RESEARCH ARTICLE

Adverse Events in Pediatric Patients Receiving Long-term Oral and Intravenous Antibiotics

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ABSTRACT

BACKGROUND AND OBJECTIVE: Children receiving long-term antibiotic therapy (LTAT) at Children's Hospital Colorado (CHCO) are treated with both oral and intravenous (IV) agents and often experience complications not comprehensively described by the literature. We sought to describe adverse drug events (ADEs) and venous access complications (VACs) in pediatric patients managed with oral and IV antibiotics so as to inform clinical decision-making, drug monitoring, and patient counseling at CHCO.

METHODS: We conducted a retrospective review of children receiving LTAT through the CHCO infectious disease service from 2006 to 2012. Demographic, microbiologic, diagnostic data, ADEs, and VACs were recorded for each patient.

RESULTS: From 2006 to 2012, 521 patients received 1876 courses, accounting for 71 306 days of antimicrobial therapy. A total of 219 patients (42 %) developed an ADE with discontinuation of the offending agent in 65% of courses associated with an ADE. The most common ADEs were neutropenia, rash, and diarrhea. Central lines were placed in 376 patients with 106 (28%) experiencing ≥1 VACs. IV agents were associated with a fourfold increase in the rate of ADEs compared with oral agents, and a fivefold increase when VACs were included.

CONCLUSIONS: Practitioners may make more informed decisions and risk assessments by using descriptive ADE information for specific agents and mode of drug delivery to mitigate risk, thereby improving the quality of care. Patients should be counseled regarding risks of LTAT, including increased risk with IV therapy, and actively monitored for side effects.

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Dr Murphy designed the data collection tool, assisted with chart review/data extraction, carried out the initial analysis, drafted the initial manuscript, and reviewed and critically revised the manuscript; Dr Fenn performed chart review/data extraction, drafted early versions of the manuscript, and reviewed and critically revised the manuscript; Dr Pyle provided statistical analysis and provided critical input; Ms Heizer and Ms Hughes kept data in shadow charts, reviewed data entry for accuracy and completeness, and critically reviewed the manuscript; Dr Child aided in study design, supervised data collection, and critically revised the manuscript; Dr Nomura aided in data analysis and provided critical input; Dr Parker conceptualized the study, coordinated and supervised data collection and analysis, and reviewed and critically revised the manuscript at all stages; and all authors approved the final manuscript as submitted.

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The practice of transitioning patients requiring prolonged intravenous (IV) antibiotics from the inpatient to the outpatient setting, known as outpatient parenteral antibiotic therapy (OPAT), is well studied and demonstrates clear advantages in terms of cost, safety, and outcomes.[1–9] Infectious Diseases Society of America (IDSA) guidelines for OPAT were published in 2004, and were widely applied at many pediatric centers, as many of the benefits, including avoidance of complications and expense of prolonged hospitalization, are generalizable to pediatrics.[10] However, children vary in drug absorption, distribution, pharmacokinetics, immunologic response, and prevalence and type of comorbidities, all of which are likely to contribute to differences in the rates and variety of complications observed in pediatric patients.[11] Current literature supports that 19% to 51% of children experience adverse drug events (ADEs) and 27% to 41% experience venous access complications (VACs) while receiving OPAT.[12–24] Most studies, however, are limited in size, often exclude children with premorbid conditions, evaluate a single clinical diagnosis, and exclude patients treated with oral antibiotics. Because the Children's Hospital Colorado (CHCO) treats patients with complex comorbidities and a wide variety of diagnoses by using both oral and parenteral agents, we use a term intended to encompass both: long-term antimicrobial therapy (LTAT). Our aim with this retrospective cohort evaluation was to comprehensively describe adverse events in our population to inform LTAT clinical decision-making by assessing the safest route, drug and drug class side-effect profiles, the need for invasive monitoring, and patient risk factors for ADEs.

TABLE 1 Characteristics of Study Cohort

Variable	Total Sample, $N = 521$		
	n	%	
Gender			
Male	311	59.7	
Female	210	40.3	
Age, y			
0–5	104	20.0	
6–11	126	24.2	
12–18	211	40.5	
19–23	72	13.8	
>24	8	1.5	
Highest level of care			
Inpatient	383	73.5	
Critical care	124	23.8	
Outpatient	13	2.5	
Emergency department	1	0.2	
Readmissions			
None	419	80	
Once	88	16.9	
>1	39	7.5	
Reason for readmission			
Unrelated to infection	38	7.3	
Due to ADE	26	5	
Related to infection[a]	24	4.6	
Comorbidities			
None	323	62	
≥1	198	38	
Comorbid conditions[b]			
Other[c]	75	14.4	
Scoliosis	53	10.2	
Cardiac anomalies	30	5.8	
Cerebral palsy	27	5.2	
Seizure disorder	25	4.8	
Musculoskeletal defects	24	4.6	
Chronic lung disease	17	3.3	
	Median	Minimum	Maximum
Age, y	10.5	0.01	32
Height, cm	140.4	25.5	195
Wright, kg	33.9	2.37	131

[a] Includes care related to underlying infectious disease process (eg, removal of infected hardware).
[b] Of the 198 patients with comorbidities, many had >1 comorbidity; each comorbid condition is counted separately.
[c] Includes neuropsychiatric disorders (25), hydrocephalus (15), endocrinopathies (11), renal (6), malignancy (6), immunodeficiencies (4), autoimmune disorders (4), pseudotumor cerebri (2), epidermolysis bullosa (1), and factor VIII deficiency (1).

METHODS

Evaluation Setting

To improve care, CHCO Pediatric Infectious Diseases (ID) has followed patients requiring LTAT since 2001. The decision to follow a patient in the LTAT clinic is made by the ID consult service in collaboration with a patient's primary service. All patients cared for in the LTAT clinic have 24-hour access to on-call ID providers. Although there is provider variation in drug choices and the timing of IV to oral transition, treatment monitoring is standardized with patients receiving regular physical and laboratory examinations in accordance with IDSA guidelines.[10] With few exceptions (central nervous system and endovascular infection), patients are generally transitioned from IV to oral therapy early.

Evaluation Design

This retrospective study was approved by CHCO Organization Research Risk and Quality Improvement Review Panel, under the authority of the Colorado Multiple Investigational Review Board. Patients were included only if they were followed in the CHCO LTAT clinic, regardless of comorbid conditions or age (some patients with complex diagnoses continue their care at CHCO past the age of 18). Patients were excluded if they received >5 days of antibiotic therapy before initiating care at CHCO (as records were unreliable), or were managed solely with antiviral or antifungal therapy (too few patients for meaningful evaluation). Because referral areas often lack compatible electronic medical records and some patients are comanaged with distant providers, shadow charts are maintained. Data were extracted (by J.L.M. and N.F.) from shadow charts and CHCO's electronic medical record (Epic Systems Corporation, Verona, WI). A standardized extraction form was built in RedCap (Vanderbilt University, Nashville, TN), and 20% of charts were audited (by H.H. and S.H.) to ensure quality of extraction. Comorbid conditions collected are in Table 1; "other" category included only serious conditions felt to affect LTAT care. Long-term antimicrobial therapy was defined as any length of outpatient IV therapy, and/or ≥2 weeks of oral antibacterial therapy. Data collection started on the day of admission.

Definitions of Adverse Events

A course of therapy is defined as receipt of at least 1 day of therapy (DOT). A DOT is defined as receiving at least 1 dose of an antimicrobial during a 24-hour period.[25] For instance, a patient receiving both vancomycin and ceftriaxone for 3 days will have 1 course of therapy and 3 DOTs ascribed to each vancomycin and ceftriaxone. Some patients developed >1 type of ADE during treatment and, at times, during treatment with >1 antimicrobial. If a patient developed an ADE while receiving >1 antimicrobial, the practitioner's charted determination of the associated antimicrobial was accepted as causing the ADE. If the practitioner could not discern or attributed the event to >1 antimicrobial, the event was ascribed to all concomitant antimicrobial agents. This is distinguished by using the terminology drug-associated ADE (DA-ADE). For example, if a child experiences adverse event X while on clindamycin and ceftriaxone, this is 1 ADE, and 1 DA-ADE each for clindamycin and ceftriaxone, so 2 DA-ADEs; in terms of percentage of courses, X will be in the numerator for both the clindamycin and ceftriaxone courses. Event rates are expressed in 2 manners: DA-ADE per 1000 DOTs as the primary analysis, which takes into account length of therapy, and percentage of DA-ADEs per total courses as a secondary analysis, to convey the proportion of courses associated with an event. The strength of presenting by DA-ADE/1000 DOTs is that one gains a sense of long-term tolerability, while by course gives a sense of tolerability on a course basis. Related readmissions are defined as readmissions related to the indication for LTAT, occurring while receiving LTAT (eg, hardware removal, management of ADE/VACs).

Adverse events were defined as reactions, conditions, or symptoms attributed to LTAT. Abnormal laboratory values were defined as those values used by the LTAT providers to signal concern, adapted from the age-specific values reported in the pediatric literature.[26] Definitions were as follows: renal impairment, increase in serum creatinine resulting in a level 1.5 times baseline, or to a value above the reference range; hepatitis, any rise in transaminases

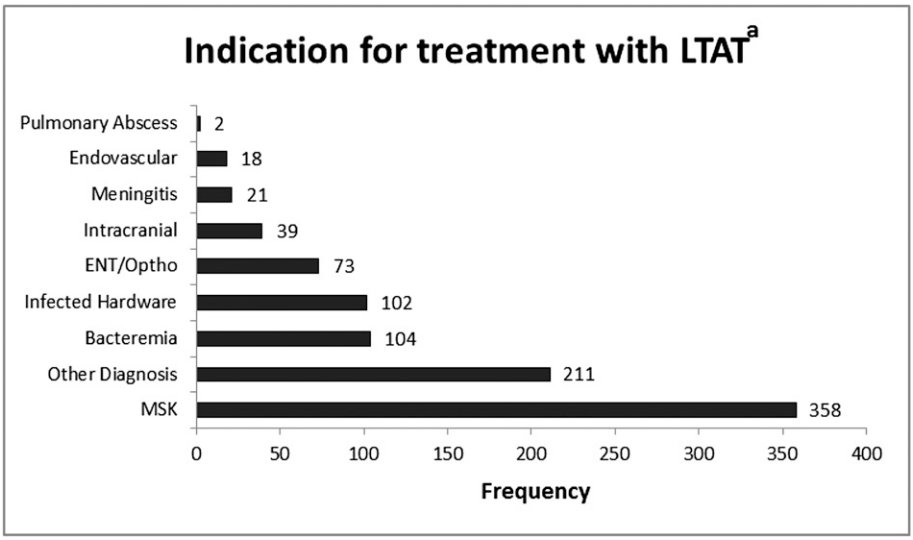

FIGURE 1 Endovascular includes endocarditis (2), Lemierre syndrome (14), and other intravascular, septic thrombus (2); intracranial infection includes brain abscesses (9) and intracranial, subdural, or epidural empyema (30); ENT/Optho (ear, nose and throat/opthalmology) includes Pott puffy tumor (5), other complicated sinusitis (27), intraorbital abscesses (5), mastoiditis (25), and orbital cellulitis (11); MSK (musculoskeletal) infection includes osteomyelitis (212), septic arthritis (80), and pyomyositis (63).[a]Many patients had multiple indications for LTAT, each is counted separately to describe the relative, frequency of diagnoses.

above normal limits resulting in symptoms and/or change in therapy; anemia, a decrease in hematocrit resulting in a value below the reference range; neutropenia, an absolute neutrophil count $<1500/\mu L$; eosinophilia, an absolute eosinophil count $>500/\mu L$, lymphopenia, an absolute lymphocyte count $<1000/\mu L$; thrombocytopenia, a thrombocyte count $<120\,000/\mu L$; *Clostridium difficile* colitis, diarrhea with a laboratory-confirmed diagnosis of *C difficile*; nausea, nausea affecting quality of life and/or ability to retain the agent; diarrhea, diarrhea affecting quality of life not attributable to *C difficile*; rash, any rash that was nonurticarial and was not associated with drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, or erythema multiforme (each collected separately). VACs are defined as line occlusion requiring fibrinolytics, infections, mechanical failure (broken caps/lumens), accidental dislodgement/removal, thrombosis, and severe local skin reactions.

Statistical Analysis

The distribution of continuous variables was assessed; most of these variables were not normally distributed, so nonparametric statistics are reported when possible. Descriptive statistics were produced for both patient-level and antibiotic-level variables. Comparison of ADEs associated with parenteral versus oral therapy was obtained by using generalized estimating equation models. Logistic regression models were used to compare the rates of ADEs and rehospitalizations by drug, drug class, and comorbid conditions.

RESULTS

Description of the Cohort

From 2006 to 2012, 521 patients received LTAT (Table 1). The most common indication for LTAT was musculoskeletal infection (Fig 1). The vast majority of patients were hospitalized, with most admitted to the general wards and 24% admitted to a critical care unit (PICU, NICU, cardiac ICU). Related readmissions occurred in 50 of 521 patients. Of those, 26 (52%, or 4.9% of total) of 50 were readmitted due to an adverse event.

ADEs

The cohort received 1876 antimicrobial courses for a total of 71 306 DOTs with 219 (42%) of 521 patients experiencing ≥1 ADE. Of the 1876 courses, 352 were associated with an ADE (27.1%) accounting for 508 DA-ADEs, with a rate of 7.1 per 1000 DOTs. Of the 352 courses with an ADE, 229 (65.1%, or 12.2% of total courses) were significant enough to prompt discontinuation of the offending agent. The most common ADEs (DA-ADE/508) were neutropenia, rash, and diarrhea (Table 2). Of the 81 patients who experienced neutropenia, 16.6% had an absolute neutrophil count (ANC) of 1000 to 1499, 41.7% had an ANC 500 to 999, 31% had an ANC 200 to 499, and 10.7% had an ANC ≤200. In terms of DA-ADE per 1000 DOTs (the primary outcome), high rates of neutropenia were noted with ampicillin, pipericillin/tazobactam, nafcillin, daptomycin, and ceftriaxone, whereas trimethoprim/sulfamethoxazole demonstrated a low event rate (Table 3). Diarrhea was the third most common ADE; including 5 episodes (6 DA-ADEs) of

TABLE 2 Description of ADEs for All Agents

Variable		All Agents	
Courses, total		1876	
DOTs, total		71 306	
Courses with ≥1 ADE, *n* (%)		352 (27.1)	
DA-ADE, *n*[a]		508	
Rate of DA-ADE/1000 DOTs		7.1	
Patients with ≥1 ADE, *n (%)*		219 (42)	
ADEs	Patients, *n*[b]	DA-ADE, *n*[a] (%)[c]	Rate[d]
Neutropenia	81	120 (6.4)	1.7
Rash	60	85 (4.5)	1.2
Diarrhea	47	61 (3.3)	0.9
Eosinophilia	29	42 (2.2)	0.6
Nausea	36	42 (2.2)	0.6
Anemia	21	36 (1.9)	0.5
Drug fever	20	26 (1.4)	0.4
Hives	15	21 (1.1)	0.3
Interstitial nephritis	10	12 (0.6)	0.2
Renal impairment	11	12 (0.6)	0.2
Thrombocytopenia	8	12 (0.6)	0.2
Candidiasis	6	8 (0.4)	0.1
Hepatitis	5	7 (0.4)	0.1
C difficile	5	6 (0.3)	0.1
Lymphopenia	4	5 (0.3)	0.1
DRESS	2	4 (0.2)	0.1
Peripheral neuropathy	3	3 (0.2)	0.04
Tendonitis	2	2 (0.1)	0.03
Elevated CPK	1	1 (0.1)	0.01
Erythema multiforme	1	1 (0.1)	0.01
Esophagitis	1	1 (0.1)	0.01
Stevens-Johnson	1	1 (0.1)	0.01

CPK, creatine phosphokinase.
[a] Number of events attributed to the individual antimicrobial agent such that an ADE ascribed to >1 agent will be represented more than once (ascribed as DA-ADE).
[b] Patients with >1 DA-ADE will be represented more than once.
[c] Percentage of courses with a DA-ADE.
[d] Rate of DA-ADE per 1000 DOTs.

C difficile colitis (not toxic megacolon), only 1 of which was associated with clindamycin. High rates of diarrhea were noted with ampicillin-sulbactam, ceftazidime, and pipericillin/tazobactam. Less common and more severe ADEs included 2 cases of peripheral neuropathy, 1 associated with metronidazole and the other in a patient receiving both metronidazole and linezolid; 2 cases of tendonitis associated with levofloxacin; 1 episode of Stevens-Johnson syndrome associated with trimethoprim/sulfamethoxazole; and 2 cases of DRESS, 1 associated with nafcillin and the other in a patient receiving both vancomycin and metronidazole. For specific agent, drug classes, and ADE data, see Tables 2, 3, and Supplemental Tables 6 to 13.

Evaluation of ADE Risk in Patients With Comorbid Conditions

A subanalysis was performed to assess risk associated with comorbidities. Of the 521 patients, 323 patients (62%) were previously healthy and 198 (38%) had ≥1 comorbid conditions (Table 1). Patients without comorbidities received on average 112 DOTs per patient, accounting for 36 227 DOTs, whereas patients with comorbidities received on average 177 DOTs per patient, accounting for 35 076 DOTs. Populations with and without comorbidities demonstrated similar DA-ADEs by course percentage (10% vs 11%) and by DOT (5.2 vs 5.1, respectively), and similar discontinuation events (11.7% vs 13.0%, and 3.7 vs 2.7, respectively).

Comparative Safety of IV Versus Oral Routes of Administration

Of the 1876 courses, 501 (26.7%) were delivered orally, 1114 (59.4%) were delivered IV, and 261 (13.9%) were delivered IV with transition to the oral equivalent at an undeterminable time. In the primary analysis evaluating DA-ADEs per 1000 DOTs, oral route was associated with fewer ADEs (Table 4). Oral agents were associated with 129 DA-ADEs stemming from 31 162 DOTs (4.1 ADEs per 1000 DOTs), whereas IV agents were associated with 294 DA-ADEs stemming from 19 503 DOTs (15.1 ADEs per 1000 DOTs, $P < .0001$). Patients receiving the IV and oral formulation (without clear date of transition) experienced 85 DA-ADEs stemming from 20 641 DOTs, a rate of 4.1 per 1000 DOTs. IV agents demonstrated higher rates of DA-ADEs per 1000 DOTs compared with oral agents, with a statistically significant difference in the rates of neutropenia, rash, diarrhea, eosinophilia, anemia, drug fever, renal impairment, and thrombocytopenia (Table 4). With the exception of the oxazolidones, IV agents within each drug class demonstrated higher rates of DA-ADEs compared with oral agents. Although analysis of DA-ADE per 1000 DOTs demonstrates more events in the IV group, the secondary analysis by percentage of courses with an ADE does not, with 19.8% of oral and 18.0% of IV courses attributed ≥1 DA-ADEs. There is a similar discordance when analyzing the need to discontinue an antimicrobial due to an ADE. When analyzed by DOT, there is a marked difference, with 1.8 oral versus 7.4 discontinuations per 1000 DOTs, whereas per course 12.9% of oral and 11.8% of IV were discontinued.

Central lines were placed in 376 (72.2%) of the 521 patients. Peripherally inserted catheters (PICCs) were the most used device (341/376, 90.7%). Of the 376 patients with central lines, 28% developed a total of 126 different VACs. The most common VACs were occlusion requiring fibrinolytics, line malfunctions, and accidental removal; a total of 41 lines were replaced, most commonly due to malfunctions and accidental removal, and 6 infections occurred (Table 5). If one includes the 126 VACs associated with drug delivery, the rate of adverse events associated with IV agents increases to 21.5 per 1000 DOTs, 5 times the rate observed with oral agents (4.1); and, as a percentage of courses, increase from 18.0% to 29.4% (compared with 19.8% of oral).

DISCUSSION

This retrospective evaluation is intended to inform clinical decision-making and LTAT choices for children cared for at CHCO. In achieving these goals, these data expand our current knowledge of LTAT for pediatric patients. Our data are reported in 2 manners: DA-ADE per 1000 DOTs (primary analysis), and DA-ADE per courses (secondary analysis); each includes inherent biases to be considered. Evaluation by DOT provides a view of long-term tolerability, in that agents with low adverse events–ADEs per 1000 DOTs are able to accumulate many days of use across our population, yet this may bias against IV agents, in that IV therapy is given to sicker patients, or because automatic transitions to oral may occur after the highest risk period for developing an adverse event.[24] Thus, a secondary analysis by percentage of courses is presented, although it may bias against oral agents, in that early conversion to oral agents (a goal of our clinic) results in shorter courses of IV therapy and thus decreases the opportunity to capture adverse events that may occur with prolonged IV therapy. Presenting both analyses is a strength of our study and allows our clinic to better assess risks and counsel patients in the following 4 manners.

First, we will leverage these data to provide improved anticipatory guidance for CHCO LTAT patients. Families may be counseled that the overall risk of experiencing a side effect is 42% for patients, 27% per antibiotic course, and 7 events for every 1000 DOTs. Of those with an ADE, these events lead to a change in therapy in 65%, giving a range in the literature of 31% to 65%.[24] The use of a central line carries additional risk of a VAC in 28% of patients with a central line, with need to replace the line in 10.9%.[13–15,18,20–22] The most common ADEs include neutropenia, rash, and diarrhea (consistent with other studies[21,23,24]). Although our definition of neutropenia was nonsevere (ANC <1500, at a level in which our clinic staff consider monitoring more closely), of the 84 patients who experienced neutropenia, 42% had an ANC in a range in which most practitioners would change the antimicrobial (200–499), and 11% had an ANC of <200, where concern for opportunistic infection is greater.

Second, children with preexisting conditions are not at higher risk for ADEs. We hypothesized that these children were at increased risk of ADEs due to their underlying condition, the likelihood of being treated with multiple agents, and longer via IV. We confirmed that they were treated

TABLE 3 Rate and Description of DA-ADEs in the 10 Most Used Antimicrobials at CHCO in Terms of DOTs and Courses (Starts)

Variable	Antibiotic												Other[a]		All Agents	
	Vanc		Clnd		Cfaz		Ctrx		Cphx		Levo		Rif		Mtro		Ctax		Nafc		TmpS		Cipro					
Courses, total	335		291		203		163		130		119		116		82		67		55		37		24		254		1876	
DOT, total	6331		17 786		3002		3651		8241		8008		5762		3120		447		1204		2930		2648		8176		71 306	
Courses with ≥1 ADE, *n* (%)	66 (19.7)		57 (19.6)		15 (7.4)		36 (22.1)		29 (22.3)		26 (16.4)		19 (16.4)		21 (25.6)		9 (13.4)		17 (30.9)		8 (21.6)		4 (16.7)		45 (17.7)		352 (27.1)	
DA-ADE, *n*[a]	97		77		23		50		38		40		27		37		18		22		13		5		61		508	
Rate of DA-ADE/1000 DOTs	15.3		4.3		7.7		13.7		4.6		5.0		4.7		11.9		40.3		18.3		4.4		1.9		7.5		7.1	
ADEs	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]	*n*[b] (%)[c]	Rate[d]
Neutropenia	18 (5.4)	3	10 (3.4)	1	7 (4.3)	2	22 (13.5)	6	14 (10.8)	2	9 (7.6)	1.1	5 (4.3)	0.9	7 (8.5)	2	2 (3)	4	9 (16.4)	7	3 (8.1)	1	—	—	14 (5.5)	2	120 (6.4)	1.7
Rash	18 (5.4)	2.8	22 (7.6)	1.2	3 (1.8)	1.0	10 (6.1)	2.7	4 (3.1)	0.5	6 (5)	0.7	1 (0.9)	0.2	4 (4.9)	1.3	2 (3)	4.5	5 (9.1)	4.2	2 (5.4)	0.7	1 (4.2)	0.4	7 (2.8)	0.9	85 (4.5)	1.2
Diarrhea	7 (2.1)	1.1	16 (5.5)	0.9	2 (1.2)	0.7	1 (0.6)	0.3	9 (6.9)	1.1	6 (5)	0.7	3 (2.6)	0.5	3 (3.7)	1.0	2 (3)	4.5	1 (1.8)	0.8	1 (2.7)	0.3	1 (4.2)	0.4	9 (3.5)	1.1	61 (3.3)	0.9
Eosinophilia	7 (2.1)	1.1	8 (2.7)	0.4	1 (0.6)	0.3	4 (2.5)	1.1	3 (2.3)	0.4	3 (2.5)	0.4	1 (0.9)	0.2	2 (2.4)	0.6	4 (6)	8.9	1 (1.8)	0.8	—	—	—	—	8 (3.1)	1.0	42 (2.2)	0.6
Nausea	5 (1.5)	0.8	6 (2.1)	0.3	—	—	2 (1.2)	0.5	1 (0.8)	0.1	5 (4.2)	0.6	8 (6.9)	1.4	8 (9.8)	2.6	—	—	—	—	4 (10.8)	1.4	2 (8.3)	0.8	1 (0.4)	0.1	42 (2.2)	0.6
Anemia	10 (3)	1.6	2 (0.7)	0.1	2 (1.2)	0.7	3 (1.8)	0.8	—	—	3 (2.5)	0.4	4 (3.4)	0.7	3 (3.7)	1.0	2 (3)	4.5	—	—	1 (2.7)	0.3	—	—	6 (2.4)	0.7	36 (1.9)	0.5
Drug fever	9 (2.7)	1.4	—	—	1 (0.6)	0.3	3 (1.8)	0.8	—	—	—	—	1 (0.9)	0.2	2 (2.4)	0.6	2 (3)	4.5	2 (3.6)	1.7	—	—	—	—	6 (2.4)	0.7	26 (1.4)	0.4
Hives	5 (1.5)	0.8	6 (2.1)	0.3	2 (1.2)	0.7	—	—	—	—	3 (2.5)	0.4	—	—	1 (1.2)	0.3	—	—	1 (1.8)	0.8	1 (2.7)	0.3	1 (4.2)	0.4	1 (0.4)	0.1	21 (1.1)	0.3
Interstitial nephritis	2 (0.6)	0.3	1 (0.3)	0.1	1 (0.6)	0.3	3 (1.8)	0.8	2 (1.5)	0.2	1 (0.8)	0.1	—	—	—	—	1 (1.5)	2.2	1 (1.8)	0.8	—	—	—	—	—	—	12 (0.6)	0.2
Renal impairment	10 (3)	—	—	—	—	—	—	—	1 (0.8)	0.1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1 (0.4)	0.1	12 (0.6)	0.2
Thrombocytopenia	2 (0.6)	0.3	1 (0.3)	0.1	1 (0.6)	0.3	—	—	—	—	1 (0.8)	0.1	1 (0.9)	0.2	1 (1.2)	0.3	1 (1.5)	2.2	1 (1.8)	0.8	—	—	—	—	3 (1.2)	0.4	12 (0.6)	0.2
Candidiasis	1 (0.3)	0.2	1 (0.3)	0.1	—	—	1 (0.6)	0.3	2 (1.5)	0.2	1 (0.8)	0.1	1 (0.9)	0.2	1 (1.2)	0.3	—	—	—	—	—	—	—	—	—	—	8 (0.4)	0.1
Hepatitis	2 (0.6)	0.3	1 (0.3)	0.1	1 (0.6)	0.3	—	—	1 (0.8)	0.1	—	—	—	—	1 (1.2)	0.3	1 (1.5)	2.2	—	—	—	—	—	—	—	—	7 (0.4)	0.1
C difficile	—	—	1 (0.3)	0.1	1 (0.6)	0.3	—	—	1 (0.8)	0.1	—	—	2 (1.7)	0.3	—	—	—	—	—	—	—	—	—	—	1 (0.4)	0.1	6 (0.3)	0.1

Amp, ampicillin; AmpS, ampicillin/sulbactam; AmxC, amoxicillin/clavulanic acid; Cfaz, cefazolin; Cipro, ciprofloxacin; Clnd, clindamycin; Cphx, cephalexin; Ctax, cefotaxime; Ctaz, ceftazidime; Ctrx, ceftriaxone; Doxy, doxycycline; Gent, gentamycin; Levo, levofloxacin; Mero, meropenem; Mtro, metronidazole; Nafc, nafcillin; Rif, rifampin; TmpS, trimethoprim/sulfamethoxazole; Vanc, vancomycin; —, event rate of zero.

[a] Includes all remaining antibiotics used by CHCO, statistics for each antimicrobial agent included in "Other" can be found in Supplemental Tables 6 to 9.

[b] Number of DA-ADEs (ADEs ascribed to >1 agent will be represented more than once).

[c] Percentage of courses with a DA-ADE.

[d] Rate of DA-ADE per 1000 DOTs.

TABLE 4 Comparison of ADEs by Route of Drug Delivery

Variable	Route of Administration						P[b]
	Oral		Parenteral		IV → PO[a]		
Courses, total	501		1114		261		
DOTs, total	31 162		19 503		20 641		
Courses with ≥1 ADE, *n* (%)	99 (19.8)		201 (18)		52 (19.9)		
DA-ADE, *n*[c]	129		294		85		
Rate of DA-ADE/1000 DOTs	4.1		15.1		4.1		<.0001
Courses stopped due to ADE, *n* (%)	56 (11.8)		144 (12.9)		29 (11.1)		
Rate of discontinuation/1000 DOTs	1.8		7.4		1.4		
ADEs	*n*[c] (%)[d]	Rate[e]	*n*[c] (%)[d]	Rate[e]	*n*[c] (%)[d]	Rate[e]	
Neutropenia	30 (6)	1.0	76 (6.8)	3.9	14 (5.4)	0.7	<.0001
Rash	22 (4.4)	0.7	50 (4.5)	2.6	13 (5)	0.6	<.0001
Diarrhea	18 (3.6)	0.6	28 (2.5)	1.4	15 (5.7)	0.7	.025
Eosinophilia	10 (2)	0.3	27 (2.4)	1.4	5 (1.9)	0.2	.0006
Nausea	17 (3.4)	0.5	10 (0.9)	0.5	15 (5.7)	0.7	NS
Anemia	7 (1.4)	0.2	23 (2.1)	1.2	6 (2.3)	0.3	.0015
Drug fever	3 (0.6)	0.1	22 (2)	1.1	1 (0.4)	0.0	<.0001
Hives	8 (1.6)	0.3	11 (1)	0.6	2 (0.8)	0.1	NS
Interstitial nephritis	3 (0.6)	0.1	9 (0.8)	0.5	—	—	NS
Renal impairment	1 (0.2)	0.03	11 (1)	0.6	—	—	.0045
Thrombocytopenia	1 (0.2)	0.03	9 (0.8)	0.5	2 (0.8)	0.1	.0153
Candidiasis	2 (0.4)	0.1	3 (0.3)	0.2	3 (1.1)	0.1	NS
Hepatitis	1 (0.2)	0.03	4 (0.4)	0.2	2 (0.8)	0.1	NS
C difficile	3 (0.6)	0.1	3 (0.3)	0.2	—	—	NS
Lymphopenia	—	—	4 (0.4)	0.2	1 (0.4)	0.0	—
DRESS	1 (0.2)	0.03	2 (0.2)	0.1	1 (0.4)	0.0	NS
Peripheral neuropathy	1 (0.2)	0.03	—	—	2 (0.8)	0.1	—
Tendonitis	—	—	1 (0.1)	0.1	1 (0.4)	0.0	—
Elevated CPK	—	—	1 (0.1)	0.1	—	—	—
Erythema multiforme	—	—	—	—	1 (0.4)	0.0	—
Esophagitis	—	—	—	—	1 (0.4)	0.0	—
Stevens-Johnson	1 (0.2)	0.03	—	—	—	—	—

A total of 219 patients experienced ADEs, with many patients experiencing >1 type of ADE. NS, no statistically significant difference was identified; —, event rate of zero events and too few events to be statistically analyzed (for *P* value).

[a] IV/oral represents patients treated with IV agents but transitioned to the oral equivalent during the course of treatment at a time that could not be determined accurately.

[b] *P* value comparing rate of DA-ADE for oral versus IV therapies.

[c] Number of events attributed to the individual antimicrobial agent such that an ADE ascribed to >1 agent is represented more than once.

[d] Percentage of courses with a DA-ADE.

[e] Rate of DA-ADE per 1000 DOTs.

longer (177 DOTs/patient with comorbidities versus 112 DOTs/patient without), yet they experienced similar rates of adverse events at every level of analysis. Overall, families of children with comorbidities may be counseled similarly to families of children without comorbid conditions, with the caveat that our evaluation is limited: ADEs may be driven by factors not extracted, and our detail on comorbid conditions was limited. Thus, more targeted studies on LTAT in populations with well-defined comorbidities are warranted.[27]

Third, early transition to oral when feasible may be desirable, as both DA-ADE and VAC events were greater in the IV group, at least in terms of DA-ADEs per 1000 DOTs. For example, IV clindamycin is associated with a 10-fold difference in the rate of DA-ADEs per 1000 DOTs compared with oral clindamycin (22.7 vs 2.9, $P < .0001$). Given equivalent bioavailability and 1:1 dosing, the oral formulation should be strongly considered in place of IV clindamycin. Although not equally as bioavailable, similar arguments may be made for transitioning from cefazolin to cephalexin and ampicillin-sulbactam to amoxicillin-clavulanate, as the oral agents have lower rates of ADEs (Supplemental Tables 6 to 9). These differences are not as apparent at the course level, consistent with previous publications,[23] but taken together with VAC risk, they support transitions to oral when appropriate clinical criteria are reached.

Finally, our evaluation supports that both clinical and laboratory monitoring are necessary for children receiving LTAT, although we did not specifically assess the need for monitoring or compare timing for monitoring. The IDSA guidelines suggest laboratory evaluation weekly for patients on IV therapy, our data do not refute this.[10] Combining conclusions from our data demonstrating lower rates of ADEs in patients receiving oral antibiotics and data from others on the timing of developing ADEs,[24] we changed our monitoring of patients receiving oral antibiotics to weekly for the first 3 to 4 weeks and every other week thereafter (excluding linezolid). Additionally, we do not monitor patients with comorbidities any differently.

The limitations of our evaluation are worth consideration. Because the transition date for oral to IV for agents with both formulations could not be determined, we created a separate IV-oral group, disproportionately affecting data for these agents (62 patients, Table 4 and Supplemental Tables 10 to 13). Second, ADEs were attributed to a specific antimicrobial or antimicrobial agent by ID specialists, and an ADE may have been ascribed to >1 agent as described in the methods; as there is no manner to prove causation, we did not endeavor to second-guess these decisions. Third, although our practice is standardized, we did not assess compliance of laboratory

TABLE 5 Description of VACs and Usage

Description of Drug Delivery	Patients, $n = 521$	%, Patients
Central venous access	376	72.2
No central venous access	145	27.8
Variable	Patients, $n = 376$	%, lines
PICC	341	90.7
Broviac	26	6.9
Broviac and PICC[a]	7	1.9
Unknown	2	0.5
Line replacement		
None	335	89.1
Once	36	9.6
≥2 times	5	1.3
Reason for replacement		
Line malfunction	17	4.5
Accidental removal	12	3.2
Line infection	3	0.8
Local skin reaction	3	0.8
Thrombus	2	0.5
Unknown	2	0.5
Duration of use	1	0.3
Culture (+) at time of placement	1	0.3
VACs		
None	270	71.8
1	87	23.1
≥2	19	5.1
Description of VACs	Events, $n = 126$	%, events
Required fibrinolytics >1 time	48	38.1
Required fibrinolytics once	37	29.4
Malfunction	17	13.5
Accidental removal	12	9.5
Line infection	6	4.8
Local skin reaction	4	3.2
Thrombus	2	1.6

[a] Seven patients had their Broviac replaced by a PICC.

monitoring, and oversampling in the IV group is a possibility. Fourth, unfortunately we did not extract the time to first adverse event in our evaluation, nor did we assess for the impact of polytherapy. Fifth, our study does not address the comparative efficacy of IV versus oral therapy, and some may argue that a better outcome may outweigh the increased risk of adverse events; however, the literature on acute musculoskeletal infection, a large proportion of CHCO LTAT patients, supports equal clinical efficacy with early transition to oral when clinical criteria are met.[28–32] Last, our analysis included all events for patients, including during their inpatient stay, and after discharge to remote areas via our shadow chart system; this renders the data less comparable, but perhaps more complete, as compared with other studies assessing outpatient therapy alone.

CONCLUSIONS

Pediatric outpatient LTAT is common practice at CHCO, but carries notable risks, particularly for those receiving IV therapy. Practitioners may make more informed decisions and risk assessments by using this descriptive adverse event information for specific agents and mode of drug delivery, and thus may be able to mitigate risk, or at least provide improved anticipatory guidance, thereby improving the quality of care. This evaluation reflects LTAT as practiced at CHCO, and will change our practice accordingly, but it may not be applicable to all populations/centers. Pediatric-specific LTAT guidelines addressing the IV to oral transition and laboratory monitoring for both IV and oral agents are warranted.

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