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ORIGINAL ARTICLE

Antibiotic-Associated Adverse Events in Hospitalized Children

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Background. Antibiotic-associated adverse events (AEs) in hospitalized children have not been comprehensively characterized.

Methods. We conducted a retrospective observational study of children hospitalized at The Johns Hopkins Hospital receiving ≥24 hours of systemic antibiotics. Consensus regarding antibiotic-associated AE definitions was established by 5 infectious diseases specialists prior to data collection. Two physicians reviewed potential AEs and determined whether they were more likely than not related to antibiotics after comprehensive manual chart review. Inpatient and post-discharge AEs were identified using the Epic Care Everywhere network. AEs evaluated from the initiation of antibiotics until 30 days after antibiotic completion included gastrointestinal, hematologic, hepatobiliary, renal, neurologic, dermatologic, cardiac, myositis, vascular access device-related events, and systemic reactions. Ninety-day AEs included *Clostridioides difficile* infections, multidrug-resistant organism infections, and clinically significant candidal infections. The impact of AEs was categorized as necessitating additional diagnostic testing, changes in medications, unplanned medical encounters, prolonged or new hospitalizations, or death.

Results. Among 400 antibiotic courses, 21% were complicated by at least one AE and 30% occurred post-discharge. Each additional day of antibiotics was associated with a 7% increased odds of an AE. Of courses complicated by an AE, 66% required further intervention. Hematologic, gastrointestinal, and renal AEs were the most common, accounting for 31%, 15%, and 11% of AEs, respectively. AEs complicated 35%, 35%, 19%, and 18% of courses of piperacillin-tazobactam, tobramycin, ceftazidime, and vancomycin, respectively.

Conclusions. More than 1 in 5 courses of antibiotics administered to hospitalized children are complicated by AEs. Clinicians should weigh the risk of harm against expected benefit when prescribing antibiotics.

Key words. adverse events; antibiotics; pediatrics.

Approximately 60% of hospitalized children receive antibiotics, with one-quarter of antibiotic use considered inappropriate [1–3]. Although antibiotics are critical to improve the clinical outcomes of children with infections, antibiotic use is not benign. In addition to the ongoing public health threat posed by multidrug-resistant organisms (MDROs) driven by antibiotic overuse, individual courses of antibiotics can be associated with adverse events (AEs) ranging from rashes to seizures to anaphylaxis.

Approximately 20% of hospitalized adult patients receiving antibiotics experience an antibiotic-associated AE [4]. Antibiotics are the cause of almost half of pediatric emergency department (ED) visits for adverse drug events and are the most commonly identified cause of medication-associated AEs in pediatric inpatients [5–7]. Nevertheless, the scope of antibiotic-associated AEs in hospitalized children, including the prevalence and types of AEs that children experience, has not been comprehensively defined. Understanding the risks associated with antibiotic use is critical for clinicians to make well-informed decisions about antibiotic prescribing (eg, avoiding an antibiotic that lowers the seizure threshold in a child with epilepsy, choosing the least nephrotoxic antibiotic for a patient with chronic kidney disease). We characterized antibiotic-associated AEs among hospitalized children using comprehensive data from a cohort of children receiving 400 antibiotic courses, including a manual review of all antibiotics received and adjudication of all potential AEs that occurred in both the inpatient and outpatient setting.

METHODS

Eligibility Criteria

We conducted a retrospective observational study of children admitted to The Johns Hopkins Hospital who received at least

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24 hours of systemic (oral or intravenous) antibiotics. We collected data on a convenience sample of 400 individual courses of antibiotics using consecutive medical record numbers from pediatric patients aged 6 months and older hospitalized from July to December 2016. Exclusion criteria for individual antibiotics consisted of the following: (1) prophylactic antibiotics with no defined end date, (2) antibiotics for noninfectious indications (eg, azithromycin for anti-inflammatory effects and erythromycin for intestinal motility) [8], and (3) topical or inhaled antibiotics. Patients were excluded if they were admitted to the neonatal intensive care unit, to the oncology service, or if the hospital admission exceeded 60 days as the large number of medical interventions in these populations make both identification of antibiotic-associated AEs and attribution of AEs to specific antibiotics challenging. This study was approved by The Johns Hopkins University School of Medicine Institutional Review Board, with a waiver of informed consent.

Data Collection

Children meeting eligibility criteria were identified using The Johns Hopkins Hospital pharmacy database. Demographic data, preexisting medical conditions, infectious diseases-related diagnosis warranting antibiotic therapy, antibiotics received, and antibiotic-associated AEs were collected by manual review of electronic health records and entered into a secure REDCap database. Both inpatient and outpatient records were reviewed to obtain data regarding antibiotics prescribed at discharge as well as AEs experienced after discharge. Epic Care Everywhere, a network that includes inpatient and outpatient records from over 1700 hospitals and 34 000 clinics in the United States [9], was reviewed for each patient to identify AEs and other relevant post-discharge data.

Definitions

An antibiotic course was defined as a single contiguous duration of antibiotics that could include multiple antibiotics administered simultaneously or in succession. The duration of the antibiotic course was defined as the day of initiation of antibiotics until the completion of all antibiotics administered without interruption and included antibiotics administered both during the inpatient stay and continued after hospital discharge. As an example, a patient prescribed 5 days of amoxicillin and azithromycin concurrently was considered to have received a single 5-day antibiotic course consisting of 2 antibiotics.

Antibiotic-Associated AE Criteria

Consensus regarding AE definitions was established by 5 pediatric infectious diseases specialists A. L. H., A. J. H., M. P. K., R. G. S., and P. D. T. before data collection began. AE definitions were based on a review of the published literature [4, 10] as well as clinical experience. The criteria used to define AEs are described in Table 1. AEs evaluated from the start of antibiotic therapy until 30 days after the discontinuation of antibiotics included (1) anaphylaxis; (2) gastrointestinal: nausea, vomiting, or antibiotic-associated diarrhea, not including *Clostridioides difficile* infection (CDI); (3) hematologic abnormalities; (4) hepatobiliary abnormalities; (5) renal dysfunction;

Table 1. Criteria Used to Classify Antibiotic-Associated Adverse Events in a Cohort of Hospitalized Children

Adverse Event	Definition
Within 30 days of antibiotic initiation	
Gastrointestinal	Diarrhea not associated with *Clostridioides difficile* infection (>3 loose stools per day associated with antibiotic administration and documented as "diarrhea" in the medical record, in the absence of laxative use or preexisting enteritis); nausea and vomiting associated with antibiotic administration, in the absence of an alternate explanation
Hematologic	Anemia (hemoglobin < 10 g/dL), leukopenia (white blood cell count < 4500 cells/mm^3), neutropenia (absolute neutrophil count < 1500 cells/ mm^3), or thrombocytopenia (platelet count < 150 000/μL) with levels below patient's baseline and in the absence of bleeding or myelosuppressive therapies, eosinophilia (absolute eosinophil count > 500/μL)
Hepatobiliary	Cholestasis (total bilirubin > 3 mg/dL or > upper limit of normal for age) or transaminitis (aspartate transaminase or alanine transaminase > 3 times patient's baseline or > 2 times upper limit of normal for age) in the absence of existing hepatobiliary pathology or recent biliary instrumentation
Renal	Increase in serum creatinine > 1.5 times patient's baseline or 0.3 mg/dL above baseline in the absence of precipitating factors for acute kidney injury such as sepsis or the receipt of intravenous contrast or other nephrotoxic agents
Neurologic	Altered mental status, peripheral neuropathy, or seizures in the absence of preexisting neurologic conditions, substance-related toxicities, or infectious syndromes; new subjective or objective hearing impairment.
Dermatologic	Rash, including hives, non-hives rashes, and Red Man's syndrome, temporally associated with antibiotic administration with resolution upon antibiotic discontinuation
Cardiac	Corrected QT interval > 440 ms in males or >460 ms in females in the absence of preexisting arrhythmias, based on at least 2 electrocardiograms
Anaphylaxis	Acute onset of respiratory compromise, hypotension, or end-organ dysfunction within minutes after the initiation of antibiotic administration, in the absence of an alternative explanation
Myositis	Increase in creatine kinase > 5 times patient's baseline, in the absence of existing myopathy or statin use
Vascular access device-related	Thrombotic or infectious complication, dislodgement, intravenous catheter infiltration
Systemic	Drug fever (fever for > 1 day without alternative explanation and with improvement after discontinuation of antibiotic), drug reaction with eosinophilia and systemic symptoms
Within 90 days of antibiotic initiation	
Clostridioides difficile infection (CDI)	Clinical signs and symptoms consistent with CDI in the setting of a positive stool assay for *C. difficile* toxin and the absence of laxative use
Emergence of multidrug-resistant organisms	New colonization or infection with any of the following: (1) bacteria with an antibiotic minimum inhibitory concentration at least 2 times the initial value, (2) carbapenem-resistant Enterobacterales, (3) multidrug-resistant *Acinetobacter baumannii*, (4) multidrug-resistant *Pseudomonas aeruginosa*, (5) methicillin-resistant *Staphylococcus aureus*, or (6) vancomycin-resistant Enterococci
Clinically significant *Candida* species infection	Infection requiring topical or systemic antifungal therapy

(6) neurologic manifestations; (7) dermatologic manifestations; (8) electrocardiogram changes; (9) myositis; (10) vascular access device-related events; and (11) other systemic reactions (eg, drug fever and drug reaction with eosinophilia and systemic symptoms [DRESS]).

AEs evaluated from the start of therapy until 90 days after completion of antibiotics included: (1) incident CDI, (2) incident MDRO infections, and (3) incident clinically significant infections caused by *Candida* species (ie, requiring topical or systemic antifungal therapy). These later events were evaluated up to 90 days after antibiotic completion as these risks remain elevated several weeks after discontinuing antibiotic therapy [11–13].

Adjudication Process

All potential AEs were systematically reviewed by 2 pediatric infectious diseases specialists (R. G. S. and P. D. T.) in the context of the patient's medical history and clinical course to ensure that they were highly likely to be attributable to antibiotics and not to underlying medical conditions, other interventions, or other medications. Disagreements were discussed with a third infectious diseases specialist (A. J. H.). Thirty-day AEs were attributed to a specific antibiotic based on the antibiotic's known likelihood to cause the AE and the temporal association with the administration of the antibiotic. For example, diarrhea that occurred in a patient receiving both amoxicillin-clavulanate and azithromycin was attributed to amoxicillin-clavulanate. Relevant medical data beyond antibiotic use were also reviewed. For example, if acute kidney injury (AKI) occurred in the setting of vancomycin use, receipt of other nephrotoxins, such as nonsteroidal anti-inflammatory drugs, intravenous contrast, and other anti-infectives (eg, acyclovir), that may have contributed to AKI was also collected. In cases where multiple factors may have contributed, indicators such as recovery from the AE after the antibiotic was discontinued and previous or future issues with the AE for the specific patient were factored into the decision-making of whether the AE was "more likely than not" to be caused by the antibiotic. Ninety-day AEs were not attributed to specific antibiotics due to the potential for any antibiotic to contribute to their development.

Appropriateness of all antibiotic regimens was assessed by both R. G. S. and P. D. T. To avoid overestimating avoidable AEs, antibiotic regimens were determined to be unnecessary only if there was no indication for antibiotics (ie, antibiotics administered for a viral or noninfectious diagnosis). Antibiotic regimens that were longer in duration than necessary or those that included broader antibiotic regimens than those recommended in national or local guidelines were not recorded as unnecessary as it is unknown if an AE would have still occurred with a shorter duration of therapy or narrower spectrum agent.

Unanticipated consequences of antibiotic-associated AEs were categorized as one or more of the following (based on agreement by both R. G. S. and P. D. T.): (1) additional laboratory tests, imaging, or electrocardiograms; (2) changes in antibiotic regimen or other additional medications; (3) unplanned ED or outpatient encounters; (4) extension of hospital stay; (5) new hospitalization; and (6) death. Planned subsequent visits with clinicians, routine laboratory monitoring, and therapeutic drug monitoring were not considered to be unanticipated consequences of AEs and were not included.

Statistical Analysis

Medians, interquartile ranges, and percentages were calculated to describe AEs. Pearson's Chi-square test or Fishers exact test, as appropriate, was used for categorical variables, and the Wilcoxon Rank Sum test was used for continuous variables. Univariable logistic regression was used to determine the increased odds of an AE for each additional day an antibiotic was prescribed. All analyses were performed using Stata 15 (StataCorp). A 2-sided P-value <.05 was considered statistically significant for all tests.

RESULTS

Overall Cohort

Four-hundred antibiotic courses administered to 352 unique patients were evaluated. The majority (58%) of children were previously healthy and 31% required admission to the intensive care unit at any point during their hospitalization. The median age was 8 years (interquartile range [IQR]: 4-14), and no association between patient age and development of antibiotic-associated AEs was observed. Forty-seven percent of patients were female. One-hundred twenty-three AEs occurred in 68 unique patients, with each patient experiencing from 1 to 5 AEs. Twenty-one percent of antibiotic courses were complicated by at least one AE. Thirty percent of AEs occurred after hospital discharge, including 23% of 30-day AEs and 65% of 90-day AEs.

The proportion of patients receiving antibiotic regimens consisting of 1, 2, and 3 or more antibiotics who developed AEs was 6%, 19%, and 44%, respectively ($P < .001$). Each additional day of an antibiotic course was associated with a 7% increase in the odds of developing an AE. Eighteen percent of antibiotic courses were determined to be not clinically indicated; 15% of AEs were associated with unnecessary courses of antibiotics.

Of AEs identified, 84% were 30-day AEs and 16% were 90-day AEs. Of antibiotics administered to at least 20 children, piperacillin-tazobactam, tobramycin, ceftazidime, and vancomycin had the highest association with AEs; 35%, 35%, 19%, and 18% of courses of piperacillin-tazobactam, tobramycin, ceftazidime, and vancomycin, respectively, resulted in a 30-day AE (Table 2). Of all courses of antibiotics that were complicated by AEs, 66% required further intervention, including additional diagnostic testing (54%), changes to the antibiotic regimen or other additional medications (66%),

Table 2. Proportion of 400 Antibiotic Courses Prescribed to Hospitalized Children Complicated by an Adverse Event (AE)

Antibiotics Prescribed	Courses Complicated by AEs; n (Numerator)	Antibiotic Courses Including Agent; n (Denominator)	Percent of Courses Complicated by an AE
Penicillins	17	150	11%
Amoxicillin	0	41	0%
Amoxicillin-clavulanate	6	47	13%
Ampicillin	2	18	11%
Ampicillin-sulbactam	0	19	0%
Oxacillin	1	3	33%
Penicillin	1	2	50%
Piperacillin-tazobactam	7	20	35%
Cephalosporins	28	283	10%
Cefadroxil	0	1	0%
Cefazolin	3	39	8%
Cefdinir	0	18	0%
Cefepime	5	50	10%
Cefoxitin	1	3	33%
Cefpodoxime	0	1	0%
Ceftaroline	0	1	0%
Ceftazidime	4	21	19%
Ceftriaxone	14	112	13%
Cefuroxime	0	1	0%
Cephalexin	1	36	3%
Fluoroquinolones	4	33	12%
Ciprofloxacin	2	26	8%
Levofloxacin	1	6	17%
Moxifloxacin	1	1	100%
Aminoglycosides	11	47	23%
Gentamicin	4	27	15%
Tobramycin	7	20	35%
Carbapenems	1	10	10%
Ertapenem	0	3	0%
Meropenem	1	7	14%
Others			
Azithromycin	0	29	0%
Clindamycin	5	68	7%
Colistin	0	1	0%
Doxycycline	0	7	0%
Linezolid	1	7	14%
Metronidazole	0	42	0%
Nitrofurantoin	0	3	0%
Rifampin	0	1	0%
Trimethoprim-sulfamethoxazole	2	35	6%
Vancomycin	10	56	18%

unplanned ED or outpatient visits (9%), prolonged hospitalization (9%), and new hospitalizations (9%)—categories not mutually exclusive. There were no deaths. AEs contributing to more than 5% of all antibiotic-associated AEs are described in further detail below.

Hematologic AEs

Thirty-eight hematologic AEs constituted 31% of all AEs (Table 3). Hematologic AEs included the following: leukopenia (29% of hematologic AEs), neutropenia (24%), eosinophilia (21%), anemia (18%), and thrombocytopenia (8%). Common antibiotics resulting in hematologic AEs were ceftriaxone (26%), piperacillin-tazobactam (21%), and ampicillin (16%). Of all courses complicated by hematologic AEs, 52% required an intervention, most commonly additional laboratory testing (43%) and changes to the antibiotic regimen (38%). None of the patients with neutropenia developed secondary bacterial infections. One patient who developed ceftriaxone-induced hemolytic anemia required a blood transfusion.

Gastrointestinal AEs

Nineteen gastrointestinal AEs accounted for 15% of all AEs (Table 3). Of these, 79% were non-CDI diarrhea and 21% were nausea or vomiting. Common antibiotics resulting in gastrointestinal AEs were amoxicillin-clavulanate (26%) and clindamycin (21%). Sixty-three percent of all gastrointestinal AEs required an intervention, most commonly changes to the antibiotic regimen (42%).

Renal AEs

Thirteen renal AEs constituted 11% of all AEs (Table 3), all of which were attributed to vancomycin and aminoglycosides (Table 3). More specifically, 35% of courses of tobramycin, 15% of courses of gentamicin, and 11% of courses of vancomycin were associated with AKI. No patients received amikacin. In 85% of antibiotic courses complicated by renal AEs, patients received combinations of multiple potentially nephrotoxic antibiotics including tobramycin and trimethoprim-sulfamethoxazole (39% of all renal AEs), vancomycin and gentamicin (31% of all renal AEs), and piperacillin-tazobactam and vancomycin (15%). Ninety-two percent of antibiotic courses complicated by AKI required interventions, most commonly additional diagnostic testing (85%) and changes in the antibiotic regimen (46%). No patients experiencing AKI required dialysis.

Hepatobiliary AEs

Eleven hepatobiliary AEs comprised 9% of all AEs (Table 3). The majority (91%) involved elevated transaminases, 70% of which required further intervention, most commonly in the form of additional diagnostic testing (60%) or changes to the antibiotic regimen (30%). Common antibiotics implicated in elevated transaminases were ceftriaxone (30%) and piperacillin-tazobactam (30%). A previously healthy 5-year-old child developed gallstones after receiving 9 days of ceftriaxone, which required additional laboratory testing, imaging, and outpatient surgical evaluation.

Dermatologic AEs

Nine dermatologic AEs constituted 7% of all AEs (Table 3). Seventy-eight percent were non-hives rashes and 22% were vancomycin-associated Red Man syndrome. Fifty-five percent

Table 3. Antibiotic-Associated Adverse Events (AEs) Experienced During 400 Antibiotic Courses Administered to Hospitalized Children

Type of AE	Number of AEs	Percent of Total AEs[a]	Antibiotics Implicated (Number of Courses With AE)[b]
30-day AEs[c]	103	84%	
Gastrointestinal	19	15%	Amoxicillin-clavulanate (5), clindamycin (4), ceftriaxone (2), ciprofloxacin (2), cefepime (1), ceftazidime (1), levofloxacin (1), linezolid (1), piperacillin-tazobactam (1), trimethoprim-sulfamethoxazole (1)
Hematologic	38	31%	Ceftriaxone (7), piperacillin-tazobactam (4), ampicillin (2), cefazolin (2), ceftazidime (1), cefepime (1), cefoxitin (1), linezolid (1), meropenem (1)
Hepatobiliary	11	9%	Ceftriaxone (3), piperacillin-tazobactam (3), cefepime (2), cefazolin (1), oxacillin (1)
Renal	13	11%	Tobramycin (7), vancomycin (6), gentamicin (4)[d]
Dermatologic	9	7%	Vancomycin (3), ceftriaxone (2), amoxicillin-clavulanate (1), ceftazidime (1), clindamycin (1), piperacillin-tazobactam (1)
Anaphylaxis	2	2%	Ceftazidime (1), trimethoprim-sulfamethoxazole (1)
Neurologic	1	1%	Cefepime (1)
Vascular access device-related	8	7%	Vancomycin (2), ceftazidime (2), ceftriaxone (1), clindamycin (1), moxifloxacin (1), penicillin (1)
Drug fever	2	2%	Piperacillin-tazobactam (2)
90-day AEs	20	16%	
Clostridioides difficile infection	5	4%	—
Infection due to multidrug-resistant organisms	8	7%	—
Clinically significant *Candida* species infections	7	6%	—

[a]Percent of total AEs rounded to nearest whole number and may not add up to 100%.
[b]Some courses of antibiotics were complicated by more than one AE (eg, both leukopenia and neutropenia). For some AEs, the total number of courses with AEs may be less than the total number of AEs.
[c]No patients developed cardiac problems or myositis.
[d]There were 13 total renal AEs, 4 of which were associated with the combination of vancomycin and gentamicin.

of dermatologic AEs led to changes in the antibiotic regimen. One patient developed hives (in association with anaphylaxis) while receiving intravenous trimethoprim-sulfamethoxazole.

Vascular Access Device-Related AEs

Eight vascular access device-related AEs comprised 7% of all AEs (Table 3). Seventy-five percent of these were drug infiltrations of peripheral intravenous catheters, and 25% were central line malfunctions. One-third of the infiltrations led to extravasation injury and required treatment with hyaluronidase. Both central line malfunctions occurred after discharge. One required an ED visit with additional imaging, and the other resulted in an additional hospitalization, imaging, and early discontinuation of antibiotic therapy.

Ninety-day AEs

Twenty 90-day AEs, which included CDI and incident infection with MDROs or *Candida* spp., accounted for 16% of all AEs. CDI occurred during or following 1% of antibiotic courses and symptoms manifested an average of 14 days (range: 10-17) after antibiotic initiation. MDRO infections constituted 8% of all AEs. Of these, 75% were caused by multidrug-resistant Gram-negative organisms and 25% were caused by methicillin-resistant *Staphylococcus aureus*. Six percent of AEs were *Candida* spp. infections, which included *Candida* dermatitis or oral candidiasis treated with topical or oral antifungals.

DISCUSSION

Evaluating 400 antibiotic courses administered to hospitalized children, 21% of courses were associated with at least one AE. Each additional day of antibiotic therapy was associated with a 7% increase in the odds of developing an AE. Of children who developed an AE, 66% required further interventions ranging from additional diagnostic testing to additional unplanned hospitalizations. Importantly, 30% of AEs occurred after hospital discharge and the prescriber may not have been aware that an AE occurred. Fifteen percent of AEs were associated with antibiotic courses that were unnecessary and were, therefore, potentially avoidable.

Our findings are consistent with the experience in hospitalized adults who receive antibiotics, 20% of whom are estimated to experience an antibiotic-associated AE [4]. Antibiotic-associated AEs contribute to nearly 70 000 emergency department visits annually in children [5, 14]. Traditionally, children have been excluded from most antibiotic trials, leading to limited premarketing safety data [15]. Although some postmarketing studies of specific antibiotics [16–19] or specific antibiotic-associated AEs [20–22] are available for children, comprehensive AE data across antibiotics in hospitalized children are lacking. Available studies frequently rely on voluntary error reporting, likely underestimating the incidence of AEs [6, 7, 23]. Furthermore, they generally do not link specific AEs with specific antibiotics.

Arguments for reducing unnecessary antibiotic exposure often focus on the risk for development of antibiotic resistance; however, clinicians tend to perceive antibiotic resistance as a public health problem that may be a national or global threat but is less relevant to their personal practice [24–26]. They also frequently underestimate the risk of AEs that can affect the individual patient and rarely discuss these risks with patients [27]. In this context, clinicians may consider a small potential benefit from antibiotics to outweigh the risk of antibiotic-associated harm [28]. Our study adds to a growing body of evidence that there are concrete dangers for patients receiving antibiotics that increase with each additional day of therapy. These findings support the value of stewardship interventions designed to optimize all aspects of antibiotic use, including limiting the use of therapy that is unnecessary altogether, choosing the right drug when therapy is needed, and using the shortest effective duration of therapy. It is not yet clear how best to communicate these risks to prescribers to promote behavior change, but evidence from another public health crisis, the opioid epidemic, suggests that giving providers feedback about the outcomes of their prescribing practices may make medication-associated risks more tangible and encourage providers to incorporate them into their decision-making. In a trial of 861 clinicians who prescribed opioids to patients who subsequently suffered a fatal opioid overdose, clinicians who received a letter notifying them of their patients' deaths along with guidance for safe opioid prescribing prescribed fewer opioids in the subsequent 3-month follow-up period [29]. Notably this contrasted with a different study showing that a letter solely notifying prescribers that they prescribed more opioids than their peers had no impact on opioid prescribing behavior [30]. Peer comparison of antibiotic prescriptions has often been used as part of stewardship activities, but the opioid experience suggests that a provider-specific "harm score" that incorporates their patients' antibiotic-associated AEs may be more consequential.

There are several limitations to our study. We evaluated a convenience sample of 400 courses of antibiotics administered at a single academic center and results may not be generalizable to other settings, especially for antimicrobials that were prescribed infrequently in this cohort. Many of the patients were medically complex, and while each AE was adjudicated by at least 2 infectious diseases specialists to determine if the AE was likely to be attributable to antibiotics, children with underlying medical conditions may have reasons to have additive effects on AEs compared with otherwise healthy children, potentially overestimating the proportion of children with antibiotic-associated AEs. On the contrary, we likely underestimated the number of AEs for a number of reasons. First, our rigorous and standardized manual chart review is a strength of this study, but because of its retrospective nature, we were only able to include events that were documented in the medical record. Clinicians are known to have lapses in their documentation of AEs in the medical record [6, 31]. Second, we excluded patients in the neonatal intensive care unit, oncology patients, and children hospitalized for greater than 60 days as the complexity of their medical interventions makes it challenging to reliably attribute AEs to an antibiotic. However, because of polypharmacy and underlying medical conditions, these patients may be at even higher risk of antibiotic-associated AEs than the patients included in this cohort. Third, we used Epic Care Everywhere to identify AEs that occurred after hospital discharge. Although this network includes data from an estimated 250 million patients, it does not include AEs if patients sought care in settings not contributing data to this network [32]. Fourth, we would not have captured AEs for patients who developed laboratory derangements but did not have laboratory monitoring or for patients with mild rashes, diarrhea, and other antibiotic-associated AEs for which they may have relied on self-discontinuation of antibiotics or over the countermeasures for symptom relief without formally seeking medical care.

Antibiotic-associated AEs are common in hospitalized children and the risk increases with each additional day of therapy and with each additional antibiotic administered. Clinicians should carefully weigh the risk of harm against expected benefit when prescribing antibiotics to children. In the future, provider-specific harm scores may help convey these risks to clinicians to encourage improved prescribing practices.

Notes

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