to consider, and during the past several years many drug shortages have forced clinicians to use alternative agents, so having this additional option in our procedural sedation tool belt and knowing how to use it optimally is beneficial for the future of pediatric

emergency practice. In this case series, the use of IN dexmedetomidine was successful for both painful and non-painful procedures for completion of procedural sedation.

When selecting which medication or combination of medications to use for a procedural sedation, considering the onset and duration is vital. Dexmedetomidine IN has an onset of about 20 minutes but does not reach peak effect for up to 30 to 40 minutes from administration and can have a duration of 45 to 60 minutes. Comparing this with other IN and IV options, the onset of dexmedetomidine is not optimal for urgent procedures. For the patients in this case series, 6 (patients A, C, D, F, H, and R) had delays in the procedure of more than 40 minutes from the time of administration of dexmedetomidine, and 4 (patients A, D, F, and H) of those 6 procedures required additional sedation or admission for full sedation to complete the procedure. Coordination of timing of administration, start of the procedure, and duration of the procedure are all important to consider with IN dexmedetomidine use. Regarding dosing, various doses have been studied, ranging from 1 to 4 mcg/kg for IN use. One study evaluated 109 patients ranging in age from 6 months to 18 years and found that doses of 3 mcg/kg of dexmedetomidine alone, or dexmedetomidine IN combined with midazolam IN, had a 92% success rate.[7] Another systematic review evaluating dexmedetomidine use in the ED included 3 studies addressing procedural sedation. Within that review, dexmedetomidine showed more rapid onset to adequate sedation in some studies, and less favorable onset in others, along with several studies with risk of bias, thus emphasizing the need for further studies in this area.[4]

Through review of the patients within this case series, a few opportunities that may lead to increased rates of success were identified. In this small case series, less success was seen in patients who required sedation for painful procedures. This is likely multifactorial; however, of the patients whose sedation was unsuccessful, none received adjunctive pain medication prior to the procedure. Two of the patients whose sedation was successful for a painful procedure received acetaminophen or ibuprofen 30 to 90 minutes prior to the procedure and had success. Pain management in the pediatric population is often difficult to recognize and manage but is influential in the success of the procedure and comfort of the patient. Routine assessment of the patient's pain, using pediatric-specific tools such as Wong-Baker FACES or Faces Legs Activity Cry Consolability Scale in younger children and Numerical Rating Scale in older children, can aid in determining the need for additional adjunctive therapies to improve success rates in these patients.[11,12]

Another factor identified, which may have influenced the success of procedures, lies within the considerations for IN medication administration. One consideration is that the nasal atomizer has a dead space of up to 0.1 mL, meaning that up to 0.1 mL of the medication may be retained in the atomizer. To overcome this, nurses are instructed to draw up an additional 0.1 mL of the medication they are administering.[13] It is also important to recognize the limits of IN absorption of medication. The largest limitation is the volume of medication required; both large volumes and very small volumes can lead to impaired absorption of the optimal dose. The maximum volume that should be used is 1 mL per nostril in larger children, and 0.5 mL per nostril in infants and smaller children. Because of this limitation, when using dexmedetomidine it is beneficial to use the most concentrated product available, which for dexmedetomidine is a 100-mcg/mL vial preparation. Specifically, the maximum weight limitation for an intranasally absorbable 3-mcg/kg dose is about 66 kg. In patient B in our case series, the dose administered equated to a total volume of 2.5 mL and the sedation was not successful. While there were other factors that may have contributed, the large volume required for the desired dose was likely contributory. On the other side, small volumes of medication may be less reliable because the nasal atomizer can retain approximately 0.1 mL of the drug being administered. Patients A, C, and Q received doses that were less than 0.2 mL, and one required administration of ketamine to complete the procedure successfully. There may have been other factors contributing to this, but in cases where the volume is ≤0.2 mL, it is especially important to ensure that an additional 0.1 mL of the medication to be administered is drawn up to account for the dead space in the atomizer and to ensure maximal drug delivery and absorption. It is unknown in these 3 patients whether there was additional dexmedetomidine drawn up to account for the dead space in the atomizer.

Study Limitations

This case series favored success in a younger patient population; however, a larger cohort is required to definitively ascertain trends regarding ideal patient population for successful use of IN dexmedetomidine. Owing to the retrospective nature and small number of patients included in this descriptive case series, there are potential limitations with documentation and extraction of information collected. Data analysis was limited to information available in the electronic medical record, and adverse events potentially may have been underreported.

Conclusion

This case series illuminates the use of IN dexmedetomidine in a pediatric ED to provide a safe and less invasive option for sedation. Through this limited case series, the use of IN dexmedetomidine led to a reduced need for admissions dedicated to obtaining

procedural sedation, thus alleviating both financial and resource burdens of the health care system. Intranasal dexmedetomidine provides a safe, less invasive, and tolerable option for pediatric procedural sedation in the ED. Future research is warranted to further evaluate optimal dosing, safety, and cost effectiveness.

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

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References

1. Poonai N, Spohn J, Vandermeer B, et al. Intranasal dexmedetomidine for procedural distress in children: a systematic review. *Pediatrics*. 2020;145(1):1-12.
2. Weerink MAS, Struys MMRF, Hannivoort LN, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. *Clin Pharmacokinet*. 2017;56(8):893–913.
3. Dexmedetomidine. *Merative Micromedex*. Ann Arbor, MI: Merative. Accessed September 2, 2024. http://www.micromedexsolutions.com
4. Baumgartner K, Groff V, Yaeger LH, Fuller BM. The use of dexmedetomidine in the emergency department: a systematic review. *Acad Emerg Med.*2023;30(3):196–208.
5. Kavya KG, Pooja N. Intranasal dexmedetomidine with intravenous midazolam: a safe and effective alternative in the paediatric MRI sedation. *Cureus*. 2023;15(10):e46787.
6. Pascolo P, Peri F, Montico M, et al. Needle-related pain and distress management during needle-related procedures in children with and without intellectual disability. *Eur J Pediatr*. 2018;177(12):1753–1760.
7. Behrle N, Birisci E, Anderson J, et al. Intranasal dexmedetomidine as a sedative for pediatric procedural sedation. *J Pediatr Pharmacol Ther*. 2017;22(1):4–8.
8. Rech MA, Barbas B, Chaney W, et al. When to pick the nose: out-of-hospital and emergency department intranasal administration of medications. *Ann Emerg Med*. 2017;70(2):203–211.
9. Gan L, Zhao X, Chen X. The safety and efficacy evaluation of dexmedetomidine for procedural sedation and postoperative behaviors in pediatric populations: a systematic review and meta-analysis. *Ann Pharmacother*. 2022;56(1):16–26.
10. Del Pizzo J, Callahan JM. Intranasal medications in pediatric emergency medicine [quiz in Pediatr Emerg Care. 2014;30(7):502–504]. *Pediatr Emerg Care*. 2014;30(7):496–501.
11. Chumpitazi CE, Chang C, Atanelov Z, et al. Managing acute pain in children presenting to the emergency department without opioids. *J Am Coll Emerg Physicians Open*. 2022;3(2):e12664.
12. Ogino J, Hilado M, Schellenberg M, Im DD. Pain management in pediatric trauma. *Clin Pediatr (Phila)*. 2022;61(12):821–825.
13. Teleflex. LMA MAD Nasal: needle-free intranasal drug delivery. Accessed September 2, 2024. https://www.teleflex.com/usa/en/product-areas/anesthesia/atomization/mad-nasal-device/index.html

JPPT | Case Report

Eslicarbazepine Overdosing in a Teenager: Case Description and Management

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Eslicarbazepine acetate has been recently licensed as an anti-epileptic medication to be used in adolescents. Data regarding dosing and overdosing are still limited in the literature. We describe a rare case of intentional eslicarbazepine overdosing in a previously healthy teenager who presented with neurological toxicity. Management of hyperhydration with diuretics, haloperidol, and midazolam proved to be helpful both in inducing rapid clearance through the kidneys and in managing symptoms of agitation, respectively.

ABBREVIATIONS IV, intravenous

KEYWORDS overdosing; eslicarbazepine acetate; neurological toxicity; adolescence; poisoning

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Information Box

What specific questions does this report address?

This case report addresses the question of eslicarbazepine acetate overdosing.

What does this report add to our current knowledge?

This case report adds knowledge to the clinical presentation and management of eslicarbazepine overdosing in adolescents.

Introduction

Eslicarbazepine acetate is a new anti-epileptic medication that has been recently licensed for the treatment of focal seizures.[1] The drug has been approved by the United States Food and Drug Administration for use in individuals 4 years and older since 2017.[2] An oral dose of 800 mg/day has been proven to be safe, effective, and well-tolerated in adults.[3] It can also be used as adjunctive therapy in adults, adolescents, and children aged older than 6 years with partial-onset seizures with or without secondary generalization.[4] Data on overdosing are limited and mainly concern seizures, status epilepticus, and cardiac toxicity (arrhythmia).[4] We report a 14-year-old female with intentional eslicarbazepine overdose and describe the clinical presentation and management.

Case Report

A 14-year-old adolescent female with a mental health history was brought to a primary health center by her foster parents, who found her unresponsive in her room. Her weight was 70 kg, and she had been prescribed eslicarbazepine for depression (off-label use) 3 months earlier. Thirteen tablets were missing from the box, so it was assumed that she had ingested 10.400 mg of eslicarbazepine 2 to 3 hours earlier. Of note, the patient had recorded the suicide attempt and had uploaded a video in a widely used video-sharing application. Hence, the exact time of ingestion became known to us a few hours later.

The National Poison Center advised gastric lavage, activated charcoal (1g/kg) administration via nasogastric tube, and transfer to a tertiary center. Upon arrival to our emergency department (6 hours postingestion), her Glasgow Coma Scale score was 7 of 15, her pupils were dilated, sluggishly responsive to light, and she was only responding to painful stimuli. She had a patent airway (SpO_2 = 97%), stable heart rate (98–120 bpm), and slightly elevated blood pressure (145/70 mm Hg). She was administered 1 mg of flumazenil, 1.2 mg of naloxone, and 100 μg of clonidine, with no effect. Cardiac monitoring revealed a sinus rhythm with a normal QTc interval (400 msec). She was admitted to the general pediatric ward of the hospital. Two hours later (8 hours postingestion), she remained in deep lethargy with stable vital signs but started having episodes of agitation with abnormal nonepileptic movements of the upper and lower extremities. She remained in a state of reduced consciousness, fluctuating between stupor and extreme agitation and irritability, with incomprehensible speech and muscle spasms or movements resembling focal seizures and myoclonus for more than 12 hours. To control the episodes of irritability, she was restrained on her bed and was given intravenous (IV) haloperidol (2.5 mg, twice), IV propofol (6 mg, once), and buccal

midazolam (10 mg, once). She was also given IV fluids and furosemide (20 mg) to maximize urine output, aided by an infusion of mannitol (50 m/l/20 min). Because of the persistent neurological symptoms, a computed tomography scan of the brain was performed, which showed no evidence of focal lesions, hemorrhage, or edema. The patient remained hemodynamically stable and gradually regained consciousness approximately 21 hours postingestion, remaining fully orientated and in good medical condition. Blood and urine toxicologic analysis detected an elevated concentration of the active metabolite eslicarbazepine, confirming overdosing (blood: 51 mcg/mL, urine: 141 mcg/mL) when the therapeutic range in urine is 5 to 35 mcg/mL. Moreover, cannabinoids were also isolated in the urine sample, indicating probable ingestion of additional drugs. She was referred for a mental health evaluation.

Discussion

Eslicarbazepine acetate is given orally and is metabolized via hydrolytic first-pass metabolism to its active metabolite eslicarbazepine, which directly blocks voltage-gated sodium channels with no involvement of cytochrome P450.[2,4,5] Its pharmacokinetic and pharmacodynamic properties have been studied in adults, and it was shown to have a half-life of 9 to 20 hours, reaching peak serum concentrations at approximately 4 hours postingestion. Subsequently, it is excreted through the kidneys.[6]

Data regarding the toxicity of eslicarbazepine acetate in children and adolescents are extremely limited. Consequently, the National Poison Center had very little information on symptoms and treatment of overdosing, and information on the upper limit of tolerated dose was unavailable. In our patient, neurological toxicity was clinically obvious and persistent. There is only 1 other reported case of intentional overdosing with this novel anti-epileptic drug. An 18-year-old female ingested 5600 mg of eslicarbazepine and suffered from clonus, seizures, and cardiac arrest. She was managed supportively and with hemodialysis.[7] Cardiac toxicity with QTc prolongation and malignant arrhythmia were also reported, a finding that was not confirmed in our patient by serial electrocardiograms.

Based on the experience gained from the described patient, we recommend the following for the management of eslicarbazepine overdose: clinicians should be aware that there is no antidote. Therefore, management is largely supportive. Apart from the cardiological side effects, overdose could cause neurological symptoms and especially a reduced level of consciousness, seizures, or agitation. The patient should be closely monitored until a full resolution of the altered level of consciousness because of possible self-harm and injury. Gastric lavage should be performed if the patient has a good level of consciousness and as soon as possible from the time of ingestion. Hemodialysis and activated charcoal are also suggested. In our case, hydration, diuretics, haloperidol, and midazolam proved helpful, but management should always be individualized and include cardiac monitoring.

In conclusion, the present case adds significant evidence to the limited data regarding eslicarbazepine acetate overdose, highlighting the persistent neurological toxicity. The use of common antidotes proved unhelpful, but haloperidol effectively controlled agitation. Rapid clearance through the renal route is recommended.

Article Information

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

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References

1. Heo Y-A. Eslicarbazepine acetate: a review in focal-onset seizures. *CNS Drugs*. 2020;34(9):989–1000.
2. Long K. Aptiom (eslicarbazepine) FDAAA Section 915 New Molecular Entity (NME) *Postmarket Safety Summary Analysis. NDA 022416*. May 30, 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022416Orig1s000OtherR.pdf
3. Fei Y, Shi R, Song Z. Adjunctive treatment with eslicarbazepine acetate for adults and children with focal-onset epilepsy: a meta-analysis. *Front Neurol*. 2022;13:909471.
4. Website.European Comission Annex I. Esclicarbazepine acetate. Summary of Product Characteristics.

Accessed May 16, 2023. https://ec.europa.eu/health/documents/community-register/2009/2009042156888/anx_56888_en.pdf
5. Chung S, Sinha SR, Shah A, et al. Long-term safety and efficacy following conversion to eslicarbazepine acetate monotherapy in adults with focal seizures. *Clinical Trial Epilepsy Res*. 2019;153:59–65.
6. Bialer M, Soares-da-Silva P. Pharmacokinetics and drug interactions of eslicarbazepine acetate. *Epilepsia*. 2012;53(6):935–46.
7. Thompson J, Powell JD, Ovakim HD. Intentional overdose of the novel anti-epileptic drug eslicarbazepine presenting with recurrent seizures and ventricular dysrhythmias. *CJEM*. 2018;20:44–47.

JPPT | Research Letter

Evaluation of Patient-Driven Constipation Action Plans for Patients Discharged From a Pediatric Hospitalist Service

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ABBREVIATION GI, gastrointestinal

KEYWORDS constipation; laxative; pediatrics; pharmacy; polyethylene glycol

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Constipation is a common gastrointestinal (GI) disorder among pediatric patients, and is associated with an increase in health care utilization.[1,2] Management of constipation poses challenges due to diverse physiologic and psychologic factors associated with childhood development.[3,4] The European Society for Paediatric Gastroenterology, Hepatology and Nutrition and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommend polyethylene glycol as the preferred first-line pharmacologic therapy for the maintenance treatment of constipation.[2]

This study serves as an extension of a prospective clinical study from the same institution, Allison et al,[5] that evaluated the implementation of patient-specific, pharmacist-driven constipation action plan and found the implementation to be associated with decreased health care utilization. For this study, emphasis on patient-driven care was the focus, with the intention for patients and caregivers to actively participate in health care decisions. With a standardized action plan, caregivers and patients followed an outlined treatment approach to prevent constipation recurrence.

The purpose of this prospective, single-center study is to investigate and analyze the application of a standardized, patient-driven constipation action plan for patients discharged from the pediatric hospital service at a large academic medical center. Patients included in the study were 2 to 18 years of age who weighed ≥ 10 kg, admitted to a pediatric hospitalist service for a primary concern of constipation, and prescribed polyethylene glycol at hospital discharge.

Three standardized action plans were developed based on weight cohorts (10 kg to < 25 kg, 25 kg to < 40 kg, and ≥ 40 kg) for all enrolled patients by a study pharmacist (Figure 1). These action plans differed in polyethylene glycol starting dose, frequency, titration suggestions, and second-line pharmacologic therapy. Passing one bowel movement daily was considered the baseline goal for all enrolled patients and could be adjusted based on patient-specific factors and caregiver input, or by the study pharmacist. Patients or caregivers titrated polyethylene glycol based on the patient's reported number of daily bowel movements, or lack thereof, and consistency of stool.

After hospital discharge, caregivers were contacted every other week by telephone for a total of 4 encounters by a study pharmacist to discuss the patient's polyethylene glycol dose, adherence to action plan, and reported bowel habits. Pharmacist-specific recommendations were provided only in emergency situations or per caregiver-specific request.

The primary outcome was to determine the effect of a standardized patient-driven constipation action plan on the rate of health care utilization for concerns of constipation. Health care utilization was defined as a hospital admission, emergency department visit, GI specialist visit, caregiver-requested or scheduled acute care office visit, or urgent care visit. The secondary outcome for this study was to identify the average number of daily bowel movements in relation to compliance with the action plan.

Nine patients (5 female) were enrolled between October 2023 and April 2024. Patient age and body weight were a median of 6 years (range, 3–14) and 23.7 kg (range, 17.4–69.4), respectively. Follow-up duration after study enrollment ranged from 50 to 67 days. For enrolled patients, 27 health care utilization encounters occurred in total, including admission at time of enrollment, in the year before study enrollment (approximately 2.25 encounters monthly). Patients had 5 total health care utilization encounters after implementation of the action plans (approximately 2.5 encounters monthly). The median number of daily bowel movements before and after implementation of the action plans increased from 0.43 (range, 0.14–2) to 1 (range, 1–2). Stool consistency reported throughout the study follow-up period is illustrated in Figure 2. The final reported median daily weight-based polyethylene glycol dose was 0.5 g/kg/day (range, 0.16–1.08).

Figure 1. Standardized patient-driven constipation action plan example (25 kg to < 40 kg).

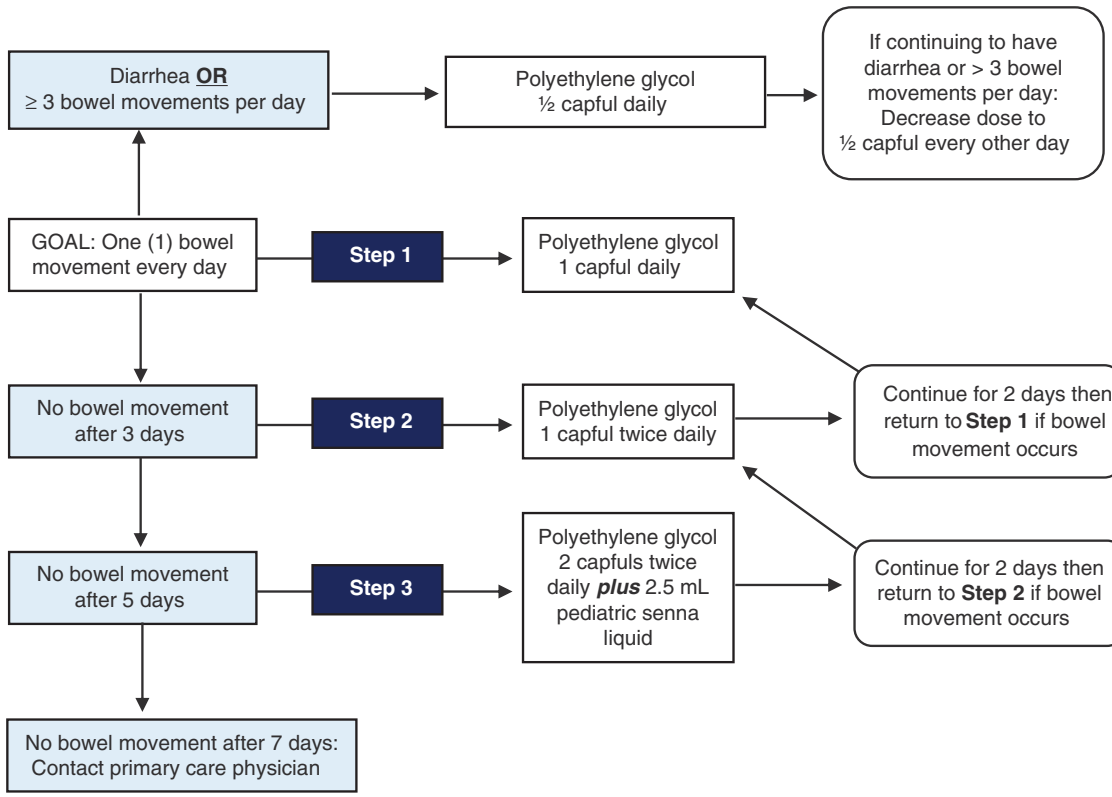
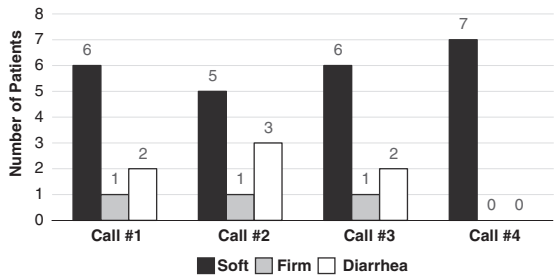


Figure 2. Reported stool consistency from pharmacist telephone encounters.



All patients required an intervention during the follow–up period, with a median of 3 dose adjustments per patient (range, 1–10). Thirty-six dose adjustments were required throughout the entire follow-up period, of which, thirteen were driven solely by the action plan and seventeen were implemented by the caregivers without pharmacist consultation based on action plan recommendations.

Our study found that health care utilization was not lower after the implementation of a standardized, patient-driven constipation action during the post-implementation follow-up period, despite improvement in the median number of daily bowel movements and stool consistency. The health care utilization post-implementation data are suggested to be skewed due to the short duration of follow-up, with approximately 2 available months of post-implementation data to compare to 1 year of baseline data. In addition, the study enrollment timeline was also significantly impacted due to hospital admission trends of the 2023–2024 respiratory syncytial virus season.

Future research should evaluate adjusted designations for the standardized constipation action plans and their need for health care utilization and post-discharge stool frequency and consistency achievement.

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. All patients and/or caregiver(s) provided written informed consent at enrollment.

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References

1. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best Pract Res Clin Gastroenterol*. 2011;25:3–18.
2. Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr.* 2014;58(2):258–274.
3. Koppen IJN, Lammers LA, Benninga MA, Tabbers MM. Management of functional constipation in children: therapy in practice. *Paediatr Drugs*. 2015;17:349–360.
4. Sandweiss DR, Allen L, Deneau M, et al. Implementing a standardized constipation-management pathway to reduce resource utilization. *Acad Pediatr*. 2018;18(8):957–964.
5. Allison A, Sweet C, Knopp M. Implementation of a constipation action plan for patients discharged from a pediatric hospitalist service. *J Pediatr Pharmacol Ther*. 2021;26(7):718–722.

JPPT | A Pediatric Pharmacy Association Position Paper

Pediatric Antibiotic Stewardship Programs: The Path Forward

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Antibiotic overuse has been well-documented in all populations, including pediatrics. Pediatric pharmacists are valuable and well-integrated within inpatient antibiotic stewardship programs (ASP) in children's hospitals. The Pediatric Pharmacy Association (PPA) believes all pharmacists, regardless of practice setting, should receive education to support entry-level stewardship activities in pediatric patients. Additionally, pediatric antibiotic stewardship pharmacist leaders should ideally be trained in both infectious diseases (ID) and pediatrics. Currently, specialized training in pediatric ID lacks standardization due to the paucity of subspecialized training opportunities. This paper provides recommendations to support pediatric ASP training, education, and pharmacist staffing for inpatient programs. Further, it is recommended to ensure protected time is available for daily and longitudinal pediatric ASP activities to support optimal care and prevent burnout. Finally, the PPA supports the evolving role of the pediatric pharmacist in the ambulatory ASP arena and recommends investigations into unique payment modalities.

ABBREVIATIONS ASHP, American Society of Health-System Pharmacists; ASP, antibiotic stewardship program; CDC, Centers for Disease Control and Prevention; CE, Continuing education; FTE, full-time equivalent; ID, infectious diseases; PPA, Pediatric Pharmacy Association; PGY2, Post-graduate year 2; TJC, The Joint Commission

KEYWORDS Antibiotic stewardship; pharmacy education; pediatric pharmacist; antimicrobial resistance; pharmacy resident; pediatric infectious diseases

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Introduction

Approximately 20% of ambulatory and 60% of inpatient pediatric visits result in an antibiotic prescription.[1,2] Antibiotic use is not without risks, as antibiotic adverse drug events are the most common medication-related cause (46%) of emergency department visits for children.[3] Additionally, increased use of unnecessary and/or broader-than-needed antibiotics has led to increases in resistant bacterial infections among children.[4] These resistant bacteria cause about 2.8 million illnesses and 35,000 deaths annually in the United States across all ages.[5] Unfortunately, a limited number of new antibiotics are in development. Newer antibiotics often have limited safety and efficacy data in pediatric patients. Thus, very limited agents are available to combat multidrug-resistant bacteria, and drug shortages of available antibiotics continue to plague clinical practice.[6]

Antibiotic stewardship programs (ASP) combat antibiotic-related problems by optimizing antibiotic use and minimizing unintended consequences. Efforts and priorities of ASPs vary among different institutions; however, the overall aim is to improve infectious disease (ID) outcomes by limiting antibiotics to only when clinically indicated and employing the narrowest effective and safest agent for the shortest duration appropriate. Most hospitals, including children's hospitals, have implemented ASPs that meet all 7 of the Centers for Disease and Control and Prevention's (CDC) Core Elements.[7] Advancement in ambulatory ASPs has unfortunately not kept pace with inpatient ASPs, despite the availability of CDC Core Elements for Outpatient Stewardship. Much of this is due to a lack of financial support. A recent survey of children's hospitals reported that only 11% have financial support for pediatric ambulatory ASP activities.[8]

Pediatric-focused ASPs in both inpatient and ambulatory settings are best to serve this population. Pediatric ontogeny of drug disposition, ID, and pathogen-resistance patterns often differ from adults; thus, it is essential that postdoctoral trainees, such as those in pharmacy and/or medicine, receive training to successfully direct and manage pediatric-specific ASPs. Organizations suggest that pharmacist leaders of ASPs should have sufficient education, training, or expertise in ID and antibiotic stewardship.[9] While The Joint Commission (TJC) does not require age-specific pharmacist

education for those who manage pediatric patients as part of their ASP duties, the American Academy of Pediatrics recommends at least 1 ASP team member with pediatric expertise.[9,10] To successfully manage pediatric ASPs, pharmacists must be knowledgeable of unique pediatric considerations (eg, ontogeny, drug dosing, adverse effects), pediatric ID knowledge (eg, exposures, pathogens, disease states), and general ID principles (eg, antibiotic coverage, common diseases, antibiotic resistance). The most direct route to acquiring this knowledge is through ID-specific pharmacist postgraduate residency training conducted within a pediatric hospital. Unfortunately, very few of these pharmacy residencies exist. In a 2020 survey, only 14% of pediatric antibiotic stewardship/ID pharmacists with specialized postgraduate year 2 (PGY2) training had completed their ID PGY2 in a children's hospital. Most (54%) completed a pediatric residency, while 32% completed an ID program.[11] The Pediatric Pharmacy Association (PPA) believes that pharmacists trained and specialized in pediatric antibiotic stewardship/ID are necessary to implement pediatric antibiotic stewardship efforts in both inpatient and ambulatory ASPs and to ensure a high level of care for pediatric patients.

In 2017, the PPA formulated a position statement with implementation and sustainability recommendations regarding pediatric ASPs.[12] As practice has evolved, the PPA has re-evaluated heightened challenges, resulting in new recommendations (Box 1). In addition to education and training needs for pharmacists (eg, student pharmacists, generalist pharmacists, and pediatric antibiotic stewardship/ID specialty pharmacists), pediatric ambulatory ASP practices should be supported and expanded. To attain these goals and ensure continued success in inpatient pediatric ASP practices, pharmacists should have time reserved to conduct pediatric ASP practice, share clinical research or quality improvement initiatives, and limit the ever-present burnout that plagues the stewardship community.

Box 1. PPA Recommendations for Pediatric Antibiotic Stewardship

Summary of Recommendations

1. Incorporate education to support entry-level pediatric ASP efforts into pharmacy school curriculums.
2. Create high quality pediatric ID/ASP continuing education programs. Enhance collaboration efforts between pediatric and infectious diseases professional organizations.
3. Expand postdoctoral training programs for pharmacists in pediatric IDs.
4. Include antibiotic stewardship as an element of training in pediatric pharmacy residencies and include pediatrics as an element of training in ID pharmacy residencies.
5. Ensure pediatric stewardship services are provided for every pediatric patient, including those who are admitted to an adult acute care hospital, via in-house or remote consultation with pediatric antibiotic stewardship/ID pharmacist.
6. Recommend inclusion of pediatric ASP consult services for institutions with limited pediatric patients and no in-house pediatric ASP.
7. Support appropriate funding and allocation of resources for inpatient pediatric antibiotic stewardship pharmacists.
8. Investigate pediatric pay for performance or other payment methods to allow for sufficient pharmacist time and resources for expansion of ambulatory antibiotic stewardship services for pediatric patients.
9. Invest adequate time and resources for pediatric pharmacists to participate in antibiotic stewardship scholarly projects including presentation of research and quality improvement initiatives at local, state, or national conferences and publication of results.
10. Protect antibiotic stewardship pharmacists from burnout through management of workload and expectations.

ASP, *antibiotic stewardship program;* ID, *infectious disease*

Pharmacist Training

Student Pharmacists and Generalist Pharmacists. ***Incorporate Education to Support Entry-Level Pediatric ASP Efforts Into Pharmacy School Curriculums.*** The Pediatrics Practice and Research Network of the American College of Clinical Pharmacy and the American Association of Colleges of Pharmacy published a PPA-endorsed opinion paper in 2020 recommending all pharmacy schools offer a minimum of 25 contact hours of pediatric education.[13] Unfortunately, incorporating this level of pediatric pharmacy education is not the reality at many schools, and training specific to subpopulations such as pediatrics and specific ID considerations (eg, unique pathogens, optimal choice, dose, and duration of antimicrobials in this population) are often limited. In 2013, a survey estimated that 94% of pharmacy schools had only a median of 16 hours of pediatric didactic education with 61% of schools providing additional education through a pediatric elective.[14,15] In addition to sparce pediatric curricula, ID education is limited. Jeffres et al[16] reported that, across 106 pharmacy schools in the US, pharmacy students receive approximately 20 hours of ID fundamentals and 40 hours for infectious conditions/diseases. In the absence of additional postgraduation training, many pharmacists graduate with little to no formal training in pediatric antibiotic stewardship/ID-related pharmacotherapy.[17]

Whether practicing in inpatient or ambulatory settings, even nonpediatric focused, pharmacists are likely to encounter pediatric patients.[15,16] As such, the PPA believes all graduating pharmacists should be educated to support entry-level antibiotic stewardship activities and management, including pediatrics, regardless of practice site. This recommendation is in

addition to the topics already recommended by the 2020 Joint Statement on Pediatric Pharmacy Curricula (Table 1).[15,18,19]

Create High-Quality Pediatric ID/ASP Continuing Education Programs. Enhance Collaboration Efforts Between Pediatric and Infectious Diseases Professional Organizations. Education programs, some with continuing education (CE) credits, are available for those seeking additional education in either pediatrics or antibiotic stewardship/ID. High-quality education offerings are limited for those seeking combined pediatric antibiotic stewardship content. The PPA's growing library of educational programs targeting achievement of the PPA-endorsed minimum core competencies for all pharmacists involved in the care of hospitalized pediatric patients is a starting point for expanding CE related to pediatric antibiotic stewardship/ID.[20] In addition to general pediatric topics, these core competencies comprise pediatric ID education, including pediatric sepsis, urinary tract infections, septic arthritis, osteomyelitis, vaccines, pneumonia and tracheitis, croup, and bronchiolitis.[20] For higher-level CE, the PPA would like to explore future formal collaborations with ID organizations to provide more focused educational programs, including both entry-level and advanced pediatric antibiotic stewardship content. Furthermore, the PPA seeks to provide educational resources to pharmacists in various practice settings, including community and other ambulatory arenas. The PPA would also like to foster collaborations with other pharmacy organizations to explore the development of additional pediatric antibiotic stewardship pharmacist educational opportunities and resources.

Table 1. Published Educational Coverage Recommendations for Student Pharmacists and Pharmacy Post-Graduate Year-2 (PGY2) Residents, With a Focus on Pediatric Infectious Diseases Topics

Doctor of Pharmacy Curricula[15]	PGY2 Pediatric Pharmacy Residency[19]	PGY2 Infectious Diseases Pharmacy Residency[18]
Pediatric Topics, Applicable to Infectious Diseases	**Infectious Diseases Topics**	**Infectious Diseases Topics**
Anatomic and physiologic differences in pediatric patients	AIDS/HIV*	Cardiovascular Infections (eg, endocarditis)
Pediatric-related calculations, including pediatric pharmacokinetics, drug dosing, renal dosing, maintenance fluids	Antibiotic prophylaxis (eg, endocarditis, surgery)	Central nervous system infections (eg, meningitis, encephalitis)
Pediatric dosage forms	Antibiotic stewardship	Fever of unknown origin*
Fever	Catheter-related blood stream infection/sepsis*	Fungal infections
Pharmacodynamic principles	*Clostridioides difficile*	Gastrointestinal infections
Infectious Diseases Topics	Conjunctivitis*	Hepatitis B*
Ear infections (eg, otitis media, otitis externa)	CNS infections (ie, viral encephalitis*, meningitis)	Hepatitis C*
Endocarditis	Croup*	HIV-infection and AIDS*
Influenza	Endocarditis*	Intra-abdominal infections
Immunization	Epiglottitis*	Neutropenic fever
Meningitis (eg, aseptic, bacterial)	Fever	Non-tubercular mycobacterial infections
Neonatal sepsis	Fungal infections	Ophthalmologic infections*
Pinworm, lice, scabies	Osteomyelitis/septic arthritis*	Opportunistic infections in immunocompromised hosts
Pneumonia	Otitis media* & otitis externa	Otitis media & otitis externa
SSTIs and osteoarticular infections (eg, cellulitis, osteomyelitis, septic arthritis)	Parasitic infections	Parasitic infections*
STIs	Pneumonia	Reproductive organ infections*
Surgical prophylaxis	Sepsis	Respiratory infections: upper and lower (eg, pneumonia, RSV bronchiolitis)
UTIs	SSTIs* and osteoarticular infections (ie, cellulitis*, impetigo*, osteomyelitis*, septic arthritis*)	Rickettsial infections*
URTI (eg, bronchiolitis, croup, pharyngitis)	STIs*	Sepsis
	Shunt infections*	STIs*
	Strep throat*	SSTIs* and osteoarticular infections* (eg, cellulitis, osteomyelitis, septic arthritis)
	Tuberculosis*	Tuberculosis*
	UTIs	Travel medicine*
		Urologic infections
		Viral infections

Data in table are adapted and modified in part from references 15, 18, and 19.
AIDS, Acquired immunodeficiency syndrome; CNS, central nervous system; HIV, Human immunodeficiency virus; PK, pharmacokinetic; PD, pharmacodynamic; STI, sexually transmitted infection; SSTIs, skin and soft tissue infections; URTI, upper respiratory tract infection; UTI, urinary tract infection

* May be met through didactic discussion, reading assignments, case presentations, and/or written assignments; other entries must be met through patient experience.

Pediatric Infectious Diseases and Antibiotic Stewardship Pharmacists. ***Expand Postdoctoral Training Programs for Pharmacists in Pediatric Infectious Diseases.*** To provide comprehensive training, the PPA supports expanding postdoctoral training programs for pharmacists in pediatric ID. Per the CDC and TJC, ASPs should be led by a specialty-trained pharmacist or co-led by an ID-trained physician and pharmacist.[9,21] The PPA believes that pediatric ASPs should have a pharmacist leader as director/co-director who is competent in both ID and pediatrics. Currently, most pharmacists leading pediatric ASPs have trained in pediatrics or ID.[11,22] Training for pharmacists seeking to specialize in pediatric antibiotic stewardship/ID lacks standardization primarily because of the paucity of subspecialized training opportunities.[23,24] The number of American Society of Health-System Pharmacists (ASHP) PGY2 residency training programs in pediatrics (N = 83) or ID (N = 144 including 4 of these pediatric ID focused within children's hospitals) are much more readily available compared with the sparce PGY2 ID un-accredited residency programs or fellowships available at children's hospitals.[24]

Include Antibiotic Stewardship as an Element of Training in Pediatric Pharmacy Residencies and Include Pediatrics as an Element of Training in Infectious Diseases Pharmacy Residencies. Per ASHP pharmacy residency requirements, those completing PGY2 pediatric pharmacy residency programs will receive at least some pediatric antibiotic stewardship/ID training. Alternatively, exposure to pediatric pharmacotherapy is not guaranteed from completing a PGY2 ID pharmacy residency program, and currently, only approximately 45% of PGY2 ID pharmacy residency programs mention pediatrics in description materials.[24] In a 2019 survey, 101 PGY2 ID pharmacy residency programs reported fewer than 30% requiring a pediatric antibiotic stewardship/ID experience, and approximately 30% did not offer pediatric antibiotic stewardship/ID experiences.[25] In the absence of pediatric ID-dedicated residencies and fellowships, the PPA supports the following minimum training requirements for pediatric antibiotic stewardship/ID pharmacists: (1) the completion of a pediatric residency AND additional antibiotic stewardship/ID-focused education, or (2) the completion of an ID residency AND additional pediatric focused education (Table 2). Given the rarity of pediatric-focused antibiotic stewardship/ID pharmacy post-graduate training to bridge the gap until more training programs are available, the PPA recommends including comprehensive antibiotic stewardship/ID training within the established core areas of PGY1 pharmacy residencies, PGY2 pediatric pharmacy residencies, and pediatric experiences incorporated into PGY2 ID pharmacy residencies. The current required and elective core areas/patient care experiences for these residencies are extensive (Table 1) and may already be challenging to achieve within the course of a single specialized residency year.[18,19] Although comprehensive training in antibiotic stewardship/ID during pediatrics residency and pediatrics during ID residency is optimal, excessive additional required experiences risk diminishing overall quality, increase residency-related stress, and reduce the feasibility of goal achievement. To minimize requirements, pediatric antibiotic stewardship should be discussed in PGY1 programs, pediatric PGY2 programs should designate antibiotic stewardship/ID as a required rotation (standard month-long block or longitudinal), and PGY2 antibiotic stewardship/ID adult programs should incorporate required pediatric-specific experiences to ensure sufficient education is attained (Table 2). For residency programs without pediatric antibiotic stewardship/ID-specific resources, we encourage collaboration between other health systems or residency programs (Table 2).

For pharmacists who received primary training in adult antibiotic stewardship/ID and have limited pediatric experience, the PPA recommends seeking additional training or mentorship in pediatrics. Similarly, pharmacists with specialty training in pediatrics and limited antibiotic stewardship/ID experience should find additional training or mentorship in antibiotic stewardship/ID. Table 3 provides examples of additional training and resources that are available. These include certificate programs, live didactic sessions, professional conferences, specialty board certification, and/or self-study modules. Antibiotic stewardship certification programs offered by various large organizations include the Society of Infectious Diseases Pharmacists, the CDC, and the Making A Difference in Infectious Diseases (See Table 3). Another excellent resource for increasing pediatric antibiotic stewardship/ID proficiency for pediatric- or ID-trained pharmacists is the Sharing Antimicrobial Reports for Pediatric Stewardship (SHARPS) Collaborative.

Antibiotic Stewardship Services. ***Ensure Pediatric Stewardship Services are Provided for Every Pediatric Patient, Including Those Who Are Admitted to an Adult Acute Care Hospital, Via In-House or Remote Consultation With Pediatric Antibiotic Stewardship/ID Pharmacist.*** Available literature has demonstrated a clear benefit of inpatient ASP services to children.[26–28] Prospective audits with feedback with or without preauthorizations are foundational activities of inpatient ASPs and are considered "priority" interventions by the CDC's Core Elements.[21] Core Element interventions should be prioritized for all patients admitted to an acute care setting, including pediatrics, regardless of the primary population served at the institution (ie, freestanding vs combined pediatric/adult hospital). The methodology of implementing these foundational stewardship practices will be dependent

Table 2. Pediatric Pharmacy Association Recommended Pediatric and/or Infectious Diseases Topics Recommended to be Added for those Completing Post-Graduate Year-2 (PGY2) Pharmacy Residencies

PGY2 Pediatric	PGY2 Infectious Diseases
Infectious Diseases Topics • Antibiotic resistance • Antimicrobial susceptibility testing • Antibiotic stewardship metrics • Diagnostic stewardship • Pediatric immunizations	**Pediatric Topics** • Introduction to pediatric pharmacokinetic/pharmacodynamics across the pediatric age continuum • Medication dosing in special populations • Medication formulation considerations and challenges • Medication adverse drug reactions/side effects/contraindications and precautions in special populations **Infectious Diseases Topics** • Bone and joint infections* to include acute hematogenous osteomyelitis • Intraabdominal infections to include NEC • Pediatric immunizations • Respiratory infections: upper and lower* to include community acquired pneumonia, croup, acute otitis media, periorbital and orbital cellulitis, retropharyngeal abscesses, respiratory syncytial virus bronchiolitis, sinusitis, and complications (eg, intracranial extension) • STIs, including chlamydial ophthalmia and chlamydial pneumonia, congenital syphilis, gonococcal ophthalmia, and perinatal HIV treatment • Sepsis including neonatal sepsis (early/late onset) • Neonatal HSV

HSV, herpes simplex virus; NEC, necrotizing enterocolitis; STI, sexual transmitted infection

* Although these topics (eg, bone and joint, respiratory) are covered in the infectious diseases' curriculum, the bulleted sub-topics may be specific to pediatric patients or have pediatric specific considerations that should be discussed.

Table 3. Continuing Education Resources for Antibiotic Stewardship Pharmacists

Program	Offerings	Links
British Society for Antimicrobial Chemotherapy	Multiple online on demand offerings	https://bsac.org.uk/education/
CDC	13 module training program on antibiotic stewardship (1 module specific to otitis and pharyngitis)	https://www.train.org/cdctrain/training_plan/3697
MAD-ID	Antimicrobial stewardship program with an elective in pediatrics	https://mad-idtraining.org/certification/
PIDS	Toolkit with links to various programs and trainings	https://pids.org/pediatric-asp-toolkit/inpatient-settings/inpatient-cdc-core-elements/drug-expertise-pharmacist-leader/
PPA	Continuing education on-demand offerings: all are pediatric-specific, some are infectious disease-related. Additionally, infectious diseases/ASP content is often part of the live meetings.	https://www.ppag.org/?pg=OnDemandCE
SHARPS	Listserv, annual live educational event, and research collaborative specific to pediatric infectious diseases	https://sharps.wustl.edu/
SIDP	ASP Training Certificate Program with pediatric elective	https://www.sidp.org/Stewardship-Certificate

ASP, antibiotic stewardship program; CDC, Centers for Disease Control and Prevention; MAD-ID, Making a Difference in Infectious Diseases; PIDS, Pediatric Infectious Diseases Society; PPA, Pediatric Pharmacy Association; SHARPS, Sharing Reports for Pediatric Stewardship; SIDP, Society of Infectious Diseases Pharmacists

on the institution's available resources and stewardship culture.

The PPA believes that every pediatric patient admitted to an acute care hospital should benefit from the services provided by the institution's ASP. Freestanding children's hospitals should not only have an ASP that incorporates the CDC's 7 Core Elements but additionally should include at least 1 pharmacist with training in pediatric antibiotic stewardship/ID as described above.[21] Children admitted to an adult institution with pediatric services should still have access to a pediatric antibiotic stewardship/ID pharmacy specialist, whether available locally or via consultation (eg, collaboration with a regional health system). Collaborations to develop pathways/processes or assist on a personal patient care level can be individualized based on the institution's needs and resources but may include telehealth services from pediatric health systems or contracting with local experts for in-depth support.

Recommend Inclusion of Pediatric ASP Consult Services for Institutions With Limited Pediatric Patients and No In-House Pediatric ASP. Institutions with limited pediatric expertise should create collaborations or consultations with institutions or organizations that have pediatric antibiotic stewardship experts. These experts can assist in developing pediatric ASP initiatives and outcomes specific to the institution (Tables 4 and 5). For example, experts can assist in developing pediatric-specific clinical pathways and any pediatric-specific antimicrobial restrictions or preauthorizations. As per the TJC standards, institutions should use national and internationally recognized guidelines, and if pediatric guidance is lacking, the pediatric antibiotic stewardship/ID pharmacy expert can help direct recommendations from additional pediatric-focused literature and/or guidelines.[9] Additionally, these individuals can provide insight into how local pediatric susceptibility data impacts pediatric ID treatment recommendations.[10] Further, performance of inpatient ASP services provided to pediatric patients should be routinely evaluated by an ASP team member as part of standards outlined for all stewardship programs.[21] Process and outcome measures should be appropriate for the given population and in-

Table 4. Recommended Pediatric Antibiotic Stewardship Program Services for Institutions With Limited Pediatric Expertise

Service	Priority	Additional Guidance
Institution-specific clinical pathways for common pediatric infectious diseases	High	Consultation and collaboration with pediatric ASPs are highly recommended. Consider prioritizing based on commonly encountered ID admissions in pediatric patients at the institution within the last year (eg, bronchiolitis, CAP, appendicitis).
Antimicrobial therapeutic drug monitoring	High	Consultation and collaboration with pediatric antibiotic stewardship pharmacists highly recommended. Consider developing pediatric-specific monitoring guidelines and/or goals of therapy.
Restricted antimicrobials and preauthorization process	Medium	Consultation and collaboration with pediatric antibiotic stewardship pharmacists is highly recommended.
Rapid diagnostic testing	Medium	For applicable rapid diagnostics available at an institution, include specific recommendations for interpretation and application within the pediatric population (eg, rapid Group A *Streptococcus* testing for pharyngitis, meningitis/encephalitis PCR panel).
Pediatric antibiogram	Medium	Development of a pediatric-focused antibiogram, depending on the number of available cultures in pediatric patients, should be completed when possible. Consultation with microbiology colleagues is highly recommended. Provide guidance for clinicians on appropriate use of focused antibiograms in settings of combined adult and pediatric patient populations.
Structured peer education	Medium	Education can be provided through daily interventions made by antibiotic stewards. Consultation and collaboration with pediatric antibiotic stewardship pharmacist is recommended, especially when considering formal education on pediatric topics.

ASP, antibiotic stewardship program; CAP, community-acquired pneumonia; ID, infectious diseases; PCR, polymerase chain reaction

Table 5. Recommended Pediatric Antibiotic Stewardship Outcomes to be Measured for All Institutions[21,33]

Area of Practice	Outcome	Guidance
Inpatient		
	Indication for antibiotic	Indication for use should be documented on all antibiotics prescribed, preferably incorporated into the order for pharmacist review upon verification.
	Percent of common pediatric infections (eg, CAP, SSTI, UTI) with evidence-based treatments (i.e., antibiotic selection, dose, and durations)	Evidence-based recommendations should be specific to pediatrics. For example, for pediatric CAP, measure the percent of narrow antibiotics (eg, ampicillin, penicillin), percent with appropriate dosing (based on local pneumococcal resistance) and total duration of therapy (eg for uncomplicated CAP 5–7 days)
Ambulatory*		
	Percent of patients with viral illness (eg, URI, including bronchiolitis) not receiving antibiotic therapy	Viral respiratory infections should not receive antibiotic therapy. Families' education that antibiotics do not treat viruses is also recommended.
	Percent of patients where watchful waiting can be recommended (eg, AOM)	Watchful waiting is highly recommended and often underutilized for older children with nonsevere AOM
	Percent of common pediatric infections (eg, AOM, ABS, CAP, SSTI) with evidence-based treatments (ie, antibiotic selection, dose, and durations)	Evidence-based recommendations should be specific to pediatrics. For example, a major shift in recent years is the evolving evidence supporting shorter durations. For example, most mild cases of pediatric CAP and SSTI can be successfully treated with 5 days of therapy.
	Percent of group A Streptococcal pharyngitis that is treated without testing or with negative results	The primary reason to treat Group A Streptococcal pharyngitis is to prevent acute rheumatic fever. Most cases of pharyngitis are caused by viruses and young children can be colonized. Antibiotics for treatment of GAS pharyngitis should be done where testing is appropriate, performed, and resulted positive.

AOM, acute otitis media; ABS,acute bacterial sinusitis; CAP, community-acquired pneumonia; GAS, group A streptococcus; SSTIs, skin and soft tissue infections; URI, upper respiratory infection; UTI, urinary tract infection

* Including Emergency Medicine Departments

tervention with special attention to differences in the pediatric population (eg, The CDC's National Health and Safety Network's Standardized Antimicrobial Administration Ratio has different categories of antibiotic groups for neonates, pediatrics, and adults). The PPA recommends that the pediatric antibiotic stewardship/ID pharmacist has unique expertise and should be at least consulted to inform recommendations, pathways, and outcomes for pediatric patients managed at the hospitals.

Support Appropriate Funding and Allocation of Resources for Inpatient Pediatric Antibiotic Stewardship Pharmacists. Antibiotic stewardship programs require support from senior administrators. Support is vital not only through allocating full-time equivalent (FTE) funding for both pediatric antibiotic stewardship physician(s) and pediatric antibiotic stewardship pharmacist(s) but also to foster acceptance of the ASP and its mission. Recent recommendations for ASP FTE allocation and support are provided in Table 6.[29–31] Doernberg and colleagues[30] reported a relationship between physician and pharmacist FTE and self-reported effectiveness of the ASP, which was attributed mostly to programs that specifically had pharmacist support for postantibiotic review and feedback. The authors conclude that an ID physician-to-infectious diseases pharmacist ratio of 1:3 provides the highest value use of available resources.[30]

The PPA recommends hospital leaders provide funding for all components (eg, physician time, information technology requirements, data analyst) of ASPs, including pediatric antibiotic stewardship/ID-trained pharmacists to lead and manage ASPs based on the number of neonatal and pediatric beds regardless of

Table 6. Summary of Minimum Recommended Personnel Support of (Pediatric) Inpatient Antibiotic Stewardship Programs[29–31]

Source	Minimum Pharmacist	Minimum Physician	Minimum Data Analyst
USNWR, Best Children's Hospitals[31]	0.4 FTE for hospitals <250 beds; 1 FTE hospitals ≥250	0.3 FTE medical director	0.2 FTE
CMS (average 124-bed hospital)[29]	0.25 FTE	0.1 FTE	0.05 FTE
Doernberg, 100–300 beds, necessary FTE for effectiveness[30]	1 FTE	0.4 FTE	—

CMS, Centers for Medicare & Medicaid Services; FTE, full-time equivalent; USNWR, US News & World Report

classification in a free-standing children's or combined adult and children's hospital. As provided in Table 6, the PPA supports US News and World Reports Best Children's Hospital minimum pediatric pharmacist FTE for stewardship of 0.4 FTE for hospitals less than 250 beds and 1 FTE hospital with 250 beds or more.[31] The PPA also recommends that pediatric antibiotic stewardship pharmacists' FTE support should be provided in-house or as a consultant at 0.1 FTE for hospitals with less than 20 pediatric licensed beds and 0.4 FTE for institutions with 20 to 250 licensed pediatric beds. In rare instances when a primarily adult institution has more than 250 licensed pediatric beds, the PPA recommends following recommendations for a similar-sized children's hospital with at least 1 FTE.

Investigate Pediatric Pay for Performance or Other Payment Methods to Allow for Sufficient Pharmacist Time and Resources for Expansion of Ambulatory Antibiotic Stewardship Services for Pediatric Patients. The importance of antibiotic stewardship in the ambulatory care setting has been recognized and regulatory authorities, like the CDC and TJC, have mandated it to ensure the safe and effective use of antibiotics in the ambulatory setting.[32,33] One report suggested that more than 60% of antibiotic expenditures occur in outpatient pharmacies and clinics.[34] More than 1 in 5 pediatric ambulatory visits results in an antibiotic being prescribed.[2] Many of these prescriptions are for broad-spectrum antibiotics (50%) to treat respiratory conditions where antibiotic therapy is often unnecessary.[2] Several publications have outlined strategies (eg, feedback to prescribers, commitment posters, delayed prescribing, communications training, documentation, diagnostic confirmation) and metrics (eg, percent of bronchiolitis visits with antibiotics prescribed, percent of all antibiotics where amoxicillin was prescribed) for pediatric ambulatory ASP services.[35–40] Of note, many of the potential metrics are claims related and, as such, are often available for tracking.[37] Because these metrics can be tracked via claims and there is strong evidence for specific quality measures (eg, percentage of bronchiolitis visits with antibiotic prescribed) and/or evidence-based guidelines for many common pediatric ID-related conditions (eg, bronchiolitis, otitis media, pharyngitis, pneumonia, skin infections), they lend themselves well to value-based payment and potential pay-for-service models.

Pediatric patients in the ambulatory setting would benefit from pediatric antibiotic stewardship pharmacist services to reduce inappropriate prescribing, optimize antibiotic choice, and dose, and limit adverse drug events. Literature supports the role of pediatric pharmacists in cost avoidance in ambulatory settings. In 1 study, pediatric pharmacist interventions resulted in approximately $307,210 of cost avoidance over a 4-month period; more than half of the costs avoided were due to the prevention or management of adverse drug events, and other costs avoided included unnecessary medications, prevention or management of allergic reactions, and drug interactions.[41] Several antibiotic stewardship approaches have successfully improved antibiotic use in the ambulatory setting. Further, the TJC requires antibiotic stewardship in its accredited ambulatory health care organizations.[32] The PPA recommends dedicating resources to support pediatric antibiotic stewardship pharmacists in developing, tracking, reporting, and sharing metrics for effective pediatric ambulatory antibiotic stewardship. We further support pilot projects investigating unique payment models, such as pay-for-performance, for pharmacists engaged in these evolving roles.

Pediatric Antibiotic Stewardship Research. ***Invest Adequate Time and Resources for Pediatric Pharmacists to Participate in Antibiotic Stewardship Scholarly Projects Including Presentation of Research and Quality Improvement Initiatives at Local, State, or National Conferences and Publication of Results.*** While publications in pediatric antibiotic stewardship have increased, many questions regarding optimal practices remain unanswered. Systematic evaluation of stewardship practices and dissemination of that information is key to moving the field forward and providing optimal patient care. Without

quality publications evaluating antibiotic stewardship interventions and treatment of ID, the uptake of effective practices will be delayed, and ineffective or unproven practices will continue.[10] Areas of particular focus include the pharmacist's role in pediatric ASPs, pediatric ASP activities in expanded settings (eg, ambulatory, community hospitals, smaller children's hospitals), specific disease-state evaluations of (including optimal antibiotic choice, dose and frequency, duration, and clinical outcomes), strategies for outpatient parenteral antimicrobial therapy/complex outpatient antimicrobial therapy, and pediatric antibiotic stewardship management in special pediatric populations (eg, neonates, cystic fibrosis, transplant, immunocompromised host).[10,42,43] Although PGY2-trained pharmacists are not specifically trained to complete research, all must complete at least 1 research project that helps to provide some experience if they have completed an ASHP-accredited residency program. Thus, clinician-researchers should aim to determine optimal implementation strategies and the factors contributing to high-intervention uptake and sustainability across settings.[42,44]

Colleagues representing the Society of Infectious Diseases Pharmacists have made a strong argument for pharmacist involvement in antibiotic stewardship quality improvement activities and research, and the PPA supports their recommendations.[42] Published reports are encouraged to describe the pharmacist's role in ASP, the pharmacy practice model, and details about the specific pediatric population served.[42] The PPA further recommends health care systems provide time for the continued development of pharmacists' quality improvement and research skills, encourage and reward research contributions, and provide sufficient time to perform scholarly activities. Additionally, the PPA supports participation in pediatric-specific collaborative networks between multiple institutions, such as the Sharing Antimicrobial Reports for Pediatric Stewardship network, to create robust and quality data.[45]

Pharmacist Burnout. ***Protect Antibiotic Stewardship Pharmacists From Burnout Through Management of Workload and Expectations.*** Like other health care providers, stewardship pharmacists are at risk of burnout and should be protected from it. Burnout drivers specific to antibiotic stewardship pharmacists have not been well studied, but many factors contribute to overwork, emotional exhaustion, depersonalization, and lack of professional accomplishment.[46] Therefore, it is vital that hospital leadership works to retain talent within ASP, particularly pediatric antibiotic stewardship talent, as they are a limited resource. Ensuring pediatric antibiotic stewardship pharmacists have adequate time off and resiliency skills are important, but these are band-aids for underlying issues. The PPA recommends hospital leadership consider actions that address the underlying drivers to prevent or minimize burnout when possible. Some potentially helpful actions to protect and retain pediatric antibiotic stewardship pharmacists include clearly communicating stewardship activities are supported and prioritized, encouraging other ID and pharmacy colleagues to support ASP activities, ensuring that the work expectations of the antibiotic stewardship pharmacists are realistic based upon available time and resources, prioritizing protected time for the administrative and scholarly ASP work activities, providing specific job descriptions for stewardship pharmacists (rather than generic "clinical specialist" position descriptions), and providing a path for career growth. Ensuring ASP activities are efficient and well-prioritized may help expand and protect current person resources.[47] The PPA recommends that efforts should be made to support the role of the pediatric antibiotic stewardship pharmacist, providing them sufficient time, resources, and continuous training to effectively conduct the program while minimizing burnout.

Conclusions

Pediatric pharmacists with dedicated expertise in antibiotic stewardship are essential to optimizing antibiotic drug therapy, in order to improve outcomes, avoid adverse effects, and limit resistance development. To improve and expand upon this, it is essential that student pharmacists and postdoctoral trainees have content focused on pediatric antibiotic stewardship/ID. Further, those who will be expected to lead or practice as pediatric antibiotic stewardship pharmacists should optimally complete an ID PGY2 pharmacy residency at a children's hospital or a pediatric ID fellowship training program. Until enough of these programs exist, it is recommended that current pediatric and ID training programs expand education surrounding ID or pediatric core competencies, respectively. For clinical pharmacists already practicing, participation in developing quality CE or certificate programs in pediatric antibiotic stewardship will help provide the expertise and guidance needed to confidently care for this patient population.

The PPA also recommends that all pediatric inpatients receive a high level of pediatric ID care that is informed by a pediatric antibiotic stewardship pharmacist (in-house or via consultation). As ambulatory ASP programs evolve, it is recommended that pediatric antibiotic stewardship pharmacists are highly involved in supporting optimal care of the ambulatory pediatric patient. Further, it is recommended that institutions investigate additional payment models to support ambulatory efforts. Knowledge sharing is essential to the improvement and expansion of important pediatric ASP efforts, and, as such, pediatric antibiotic stewardship pharmacists should be given resources and time to conduct scholarly activities. Last, it is important not to lose well-trained pediatric antibiotic stewardship

pharmacists to burnout. The PPA recommends strategies to help protect these individuals and their efforts.

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References

1. Gerber JS, Newland JG, Coffin SE, et al. Variability in antibiotic use at children's hospitals. *Pediatrics.* 2010;126(6):1067–1073.
2. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics.* 2011;128(6):1053–1061.
3. Lovegrove MC, Geller AI, Fleming-Dutra KE, et al. US emergency department visits for adverse drug events from antibiotics in children, 2011–2015. *J Pediatric Infect Dis Soc.* 2019;8(5):384–391.
4. Milstone AM, Bryant KA, Huskins WC, Zerr DM. The past, present, and future of healthcare-associated infection prevention in pediatrics: multidrug-resistant organisms. *Infect Control Hosp Epidemiol.* 2010;31 Suppl 1:18.
5. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Updated 2019. Accessed July 19, 2023. https://www.cdc.gov/antimicrobial-resistance/data-research/threats/.
6. Lockwood KL SR. Advice on antibiotics for kids during shortages. *Medscape Commentary*. 2023. Accessed November 20, 2023. https://www.medscape.com/viewarticle/987769
7. Centers for Disease Control and Prevention. Current stewardship report. Antibiotic use in the United States, 2024 update: progress and opportunities. Accessed May 21, 2025. https://www.cdc.gov/antibiotic-use/hcp/data-research/stewardship-report.html?CDC_AAref_Val=https://www.cdc.gov/antibiotic-use/stewardship-report/current.html
8. El Feghaly RE, Monsees EA, Burns A, et al. Outpatient antimicrobial stewardship programs in pediatric institutions in 2020: Status, needs, barriers. *Infect Control Hosp Epidemiol.* 2022;43(10):1396–1402.
9. Allen C, Dodds ES, Davidson L, et al. *New and revised requirements for antibiotic stewardship. R3 report: requirement, rationale, reference. a complimentary publication of The Joint Commission.* 2022(35):1–5. Accessed November 20, 2023. https://www.jointcommission.org/-/media/tjc/documents/standards/r3-reports/r3_antibioticstewardship_july2022_final.pdf
10. Gerber JS, Jackson MA, Tamma PD, et al. Antibiotic stewardship in pediatrics. *Pediatrics*. 2021;147(1):e2020040295.
11. Puckett LM, Newland JG, Girotto JE. Advancing pediatric antimicrobial stewardship: has pharmacodynamic dosing for gram-negative infections taken effect? *Antimicrob Steward Healthc Epidemiol.* 2021;1(1):e61.
12. Nichols K, Stoffella S, Meyers R, et al. Pediatric antimicrobial stewardship programs. *J Pediatr Pharmacol Ther.* 2017;22(1):77–80.
13. LaRochelle JM, Smith KP, Benavides S, et al. Evidence demonstrating the pharmacist's direct impact on clinical outcomes in pediatric patients: An opinion of the pediatrics practice and research network of the American College of Clinical Pharmacy. *J Am Coll Clin Pharm.* 2020;3(4):786–792.
14. Prescott WAJ, Dahl EM, Hutchinson DJ. Education in pediatrics in US colleges and schools of pharmacy. *Am J Pharm Educ.* 2014;78(3):51.
15. 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.
16. Jeffres MN, Kufel WD, Biehle LR, et al. A comprehensive survey of infectious diseases curriculum among US pharmacy schools. *Am J Pharm Educ.* 2019;83(9):7168.
17. Ferguson CL, Ferrell S, Kovey K, et al. Implementation of a pediatric pharmacy education program at a community regional medical center. *J Pediatr Pharmacol Ther.* 2020;25(1):25–30.
18. American Society of Health-System Pharmacists. Required competency areas, goals, and objectives for postgraduate year two (PGY2) infectious diseases pharmacy residency. Updated 2017. Accessed February 23, 2024. https://www.ashp.org/-/media/assets/professional-development/residencies/docs/pgy2-infectious-diseases-pharmacy-residency-competency-areas-goals-objectives-2017.pdf
19. American Society of Health-System Pharmacists. Required competency areas, goals, and objectives for postgraduate year two (PGY2) pediatric pharmacy residency. Updated 2016. Accessed July 7, 2023. https://www.ashp.org/-/media/assets/professional-development/residencies/docs/pgy2-newly-approved-pediatric-pharmacy-2016.pdf
20. Boucher EA, Burke MM, Klein KC, Miller JL. Update to the minimum requirements for core competency in pediatric hospital pharmacy practice. *J Pediatr Pharmacol Ther.* 2021;26(7):762–766.

21. Centers for Disease Control and Prevention. Core elements of hospital antibiotic stewardship programs. Updated 2019. Accessed May 21, 2025. https://www.cdc.gov/antibiotic-use/hcp/core-elements/hospital.html?CDC_AAref_Val=https://www.cdc.gov/antibiotic-use/core-elements/hospital.html.
22. Esadah E, Bio L. The role of pharmacists in the world of pediatric antimicrobial stewardship. *Contagion.* 2022;9(7):4.
23. American College of Clinical Pharmacy. Directory of residency, fellowships, and graduate programs. Accessed May 21, 2025. https://www.accp.com/resandfel/search.aspx. Updated 2025.
24. American Society of Health System Pharmacists. Residency directory. Updated 2025. Accessed May 21, 2025. https://accreditation.ashp.org/directory/#/program/residency.
25. Cho JC, Crotty MP, Kufel WD, et al. Learning experiences within infectious diseases pharmacy residency programs in the United States: a cross-sectional survey. *Open Forum Infect Dis.* 2019;6(10):ofz387.
26. Donà D, Barbieri E, Daverio M, et al. Implementation and impact of pediatric antimicrobial stewardship programs: a systematic scoping review. *Antimicrob Resist Infect Control.* 2020;9(1):3.
27. Araujo da Silva AR, Albernaz de Almeida Dias DC, Marques AF, et al. Role of antimicrobial stewardship programmes in children: a systematic review. *J Hosp Infect.* 2018;99(2):117–123.
28. Smith MJ, Gerber JS, Hersh AL. Inpatient antimicrobial stewardship in pediatrics: a systematic review. *J Pediatric Infect Dis Soc.* 2015;4(4):127.
29. Centers for Medicare & Medicaid Services. Regulatory provisions to promote program efficiency, transparency, and burden reduction; fire safety requirements for certain dialysis facilities; hospital and critical access hospital (CAH) changes to promote innovation, flexibility, and improvement in patient care. *Federal Register.* 2019;84(189):51732.
30. Doernberg SB, Abbo LM, Burdette SD, et al. Essential resources and strategies for antibiotic stewardship programs in the acute care setting. *Clin Infect Dis.* 2018;67(8):1168–1174.
31. Olmsted MG, Lessem S, Powell R, et al. Methodology: U.S. news & world report best children's hospitals 2023-24. 2023. Accessed March 12, 2024. https://health.usnews.com/media/best-hospitals/BCH_Methodology_2023-2024.pdf
32. The Joint Commission. Antimicrobial stewardship in ambulatory health care. R3 report: requirement, rationale, reference. a complimentary publication of The Joint Commission. 2019(23). Accessed November 21, 2023. https://www.jointcommission.org/-/media/tjc/documents/standards/r3-reports/r3_23_antimicrobial_stewardship_amb_6_14_19_final2.pdf
33. Sanchez GV, Fleming-Dutra KE, Roberts RM, Hicks LA. Core elements of outpatient antibiotic stewardship. *MMWR Recomm Rep.* 2016;65(6):1–12.
34. Suda KJ, Hicks LA, Roberts RM, et al. A national evaluation of antibiotic expenditures by healthcare setting in the United States, 2009. *J Antimicrob Chemother.* 2012;68(3):715–718.
35. Keller SC, Cosgrove SE, Miller MA, Tamma P. A framework for implementing antibiotic stewardship in ambulatory care: lessons learned from the Agency for Healthcare Research and Quality Safety Program for Improving Antibiotic Use. *Antimicrob Steward Healthc Epidemiol.* 2022;2(1):e109.
36. Frost HM, Knepper BC, Shihadeh KC, Jenkins TC. A novel approach to evaluate antibiotic utilization across the spectrum of inpatient and ambulatory care and implications for prioritization of antibiotic stewardship efforts. *Clin Infect Dis.* 2020;70(8):1675–1682.
37. Poole NM, Frost H. Targets and methods to improve outpatient antibiotic prescribing for pediatric patients. *Infect Dis Clin North Am.* 2022;36(1):187–202.
38. Bozzella MJ, Harik N, Newland JG, Hamdy RF. From paper to practice: Strategies for improving antibiotic stewardship in the pediatric ambulatory setting. *Curr Probl Pediatr Adolesc Health Care.* 2018;48(11):289–305.
39. El Feghaly RE, Herigon JC, Kronman MP, et al. Benchmarking of outpatient pediatric antibiotic prescribing: results of a multicenter collaborative. *J Pediatric Infect Dis Soc.* 2023;12(6):364–371.
40. Vernacchio L, Herigon JC, Hatoun J, et al. The antibiotic likelihood index: a new measure of antimicrobial stewardship for pediatric primary care based on reason for visit. *J Pediatric Infect Dis Soc.* 2022;11(4):142–148.
41. Yung E, McNicol M, Lewis D, et al. Economic impact of pharmacist interventions in pediatric ambulatory care clinics. *J Am Pharm Assoc (2003).* 2021;61(2):198–205.e1.
42. Mercuro NJ, Pillinger KE, Cwengros L, et al. A report on infectious diseases pharmacist involvement in antimicrobial stewardship research: a call to action on behalf of the Society of Infectious Diseases Pharmacist. *J Am Coll Clin Pharm*. 2022;5:266–269.
43. Kronman MP, Banerjee R, Duchon J, et al. Expanding existing antimicrobial stewardship programs in pediatrics: what comes next. *J Pediatric Infect Dis Soc.* 2018;7(3):241–248.
44. McGregor JC, Fitzpatrick MA, Suda KJ. Expanding antimicrobial stewardship through quality improvement. *JAMA Netw Open.* 2021;4(2):e211072.
45. Newland JG, Gerber JS, Kronman MP, et al. Sharing antimicrobial reports for pediatric stewardship (SHARPS): a quality improvement collaborative. *J Pediatric Infect Dis Soc.* 2018;7(2):124–128.
46. Nori P, Stevens MP, Patel PK. Rising from the pandemic ashes: reflections on burnout and resiliency from the infection prevention and antimicrobial stewardship workforce. *Antimicrob Steward Healthc Epidemiol.* 2022;2(1):e101.
47. Heil EL, Justo JA, Bork JT. Improving the efficiency of antimicrobial stewardship action in acute care facilities. *Open Forum Infect Dis.* 2023;10(9):ofad412.

JPPT | Invited Commentary

Risk Management of Valproate and Other Teratogenic Anticonvulsants in the Era of Proliferating Use

Almut G. Winterstein, PharmD, PhD

Valproic acid, carbamazepine and topiramate have well-known teratogenic risk and all 3 rank among the top 10 teratogenic medications with the highest prenatal exposure risk. Importantly, pregnancies exposed to valproic acid are not dominated by patients with epilepsy but rather with less serious conditions such as migraine. In the United States, only a weight loss combination product containing topiramate has a mandatory pregnancy prevention program, a so-called Risk Evaluation and Mitigation Strategy (REMS), while prevention of fetal exposure to all three single ingredient products relies on information in the product labeling and a medication guide provided at dispensing.

REMS have been avoided for antinconvulsants because of concerns about reduced medication access for patients with serious conditions such as epilepsy, hence weighting maternal harm due to uncontrolled disease against adverse pregnancy or infant outcomes. However, the broad and growing spectrum of indications for all three medications, paired with increasingly strict abortion laws that may not allow pregnancy termination if accidental fetal exposure occurs, may require re-assessment of the benefit-risk of REMS. Here we argue that formal quantitative approaches are needed that allow assessments of maternal and infant risk, considering maternal disease, adverse pregnancy outcomes and teratogenic effects on infants, and the overall public health impact of REMS for anticonvulsants. For valproic acid, given its broad use, high risk of fetal exposure, and profound impact on child health, we predict the public health impact of a REMS will be favorable.

ABBREVIATIONS FDA, US Food and Drug Administration; REMS, Risk Evaluation and Mitigation Strategies

KEYWORDS anticonvulsants; drug safety; risk management; teratogenicity; valproate

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Introduction

Regulatory agencies use risk management programs—in the United States, so-called Risk Evaluation and Mitigation Strategies (REMS)—to prevent medication-related harm and to ensure that the benefit-risk of a medication is favorable. REMS might include requirements for blood tests to detect early signs of drug toxicity or mandatory provider or patient training to ensure certain safe use behaviors. Among several anticonvulsants with established teratogenic risk, the only marketed product that has currently a REMS to prevent prenatal exposure in the United States is the combination product topiramate-phentermine (Qsymia, Vivus LLC, Campbell, CA), approved for weight loss. This commentary discusses the need for and obstacles to enhanced risk mitigation involving teratogenic anticonvulsants, especially valproate, in an era of expanding use and increasingly strict abortion restrictions.

Teratogenic Risk of Anticonvulsants

Anticonvulsants are one of the most comprehensively evaluated medication classes in pregnancy, with epilepsy-pregnancy registries that have been ongoing for more than 2 decades[1,2] and a broad array of claims-based studies. Well-accepted evidence places valproate among one of the most potent teratogenic medications with links to spina bifida, cardiac septal defects, oral clefts, and adverse neurodevelopmental outcomes.[3] Among other commonly used anticonvulsants, carbamazepine and topiramate have also accumulated substantial evidence supporting teratogenicity. Although associations are less pronounced when compared with valproate, carbamazepine shows consistent links with major malformations,[3] especially with neural tube defects,[4] while topiramate has been closely linked with oral clefts.[5]

Prenatal Exposure to Anticonvulsants

Prenatal exposure to anticonvulsants, whether intended or unintended, is common. Our recent analysis of women in private insurance places valproate, topiramate, and carbamazepine among the top 10 teratogenic medications with exposure during pregnancy.[6] Notably, although initially approved for epilepsy, valproate, topiramate and carbamazepine have several approved and a multitude of off-label indications outside of

epilepsy that account for the vast majority of users and exposures during pregnancy.[7] This is important because the maternal and fetal risk imposed by uncontrolled epilepsy might justify valproate use during pregnancy in rare circumstances, while its more prevalent use for migraine has undoubtedly a negative benefit-risk. Interestingly, we found the highest risk for pregnancy onset among valproate users with migraine or headache (2.7 pregnancies per 100 user-years), which was double the rates observed among patients with epilepsy.[7] Thus, the indications that account for the most valproate use and that have the least favorable benefit-risk during pregnancy account for the largest proportion of pregnancies exposed to valproic acid.

Considering a 10% risk for major malformations[3] or 10% risk for autism,[8] it would seem intuitive that most women with migraine either did not intend to use valproate during pregnancy or did not know about the teratogenic risk. Supporting data are provided by our analysis of the timing of prenatal care initiation: we found that among pregnancies with teratogenic anticonvulsant exposure, most (>80%) of prescription fills occurred during the first trimester when pregnancy may not have been recognized yet.[9] Furthermore, only 10% had prenatal care initiated before the prescription fill, suggesting that discussions about the benefit-risk of use during pregnancy had not commenced.

Mitigation of Prenatal Exposure Risk to Teratogenic Anticonvulsants

These findings then lead to the question of how prenatal exposure to valproate, but also carbamazepine and topiramate, can be prevented. In the United States, valproate carries a black box warning about its teratogenic risk, while the labelling for carbamazepine and topiramate addresses teratogenicity only in the warning and precaution section. All 3 medications have a requirement for a medication guide with varying messaging regarding use during pregnancy, which must be dispensed by pharmacies. Knowledge assessments following exposure to medication guides have shown limited value and whether and how such knowledge might translate into enhanced safe use behaviors is largely unknown.[10]

For reference, REMS programs for other teratogenic medications include a combination of mandatory provider and/or patient training, pharmacy registration, pregnancy tests, restricted medication quantities or restricted distribution, or written patient consent regarding use of contraception. Although the effectiveness of each individual component is unclear, several implemented REMS programs have demonstrated a reduction in prenatal exposure risk.[11–13]

Considering the magnitude (risk, severity, and certainty) of teratogenicity and the benefit of REMS programs, we must wonder why no REMS programs for pregnancy prevention have been considered for these agents. Some insight is provided by experience with the topiramate-phentermine weight loss product, which was approved with a REMS that required patient education through specialty pharmacies. In its advisory committee briefing document, the US Food and Drug Administration (FDA) noted that although it might be preferable to institute a more restrictive REMS that requires pregnancy testing, this would cause undue burden on patients receiving topiramate for seizure disorders or migraine prophylaxis.[14] In other words, the burden of a REMS, which potentially reduces access to a lifesaving medication that in certain circumstances may even retain a favorable benefit-risk during pregnancy, must be weighed against its benefit in preventing fetal harm. Limiting such a restrictive REMS to the weight loss product only, the FDA noted, may in turn result in use of the single generic ingredients without a REMS, hence circumventing the burden but also the benefit of risk mitigation. Indeed, topiramate initiation rates more than doubled within 1 year of the combination product approval, likely not because of REMS burden but because of lower costs.[15] Importantly, the REMS attached to the combination product has indeed demonstrated benefit in reducing exposure during pregnancy, while topiramate shows similar pregnancy rates as other non-teratogenic weight loss products.[13]

Rethinking the REMS Benefit-Risk Equation

Where does this leave us in promoting healthier pregnancies? As demonstrated for topiramate, it appears that the public health impact of a REMS is indication specific. For severe indications, a REMS may reduce access to a lifesaving medication while potentially having only a minor impact on preventing fetal harm because of patients' and providers' commitment to pregnancy planning (given disease severity). For less severe indications, a REMS may have a significant benefit in reducing unintended and unnecessary exposure during pregnancy with limited concern about (reduced) access.

Importantly, this relationship defining the positive or negative public health impact of a REMS hinges on the assumption that REMS programs reduce access to a medication, which has yet to be quantified. Recent data suggest that providers might actually get reassurance from additional oversight provided by REMS, which might therefore increase rather than reduce prescribing and patient access to a medication.[16] This is particularly important in light of increasing restrictions to abortion, which might persuade physicians to omit teratogenic medications when treating persons of child-bearing potential.[17] This would imply that a REMS could actually become an enabling component in health care delivery, for example, by ensuring that effective contraception is in place before teratogenic medications are initiated. More research that quantifies

the effect of REMS on reduced medication access is needed to facilitate a comprehensive assessment of their public health benefit.

Moving Ahead

Assuming that indications do play a role in whether the public health impact of a REMS is overall positive or negative, there are 2 ways forward. Designing indication-specific REMS programs is complicated because in the United States, indications are currently not captured in the prescribing process. Cost containment strategies implemented by payers (e.g., for diagnostic procedures) have solved this problem by requiring that specific diagnoses accompany procedural charges, which raises the question of whether similar requirements could not be embedded into electronic prescriptions. If such a solution remains elusive, decisions about REMS should consider their overall public health impact, as aggregate of the net benefit for each indication, considering the probability and severity of uncontrolled maternal disease(s) on one hand, and of infant morbidity on the other. Quantification of these probabilities, while complex, is feasible with pharmacoepidemiologic methods, and tradeoffs between consequences for the mother versus child and the types of adverse outcomes can be captured with decision-science approaches. Such an evidence-based approach in regulatory decision-making would ensure that the public health benefit of REMS is optimized. For anticonvulsants, the myopic focus on epilepsy in evaluating REMS benefit needs to be broadened to consider the evolving spectrum of users. For valproate, given its broad uses and prenatal exposure risk, I predict the overall public health benefit is dominated by its profound impact on child health, arguing strongly in favor of a REMS.

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References

1. Holmes LB, Quinn M, Conant S, et al. Ascertainment of malformations in pregnancy registries: lessons learned in the North American AED Pregnancy Registry. *Birth Defects Res*. 2023;115(14):1274–1283.
2. Battino D, Tomson T, Bonizzoni E, et al. Risk of major congenital malformations and exposure to antiseizure medication monotherapy. *JAMA Neurol*. 2024;81(5):481–489.
3. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev*. 2016;11(11):CD010224.
4. Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol*. 2001;153(10):961–968.
5. Alsaad AM, Chaudhry SA, Koren G. First trimester exposure to topiramate and the risk of oral clefts in the offspring: a systematic review and meta-analysis. *Reprod Toxicol*. 2015;53:45–50.
6. Wang Y, Smolinski NE, Thai TN, et al. Common teratogenic medication exposures—a population-based study of pregnancies in the United States. *Am J Obstet Gynecol MFM*. 2024;6(1):101245.
7. Smolinski NE, Sarayani A, Thai TN, et al. Prenatal exposure to valproic acid across various indications for use. *JAMA Netw Open*. 2024;7(5):e2412680.
8. Hernández-Díaz S, Straub L, Bateman BT, et al. Risk of autism after prenatal topiramate, valproate, or lamotrigine exposure. *N Engl J Med*. 2024;390(12):1069–1079.
9. Winterstein AG, Wang Y, Smolinski NE, et al. prenatal care initiation and exposure to teratogenic medications. *JAMA Netw Open*. 2024;7(2):e2354298.
10. Knox C, Hampp C, Willy M, et al. Patient understanding of drug risks: an evaluation of medication guide assessments. *Pharmacoepidemiol Drug Saf*. 2015;24(5):518–525.
11. Albogami Y, Sarayani A, Hincapie-Castillo JM, Winterstein AG. Real-world fetal exposure to acne treatments in the United States: a retrospective analysis from 2006 to 2015. *Drug Saf*. 2021;44(4):447–454.
12. Sarayani A, Albogami Y, Elkhider M, et al. Comparative effectiveness of risk mitigation strategies to prevent fetal exposure to mycophenolate. *BMJ Qual Saf*. 2020;29(8):636–644.
13. Sarayani A, Donahoo WT, Hampp C, et al. Assessment of the Risk Evaluation and Mitigation Strategy (REMS) for phentermine-topiramate to prevent exposure during pregnancy. *Ann Intern Med*. 2023;176(4):443–454.
14. Clinical Briefing Document. Endocrinologic and Metabolic Drugs Advisory Committee Meeting; February 22, 2012. New Drug Application 22580: VI-0521 QNEXA (phentermine/topiramate). Silver Spring, MD: US Food and Drug Administration; 2012:200.
15. Sarayani A, Hampp C, Brown JD, et al. Topiramate utilization after phentermine/topiramate approval for obesity management: risk minimization in the era of drug repurposing. *Drug Saf*. 2022;45(12):1517–1527.
16. Sarpatwari A, Brown BL, McGraw SA, et al. Physician experiences with and perceptions of risk evaluation and mitigation strategy programs with elements to assure safe use. *PLoS One*. 2023;18(7):e0288008.
17. Clowse MEB, Saag KG. Unintended consequences of SCOTUS abortion decision for patients with rheumatic diseases. *Ann Intern Med*. 2022;175(9):1328–1329.

JPPT | Invited Commentary

Acne Vulgaris in Children and Adolescents: What's the Cause and How to Combat It

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ABBREVIATIONS FDA, US Food and Drug Administration

KEYWORDS acne vulgaris; adolescence; benzoyl peroxide; isotretinoin; macrolides; retinoids; tetracyclines

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Introduction

Acne vulgaris is a chronic disease of the pilosebaceous unit of the skin, characterized by open or closed comedones and the development of inflammatory papules, pustules, or nodules.[1] Acne is one of the most common skin disorders in adolescents and young adults, affecting up to 87% of teenagers.[2] During the young adult years acne typically exhibits a male predominance, while postadolescent acne mainly affects females.[3] Acne is not solely a disorder of adolescence, nevertheless overall incidence declines with increasing age and typically resolves by the third decade. Pediatric acne is acne that manifests prior to adolescence, classified into 4 main groups on the basis of age at symptom onset: neonatal acne, infantile acne, mid-childhood acne, and preadolescent acne (Table 1).[2] Although acne is not associated with mortality, complications such as hyperpigmentation and scarring may arise. Additionally, the negative psychosocial effects of having acne can be detrimental to our young patients, therefore appropriate care and treatment is vital.

Pediatric Acne Categorization and Pathogenesis

Acne vulgaris lesions can be either comedonal or papulopustular[3]:

- Comedonal lesions are milder in severity and characterized by closed comedones, or "whiteheads," or open comedones, also known as "blackheads." Comedonal lesions are noninflammatory and typically smaller than 5 mm.
- Papulopustular acne has a more inflamed presentation with relatively superficial papules or pustules, although still typically smaller than 5 mm.
- Nodular acne is a more severe variation of papulopustular acne with deep-seated, inflamed, and often tender, large papules or nodules.

Acne in young children is usually mild; however, as adolescence progresses it can vary greatly. Neonatal acne occurs anytime from birth to less than 6 weeks of age and affects an estimated 20% of newborns.[2] This is typically mild and self-limited and does not require treatment. Infantile acne begins around 6 weeks of age and can last up to a year or sometimes a bit longer. It is more common in males and may present with both inflammatory lesions and comedones. As with neonatal acne, most infantile acne is typically self-limited and not associated with underlying endocrine pathology. On the rare occasion that infantile or neonatal acne is severe or if the child has other potential signs of hormonal abnormality, clinicians should submit a referral to a pediatric endocrinologist for further work-up. Acne that occurs in children between the ages of 1 and 7 years is known as mid-childhood acne and is typically a sign of an endocrine abnormality.

In adults, several different host factors play a role in contributing to the pathogenesis of acne, which leads to lesion formation. The 4 main players associated with acnegenesis include hyperkeratinization of follicles, increased sebum production, *Cutibacterium acnes* bacteria, and inflammation.[3] In children, particularly infants, transient increased physiologic concentrations of adrenal androgens may be the culprit.[4] Because androgens stimulate the growth and secretory function of sebaceous glands, they increase sebum production and thus facilitate the development of acne.[3] Infants

Table 1. Pediatric Acne Categorization[2]

Age of Onset	Acne Type
Birth to ≤6 wk	Neonatal
6 wk to ≤1 yr	Infantile
1 yr to <7 yr	Mid-childhood
≥7 to ≤12 yr or menarche in females	Preadolescent
≥12 to ≤19 yr or after menarche in females	Adolescent

experience what is known as "mini-puberty," which consists of activation of the hypothalamic-pituitary-gonadal axis during the neonatal period, resulting in elevated gonadotropin and sex steroid levels during the first 3 to 6 months of life.[5] This transient elevation in androgens allows for the maturation of sex organs, and in male infants results in the production of gonadal testosterone, which can contribute to acne formation. Once hormone levels normalize, infantile acne typically subsides. Mid-childhood acne is rare and usually due to an endocrine imbalance, as children at this age do not normally produce a significant number of androgens; these children warrant an endocrine work-up.

Treatment for Mild to Moderate Acne

The treatment of acne in children and young adults varies depending on age and presentation; however, there are no large randomized controlled trials or observational studies of acne treatment in infants and young children.[6] The guidelines published by the American Academy of Dermatology offer evidence-based recommendations for patients aged 9 years or older[1]; additionally, an expert panel convened by the American Acne and Rosacea Society developed recommendations for the treatment of pediatric acne, which also encompasses younger patients.[2] Ultimately, the goal of treatment in pediatric acne is to mitigate as many age-appropriate pathogenic factors as possible by reducing sebum production, preventing the formation of microcomedones, suppressing *C acnes* bacteria, and minimizing inflammation to prevent scarring.[2]

Like the treatment of acne in adults, clinicians treat mild pediatric acne with topical medications (Table 2). Monotherapy with benzoyl peroxide or a topical retinoid is the recommended initial treatment of choice; if monotherapy is ineffective, consider combination therapy.[2] Other potential options include topical antibiotics in combination with benzoyl peroxide or topical dapsone.[1,7]

Benzoyl peroxide acts by killing the bacteria on the skin, stopping the production of sebum, and breaking down the outermost layer of the skin. It is an oxidizing agent that has potential to improve both inflammatory and noninflammatory acne lesions.[7] Benzoyl peroxide is the most widely studied over-the-counter product and is one of the most versatile, safe, inexpensive, and effective acne therapies.[2] While benzoyl peroxide is available over the counter in various dosage forms including

Table 2. Topical Medications Used for Pediatric Acne Vulgaris[2,7]

Category	Medication	Age per FDA Indication	Expert Panel Recommendation
Topical retinoid	Adapalene	12 yr and older	May be used as monotherapy or in combination regimens for all types and severities of acne in children and adolescents of all ages
	Tazarotene	9 yr and older for lotion, 12 yr and older for all other dosage forms	
	Tretinoin	9 yr and older for lotion, 10 yr and older for 0.05% gel, 12 yr and older for all other dosage forms	
	Trifarotene	9 yr and older	
Antimicrobial	Benzoyl peroxide	Adolescents	Safe and effective as monotherapy or in combination for mild pediatric acne or in regimens for acne of all types
	Clindamycin	12 yr and older	Monotherapy is not recommended, must be used in combination with benzoyl peroxide
	Dapsone	9 yr and older for 7.5% gel, 12 yr and older for 5% gel	May be considered in pediatric acne
Topical androgen receptor inhibitor	Clascoterone	12 yr and older	FDA approved after expert panel review; has been studied in children as young as 9 yr

FDA, US Food and Drug Administration

creams, gels, washes, and foams and in concentrations ranging from 2.5% to 10%, washes should be avoided or used cautiously in children to prevent eye irritation or accidental ingestion.[6] Concentration-dependent irritation, staining, and bleaching of fabric and hair is a limiting factor in treatment with benzoyl peroxide.[1]

Topical retinoids work by normalizing follicular hyperkeratosis and preventing the formation of the microcomedo, the primary lesion of acne.[2] The 4 currently available topical retinoid therapies for acne vulgaris include adapalene, tazarotene, tretinoin, and trifarotene. The safety and efficacy of retinoids in pediatric patients ages 12 years and older has been well documented in the literature, and several retinoid formulations have been approved by the US Food and Drug Administration (FDA) for children as young as 9 years.[2,7] Experts agree that topical retinoids may be used as monotherapy or in combination regimens for all types and severities of acne in children and adolescents of all ages.[2] As with most medications, the lowest strength should be trialed first. If used in combination, apply benzoyl peroxide and tretinoin at different times of the day to avoid oxidation or degradation of the tretinoin product. The most common adverse effects of retinoids include dryness, burning, stinging, and scaling.[2] Retinoids can also cause photosensitivity; thus, encourage the routine use of sunscreen in these patients to improve tolerability.

Topical antibiotics such as clindamycin and erythromycin have not been studied for the treatment of acne in children younger than 12 years; however, clinicians may use them in the pediatric population as an alternative to retinoids and benzoyl peroxide.[2] The guidelines discourage monotherapy with topical antibiotics owing to concerns for antibiotic resistance, so patients should always use them in combination with benzoyl peroxide.[1]

Topical dapsone is an antimicrobial agent that shows modest to moderate efficacy, particularly in the reduction of inflammatory acne lesions.[8] Dapsone is thought to possess both anti-inflammatory and antimicrobial properties. While efficacy and tolerability of dapsone is favorable in both males and females, a subgroup analysis has demonstrated superior efficacy in females.[9] The exact mechanism behind this sex difference is not well understood; however, differences in skin surface pH, skin thickness, and sex hormones may play a role. Dapsone does have a formulation available that is FDA approved for patients aged 9 years and older, and the expert panel suggests that it may be considered secondarily in pediatric acne.[2,7]

Treatment for Moderate to Severe Acne

Moderate pediatric acne is often initially treated with topical combinations including a retinoid and benzoyl peroxide and/or topical antibiotics; however, more severe acne typically requires addition of systemic therapy (Table 3).[2] Whenever topical or systemic antibiotics are used in acne, they should be combined with topical benzoyl peroxide to prevent antimicrobial resistance.[6] Additionally, clascoterone is a novel, first-in-class topical androgen receptor inhibitor indicated for the treatment of acne vulgaris in individuals aged 12 years and older. Several clinical studies for clascoterone have included patients as young as 9 years and have demonstrated favorable safety and efficacy.[10]

Tetracycline antibiotics such as doxycycline and minocycline are first-line medications for the treatment of moderate to severe acne vulgaris[1]; however, clinicians do not use them in children younger than 8 years owing

Table 3. Systemic Medications Used for Pediatric Acne Vulgaris[2,7]

Category	Medication	Age per FDA Indication	Expert Panel Recommendation
Tetracycline antibiotic	Doxycycline	8 yr and older	Oral antibiotics are appropriate for moderate to severe inflammatory acne vulgaris at any age. Tetracycline antibiotics should not be used in children younger than 8 yr
	Minocycline	9 yr and older	
	Sarecycline	9 yr and older	
Macrolide antibiotic	Azithromycin Erythromycin	Not FDA approved for acne but used in infants and children for other indications	
Oral retinoid	Oral isotretinoin	12 yr and older	Recommended for severe, scarring and/or refractory acne in adolescents and may be used in younger patients
Combination oral contraceptives	Various estrogen/progestin combinations	Females 14 yr and older or at least 2 yr after menarche	May be useful as second-line therapy in regimens of care in pubertal females with moderate to severe acne

FDA, US Food and Drug Administration

to their propensity to stain the developing tooth enamel. Additionally, we do not typically use systemic antibiotics and topical antibiotics simultaneously in the treatment of acne. Sarecycline is a newer, narrow-spectrum tetracycline antibiotic indicated for inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.[7] In patients younger than 8 years who require systemic antibiotic therapy for acne, macrolides such as azithromycin and erythromycin are the antibiotics of choice.[2] Educate young patients and their caregivers on potential side effects of systemic antibiotics and inform them that the typical duration of therapy is 3 months. Both tetracyclines and macrolides can cause gastrointestinal distress; tetracyclines are also known to cause photosensitivity.[7]

For severe, nodular acne and acne unresponsive to systemic antibiotics, oral isotretinoin is the recommended treatment; it tackles all 4 major factors in acne pathogenesis. Oral isotretinoin is the only medication that can permanently alter the natural course of acne vulgaris and has the potential to induce long-term remission.[11] While isotretinoin is not FDA approved for use in children younger than 12 years, the expert panel agrees that it may be used in younger patients with severe, refractory, and scarring acne.[2] The most common side effects include dry skin and mucous membranes, visual changes, and myalgias.[2] Isotretinoin is teratogenic and contraindicated in pregnancy,[7] which may be pertinent in our older adolescent population.

Hormonal therapy with combination oral contraceptive medications may be a reasonable second-line therapeutic option for female patients with moderate to severe acne vulgaris. We do not typically use combined oral contraceptives in children younger than 14 years or within the first 2 years of starting menses.[1,2] Additionally, patients with select cardiovascular and gastrointestinal comorbidities are not good candidates for treatment with these medications.[1]

Benzoyl Peroxide and Benzene—Where Are We

As I have noted above, benzoyl peroxide has been used for decades in the treatment of acne vulgaris, however recently there have been several reports which highlight potential safety concerns. Benzoyl peroxide, particularly when exposed to high temperatures, is known to degrade into benzene, a potent human carcinogen.[12] Aside from its use in the production of various chemicals, benzene may be found in natural sources as it is emitted as a vapor into the atmosphere by forest fires and volcanoes, and it is a natural part of crude oil, gasoline and cigarette smoke.[13] Even low levels of exposure to benzene at 1 part per million (ppm) or less have been shown to increase the risk of hematotoxicity.[14]

In March of 2024, Valisure LLC, an independent testing laboratory filed a Citizen's Petition with the FDA requesting a recall and suspension of the sale of products containing benzoyl peroxide.[15] Valisure conducted a study of 66 benzoyl peroxide containing products incubated at 50°C for 18 days. Subsequently, any products that showed relatively high stability were placed in 70°C incubation for 18 days. While in 70°C is an elevated temperature, 50°C is within a reasonable expected range that the product could be exposed to during routine handling. Elevated concentrations of benzene were detected in the majority of the benzoyl peroxide products tested, most of which were well over the 2 ppm acceptable concentrations set by the FDA. These levels ranged from about 0.2 ppm in a handful of the more stable products to over 1600 ppm in some of the worst offenders. Their results showed that even the most stable benzoyl peroxide formulations still produced over 2 ppm of benzene when incubated at 70°C for 14 or 18 days. They also discovered that benzene could leak outside of unopened benzoyl peroxide-containing acne treatment products at concerningly high levels.

A second group of researchers tested 111 different benbzoyl peroxide formulations shortly after taking them off the shelf. They noted that 34% of products tested contained benzene above the 2 ppm limit.[16] They also examined the effects of sunlight on degradation of benzoyl peroxide and concluded that UV exposure at levels expected outdoors are another concerning mechanism for the formation of benzene and may be more rapid than heat exposure. Additionally, they conducted a cold incubation experiment which did confirm that cold storage may stabilize benzoyl peroxide formulations.

Given this emerging data, the American Acne and Rosacea Society put out a statement recognizing these concerns, however stated that until further guidance is put out by the FDA upon confirmation of the data, patients should work with their providers to determine the best course of action to take.[17] They note that switching to another treatment may be an option for some, however there is no formal mandate to stop the use of benzoyl peroxide at this time. They also highlight the importance of following appropriate storage instructions, and directions for when to discard products. Additionally, storing benzoyl peroxide-containing products under refrigeration to reduce degradation, and replacing products every 3 months is recommended. At this point in time, benzoyl peroxide continues to be considered safe and effective by the FDA. Reassuringly, two recent studies published in the Journal of American Academy of Dermatology suggest that routine use of benzolyl peroxide-containing products for acne was not associated with meaningful risk of benzene in the blood or increased risk of cancer.[18,19]

While these initial reports of potential for high levels of benzene exposure should not be taken lightly, it is unclear if these findings have any clinically significant

impact at this time. As we await official guidance from the FDA, patients should collaborate with their providers to assess what is right for them. At a minimum, it is reasonable to store benzoyl peroxide-containing products away from direct sunlight and heat, and when not in use, in a cool place or even the refrigerator.

Most recently following the receipt of third-party testing results submitted to the FDA regarding elevated benzene concentrations in select benzoyl peroxide containing acne products, the FDA initiated independent testing to validate these findings. While the FDA testing results indicated fewer products with benzene contamination as compared to the third-party findings, this did result in a small amount of voluntary recalls at the retail level.[20] On March 11, 2025, several manufacturers volunteered to recall six over-the-counter acne products that the FDA found to have elevated benzene concentrations. An additional manufacturer volunteered to recall its Zapzyt Acne Treatment Gel after an elevated benzene concentration was found during in-house testing. The retail-level recall calls on stores and online retailers to remove these products from their shelves, but the FDA has not recommended that consumers take any action at this time. Even with daily use of these products for decades, the risk of a person developing cancer because of exposure to benzene found in these products is very low. The FDA is continuing to monitor the issue of benzene contamination in drug products, any newly available information will be published as it emerges.

Conclusion

The appearance of acne can be very troublesome for our pediatric patients, therefore timely and effective treatment is of utmost importance. In pediatric acne, treatment selection is based on lesion severity, patient age, and patient preference. Infantile acne is typically mild; when treatment is necessary, topical monotherapy is first line. Children with mid-childhood acne should have a consultation with an endocrinologist, as this is typically due to a hormonal imbalance; several topical and systemic treatments may also be used, based on expert opinion. Severe acne in pediatric patients may require the use of systemic antibiotics or isotretinoin, although age does play a factor in medication selection. Hormonal therapies are another option for some of our adolescent female patients with acne, depending on their age and onset of puberty. Treatment for acne in preadolescents uses the same principles as we use for adolescents and adults, with the exceptions of some therapies such as tetracycline antibiotics and hormonal therapies. Recently, benzoyl peroxide, a common ingredient found in many topical acne products, was linked to potential benzene exposure. While this did result in a small retail-level recall, benzoyl peroxide still continues to be considered safe and effective by the FDA.

Article Information

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References

1. Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris [published online ahead of print January 30, 2024]. *J Am Acad Dermatol*. 10.1016/j.jaad.2023.12.017
2. Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131(suppl 3):S163–S186.
3. Thiboutot D, Zaenglein AL. Pathogenesis, clinical manifestations, and diagnosis of acne vulgaris. In: Dellavalle RP, Levy ML, Owen C, eds. *UpToDate*. Waltham, MA: Wolters Kluwer. Updated July 2, 2024. Accessed August 5, 2024. https://www.uptodate.com/contents/pathogenesis-clinical-manifestations-and-diagnosis-of-acne-vulgaris URL
4. Kuiri-Hänninen T, Haanpää M, Turpeinen U, et al. Transient postnatal secretion of androgen hormones is associated with acne and sebaceous gland hypertrophy in early infancy. *J Clin Endocrinol Metab*. 2013;98(1):199–206.
5. Lanciotti L, Cofini M, Leonardi A, et al. Up-to-date review about minipuberty and overview on hypothalamic-pituitary-gonadal axis activation in fetal and neonatal life. *Front Endocrinol (Lausanne)*. 2018;9:410.
6. Zaenglein AL. Acne in infants, young children and preadolesents. In: Levy ML, Corona R, eds. *UpToDate*. Waltham, MA: Wolters Kluwer. Updated October 16, 2023. Accessed August 5, 2024. https://www.uptodate.com/contents/acne-in-infants-young-children-and-preadolescents
7. Clinical Pharmacology powered by ClinicalKey. Elsevier. 2024. Accessed August 5, 2024. https://www.clinicalkey.com/pharmacology/
8. Draelos ZD, Carter E, Maloney JM, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. *J Am Acad Dermatol*. 2007;56(3):439.e1–10.
9. Tanghetti E, Harper JC, Oefelein MG. The efficacy and tolerability of dapsone 5% gel in female vs male patients with facial acne vulgaris: gender as a clinically

relevant outcome variable. *J Drugs Dermatol.* 2012;11(12): 1417–1421.
10. Hebert A, Thiboutot D, Stein Gold L, et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two phase 3 randomized clinical trials. *JAMA Dermatol*. 2020;156(6):621–630.
11. Graber E. Acne vulgaris: management of moderate to severe acne in adolescents and adults. In: Dellavalle RP, Levy ML, Owen C, eds. *UpToDate*. Waltham, MA: Wolters Kluwer. Updated August 2, 2024. Accessed August 6, 2024. https://www.uptodate.com/contents/acne-vulgaris-management-of-moderate-to-severe-acne-in-adolescents-and-adults
12. Kucera K, Zenzola N, Hudspeth A, et al. Benzoyl Peroxide Drug Products Form Benzene. *Environ Health Perspect*. 2024;132(3):37702.
13. Centers for Disease Control and Prevention, Facts About Benzene (2018) https://emergency.cdc.gov/agent/benzene/basics/facts.asp. Accessed November 15, 2024
14. Lan Q, Zhang L, Li G, et al. Hematotoxicity in workers exposed to low levels of benzene. *Science*. 2004;306(5702):1774–1776.
15. Valisure citizen petition on benzene in benzoyl peroxide drug products. Valisure. March 5, 2024. https://assets-global.website-files.com/6215052733f8bb8fea016220/65e8560962ed23f744902a7b_Valisure%20Citizen%20Petition%20on%20Benzene%20in%20Benzoyl%20Peroxide%20Drug%20Products.pdf. Accessed November 15, 2024.
16. Kucera K, Zenzola N, Hudspeth A, et al. Evaluation of Benzene Presence and Formation in Benzoyl Peroxide Drug Products. *J Invest Dermatol*. Published online September 27, 2024.
17. Response statement from the AARS to the Valisure citizen petition on benzene in benzoyl peroxide drug products. News release. American Acne and Rosacea Society. March 20, 2024. https://acneandrosacea.org/uncategorized/american-acne-rosacea-society-aars-responds-to-citizen-petition-submitted-by-valisure-regarding-benzene-in-benzoyl-peroxide-drug-products/ Accessed November 15, 2024.
18. Sadr N, Troger A, Chai PR, Barbieri JS. No evidence for an association between benzoyl peroxide use and increased blood benzene levels in the National Health and Nutrition Examination Survey. *J Am Acad Dermatol*. 2024;91(4):763–765.
19. Garate D, Thang CJ, Lai J, Golovko G, Wilkerson MG, Barbieri JS. Benzoyl peroxide for acne treatment is not associated with an increased risk of malignancy: A retrospective cohort study. *J Am Acad Dermatol*. 2024;91(5):966–968.
20. Center for Drug Evaluation and Research. Limited number of voluntary recalls initiated after FDA testing of acne products for benzene; findings show a small number of products with elevated levels of benzene contamination. U.S. Food and Drug Administration. March 11, 2025. Accessed March 27, 2025. https://www.fda.gov/drugs/drug-safety-and-availability/limited-number-voluntary-recalls-initiated-after-fda-testing-acne-products-benzene-findings-show.

JPPT | Invited Commentary

A Cautionary Tale of Combination Ceftriaxone and Lansoprazole: Should Pediatric Clinicians Heed the Warning?

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ABBREVIATIONS hERG, human ether a-go-go; ICU, intensive care unit; LQTS, long QT syndrome; PPI, proton pump inhibitor; QTc, corrected QT interval TdP, Torsades de Pointes

KEYWORDS adverse drug events; ceftriaxone; lansoprazole; pediatrics; ventricular arrhythmia

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Torsades de Pointes (TdP) is a life-threatening polymorphic ventricular arrhythmia associated with prolongation of the heart-rate corrected QT interval (QTc) as measured via electrocardiogram.[1] Prolonged QTc may result from heritable causes related to dysfunction of cardiac repolarization or it can be acquired; most acquired cases of prolonged QTc are drug related.[1] Given the potential catastrophic impact of TdP, much attention has been given to mitigating the risk of QTc prolongation in adults. Children are also vulnerable to drug-induced QTc prolongation and the risk of TdP, although the incidence is poorly defined.[2] Emerging data about drug-related QTc prolongation in adults must also be considered in the context of pediatric patient risk, particularly when the drugs are commonly used in children.

A study published in the sixth 2023 issue of *JAMA Network Open*, "Ceftriaxone and the Risk of Ventricular Arrhythmia, Cardiac Arrest, and Death Among Patients Receiving Lansoprazole," is one such example of emerging evidence with potential implications in the pediatric population.[3] Bai and colleagues[3] explored the association of adverse cardiac outcomes with a combination of ceftriaxone and lansoprazole, building on initial identification of an association with the medication combination and QTc prolongation by Lorberbaum and colleagues,[4] by using data mining and laboratory experimentation. The article by Bai et al[3] described a multicenter, retrospective cohort study evaluating adult inpatients in 13 hospitals in Ontario, Canada, during a 7-year period from 2015 to 2021. Patients were included if they were prescribed 1 or more doses of ceftriaxone during their hospital stay, and a proton pump inhibitor (PPI) at any time between the first and final dose of ceftriaxone. Patients who received lansoprazole in combination with ceftriaxone were compared with those who received any other PPI in combination with ceftriaxone. Patients were followed up until hospital discharge for a primary composite outcome of ventricular arrhythmia or cardiac arrest during the hospital stay (which did not occur prior to hospital admission), based on International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-CA) codes.[5] All-cause in-hospital mortality was a secondary outcome.

Included in the study were 31,152 patients with a mean ± SD age of 71.7 ± 16 years who were further categorized into those who received lansoprazole (n = 3747) and those prescribed other PPIs (n = 27,405).[3] Differences in baseline characteristics between the groups (e.g., age, intensive care unit [ICU] admission, and risk factors for ventricular arrhythmia) were accounted for by using adjustment based on propensity scoring. The primary composite outcome occurred in 3.4% of patients in the lansoprazole group compared with 1.2% in the other PPI group ($p < 0.001$). All-cause in-hospital mortality was also greater in the lansoprazole than in the other PPI group (19.9% vs 10.1%, respectively; $p < 0.001$). After propensity score adjustment, the adjusted risk ratios for the lansoprazole group for the composite outcome and all-cause in-hospital mortality were statistically significantly different at 2.2 (95% CI, 1.7–2.2) and 1.6 (95% CI, 1.5–1.7), respectively. The adjusted risk difference for the lansoprazole group for the composite outcome was 1.7% (95% CI, 1.1–2.3), corresponding to a number needed to harm of approximately 58. The adjusted risk difference for all-cause in-hospital mortality was 7.4% (95% CI, 6.1–8.8), corresponding to a number needed to harm of 13.

It is striking that this large, multicenter study reported increased risk for ventricular arrhythmias, cardiac arrest, and death among adults receiving the combination of ceftriaxone and lansoprazole, given the lack of attention to this combination previously. The study built upon the results of a 2016 data mining study, in which 1.6 million electrocardiogram results from 380,000 adult patients were reviewed.[4] Signals for increased

incidence of prolonged QT interval in patients receiving both ceftriaxone and lansoprazole as compared with either drug alone emerged and were validated with patch-clamp electrophysiology experiments.[4] The drug-drug interaction was not observed with PPIs other than lansoprazole. Other literature addressing this interaction is limited to a letter responding to the 2016 study by Lorberbaum and colleagues,[4] in which Lazzerini and colleagues[6] briefly describe limited experience with patients receiving the combination who subsequently experienced acquired long QT syndrome or TdP.

The proposed mechanism of the drug-drug interaction between ceftriaxone and lansoprazole resulting in prolonged QTc is an additive blockade of the human ether a-go-go (hERG) potassium channel.[4,7] A 2022 study of nearly 25,000 adults admitted to the ICU reported an association of PPIs with QT interval prolongation, with pantoprazole and lansoprazole associated with the greatest risk.[8] Less has been reported with ceftriaxone, though a retrospective pharmacovigilance study published in 2021 reported a nearly 2-fold higher odds (OR, 1.92; 95% CI, 1.8–2.05) of experiencing a cardiac disorder among ceftriaxone-receiving adults without coronavirus infection.[9]

Is this relevant in children? Should pediatric practitioners be wary of or even avoid the combination of ceftriaxone and lansoprazole in their patients? The medication combination is certainly used in pediatric patients. A point prevalence study conducted in 32 US children's hospitals determined that ceftriaxone was the second most prescribed antibiotic.[10] In another evaluation of 51 children's hospitals in 2017 and 2018, ceftriaxone was the most common antibiotic prescribed in nonsurgical patients, with 5% of medical unit patients and 9% of pediatric ICU patients receiving ceftriaxone.[11] Ceftriaxone is also frequently administered to ambulatory children in the emergency department.[12] Proton pump inhibitors such as lansoprazole are commonly used in both ambulatory and hospitalized pediatric patients.[13–15]

While no publication has specifically reported the frequency of use of both drugs in combination, internal data from the authors' local institution provide some insight. Medication usage data were queried from admissions during a 10-year period at this free-standing, academic pediatric hospital. Of the 230,212 hospital admissions from the start of 2014 through the end of 2023, a total of 335 patient admissions received at least 2 ceftriaxone doses with at least 1 lansoprazole dose in between. This equates to approximately 3 children each month who received the combination of ceftriaxone and lansoprazole. Depending on institutional formularies, patient acuity, and local prescribing patterns, this drug combination may also be commonly observed at other pediatric hospitals.

If pediatric patients do receive this drug combination, how likely is it that the findings of Bai and colleagues[3] apply to children? To date there have been no published reports of negative cardiac outcomes in pediatric patients receiving the combination of ceftriaxone and lansoprazole. Of course, absence of evidence should not imply evidence of absence. If a child had experienced prolonged QTc or TdP due to this drug combination, the interaction is unlikely to have been recognized owing to lack of evidence in children. Torsades de Pointes is rare, difficult to detect, and generally underreported. Because the incidence of drug-induced TdP is not well defined in pediatric patients, it is challenging to compare the incidence with that observed in adults.[2] Drug-induced QTc prolongation in adults is exceptionally rare in patients without predisposing risk factors.[1] It is unknown whether patient-specific factors associated with increased risk in adults, such as female sex, electrolyte abnormalities, and heart failure with reduced ejection fraction, also predispose children to drug-related TdP. Importantly, many of these underlying cardiac risk factors are rare in children, making research challenging.

Is the mechanism of this interaction likely to occur in pediatric patients? The full ontogeny of the hERG potassium channel is not well described, but evidence supports the presence of this channel from birth. Expression of the *KCNH2* gene, encoding the fast potassium channel hERG, was found to be higher in patients younger than 15 years than in adults.[16] Given that most drug-induced QT interval prolongation is due to binding to and interference with hERG potassium channels, this increased expression has been suggested as a reason why many QTc-prolonging medications may be associated with a lower impact in children than in adults.[1,17] However, QTc prolongation due to hERG-blocking medications has been reported in all age ranges of patients, including preterm infants, indicating at least some degree of risk.[17–22] Interestingly, in 1 case series, 8 of 22 patients <2 years of age who received domperidone experienced QTc prolongation, with only 2 experiencing QTc ≥450 msec. Those 2 patients were receiving concomitant lansoprazole.[21] Finally, the average age at diagnosis of long QT syndrome (LQTS) in one study was 6.8 years, with 20% of patients presenting before 1 month of age.[23] Defective hERG potassium channels, due to pathogenic *KCNH2* gene variants, cause 25% to 40% of congenital LQTS.[24] This variation, called LQTS type 2, is the second most common cause of congenital LQTS.

In conclusion, the 2023 study by Bai and colleagues[3] highlights a potentially important drug-drug interaction between ceftriaxone and lansoprazole, which may increase an adult patient's risk for ventricular arrhythmia, cardiac arrest, and in-hospital mortality. Despite the absence of evidence supporting the impact of this interaction in pediatric patients, the potential for associated negative cardiac outcomes in pediatric patients receiving the combination of ceftriaxone and lansoprazole

are concerning, given the proposed pathophysiologic mechanism of the interaction. Clinicians should consider diligent monitoring in those children receiving concomitant ceftriaxone and lansoprazole, particularly in children who are receiving other medications that may prolong QTc or in the context of electrolyte abnormalities. Use of alternative PPIs or histamine (H2) antagonists could also be considered in place of lansoprazole. Children with congenital LQTS may also be at risk and providers should consider alternative combinations, when possible. Additional research is needed to evaluate the clinical outcomes associated with this combination in the pediatric cohort.

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References

1. Tisdale JE, Chung MK, Campbell KB, et al; American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology, the Council on Cardiovascular and Stroke Nursing. Drug-induced arrhythmias: a scientific statement from the American Heart Association. *Circulation*. 2020;142(15):e214–e233.
2. Tisdale JE. Drug-induced QT interval prolongation in children: are the kids alright? *Can J Hosp Pharm*. 2016;69(3):183–184.
3. Bai AD, Wilkinson A, Almufleh A, et al. Ceftriaxone and the risk of ventricular arrhythmia, cardiac arrest, and death among patients receiving lansoprazole. *JAMA Netw Open*. 2023;6(10):e2339893.
4. Lorberbaum T, Sampson KJ, Chang JB, et al. Coupling data mining and laboratory experiments to discover drug interactions causing QT prolongation. *J Am Coll Cardiol*. 2016;68(16):1756–1764.
5. Canadian Institute for Health Information. Canadian Coding Standards for Version 2022 ICD-10-CA and CCI. Ottawa, ON: CIHI; 2022.
6. Lazzerini PE, Bertolozzi I, Rossi M, et al. Combination therapy with ceftriaxone and lansoprazole, acquired long QT syndrome, and Torsades de Pointes risk. *J Am Coll Cardiol*. 2017;69(14):1876–1877.
7. Lazzerini PE, Cartocci A, Qu YS, et al. Proton pump inhibitors directly block hERG-potassium channel and independently increase the risk of QTc prolongation in a large cohort of US veterans. *Circ Arrhythm Electrophyiol*. 2021;14(7):e010042.
8. Fan W, Liu H, Shen Y, Hong, K. The association of proton pump inhibitors and QT interval prolongation in critically ill patients *Cardiovasc Drugs Ther*. 2024;38(3):517–525. 10.1007/s10557-023-07425-4
9. Yuan J, Li M, Yu Y, et al. Pharmacotherapy management for COVID-19 and cardiac safety: a data mining approach for pharmacovigilance evidence from the FDA adverse event reporting system (FAERS). *Drugs Real World Outcomes*. 2021;8(2):131–140.
10. Ferguson RA, Herigon JC, Lee BR, et al. Variability in ceftriaxone dosing across 32 US acute care children's hospitals. *J Pediatr Infect Dis Soc*. 2021;10(5):677–681.
11. Griffith HG, Gantuluri K, Thurm C, et al. Considerable variability in antibiotic use among United States children's hospitals in 2017-2018. *Infect Control Hosp Epidemiol*. 2020;41(5):571–578.
12. Howard LM, Thurm C, Dantuluri, et al. Parenteral antibiotic use among ambulatory children in United States children's hospital emergency departments. *Open Forum Infect Dis*. 2020;7(10):ofaa357.
13. Arnoux A, Bailhache M, Tetard C, et al. Proton pump inhibitors are still overprescribed for hospitalized children. *Arch Pediatr*. 2022;29(4):258–262.
14. Hales CM, Kit BK, Gu Q, Ogden CL. Trends in prescription medication use among children and adolescents–United States, 1999-2014. *JAMA*. 2018;319(19):2009–2020.
15. Locci C, Cuzzolin L, Cheri G, et al. Clinical use of gastric antisecretory drugs in hospitalized pediatric patients. *J Clin Med*. 2023;12(1):368.
16. Moric-Janiszewska E, Glogowska-Ligus J, Paul-Samojedny M, et al. Age- and sex-dependent mRNA expression of KCNQ1 and HERG in patients with long QT syndrome type 1 and 2. *Arch Med Sci*. 2011;7(6):941–947.
17. Heath TS, Greenberg RG, Hupp SR, et al. Effects of methadone on corrected Q-T interval prolongation in critically ill children. *J Pediatr Pharmacol Ther*. 2018;23(2):119–124.
18. Fobe C, Van Grambezen B, Moniotte S, et al. Torsade de pointe due to QT prolongation following erythromycin administration in a preterm infant. *Acta Cardiol*. 2022;77(7):597–601.
19. Günlemez A, Babaoğlu A, Arisoy AE, et al. Effect of domperidone on the QTc interval in premature infants. *J Perinatol*. 2010;30(1):50–53.
20. Chhina S, Peverini RL, Deming DD, et al. QTc interval in infants receiving cisapride. *J Perinatol*. 2022;22(2): 144–148.
21. Ngoenmak T, Treepongkaruna S, Buddharaska Y, Khositseth A. Effects of domperidone on QT interval in children with gastroesophageal reflux disease. *Pediatr Neonatol*. 2016;57(1):60–64.
22. Vieira MC, Miyague NI, Van Steen K, et al. Effects of domperidone on QTc interval in infants. *Acta Pediatr*. 2012;101(5):494–496.
23. Garson A Jr, Dick M II, Fournier A, et al. The long QT syndrome in children: an international study of 287 patients. *Circulation*. 1993;87(6):1866–1872.
24. Schwartz PJ, Ackerman MJ, George AL, Wilde AAM. *J Am Coll Cardiol*. 2013;62(3):169–180.

JPPT | Commentary

The Pitfalls and Opportunities With Posaconazole DR Oral Suspension

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ABBREVIATIONS DR, delayed release; EMR, electronic medical record; IR, immediate release; ISMP, Institute for Safe Medication Practices; IV, intravenous; NG, nasogastric

KEYWORDS antifungal; drug development; drug supply; inpatient pharmacy; medication administration; medication safety

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Posaconazole is a triazole antifungal that plays an important role in the treatment and prevention of various fungal infections, particularly in immunocompromised patients. It has historically been available as delayed-release (DR) 100-mg tablets, immediate-release (IR) oral suspension 40 mg/mL, and as an intravenous (IV) solution; at the end of 2022, a DR oral suspension for preparation became available on the market in the United States.

Owing to erratic bioavailability of the IR oral suspension, the DR oral suspension has been highly anticipated in the pediatric setting because of the opportunity to provide patient-specific doses in a safe and effective manner.[1,2] The DR oral suspension avoids the crushing of DR tablets (which is not formally approved though studies supporting the practice exist) and associated difficulties in optimizing a dose given tablet sizes; administering the IR suspension multiple times per day (some patients may require dosing 4 times a day to achieve appropriate therapeutic concentrations); and using a less optimal antifungal for the patient.[3–6]

Unfortunately, the currently available product poses several barriers for use in patient care, and particularly in the inpatient setting. This commentary presents identified challenges and solutions with the current formulation of posaconazole DR oral suspension, identified at a large, tertiary pediatric academic medical center.

Product Availability

Posaconazole DR oral suspension is only available for purchase as a drop-ship item; drop-ship medications take more time for order and delivery than other medications. Available in an 8-day supply package, each kit comes with 1 bottle of solution for reconstitution.[1] The medication is supplied in packets with 4 syringes (2 blue [10 mL] syringes and 2 green [3 mL] syringes), 2 mixing cups, a bottle of mixing liquid (contains preservatives), and a bottle adapter.[1]

Challenges.

- Inpatient: The product is available as a medication box/kit and these are essentially patient-specific, complicating medication preparation and dispensing from an inpatient setting. Questions considered by our institution's pharmacy team include:
  - How should packets be prepared when there is 1 primary diluent bottle for each of 8 packets? Would this look different if there were multiple patients needing the medication at once?
  - Where should doses be dispensed from (and are the packets all dispensed at once or individually)?
  - What to do with extra packets?
  - How to allow for appropriate barcode medication administration scanning of the doses?
- Ambulatory: The 8-day supply/counts are challenging for families who are accustomed to receiving medications every 30 days, particularly if an insurance company will not allow a 32-day supply. This requires families to come to the pharmacy more frequently (particularly if receiving other maintenance medications), and both family and pharmacy must identify the need to refill the medication (usually patient-specific ordering by the pharmacy given the cost) in advance. Additionally, this may subject families to a greater number of copayments, adding an additional financial burden.

Solutions.

- Inpatient: The full box is dispensed with the same barcode being used for the multiple packets. An educational handout (see Supplement S1) was created in conjunction with medication safety, pharmacy, and nursing leadership to provide clear instructions on how to prepare individual doses on the floor, and to ensure each dose was appropriately scanned prior to administration. In addition to the educational

handout, administration instructions were added to the medication administration report in the electronic medical record (EMR). The inpatient pharmacist was in close contact with the pharmacy inventory team regarding discharge plans to ensure adequate supply of drug without over-purchasing. Use of the product is strictly limited, and there have not been multiple cases of patients needing treatment simultaneously because of the complexities of the medication and medication safety concerns.[7] If the need were to arise, continuing with an individual supply (1 box per patient) at this time is anticipated.

- Ambulatory: When able and appropriate, change prescription of maintenance medications to a 90-day supply and an 88-day supply for posaconazole DR oral suspension (assuming ongoing clinical need). Have families call for a refill when opening the final box of posaconazole DR suspension (essentially 8 days before the supply is exhausted) to allow adequate time for refill, and as an easy way for families to remember to call.

Preparation and Stability

The product must be prepared by the family/caregiver prior to each dose and expires 1-hour after preparation. Additionally, the preparation is multistep and requires first measuring the correct amount of diluent, then mixing it with the full powder packet, and finally measuring the appropriate patient-specific dose (2 syringes, 1 mixing cup required in addition to the active medication and diluent).[8]

Challenges.

- Inpatient: The short stability of the medication makes it nearly impossible for the medication to be prepared in the inpatient pharmacy, delivered to the floor, and given to the nurse to administer without any delays, which would elapse the beyond-use time.
- Ambulatory: A parent/guardian could not make premeasured doses if the patient were to be cared for by another family member or friend. This means the trained family member would not be able to miss any dosing time for the patient, education would need to extend to multiple family members/friends, or the patient would be at risk of missing a dose.

Solutions.

- Inpatient: Education sheets were created for nursing (Supplement S1), and the inpatient clinical pharmacist checked in daily to ensure there was no confusion or questions about the preparation or administration process (facilitated by nursing in this unique situation only). Comments were also placed in the EMR and dose labels about reviewing these instructions (completed by the verifying inpatient pharmacist).
- Ambulatory: The manufacturer provides a detailed education sheet for families, but it is multiple pages and includes 15 steps, which can be quite overwhelming. A simplified, patient-specific education sheet for families was created and the education process started with the first dose, to ensure families felt confident preparing and administering the correct dose (Supplement S2). Families were observed by nursing and the inpatient pharmacist prior to discharge to "self-lead" the preparation and administration and were asked about the need for additional family member education. How many family members were taught was left up to the family, but all were counseled on the importance of adherence and not missing doses.

The product comes with its own syringes for administration, specified by color; unfortunately, they are not compatible with nasogastric (NG) tubes or ENFit (Multiple manufacturers)) feeding tubes.

Challenges.

- Inpatient: For patients requiring feeding tube administration, the posaconazole DR suspension is not an option at this time because only the manufacturer-provided notched tip syringes should be used when administering the product. Additionally, incompatibility with ENFit syringes/feeding tubes poses a safety risk for route of administration. Color vision–deficient staff need to differentiate syringes by size and cannot rely on the manufacturer's directions, which uses colors specifically.
- Ambulatory: If families are color vision–deficient, manufacturer directions may be confusing, and alternative education would be needed to ensure proper preparation. Patients with NG tubes need alternative formulations.

Solutions. Education sheets (see Supplements S1 and S2) that are not reliant on colors alone, but also clearly relate colors to syringe size, were created for nursing and families. For patients with feeding tubes, the use of crushed posaconazole DR tablets is preferred owing to incompatibility of manufacturer syringes and ENFit system; institutional directions (see Supplement S2) have been created for families and caregivers on how to do this. Therapeutic drug monitoring is used to ensure adequate dosing.

Product Differences

The IV formulation, DR tablets, IR suspension, and DR suspension are not 1:1 dosing conversions. While IR suspension was removed from the market in 2024, orders for the product may still exist in the EMR and cause confusion.

Challenges. When patients are transitioning between products (IV to oral or oral to NG tube), special attention to detail is required. Both suspension

formulations are now hidden in the EMR so that only pharmacists are able to place orders—to prevent confusion for providers during switching. Patient safety events may occur during feeding tube placement and the formulation is switched 1:1 to liquid IR suspension from DR tablets.

Solutions. In conjunction with this, alerts were added to the EMR when ordering posaconazole, and pharmacist education (in the form of a clinical pearl presentation and internal guidance document for further reference) was provided to assist in ordering the right dose/conversion.

Insurance

Challenges. Because the DR suspension is now preferred for pediatric patients, there have been instances where insurance companies specifically prefer the DR suspension product. There have also been instances where insurance-preferred pharmacies are not able to order the product, and on 1 occasion the insurance strictly preferred the DR suspension but would only allow the family to fill the prescription at a pharmacy that was unable to order the product.

Solutions. Early ambulatory prescribing of any posaconazole prescription is recommended (e.g., sending prescriptions as soon as it is known that a patient may require therapy) to allow for prior authorizations and peer to peer, time to order the product, and adequate education for all involved. Historically, most patients requiring any formulation of posaconazole require a minimum of a prior authorization. Several have required significant advocacy in order to receive the medication, with more than a week to receive approval for the medication, and potentially longer to get the product in stock and dispensed. It is an important reminder for all pharmacists, because most (if not all) patients starting to take posaconazole as an inpatient will require continuation in the outpatient setting, and thus early preparation is best.

Discussion

In September 2023, the Institute for Safe Medication Practices (ISMP) issued a safety brief highlighting many of the above concerns.[7] ISMP ultimately recommended carrying only one of the posaconazole suspension formulations to avoid confusion; and emphasized that the inability to use ENFit syringes, as well as the kit design and supply, and the short time frame from preparation to administration all pose significant safety and feasibility issues in the inpatient setting. ISMP highlights the need to develop a plan to operationalize use of the DR suspension (from preparation to administration), prevent the risk of wrong-route drug administration or dosing errors, and provide education to patients/caregivers about home preparation and administration.

In summary, while the posaconazole DR suspension seems like a promising option for pediatric patients, based on trial data, in the real world it falls short. The complexities of preparation, product packaging that is essentially patient-specific (not friendly for multipatient use with no consideration to inpatient administration), incompatibility with feeding tubes, and medication safety concerns, in combination with concern for dosing errors between other formulations, make it essentially unusable in the inpatient setting (which translates to the outpatient setting). Because of these challenges, strong preference has been given to avoid use of the DR suspension in pediatric patients. In situations where DR suspension cannot be avoided, the above solutions provide guidance on safe use and can be adapted to your institution and practice.

Importantly, this should be a call for the manufacturer (and other drug manufacturers) to consider the highlighted issues when developing any medication—these are not challenges unique to the pediatric population, although these challenges disproportionately affect pediatric patients. Continued changes to the formulation, investigation into product compatibility with the ENFit system, and future consideration of pediatric patients during drug development are encouraged.

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References

1. McCreary EK, Davis MR, Narayanan N, et al. Utility of triazole antifungal therapeutic drug monitoring: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy.* 2023;43(10):1043–1050.
2. Ashok A, Mangalore RP, Morrissey CO. Azole therapeutic drug monitoring and its use in the management of invasive fungal disease. *Curr Fungal Infect Rep*. 2022;16:55–69.

3. Dieringer TD, Shaenman JM, Davis MR. Enteral feeding tube administration with therapeutic drug monitoring of crushed posaconazole tablets and opened isavuconazonium sulfate capsules. *J Antimicrob Chemother*. 2022;77(5):1417–1423.
4. Neuhas K, Chemali X. Serum concentrations of crushed posaconazole delayed release tablets in lung transplant recipients. *J Heart Lung Transplantation*. 2023;42(4S):S98.
5. Mason MJ, McDaneld PM, Musick WL, Kontoyiannis DP. Serum levels of crushed posaconazole delayed-release tablets. *Antimicrob Agents Chemother*. 2019;63(5):e02688-18.
6. Stevens RW, O'Connell C, Huang A, et al. Therapeutic drug monitoring following crushed administration of delayed-release posaconazole tablets via enteral feeding tubes. *J Antimicrob Chemother*. 2023;78(2):553–555.
7. Safety briefs: limitations of the most recent posaconazole formulation. *Acute Care: ISMP Medication Safety Alert!* 2023;28(18):1–4.
8. Noxafil PowderMix [package insert]. Rahway, NJ: Merck; 2022.

JPPT | Letter to the Editor

Concern for Patient Harm Due to Potentially Supratherapeutic Clonidine Dosing Resulting From Physiologically Based Pharmacokinetic Modeling

To the Editor—We read with interest the recent publication by Yellepeddi et al[1] describing an innovative physiologically based pharmacokinetic (PBPK) model for predicting optimal clonidine doses for neonatal and pediatric indications. We agree with the authors' assertions regarding the dosing and pharmacokinetic challenges of using clonidine to effectively manage a variety of neonatal and pediatric disease states in which use has become common. Nonetheless, we have significant concerns that dosing up to 30 µg/kg/dose for neonates and 0.9 mg/day for older children and adolescents may cause patient harm if applied broadly.

As noted by the authors, excessive clonidine dosing may result in severe adverse drug events (ADEs), including hypotension, bradycardia, and somnolence; in younger age groups with unintentional ingestion, respiratory depression, and coma have been reported.[2–4] ADEs are thought to be dose related and have been observed in pediatric patients receiving labeled doses up to 0.4 mg/day.[5] Off-label use occurs frequently, potentially confounding ADE risk.

In neonates receiving clonidine for neonatal abstinence or neonatal opioid withdrawal syndromes, literature has consistently demonstrated the safety of doses up to 24 µg/kg/day divided every 3 to 6 hours, and up to 46% of these patients may be managed in the outpatient setting.[6,7] The PBPK model's proposal for single doses up to 30 µg/kg, roughly 500% of published dosing, has not been described in vivo. Investigators evaluating toxic clonidine ingestions have proposed 10 µg/kg or 0.1 mg as the dose thresholds at which patients younger than 4 years should receive medical evaluation.[2,3] Considering a mean term birthweight of 3.4 kg, most term neonates meet both thresholds at the PBPK model's proposed dose.[8] Additionally, while Yellepeddi et al[1] recommend the application of the PBPK model to develop clonidine dosing regimens for preterm neonates, modification to account for premature renal function at specific gestational ages was not further described. As gestational age of viability continues to decrease, the assumed rates of renal development included in the model become less reliable, requiring additional caution. Given that numerous studies have demonstrated the effectiveness of clonidine for neonatal abstinence and neonatal opioid withdrawal syndromes with standard dosing strategies, we question the utility of higher dosing and strongly support the authors' statement that prospective confirmation of safety and benefit resulting from higher dosing is imperative before such use becomes routine.

In older children and adolescents, defined within the PBPK model as 6 to 17 years of age, clonidine is prescribed for an array of psychiatric indications at a usual range of 0.1 to 0.4 mg/day.[1,4,9] Inconsistent benefit for some conditions validates the authors' assertion that dose escalation may be warranted, but established effectiveness for numerous indications challenges the suggestion that typical dosing is generally insufficient.[9] Current Centers for Disease Control and Prevention growth percentiles estimate a 20 kg mean weight for United States children at age 6. At this weight, 0.9 mg/day dosing corresponds to 15 to 23 µg/kg/dose divided 2 to 3 times daily. In a 2023 study of toxic clonidine ingestions in 70 patients aged 7 to 17 years, Duong et al[10] reported a median ingested dose of 13 µg/kg (IQR, 7–38). Bradycardia, hypotension, or altered mental status occurred in 91% of cases. At doses of only 5 to 10 µg/kg, moderate to severe bradycardia and hypotension occurred in 26% and 29% of patients, respectively, challenging the tolerability of PBPK-proposed doses.

The PBPK model represents an innovative approach to ontogenic pharmacokinetics and warrants further application to medications without established optimal dosing. Yellepeddi et al[1] acknowledge that extrapolating target clonidine concentrations from measurements of α-2 agonist activity in animal models is a limitation. If concentration-based activity proves similar in humans, we question whether maximal α-2 agonism is the appropriate target for symptom control rather than patient-specific, symptom-based approaches. We encourage judicious consideration of patient safety in the development of clinical trials evaluating higher clonidine-dosing strategies and emphasize that such research is necessary before applying the PBPK model to clinical practice.

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Ethical Approval and Informed Consent. Given the nature of this letter, the authors assert that the project was exempt from institutional and ethics committee review.

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References

1. Yellepeddi V, Bayless S, Parrot M, Sherwin CM. Optimal dosing recommendations of clonidine in pediatrics using physiologically based pharmacokinetic modeling. *J Pediatr Pharmacol Ther*. 2024;29(6):636–644.
2. Spiller HA, Klein-Schwartz W, Colvin JM, et al. Toxic clonidine ingestion in children. *J Pediatr*. 2005;146(2):263–266.
3. Amico K, Cabrera R, Ganti L. Outcomes following clonidine ingestions in children: an analysis of poison control center data. *Int J Emerg Med*. 2019;12:14.
4. Wiley JF, Wiley MC, Torrey SB, Henretig FM. Clonidine poisoning in young children. *J Pediatr*. 1990;116(4):654–658.
5. Onyda XR *(clonidine HCl) [package insert]*. Monmouth Junction, NJ: Tris Pharm, Inc.; 2024.
6. Meddock RP, Bloemer D. Evaluation of the cardiovascular effects of clonidine in neonates treated for neonatal abstinence syndrome. *J Pediatr Pharmacol Ther*. 2018;23(6):473–478.
7. Maalouf FI, Cooper WO, Slaughter JC, et al. Outpatient pharmacotherapy for neonatal abstinence syndrome. *J Pediatr*. 2018;199:151–157.e1.
8. Johnson W, Choh AC, Soloway LE, et al. Eighty year trends in infant weight and length growth: the Fels Longitudinal Study. *J Pediatr*. 2011;160(5):762–768.
9. Naguy A. Clonidine use in psychiatry: panacea or panache? *Pharmacology*. 2016;98(1-2):87–92.
10. Duong C, Lovett C, Downes MA, Isbister GK. Reality of clonidine poisoning in children and adolescents. *J Pediatr Child Health*. 2023;59(6):827–832.

AUTHORS RESPONSE: Thank you for the opportunity to reply to the recent letter about our paper, "Optimal Dosing Recommendations of Clonidine in Pediatrics Using Physiologically Based Pharmacokinetic Modeling,"[1] which was published in *The Journal of Pediatric Pharmacology and Therapeutics*. We appreciate the authors' interest in our work and their efforts to raise awareness of the critical problem of clinical translation of model-based suggestions. We value the conversation regarding the possible clinical ramifications of our suggested modeling-based dosage strategies and recognize how crucial it is to guarantee patient safety. Below, each of the issues that were raised in the letter has been addressed.

1. Concern Regarding Potentially Supratherapeutic Clonidine Dosing and Adverse Drug Events

It is acknowledged that clonidine's adverse effects, including hypotension, bradycardia, and sedation, are dose-dependent and that pediatric patients may be particularly susceptible to these effects. However, we believe there may be a misconception regarding the intent of our study, as our article explicitly states that model-derived dosing recommendations must not be applied in clinical settings without validation through appropriate clinical data in the target population. The primary objective of the study was to demonstrate the utility of physiologically based pharmacokinetic (PBPK) modeling in characterizing clonidine pharmacokinetics across pediatric age groups, thereby providing insights that may guide future research and inform dose-optimization efforts. We stress that our model offers a platform for generating hypotheses rather than rapid practical application. We agree with your recommendation that caution must be exercised before adopting these doses widely and reiterate that our model provides a framework for guiding research rather than immediate clinical application implementing these doses.

2. Neonatal Dosing and Safety Considerations

We are aware that newborn opioid withdrawal syndrome and neonatal abstinence syndrome have been linked to clonidine dosages of up to 24 mcg/kg/day in recent research.[2,3] The 30 mcg/kg dose recommended for neonates in our paper was based on PBPK model simulations and resulted in plasma clonidine concentrations that are optimal for achieving target plasma concentrations for maximal α-2 adrenergic activity. This recommendation was not intended to be a "single" dose for administration in neonates. We want to clarify that our simulations were not used to establish a strict dosing schedule but rather to forecast exposure matching.

Regarding the safety threshold for medical evaluation at 10 mcg/kg or 0.1 mg,[4] we agree that caution is warranted. As we indicated in the discussion section, the availability of clonidine pharmacokinetic data in preterm newborns is necessary to guarantee the accuracy of model predictions when using our PBPK model for these patients. In the discussion section, we also stated that, depending on the gestational age of the preterm neonates, our PBPK model can be extrapolated to them. However, we did not go into greater detail about how to extrapolate our model to preterm infants because that was outside the purview of the manuscript.

3. Older Children and Adolescents: Risk of Toxicity

The authors of the letter have valid concerns about the 0.9 mg/day dose in older children and adolescents. Current dose recommendations range from 0.1 to 0.4 mg/day[5] as mentioned in their letter. Our model, however, showed that these dosages might not produce the desired α-2 adrenergic activity needed for the best possible treatment outcomes for Tourette's syndrome and attention-deficit/hyperactivity disorder. We appreciate the reference to Duong et al,[6] which highlights the risk of bradycardia and hypotension at doses as low as 5 to 10 mcg/kg. However, the findings given may not be applicable to a more controlled dosing of clonidine for therapeutic purposes because it came from acute clonidine poisoning caused by children accidentally consuming large quantities of clonidine. Our findings suggest that dose-optimization studies are warranted, but we emphasize in our manuscript that such recommendations must be verified through rigorous clinical studies before implementation.

4. Extrapolation From Animal Studies and Clinical Relevance of Target Concentration

Our selection of 40.5 nM as the plasma target concentration was derived from animal models,[7] and it has not yet been established if it can be directly applied to pediatric patients. Nevertheless, using PBPK modeling to define exposure-response relationships is a well-established approach in pediatric pharmacology.[8,9] Our results provide an initial estimate that should be validated through exposure-response studies in clinical settings. We concur that in dose-optimization trials, a symptom-based strategy is still essential.

5. Clinical Implementation and Need for Prospective Trials

We completely concur with the authors' concerns and reiterate the fundamental principle that model-based predictions need thorough verification before clinical implementation, even though they are useful for developing hypotheses and designing studies. Our manuscript makes it very evident that the PBPK model is not a final clinical recommendation but rather an evidence-based basis for additional research and not a definitive clinical guideline. Before applying model predictions, real-world verification through prospective pharmacokinetic or pharmacodynamic investigations is crucial, as mentioned in previous PBPK-based pediatric dose-optimization studies.[10–12]

Conclusion

We appreciate this conversation as a chance to emphasize how crucial it is to understand model-based results carefully and validate them appropriately in pediatric pharmacotherapy. Thank you for the authors' engagement, and we look forward to continued dialogue on the responsible application of pharmacokinetic modeling and more discussions about the appropriate use of pharmacokinetic modeling in clinical judgment.

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References

1. Yellepeddi V, Bayless S, Parrot M, Sherwin CM. Optimal dosing recommendations of clonidine in pediatrics using physiologically based pharmacokinetic modeling. *J Pediatr Pharmacol Ther*. 2024;29(6):636–644.
2. Meddock RP, Bloemer D. Evaluation of the cardiovascular effects of clonidine in neonates treated for neonatal abstinence syndrome. *J Pediatr Pharmacol Ther*. 2018;23(6):473–478.
3. Maalouf FI, Cooper WO, Slaughter JC, et al. Outpatient pharmacotherapy for neonatal abstinence syndrome. *J Pediatr*. 2018;199:151–157 e151.
4. Spiller HA, Klein-Schwartz W, Colvin JM, et al. Toxic clonidine ingestion in children. *J Pediatr*. 2005;146(2):263–266.
5. Naguy A. Clonidine use in psychiatry: panacea or panache. *Pharmacology*. 2016;98(1-2):87–92.

6. Duong C, Lovett C, Downes MA, Isbister GK. Reality of clonidine poisoning in children and adolescents. *J Paediatr Child Health.* 2023;59(6):827–832.
7. Gil DW, Cheevers CV, Kedzie KM, et al. Alpha-1-adrenergic receptor agonist activity of clinical alpha-adrenergic receptor agonists interferes with alpha-2-mediated analgesia. *Anesthesiology*. 2009;110(2):401–407.
8. Zhao P, Zhang L, Grillo JA, et al. Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. *Clin Pharmacol Ther*. 2011;89(2):259–267.
9. Yellepeddi V, Rower J, Liu X, et al. State-of-the-art review on physiologically based pharmacokinetic modeling in pediatric drug development. *Clin Pharmacokinet*. 2019;58(1):1–13.
10. van der Heijden JEM, de Hoop-Sommen M, Hoevenaars N, et al. Getting the dose right using physiologically-based pharmacokinetic modeling: dexamethasone to prevent post-extubation stridor in children as proof of concept. *Front Pediatr*. 2024;12:1416440.
11. Maharaj AR, Edginton AN. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT Pharmacometrics Syst Pharmacol.* 2014;3(11):e150.
12. Maharaj AR, Barrett JS, Edginton AN. A workflow example of PBPK modeling to support pediatric research and development: case study with lorazepam. *AAPS J.* 2013;15(2):455–464.