Adverse Events in Pediatric Patients Receiving Long-Term Outpatient Antimicrobials

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Background. Although long treatment courses of outpatient antimicrobials are often used in pediatric patients, few data exist regarding the frequency of adverse events (AEs) associated with these medications.

Methods. We performed a retrospective cohort study of all patients seen in the Infectious Diseases clinic at a tertiary referral children's hospital from August 1, 2009 to August 1, 2011. We included patients who received ≥ 14 days of oral or intravenous antibiotic, antiviral, or antifungal medications. Patients receiving only prophylactic medications or human immunodeficiency virus treatment were excluded.

Results. Three hundred thirty-five subjects met inclusion criteria, with a median age of 7.4 years at start of therapy. The cohort was predominantly male (60%), white (54%), and previously healthy (59%). A majority (88.4%) of subjects were treated for bacterial infections. β -Lactam agents were the most commonly used antimicrobial class (210 subjects; 62.7%), followed by clindamycin (86; 25.7%), rifampin (76; 22.7%), and vancomycin (62; 18.5%). Overall, 107 (31.9%) subjects experienced 151 distinct AEs. The most common individual AE noted was diarrhea (44; 29.1% of all AEs). Serious AEs developed in 42 (12.5%) subjects, including allergic reactions (15; 11.3% of all AEs), venous catheter-related complications (14; 13.0% of those with catheters), neutropenia (9; 3.0%), renal insufficiency (7; 2.5%), and hepatotoxicity (3; 1.1%). Rates of AEs were similar between those on oral and intravenous antimicrobials.

Conclusions. In our study population, patients on prolonged oral or intravenous outpatient antimicrobials experienced AEs frequently. These findings support the need for close monitoring of pediatric patients on prolonged antimicrobial therapy and vigilance for unwanted effects of these medications.

Key words. adverse events; antimicrobial stewardship; antimicrobials; outpatient; pediatrics

BACKGROUND

Many serious pediatric infections are initially evaluated and diagnosed during an acute hospitalization, with directed antimicrobial therapy begun in the inpatient setting. Because adverse events (AEs) may be associated with prolonged hospitalizations (such as the psychologic effects of hospitalization on children, increased risk for nosocomial infections, or the expense of inpatient care), prolonged antimicrobial courses are often completed in the outpatient setting [1]. Although most severe infections in pediatric patients were historically managed with parenteral antimicrobials, prolonged oral treatment is increasingly used, because studies have shown both safety and efficacy in diseases such as osteomyelitis [2].

Despite the frequency of prolonged outpatient antimicrobial therapy, there remains a paucity of data evaluating

the safety of, and appropriate monitoring for, long-term intravenous and oral antimicrobial treatment in the pediatric population [3]. Knowing the rate of overall AEs, frequency of specific AEs, and whether certain antimicrobial classes are associated with specific AEs would aid clinicians in monitoring children on long-term antimicrobials and would guide follow-up scheduling and choice of monitoring studies. Guidelines exist for management and monitoring of outpatient parenteral antimicrobials in adult patients [3], but pediatric practice is currently mainly driven by opinion and personal experience.

In previous studies, the safety of prolonged intravenous therapy [2, 4–6] or prolonged antimicrobials in specific infectious processes [7, 8] were evaluated; but no studies to date have examined long-term oral antimicrobial therapy in children to assess AEs. We aimed to characterize the

associated rate and impact of AEs in children treated with prolonged outpatient oral or intravenous antimicrobial therapy at a single, academic Pediatric Infectious Diseases clinic over a 2-year period.

METHODS

Design and Data Source

We conducted a retrospective cohort study of all children seen in the Infectious Diseases clinic at Seattle Children's Hospital (SCH) between August 1, 2009 and August 1, 2011. Seattle Children's Hospital is a tertiary care pediatric hospital with a broad geographic referral base; the outpatient Infectious Diseases clinic typically occurs 1–2 times per week and is staffed by physicians, nurse practitioners, and learners including medical students, pediatric residents, and pediatric infectious diseases fellows. A custom electronic data query identified all patients who visited the clinic during the study period. Patient charts were reviewed using the computerized medical record system (CIS, Cerner), which was used continuously during the study period. Two authors performed chart reviews (S. C. O., M. P. K.), and data were collected using a standardized electronic chart abstraction tool. We included subjects who received ≥ 14 days of oral or intravenous antibiotic, antiviral, or antifungal medications. We excluded subjects whose medication was given for prophylactic purposes only (eg, longstanding trimethoprim-sulfamethoxazole for *Pneumocystis carinii* prophylaxis in a heart transplantation patient), for treatment of human immunodeficiency virus, or if the infection was managed at other hospitals or remote clinics (because of lack of follow-up data in the SCH electronic medical record).

Antimicrobial Exposures

We recorded all systemic antimicrobial medications administered during the treatment period and recorded start and stop dates for each medication administered. When a medication was stopped, the reason for discontinuation was recorded. The infectious diseases practitioners make medication changes during clinic visits; we also recorded when these were made by telephone. Because patients are not routinely monitored in the clinic after discontinuation of antimicrobial therapy, subjects' time in the cohort was censored at the end of their antimicrobial therapy.

Outcomes

We used predefined AE categories. Adverse events based on clinical evaluation (eg, rash or diarrhea) were collected from clinical notes, and the date of events were recorded. Laboratory outcomes of interest and their dates were recorded; all laboratory values occurring during antimicrobial therapy were captured, whether ordered by the infectious diseases physicians or other practitioners. Routine

practice in the Infectious Diseases clinic is to monitor complete blood count, creatinine, and liver function tests for most patients on prolonged antimicrobials weekly. Most subjects (303; 90.5%) received laboratory monitoring. We defined neutropenia as an absolute neutrophil count < 500 cells/mL but also evaluated a cutoff of < 1000 cells/mL as a secondary analysis. Renal insufficiency was defined as a new serum creatinine > 1.0 mg/dL. This value was chosen because the majority of children have a creatinine < 1.0 mg/dL, and often < 0.5 mg/dL, and thus a level > 1.0 mg/dL will typically indicate some degree of renal impairment. Hepatotoxicity was defined as alanine aminotransferase > 200 IU/L [9]. All laboratory results obtained at SCH were available in the subjects' computerized records. Results obtained at outside facilities were retrieved from laboratory reports scanned into the SCH medical record when available.

We only included laboratory AEs (neutropenia, hepatotoxicity, and acute renal insufficiency) that developed after antimicrobial exposure. For neutropenia, we excluded all subjects with preexisting hematologic, oncologic, or transplantation histories. For acute renal insufficiency, we excluded all subjects with preexisting renal disease. We further defined neutropenia, acute renal insufficiency, hepatotoxicity, catheter-related events, provider-defined allergic reactions, and medication interactions collectively as serious AEs (to contrast them with milder AE such as rash or diarrhea).

Covariates

We collected demographic data including age, gender, race, and past medical history prior to infection onset as potential confounders. We grouped past medical history by organ system, such that past medical history for a subject with surgically repaired scoliosis would be categorized as musculoskeletal, for a subject with cystic fibrosis as pulmonary, etc. The type of infection treated was categorized according to a predefined list of common infections expected to be treated in the outpatient Infectious Diseases clinic (such as osteomyelitis, endocarditis, intracranial infection or meningitis, etc) or listed as "other."

Statistical Analysis

Descriptive demographic and antimicrobial exposure data were reported using proportion, mean, median, and interquartile range (IQR). Associations between antimicrobial class or route and the outcomes of interest were evaluated using the log-rank test. All analyses were performed with STATA version 12 (STATA Corp, College Station, TX). We considered a 2-tailed P value $< .05$ to be significant. This study was approved by the SCH institutional review board.

Table 1. Baseline Characteristics of 335 Included Subjects

Characteristic	N (%) or median (interquartile range)
Age	7.4 (2.3–13.3) years
Male gender	201 (60.0%)
Race/Ethnicity	
Caucasian	180 (53.7%)
Other	32 (9.6%)
African American	24 (7.2%)
Latino	20 (6.0%)
Asian/South Asian	20 (6.0%)
Mixed	8 (2.4%)
Native/Alaskan	7 (2.1%)
Missing	44 (13.1%)
Past Medical History	
None	196 (58.5%)
Musculoskeletal	34 (10.2%)
Pulmonary	26 (7.8%)
Cardiovascular	22 (6.6%)
Neurologic	19 (5.7%)
Gastrointestinal	19 (5.7%)
Oncologic	15 (4.5%)
Hematologic	7 (2.1%)
Immunologic	7 (2.1%)
Renal	3 (0.9%)
Hepatic	0 (0%)
Other	41 (12.2%)

RESULTS

Demographics

Of the 938 total individuals seen in the Pediatric Infectious Diseases clinic during the study period, 335 (35.7%) were managed with prolonged outpatient antimicrobial therapy and met inclusion criteria (Table 1). Most subjects (281; 83.9%) were hospitalized at least once for management of the infectious illness prior to being followed in the outpatient clinic, with 35 (10.4%) requiring more than 1 hospitalization. Likewise, most subjects (277; 82.7%) had been seen by the inpatient consultation service before their first outpatient clinic visit. Subjects had a median of 2 follow-up visits in the outpatient clinic (IQR, 1–3; range, 1–25 visits). The median duration of follow-up was 45 days (IQR, 30–99), with fewer than 5% of subjects followed more than 1 year.

Infections

Infections of the musculoskeletal system predominated, with septic arthritis, acute osteomyelitis, and chronic osteomyelitis being the three most common infections managed (Tables 2 and 3). The majority of all subjects in the cohort (258; 77.0%) were treated for 1 infection, with 77 (23.0%) treated for more than 1 simultaneous infection, such as concomitant septic arthritis and osteomyelitis.

Antimicrobial Agents

The majority of subjects (296; 88.4%) were treated for bacterial infections; 14 (4.2%) subjects received antivirals and 25 (7.5%) received antifungals. Antimicrobial changes were made in clinic for 298 (89.0%) subjects and by telephone for 37 (11.0%). β -Lactam antibiotics were the most

Table 2. Principal Infections Treated in 335 Subjects

Principal Infection Treated	N (%)	Prior Inpatient Consultation, N (%)
Septic arthritis	59 (17.6%)	56 (94.9%)
Acute osteomyelitis	51 (15.2%)	45 (88.2%)
Chronic osteomyelitis	26 (7.8%)	19 (73.1%)
Hardware-associated infection	24 (7.2%)	22 (91.7%)
Soft tissue infection	21 (6.3%)	14 (66.7%)
Intracranial/meningitis	20 (6.0%)	20 (100%)
Pulmonary infection	16 (4.8%)	11 (68.8%)
Lymphadenitis	15 (4.5%)	5 (33.3%)
Endocarditis/endovascular	13 (3.9%)	12 (92.3%)
Bacteremia	12 (3.6%)	12 (100%)
Orbital, periorbital, sinus infections	8 (2.4%)	6 (75.0%)
All other	70 (20.9%)	55 (78.6%)

Table 3. Principal Pathogens Identified in 335 Subjects

Principal Pathogen Identified	N (%)
<i>Staphylococcus aureus</i>	81 (24.2%)
Methicillin-sensitive	59 (17.6%)
Methicillin-resistant	22 (6.6%)
Nontuberculous <i>Mycobacteria</i>	26 (7.8%)
Polymicrobial infection	23 (6.9%)
Coagulase-negative staphylococci	16 (4.8%)
<i>Streptococcus pyogenes</i>	10 (3.0%)
<i>Streptococcus pneumoniae</i>	10 (3.0%)
<i>Mycobacterium tuberculosis</i>	8 (2.4%)
<i>Aspergillus</i> species	6 (1.8%)
Herpes simplex virus	6 (1.8%)
Viridans group streptococci	6 (1.8%)
All others combined	45 (13.4%)
No pathogen identified	98 (29.3%)

commonly used class of antimicrobials, with 210 (62.7%) subjects receiving at least 1 β -lactam. The most commonly used antimicrobials are presented in Table 4. Many subjects (114; 34.0%) remained on only 1 medication for the entirety of their treatment course, whereas 91 (27.2%) were treated with 2 medications, 45 (13.4%) with 3 medications, and the remaining 85 (25.4%) received 4 or more medications (range, 4–14). The most common combination regimens to be used were clarithromycin plus rifampin (11 subjects; 3.3%), clindamycin plus rifampin (7 subjects; 2.1%), and ceftriaxone plus metronidazole (6 subjects; 1.8%).

One third of subjects (108; 32.2%) were treated with intravenous antimicrobials in the outpatient setting, 269 (80.3%) received oral antimicrobials at any time, and almost half of the subjects (146; 43.6%) were only treated with oral antimicrobials. The median duration of all antimicrobial courses was 45 days (IQR, 30–99) across all illnesses treated. Intravenous antimicrobials were administered for a median duration of 24 days (IQR, 8–44).

Adverse Outcomes

Of all subjects in the cohort, 107 (31.9%) developed at least 1 distinct AE during antimicrobial therapy, with 76

Table 4. Most Commonly Administered Antimicrobials and Adverse Events, by Route

Antimicrobial	N (%)	Adverse Events (N, %*)	Serious Adverse Events [†] (N, %*)
Oral Route			
Cephalexin	97 (28.9%)	13 (13.4%)	1 (1.0%)
Clindamycin	86 (25.7%)	19 (22.1%)	2 (2.3%)
Rifampin	76 (22.7%)	15 (19.7%)	3 (3.9%)
Clarithromycin	26 (7.6%)	7 (26.9%)	3 (11.5%)
Moxifloxacin	21 (6.3%)	2 (9.5%)	1 (4.8%)
Metronidazole	21 (6.3%)	4 (19.0%)	2 (9.5%)
Trimethoprim-sulfamethoxazole	18 (5.4%)	2 (11.1%)	1 (5.6%)
Linezolid	17 (5.1%)	3 (17.6%)	3 (17.6%)
Parenteral			
Cefazolin	68 (20.3%)	3 (4.4%)	2 (2.9%)
Ceftriaxone	63 (18.8%)	17 (27.0%)	6 (9.5%)
Vancomycin	62 (18.5%)	6 (9.7%)	3 (4.8%)
Meropenem	22 (6.6%)	2 (9.1%)	1 (4.5%)

*Percentages in this column represent proportion of adverse events or serious adverse events per total courses of that specific antimicrobial.

[†]Defined as neutropenia, acute renal insufficiency, hepatotoxicity, catheter-related events, allergic reactions, and medication interactions.

Table 5. Adverse Events and Time to First Adverse Event Onset for 335 Included Subjects, by Type and Route of Antimicrobial Administration

Adverse Event	Subjects (N, %)	Number at Risk*	Days to First Onset (median, IQR)
Subjects on Any Antimicrobial			
Any [†]	107 (31.9%)	335	19 (9–30)
Clinical event [‡]	93 (27.8%)	335	20 (14–34)
Serious [†]	42 (12.5%)	335	23 (8–45)
Allergy	15 (4.5%)	335	8 (0–45)
Catheter-related	14 (13.0%)	108	38 (24–96)
Neutropenia	9 (3.0%)	298	22 (15–23)
Renal insufficiency	7 (2.5%)	276	12 (8–343)
Elevated liver enzymes	3 (1.1%)	272	56 (16–186)
Subjects on Intravenous Antimicrobials			
Any [†]	34 (31.5%)	108	17 (6–25)
Clinical event [‡]	22 (20.4%)	108	19 (11–29)
Serious [†]	21 (19.4%)	108	16 (6–29)
Allergy	5 (4.6%)	108	0 (0–8)
Catheter-related	14 (13.0%)	108	38 (24–96)
Neutropenia	5 (4.8%)	104	20 (11–23)
Renal insufficiency	3 (2.9%)	104	11 (7–26)
Elevated liver enzymes	0 (0%)	96	N/A
Subjects on Oral Antimicrobials			
Any [†]	73 (27.1%)	269	14 (4–25)
Clinical event [‡]	71 (26.4%)	269	15 (7–25)
Serious	21 (7.8%)	269	15 (0–51)
Allergy	10 (3.7%)	269	17 (0–51)
Neutropenia	4 (1.7%)	237	19 (7.5–127)
Renal insufficiency	4 (1.9%)	216	11 (8–27)
Elevated liver enzymes	3 (1.4%)	215	56 (16–186)

Abbreviations: IQR, interquartile range; N/A, not applicable.

*Number at risk is the number of subjects who could have experienced the adverse event, based on receiving the specified antimicrobial route and having monitoring for the adverse event. For example, 237 subjects were at risk for having neutropenia on oral antimicrobials because they received oral antimicrobials and had neutrophil levels monitored.

[†]Numbers of subjects in subcategories (eg, clinical events and serious adverse events) sum to more than the overall category number due to subjects who experienced multiple AE types.

[‡]Includes diarrhea, rash, nausea, abdominal pain, yeast infection, or other clinical adverse event.

subjects having 1 AE (71.0% of those with AE), 23 subjects (21.5% of those with AE) experiencing 2 AEs, and 8 (7.5% of those with AEs) experiencing 3 or more AEs (Table 5). These 107 subjects experienced a total of 151 distinct AEs, with 34 subjects (31.8% of those with AEs) experiencing AEs during intravenous treatment. The most common clinical AE included 44 (13.1%) subjects with diarrhea (29.1% of all AEs); 12 (3.6%) subjects with rash (8.0%

of all AEs); and 11 (3.3%) subjects with nausea, vomiting, or abdominal pain (7.3% of all AEs). Adverse events occurred in 52 previously healthy subjects and 55 subjects with a prior medical history, and there was no statistical association between prior medical history and either AE ($P = .36$) or serious AE ($P = .82$). There was likewise no association between race ($P = .95$) or gender ($P = .86$) and developing any AEs. The risk of developing any AE

Figure 1. Proportion of subjects experiencing any adverse event and time to first adverse event after initiation of antimicrobials, for all subjects (a) and by antimicrobial route (b).

continued to increase with ongoing antimicrobial exposure, although the most significant increase in risk occurred in the first 100 days of treatment (Figures 1a and 1b).

Serious AEs occurred in 42 subjects (12.5%, Table 5). Allergic reactions occurred in 15 (4.5%) subjects. Catheter-related AEs, including catheter occlusion, displacement, and infection, occurred in 14 subjects (4.2% of all subjects, 13.0% of those treated with intravenous medications) at a median of 37 days (IQR, 24–96). Of all AEs, 47 (31.1%) were associated with a change in medication on the date of the reported AE. Diarrhea (8 episodes), rash (8 episodes), and catheter complications (5 episodes) were the most common AEs to be associated with change in therapy.

There was no difference between those on oral and intravenous antimicrobials in rates of having any AE ($P = .84$), allergic reaction ($P = .72$), hepatotoxicity ($P = .32$), or renal insufficiency ($P = .33$). There was a trend toward increased clinical AE among those on oral antimicrobials, but this result was not statistically significant ($P = .08$). Although the frequency of serious AE was higher among those on intravenous medications than among those on oral treatment ($P = .01$), there was no significant difference in rates of serious AEs between the 2 administration routes when catheter-related complications (which could only occur among those with intravenous therapy) were excluded ($P = .46$). Neutropenia occurred in 9 (3.0%) subjects, but it was more common if a neutrophil cutoff of 1000 cells/mL

was used (36 subjects; 12.1%). Median time to neutropenia was the same regardless of which neutrophil cutoff was used. There was a higher rate of neutropenia among those on intravenous antimicrobials, although this rate was not statistically significant at either the 500 cells/mL ($P = .15$) or 1000 cells/mL ($P = .17$) neutropenia cutoff.

There was no association between neutropenia, the most frequent laboratory AE observed in this study, and β -lactam medications: neutropenia occurred in 4 subjects being treated with β -lactam antibiotics and 5 being administered other antimicrobial medications ($P = .99$). There were too few discrete events of acute renal insufficiency or hepatotoxicity to examine associations with specific antimicrobial classes.

DISCUSSION

In this retrospective cohort study of 335 children treated at a tertiary care pediatric center over a 2-year period, one third of subjects treated with ≥ 14 days of antimicrobials experienced an AE. These events occurred early in the course of therapy, at a median of 19 days after starting therapy. Although the majority of these AEs were classified as nonserious, many were considered important enough by treating providers to merit a change in therapy (31% of all AE). These data highlight the importance of close clinical follow-up of pediatric patients treated with prolonged antimicrobial courses. The high rate of AEs on both oral and intravenous antimicrobials across a cohort of subjects treated for a variety of infections suggests that it may be beneficial for some patients on prolonged antimicrobials to be monitored closely for antimicrobial-associated AEs.

The overall rate of AEs observed in our study population was similar to that demonstrated in other studies evaluating outpatient antimicrobial use in pediatric patients. Most published studies, however, specifically evaluated outpatient parenteral antimicrobial therapy (OPAT), without examining AEs among those subjects with prolonged oral antimicrobial treatment, and typically focused on a single infectious diagnosis, such as osteomyelitis. Our population demonstrated a lower rate of catheter-associated complications than in other series [4, 5, 8, 10]; this lower rate may reflect our institution's practice of early transition from intravenous to oral treatment, particularly in the setting of osteomyelitis and septic arthritis. In our study, the median duration of all parenteral therapy was 24 days, and only 13.0% of those with catheters experienced catheter-related AEs. In contrast, in 1 study of OPAT for bone and joint infections [8], subjects received an average of 29.6 days of intravenous therapy for septic arthritis, 42.2 days for acute osteomyelitis, and 58 days for chronic osteomyelitis.

In that cohort, 31.1% of all courses were associated with catheter-related complications and 32% were associated with noncatheter-related complications.

Due in part to the low number of serious AEs experienced, we may not have had the statistical power to demonstrate an association between these AEs and either route of administration or specific antimicrobial classes. However, these data demonstrate that serious AEs can develop at almost any time during therapy and even while taking oral antimicrobials, supporting Infectious Diseases Society of America (IDSA) recommendations for regular monitoring of complete blood count, serum creatinine, and alanine aminotransferase throughout the entire treatment course [3]. These monitoring recommendations are also supported by the fact that the proportion of subjects experiencing any AEs continues to increase over the duration of therapy (Figure 1, a and b). However, it is unclear whether the frequency of such monitoring must be as often as twice weekly, as is recommended in the current IDSA guidelines for parenteral therapy monitoring [3].

The strengths of this study include the large number of subjects evaluated and the inclusion of subjects receiving either parenteral or oral therapy. The largest limitation of this study is its retrospective design. Data collection for antimicrobial medications prescribed was based on the medical record and could therefore have resulted in misclassification of particular antimicrobial exposures and timing. Clinical AEs were likewise only obtained from the medical record, and some laboratory data collected outside our center may not have been captured in our medical record. Furthermore, because subjects were censored at the end of their antimicrobial exposure, we would have missed AEs that occurred after discontinuing antimicrobial therapy. These design features would be likely to result in an underestimate of actual AEs, however. The findings of our study may not be readily generalizable because subjects followed in a tertiary care Pediatric Infectious Diseases clinic may have additional comorbidities compared to other, generally well, children treated in the outpatient setting with prolonged antimicrobials. Future prospective studies could help determine whether children treated with prolonged antimicrobials in other settings have a similarly high rate of antimicrobial-associated AEs, whether those followed by infectious diseases specialists are more likely to have these events identified, and whether patients with specific infections or treated with specific antimicrobials are more likely to experience these events. Because we included any subjects receiving more than 14 days of antimicrobials, regardless of infection being treated or medication route, some outcomes could have been associated with the specific underlying infections themselves, as opposed to the

antimicrobial medications used to treat them. The low number of serious AEs—in particular neutropenia, acute renal insufficiency, and hepatotoxicity—prevented us from having the statistical power to determine associations between these AEs and any particular antimicrobial class.

CONCLUSIONS

Pediatric patients on prolonged outpatient oral and intravenous antimicrobial therapy and followed at a tertiary care Pediatric Infectious Diseases clinic experienced a high rate (>30%) of AEs overall. These findings support the need for close monitoring of pediatric patients on prolonged antimicrobial therapy and vigilance for unwanted effects of these medications.

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References

1. Rathore MH. The unique issues of outpatient parenteral antimicrobial therapy in children and adolescents. *Clin Infect Dis* 2010; 51 (Suppl 2):S209–15.
2. Zaoutis T, Localio AR, Leckerman K, et al. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. *Pediatrics* 2009; 123:636–42.
3. Tice AD, Rehm SJ, Dalovisio JR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. *Clin Infect Dis* 2004; 38:1651–72.
4. Gomez M, Maraqa N, Alvarez A, Rathore M. Complications of outpatient parenteral antibiotic therapy in childhood. *Pediatr Infect Dis J* 2001; 20:541–3.
5. Hussain S, Gomez MM, Wludyka P, et al. Survival times and complications of catheters used for outpatient parenteral antibiotic therapy in children. *Clin Pediatr (Phila)* 2007; 46:247–51.
6. Le J, San Agustin M, Hernandez EA, et al. Complications associated with outpatient parenteral antibiotic therapy in children. *Clin Pediatr (Phila)* 2010; 49:1038–43.
7. Faden D, Faden HS. The high rate of adverse drug events in children receiving prolonged outpatient parenteral antibiotic therapy for osteomyelitis. *Pediatr Infect Dis J* 2009; 28:539–41.
8. Maraqa NF, Gomez MM, Rathore MH. Outpatient parenteral antimicrobial therapy in osteoarticular infections in children. *J Pediatr Orthop* 2002; 22:506–10.
9. Molleston JP, Fontana RJ, Lopez MJ, et al. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN prospective study. *J Pediatr Gastroenterol Nutr* 2011; 53: 182–9.
10. Ruebner R, Keren R, Coffin S, et al. Complications of central venous catheters used for the treatment of acute hematogenous osteomyelitis. *Pediatrics* 2006; 117:1210–5.