RESEARCH ARTICLE

Risk Factors for Adverse Events in Children Receiving Outpatient Parenteral Antibiotic Therapy

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ABSTRACT

BACKGROUND: Outpatient parenteral antibiotic therapy (OPAT) can decrease length of hospital stay but is associated with adverse events (AEs). The purpose of this study was to quantify and identify risk factors for OPAT-associated AEs in children.

METHODS: Retrospective single-center study of children ≤21 years old discharged on OPAT from January 2016 to April 2019 with infectious diseases follow-up. Demographic and clinical factors and medication and central venous catheter (CVC)–associated AEs were assessed through chart review. Univariable and multivariable analyses were performed.

RESULTS: Among 181 OPAT courses, an AE occurred in 70 (39%). Medication AEs occurred in 30 of 181 courses (16.6%). Children residing in an urban area had a 4.5 times higher risk of having a medication-related AE compared with those in a rural area (odds ratio: 4.51; 95% confidence interval: 1.60–12.77; $P = .005$). CVC AEs occurred in 47 of 181 courses (26%). Every additional day of OPAT increased the odds of having a CVC-related AE by 4% (odds ratio: 1.04; 95% confidence interval: 1.01–1.07; $P = .003$). Twenty (11.1%) courses resulted in readmission to the hospital because of an AE.

CONCLUSIONS: In this cohort, 39% of children experienced an OPAT-associated AE, and CVC AEs were more common than medication AEs. Longer duration of intravenous therapy and urban residence were independently associated with OPAT-associated AEs, highlighting the importance of converting to oral antibiotic therapy as soon as feasible to reduce OPAT-associated AEs.

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Outpatient parenteral antibiotic therapy (OPAT) has increased since it was first used in the United States in 1974 in pediatric patients with cystic fibrosis.[1] Studies have revealed that OPAT improves patient and caregiver satisfaction and reduces caregiver burden by shortening hospital stays and allowing patients more freedom and flexibility when prolonged intravenous (IV) antibiotic courses are required.[2–4] Despite these benefits, there is risk of OPAT-associated adverse events (AEs), including central venous catheter (CVC) malfunction, CVC infections, and medication toxicities.[5,6] These AEs occur with a reported frequency between 4.6% and 41.0% in both the adult and pediatric literature.[5,7–15] However, these AE rates may underrepresent the true burden of OPAT because, in most studies, researchers focus on a limited scope of AEs. Furthermore, OPAT is frequently prescribed without formal oversight of infectious diseases (ID) or antibiotic stewardship providers and may be unnecessary in situations when oral, rather than IV, antibiotics may be effective.[16] There is increasing awareness that many infections that have traditionally been treated with parenteral therapy can be partially or completely treated with a course of oral antibiotics.[17–22] Without systematic tracking of OPAT use and outcomes, it is likely that prescribers underestimate the rate of AEs among patients receiving OPAT. In recent years, many groups, including the Infectious Diseases Society of America, have emphasized the importance of institutional stewardship of OPAT.[2,23–26] Because of the lack of comprehensive pediatric literature on OPAT AEs, we performed a retrospective cohort study to quantify the AEs that occurred among children discharged with OPAT with ID follow-up and evaluated risk factors for the development of medication- and CVC-associated AEs.

METHODS

Study Design

We conducted a retrospective single-center study of patients ≤21 years old discharged with OPAT from January 1, 2016, to April 30, 2019. This study was performed at our 300-bed freestanding children's hospital in the southeastern United States, which provides tertiary and referral care. Overall, this facility has ∼16 000 inpatients and 50 000 pediatric emergency department (ED) visits annually.

Only patients with pediatric ID follow-up at discharge were included in this cohort. Treating providers determined appropriateness of OPAT for all patients without input from the study team. Any local home health care company that was able to make weekly home visits and care for pediatric patients and was covered by the patient's insurance was used for OPAT. The percentage of patients discharged with OPAT without ID follow-up at our institution is low; in general, gastroenterology, oncology, and pulmonology services often manage their own patients receiving OPAT, whereas patients discharged from the hospital medicine and orthopedic services with OPAT are typically managed by the ID service. During the study period, all OPAT follow-up was done via in-person visits to the ID clinic, which is staffed by ID physicians and an ID nurse 4 days per week. Monitoring laboratory tests could be drawn locally or by the home health nurse and faxed to the ID service for evaluation. If any AEs occurred when the clinic was not open (nights and weekends), families could call the ID fellow on call. If it was determined that the patient needed to be evaluated, they were instructed to go to their nearest ED.

Demographic and clinic data were obtained by using chart review, including available records from outside hospitals when patients were seen at another institution during their course of OPAT.

We determined if each patient lived in an urban, suburban, or rural setting by mapping their zip code of residence using the National Center for Health Statistics (NCHS) database.[27] We defined urban as NCHS large central metropolitan, suburban as NCHS large fringe metropolitan and medium metropolitan, and rural as NCHS small, micropolitan, and noncore.

Study Outcomes

AEs during OPAT were determined through chart review and were categorized as medication-associated or CVC-associated. We only captured AEs that occurred after discharge and did not include AEs that occurred while patients were receiving IV antibiotics in the hospital. We defined an AE as any event that required extra medical care or resulted in a change in antibiotic therapy. We compared final outcomes of OPAT among patients with and without AEs. Days of therapy were calculated from the time of hospital discharge.

Medication-associated AEs included the following: rash, neutropenia (absolute neutrophil count <500 or declining absolute neutrophil count on serial testing that was documented as neutropenia by an ID clinician and resulted in increased monitoring or a change of antibiotic therapy), hepatitis (rising aspartate transaminase or alanine transaminase levels documented as hepatitis by an ID clinician or that resulted in increased monitoring or a change of antibiotic therapy), increased serum creatinine levels (twofold increase or diagnosis with acute kidney injury that resulted in increased monitoring or a change of antibiotic therapy), diarrhea, or *Clostridium difficile* infection.

CVC-associated AEs included the following: CVC dysfunction (anything, including thrombus or accidental removal, that prevented home antibiotic infusions), infection, and rash around the CVC site. We defined "other" AE as any CVC or medication event that providers felt may have been caused by the OPAT medication or CVC and resulted in a change in therapy.

Statistical Methods

Descriptive analyses were performed by using the Wilcoxon rank test for continuous variables and Pearson's χ^2 test or Fisher's exact test, as appropriate, for categorical variables. To evaluate risk factors for AEs, multivariable generalized estimating equation models were performed separately for any AEs (medication-related AEs and CVC-related AEs) to account for repeated courses of OPAT in some patients. Because of sample size limitations, we included variables that we thought a priori could potentially play a role in the development of AEs. The number of variables was limited to 1 for every 10 AEs to avoid overfitting the model. Antibiotics

were grouped by class because the study was not properly powered to detect differences in the rate of AEs between individual antibiotics. Data were analyzed by using Stata 14.2 (Stata Corp, College Station, TX).

RESULTS

Description of the Cohort

From January 2016 to April 2019, 169 unique patients received 181 courses of OPAT and were followed-up by the division of pediatric ID at our institution (Fig 1, Table 1). Of the 169 unique patients, 10 children had 2 courses of OPAT and 1 child had 3 courses of OPAT. In 28 of the 181 courses, children received >1 parenteral antibiotic simultaneously during their OPAT course. Cohort demographics are outlined in Table 1. Of 181 courses, 70 (38.7%) resulted in at least 1 AE. Among these, 23 (32.8%) were a medication AE, 40 (57.1%) were a CVC AE, and 7 (10.0%) included both a medication and a CVC AE (Fig 1). The most frequent medication AEs were rash, seizure, increased aspartate transaminase or alanine transaminase levels, and neutropenia. The most frequent CVC AEs were CVC malfunction and CVC infection.

Of the 30 courses resulting in a medication AE, a second medication AE occurred in 6 (20.0%) (Fig 1). Among the 47 courses that resulted in a CVC AE, a second CVC AE occurred in 9 (19.1%) (Fig 1). In univariable analyses, having a bone and joint infection or multiple infectious diagnoses, having a longer duration of IV therapy, and not having monitoring laboratory tests drawn as ordered were associated with AEs (Table 1).

Risk Factors for AEs

Multivariable analysis revealed that each additional day of OPAT was independently associated with a 4% increased odds of having any AE (odds ratio [OR]: 1.04; confidence interval [CI]: 1.02–1.07; Table 2) and of having a CVC AE (OR: 1.04; CI: 1.01–1.07; Table 2). Living in an urban area compared with a rural area was independently associated with developing a medication-associated AE, with an OR of 4.51 (CI: 1.60–12.77; Table 2). We found no association between the antibiotic class received and the development of a medication AE. There was no association between the type of CVC and the development of a CVC AE. Because multivariable analysis is limited by the number of patients in each group, we were able to analyze a slightly different group of risk factors for each analysis, as shown in Table 2.

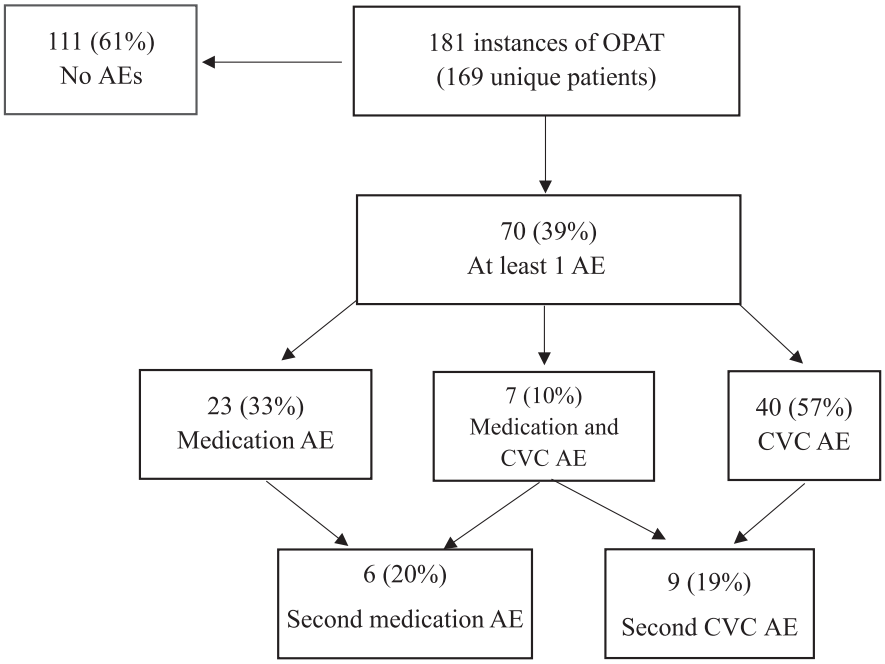

FIGURE 1 Patients who were discharged between January 2016 and April 2019 with OPAT and AEs experienced.

Outcomes After an AE

Of the 181 OPAT courses, OPAT was discontinued in 28 (15.5%), most commonly (27 of 28) because of an OPAT-associated AE. Among these 181 courses, 25 (13.8%) resulted in ED or clinic visits to address AEs and 20 (11.1%) resulted in hospital admission secondary to an AE. In 43 of 181 courses (23.8%), an OPAT-associated AE led to modification of the antibiotic used to complete the OPAT course. Children were more likely to complete the original course of antibiotics if their AE was CVC-associated than medication-associated (33 of 47 [70.2%] vs 12 of 30 [40.0%]). Children were more likely to require additional clinic or hospital visits if they had a CVC AE rather than a medication AE (39 of 47 [82.9%] vs 16 of 30 [53.3%]; Fig 2). Courses of OPAT that were not completed were typically converted to oral antibiotics; in rare cases in which the course was a few days from completion, providers discontinued all antibiotic therapy.

DISCUSSION

In this single-center study of pediatric patients receiving OPAT, we found that nearly 40% of children discharged with OPAT had AEs that required substantial additional health care use, including readmission or a follow-up visit in the clinic or ED. Among these AEs, approximately one-third were medication related and more than half were CVC related.

The proportion of subjects with AEs was slightly higher in our study than in others, likely because we used a broader definition of CVC AE,[5,10,11,13,14,28–30] whereas several previous studies have included only a single concern, such as CVC occlusions, as an AE.[10,13,14,28,29,31] We defined an AE as any event that required extra medical care or resulted in a change in antibiotic therapy, including, but not limited to, all concerns about CVC infections (fever, erythema at the site, oozing at the site) and CVC malfunctions, even if, on presentation to the ED, the malfunction was resolved quickly or

TABLE 1 Demographic and Clinical Characteristics of Children Receiving OPAT

Variable	Total (N = 181)	Any AE (n = 70)[a]	No AE (n = 111)[a]	P
Age, median (IQR), y	6.7 (1.6–13.2)	9.2 (1.0–14.8)	5.3 (2.1–12.7)	.242[a]
Sex, female, *n* (%)	82 (45.3)	32 (45.7)	50 (45.1)	.930[b]
County code, *n* (%)[c]				.523[b]
Rural	74 (40.9)	26 (37.1)	48 (43.2)	N/A
Urban (≥1 000 000 population)	32 (17.7)	15 (21.4)	17 (15.3)	N/A
Suburban (≥250 000 population)	75 (41.4)	29 (41.4)	46 (41.4)	N/A
English speaking, *n* (%)	175 (96.7)	66 (97.1)	106 (96.4)	.803[b]
Laboratory tests drawn as ordered, *n* (%)	136 (75.1)	54 (84.4)	82 (98.8)	.001[b]
No. infectious diagnoses, median (IQR), mean	1 (1–2), 1.36	1 (1–2), 1.5	1 (1–2), 1.27	.046[a]
Diagnosis,[e] *n* (%)				
Bone and joint infection	45 (24.9)	23 (32.9)	22 (19.8)	.048[b]
Skin and soft tissue infection	30 (16.6)	15 (21.4)	15 (13.5)	.163[b]
Central nervous system infection	45 (24.9)	19 (27.1)	26 (23.4)	.573[b]
Bloodstream infection	71 (39.2)	30 (42.9)	41 (36.9)	.427[b]
Intraabdominal infection	4 (2.2)	1 (1.4)	3 (2.7)	1.000[d]
Urinary tract infection	20 (11.1)	6 (8.6)	14 (12.6)	.398[d]
Pulmonary infection	17 (9.4)	5 (7.1)	12 (10.8)	.442[d]
Endovascular infection	6 (3.3)	3 (4.3)	3 (2.8)	.681[d]
Other	8 (4.4)	3 (4.3)	5 (4.5)	1.000[d]
Days of IV antibiotic therapy at home, median (IQR)	12 (8–27)	19.5 (11–34)	10 (7–17)	<.001[a]
Therapy with >1 antibiotic, *n* (%)	28 (15.5)	9 (12.9)	19 (17.1)	.440[b]
Antibiotic allergy, *n* (%)	32 (17.7)	14 (20.0)	18 (16.2)	.516[b]
Antibiotic used, *n* (%)				
Penicillin (includes penicillin, ampicillin, nafcillin, and meropenem)	36 (19.9)	11 (15.71)	25 (22.5)	.264[b]
Cephalosporin (includes ceftriaxone, cefepime, and cefazolin)	86 (47.5)	30 (42.9)	56 (50.5)	.319[b]
Aminoglycoside (includes amikacin, tobramycin, and gentamicin)	4 (2.2)	2 (2.9)	2 (1.8)	.641[b]
Vancomycin	30 (16.6)	12 (17.1)	18 (16.2)	.870[b]
Piperacillin and tazobactam	13 (7.2)	5 (7.1)	8 (7.2)	1.000[d]
Fluoroquinolones (includes ciprofloxacin, levofloxacin, and moxifloxacin)	1 (0.6)	1 (1.4)	0 (0.0)	.387[d]
Clindamycin	1 (0.6)	1 (1.4)	0 (0.0)	.387[d]
Other (includes metronidazole and micafungin)	11 (6.1)	8 (11.4)	3 (2.7)	.024[d]
Type of CVC, *n* (%)				.960[d]
PICC	164 (90.6)	64 (91.4)	100 (90.1)	N/A
Broviac	8 (4.4)	3 (4.3)	5 (4.5)	N/A
Hickman	2 (1.1)	1 (1.4)	1 (0.9)	N/A
Port	7 (3.9)	2 (2.9)	5 (4.5)	N/A
PICC versus all CVCs	164 (90.6)	64 (91.4)	100 (90.1)	.764[b]
No. (%) with >1 AE	14 (7.7)	14 (20.0)	N/A	N/A
Type of AE, *n* (%)				N/A
Medication-related only	23 (12.7)	23 (32.9)	N/A	N/A
CVC-related only	40 (22.1)	40 (57.1)	N/A	N/A
Both	7 (3.9)	7 (10.0)	N/A	N/A

Percentages should be read from top to bottom for each column. IQR, interquartile range; N/A, not applicable; PICC, peripherally inserted central catheter.

[a] Wilcoxon rank test.

[b] Pearson's χ^2 test.

[c] Centers for Disease Control and Prevention. NCHS urban-rural classification scheme for counties. Available at: https://www.cdc.gov/nchs/data_access/urban_rural.htm. Accessed December 11, 2020. Urban defined as large central metropolitan; suburban defined as large fringe metropolitan and medium metropolitan; rural defined as small, micropolitan, noncore.

[d] Fisher's exact test.

[e] Some subjects had >1 diagnosis.

TABLE 2 Multivariable Models for Risk of the Development of Any AE ($n = 70$), CVC-Associated AE ($n = 47$), and Medication-Associated AE ($n = 30$)

Variable	Any AE			CVC-Associated AE			Medication-Associated AE		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Country code[a]									
Rural	Reference	—	—	—	—	—	—	—	—
Suburban	1.37	0.66–2.85	.402	1.03	0.46–2.29	.945	1.40	0.54–3.66	.489
Urban	1.87	0.70–5.00	.209	0.75	0.25–2.27	.607	4.51	1.60–12.77	.005
Days of IV antibiotics at home	1.04	1.02–1.07	.002	1.04	1.01–1.07	.003	—	—	—
No. diagnoses	1.58	0.88–2.83	.128	1.60	0.90–2.83	.110	—	—	—
PICC versus other CVC	1.48	0.31–7.19	.627	1.60	0.33–7.80	.560	—	—	—
Vancomycin versus other antibiotic	0.27	0.08–0.88	.031	—	—	—	—	—	—
β-lactam[b] versus other antibiotic	0.17	0.06–0.50	.001	—	—	—	0.44	0.19–1.04	.060

Variables were limited to 1 per 10 events and were chosen on the basis of relevance (eg, drug versus CVC AE), review of the literature, and review of univariate analysis. PICC, peripherally inserted central catheter; —, not applicable.

[a] https://www.cdc.gov/nchs/data_access/urban_rural.html. Urban = large central metropolitan; suburban = large fringe metropolitan and medium metropolitan; rural = small, micropolitan, noncore.

[b] Includes penicillins, cephalosporins, and piperacillin and tazobactam.

required no intervention. Thus, this study may more accurately reflect the true burden of OPAT on families and the health care system.

We believe that ongoing monitoring of AEs among patients receiving OPAT is essential for patient safety. Awareness of institutional OPAT-associated AE rates and the factors associated with them is important when making clinical decisions about whether it is appropriate to discharge a patient with OPAT. In 2014, Lane et al[32] evaluated physician perception of OPAT-related AEs and found that ID physicians perceived complications to be rare. Many of the providers who initially prescribe OPAT do not provide follow-up care for these patients and thus may underestimate complications. Additionally, without a group dedicated to managing patients receiving OPAT, many AEs are likely never captured. Discharge stewardship by adequately resourced and trained providers who can ensure regular laboratory monitoring and follow-up is essential both to tracking and preventing AEs.[16,26,33]

These data allowed us to begin conversations about OPAT use at our institution among ID providers and led to a request for individual provider-level feedback regarding the number of OPAT discharges ordered. We did not adjudicate appropriateness of OPAT in this retrospective analysis. Appropriateness is difficult to assess retrospectively and should be evaluated in future prospective studies. However, we highlight the risks associated with OPAT so that clinicians can assess the risks and benefits that OPAT offers their patients.

We found that each additional day of OPAT increased the odds of having an AE by 4%. This was the most consistent association with increased risk in our study, highlighting the potential benefits of shortening IV antibiotic courses when feasible. This study emphasizes the need for additional studies to determine which pediatric infections can be effectively treated with oral therapy or short-course IV treatment rather than prolonged IV therapy.

Although we initially hypothesized that patients in rural settings might have less access to home health agencies and therefore would be at higher risk for AEs, we found the opposite to be true. We noted that living in an urban setting was independently associated with having a medication AE. We speculate that socioeconomic factors in urban settings near our medical center, such as poverty, level of parental education and health literacy, number of children in the home, and home health care nurses' comfort with pediatric patients, may be associated with higher AE risk. Patients who seem most at risk for AEs, such as uninsured patients or those who live in areas without home health, are likely seen in clinic for all their follow-up, which may be protective against AEs. It is also possible that providers were less likely to prescribe OPAT for children living in rural settings, that patients in rural settings were less likely to travel to our institution for follow-up, or that proximity to health care settings enabled better recognition of medication AEs in urban settings. Given the small sample size, we were not able to evaluate whether factors such as missed laboratory test draws or appointments were associated with AEs.

Our study had several limitations, including a relatively small sample size, a retrospective nature, and restriction of the cohort to patients managed by the ID service. This means that we were underpowered to identify significant differences in the univariate analysis. Additionally, this study does not capture all the OPAT prescribed at our institution, which may introduce bias. Our findings may not be generalizable to gastrointestinal, oncology, and pulmonology patients receiving OPAT because these patients were not well represented in our cohort and may have different AE rates. Additionally, we do not have a comparator population, such as patients discharged on oral antibiotics or patients discharged with OPAT by other

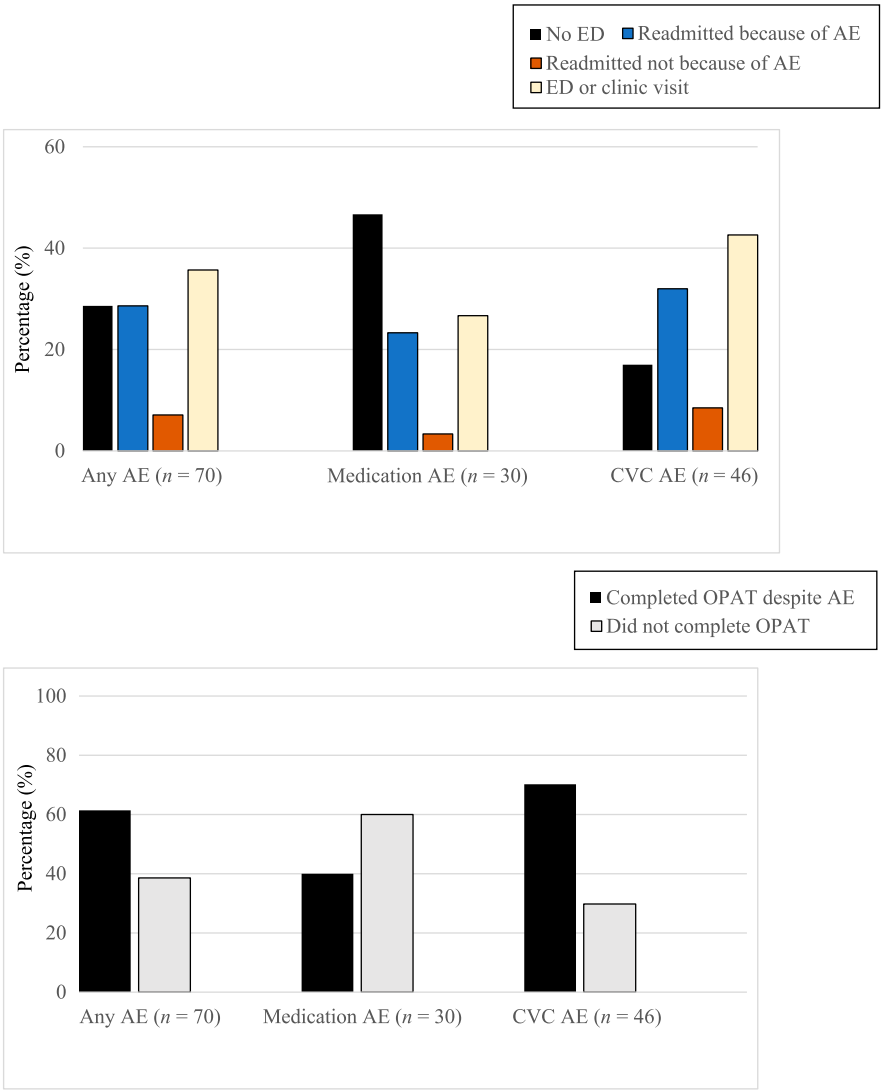

FIGURE 2 Effect of AEs on completion of OPAT courses and additional care required.

services. Because of small sample size, we are not able to break down AEs by home health agency or other factors we think might contribute to some of the differences in AEs observed between the rural and the urban population. It is possible that AEs may have been missed because some patients sought care for AEs at outside institutions. Additionally, we did not collect data about timing of AEs, cost, or patient satisfaction. We did not adjudicate appropriateness of OPAT, which we felt would be difficult to do accurately in a retrospective study. Our findings may not be generalizable to patients with different sociodemographic or clinical characteristics from our cohort.

Despite these limitations, our study reveals that patients receiving OPAT continue to use health care resources heavily, with children either being readmitted or seen in the ED or clinic (related or unrelated to OPAT) in one-third of OPAT courses, a finding that should be considered in a formal cost-effectiveness analysis. This study highlights the need for further pediatric studies that look at cost, effectiveness, and burden on the family of IV antibiotics versus oral antibiotics for a wide variety of diagnoses.[19]

CONCLUSIONS

We observed a high proportion of OPAT-associated AEs and resulting health care use among children. In our center, AEs were significantly associated with duration of IV therapy and urban residence. Institutions should assess their OPAT-associated AEs and expand antibiotic stewardship programs to enable judicious and safe use of OPAT.

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