Cost and Potential Avoidability of Antibiotic-Associated Adverse Drug Reactions in Children

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We identified 375 children who visited the emergency department or urgent care clinic at Children's Mercy Hospitals & Clinics for antibiotic adverse drug reactions over a 1-year period, and the total cost for these visits was \$170 893.20. Of these ADRs, 17% were likely avoidable. The potential negative consequences of antibiotics should be considered at the point of prescribing.

Keywords. adverse drug reactions; antibiotics; pediatrics.

An adverse drug reaction (ADR) is a response to a drug that is noxious and unintended and occurs when the drug is taken at a normal dose [1]. ADRs can result in undesired morbidity and significant health care utilization by children, which lead to approximately 500 000 pediatric visits to the outpatient clinics and emergency departments (EDs) in the United States each year [2].

Antibiotics are identified repeatedly as the most common drug class to cause ADRs in children [3]. The implications of unnecessary antibiotic prescribing in children as they relate to ADRs are poorly understood; however, it has been estimated that up to 30% of prescribed outpatient oral antibiotics are unnecessary, which results in 34 million antibiotic prescriptions annually that could have been avoided [4]. The objective of this study was to characterize the scope and burden of antibiotic-associated ADRs in children that result in a visit to the ED

or urgent care clinic (UCC) and to determine their associated costs and potential avoidability.

METHODS

Setting and Population

A retrospective observational study was performed to characterize clinical characteristics of children seeking medical care for antibiotic-associated ADRs. Chart abstraction was performed for children ≤ 21 years of age who presented to a Children's Mercy Hospitals & Clinics ED or UCC between July 1, 2013, and June 30, 2014, and received a diagnosis of ADR by a clinician according to documentation in the electronic medical record clinical notes. Patients were identified by the Children's Mercy Hospitals & Clinics pharmacovigilance program as previously described [5]. In brief, a drug safety pharmacist within the Division of Clinical Pharmacology is dedicated to identifying, clarifying, and documenting ADRs within the electronic medical record for all patients who seek medical care in our hospital, UCC, ED, or outpatient clinics. A standardized form within the electronic medical record is used by the pharmacovigilance pharmacist to classify ADR type and severity. ADRs are classified as an allergy/hypersensitivity reaction (eg, rash, anaphylaxis) or an adverse effect (eg, diarrhea, diaper rash). Severity is classified as mild when the implicated drug is continued, moderate when the implicated drug is discontinued and/or a treatment for the reaction is required, or severe when the reaction is life-threatening (ie, epinephrine administration is required) or necessitates hospitalization.

Data Collection, Case Definitions, and Cost

A patient was included in the study if supporting documentation by the ED or UCC clinician confirmed the presence of an ADR. Data extracted from the electronic medical record included date, site, race, age, sex, implicated medication(s), symptoms, severity, type, days of exposure, indication for the implicated medication, treatment of the ADR, disposition after the ED/UCC visit, and charges. ADR visit charges were converted to estimated costs by applying a based annual cost-to-charge ratio (RCC) submitted to the Centers for Medicare and Medicaid Services. Total costs included ED/UCC visits and hospitalizations associated with the initial ADR-related visit.

Classification of ADR Avoidability

ADR avoidability (or preventability) was based on a concept described by Hallas et al [6], which focuses on the appropriateness of medication prescribing related to ADRs. The Hallas et al classification defines "an ADR as definitely avoidable if the event is due to a drug treatment inconsistent with present day knowledge of good medical practice or is clearly unrealistic.

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A possibly avoidable ADR is defined as situations where the prescription is not erroneous but the event could have been avoided by an effort exceeding the obligatory demands.” [6] For our study, an ADR was deemed definitely or probably avoidable if an antibiotic was prescribed for an indication for which no antibiotic was indicated (eg, viral respiratory infection) or if the antibiotic was prescribed 3 days or less before the point of ADR presentation and the treating clinician at the ED or UCC discontinued the inciting antibiotic without prescribing another antibiotic. Summary statistics were constructed using frequencies and proportions for categorical data by using GraphPad Software (La Jolla, California). Our study protocol was approved by the Children’s Mercy Hospitals & Clinics Institutional Review Board.

RESULTS

Characteristics of Children Seeking Medical Care for an Antibiotic-Associated ADR

There were 166 872 ED and UCC visits during the study period, and 430 children were identified as seeking care for an ADR. The total number of ADRs attributed to a systemic antibiotic was 375. Children with an ADR were most frequently Caucasian/white (235 [63%]), male (200 [53%]), and 1 to 5 years of age (203 [54%]).

Implicated Antibiotics and ADR Clinical Symptoms

The most frequently implicated antibiotics were amoxicillin (222 [59%]), trimethoprim-sulfamethoxazole (41 [11%]), and cefdinir (34 [9%]). The primary prescribing indication was otitis media (182 [49%]), skin and soft tissue infection (58 [15%]), and pharyngitis (37 [10%]) (Table 1). Rash was the most common clinical manifestation reported (97%), followed by angioedema (10%) and gastrointestinal symptoms (8%). The majority of the reactions were classified as allergic (361 [96%]) and were moderate in severity (336 [90%]); 13 (3%) were classified as severe.

Table 1. Indications for Antibiotics Associated With ADRs

Reason for Prescribing Antibiotic	No. (%) of Patients (N = 375)
Otitis media	182 (49)
SSTI	58 (15)
Pharyngitis	37 (10)
Pneumonia	22 (6)
≥2 indications	20 (5)
Sinusitis	14 (4)
Respiratory virus	12 (3)
UTI	9 (2)
Bronchitis/wheeze	8 (2)
Prophylaxis	4 (1)
Bacteremia	1 (0.2)
Other/unknown	8 (2)

Abbreviations: ADR, adverse drug reaction; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

ADR Treatment and Cost

The majority (240 [64%]) of patients required additional medical treatment(s), including an antihistamine (92%), a steroid (17%), epinephrine (3%), and/or albuterol (3%). Two or more treatment medications were prescribed in 32% of the cases. The 375 antibiotic-associated ADR visits resulted in a total cost of \$170 893.20. Nine patients were admitted to the hospital directly from the ED/UCC ADR-related visit.

Subsequent Antibiotic Prescribing and Avoidability

Of the 375 children, 241 (64%) were not prescribed an additional antibiotic. A total of 52 children who received 3 days or less of antibiotics before the ADR occurred were not prescribed an additional antibiotic, which suggests that the initial antibiotic prescribed and subsequent ADR could have been avoided. The most common indications for an antibiotic were otitis media (27), skin and soft tissue infection (5), pharyngitis (3), and sinusitis (3). An additional 13 ADRs were deemed avoidable because the patients had been prescribed an antibiotic for a presumptive viral respiratory infection or bronchitis/wheeze symptoms. In total, 65 (17%) children likely experienced an avoidable ADR that resulted in a UCC or ED visit, the total costs of which were \$27 382.91. This avoidable cost accounted for 16% of overall antibiotic-associated ADR-related ED/UCC visit costs.

DISCUSSION

To our knowledge, this study is the first to have estimated the potential avoidability of antibiotic-associated pediatric ADRs that result in a visit to an ED or UCC. In our study, an average of more than 1 child per day sought medical care in the ED or UCC because of an unintended consequence of antibiotics. The results of this study show that pediatric antibiotic-associated ADRs are frequent, a substantial proportion of them are avoidable, they are costly, and they result in excess treatment.

In children, antibiotics are recognized as the leading class of drugs that result in ADRs [3]. The potential avoidability of ADRs attributable to unnecessary antibiotic prescribing has gone mostly unexamined. Our data suggest that almost 1 in 5 antibiotic-associated ADRs are avoidable. A recent study by Tamma et al [7] similarly showed that 20% of non-clinically indicated antibiotic regimens were associated with an adverse drug event in the hospital setting. Overall, an estimated 142 505 patients seek medical care in US EDs annually as a result of adverse events associated with antibiotics. Many others are hospitalized or seek medical care elsewhere [2, 8]. Thus, tens of thousands of ADRs attributable to unnecessary antibiotic prescribing are potentially avoidable.

The risk of antibiotic prescribing often goes underrecognized, yet reducing unnecessary antibiotic use in children is a key approach for decreasing ADRs. In our study, otitis media, pharyngitis, and skin and soft tissue infections were the most common

diagnoses associated with antibiotic-related ADRs. It is interesting to note that 64% of the antibiotics prescribed for these 3 diagnoses were discontinued at the time of ADR presentation, and no subsequent antibiotic was prescribed. Existing guidelines for otitis media suggest that observation with close follow-up before prescribing an antibiotic should be considered [9]. For mild skin and soft tissue infections, incision and drainage alone are adequate [10]. In these clinical situations, the risks of ADRs should be addressed at the time of decision-making between the caregiver and provider when observation without antibiotics is a rational option.

Our study had limitations. Our hospital-wide pharmacovigilance program relies on computerized triggers, including diagnostic codes, and therefore our findings likely underestimate the number of children who seek medical care for an ADR. The potential and probable avoidable ADRs are also likely underestimated, because we used a conservative definition of “avoidable.” In addition, we were unable to determine the incidence of ADRs in children prescribed antibiotics, because the majority of these children were prescribed antibiotics in an outpatient setting and sought medical care only in our ED or UCC. Because our study was retrospective, the reason for the antibiotic prescription and determination of the cause of the ADR were limited to clinician interpretation. Differentiating true allergic reactions from those with another etiology, such as viral infection, was beyond the scope of this study, and details of the ADR clinical symptoms depended on medical record documentation. Last, this study lacks generalizability, because it was performed with data from a single pediatric center.

In conclusion, antibiotics are a common culprit of pediatric ADRs and result in potentially unnecessary visits to the ED or UCC. These ADRs are costly, and at least 17% of them are avoidable. ADR risk is a patient-centric outcome that should be communicated to patients and caregivers.

Notes

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