JAMA Internal Medicine | Original Investigation

Association of Adverse Events With Antibiotic Use in Hospitalized Patients

Pranita D. Tamma, MD, MHS; Edina Avdic, PharmD, MBA; David X. Li, BS; Kathryn Dzintars, PharmD; Sara E. Cosgrove, MD, MS

IMPORTANCE Estimates of the incidence of overall antibiotic-associated adverse drug events (ADEs) in hospitalized patients are generally unavailable.

OBJECTIVE To describe the incidence of antibiotic-associated ADEs for adult inpatients receiving systemic antibiotic therapy.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort of adult inpatients admitted to general medicine wards at an academic medical center.

EXPOSURES At least 24 hours of any parenteral or oral antibiotic therapy.

MAIN OUTCOMES AND MEASURES Medical records of 1488 patients were examined for 30 days after antibiotic initiation for the development of the following antibiotic-associated ADEs: gastrointestinal, dermatologic, musculoskeletal, hematologic, hepatobiliary, renal, cardiac, and neurologic; and 90 days for the development of *Clostridium difficile* infection or incident multidrug-resistant organism infection, based on adjudication by 2 infectious diseases trained clinicians.

RESULTS In 1488 patients, the median age was 59 years (interquartile range, 49-69 years), and 758 (51%) participants were female. A total of 298 (20%) patients experienced at least 1 antibiotic-associated ADE. Furthermore, 56 (20%) non-clinically indicated antibiotic regimens were associated with an ADE, including 7 cases of *C difficile* infection. Every additional 10 days of antibiotic therapy conferred a 3% increased risk of an ADE. The most common ADEs were gastrointestinal, renal, and hematologic abnormalities, accounting for 78 (42%), 45 (24%), and 28 (15%) 30-day ADEs, respectively. Notable differences were identified between the incidence of ADEs associated with specific antibiotics.

CONCLUSIONS AND RELEVANCE Although antibiotics may play a critical role when used appropriately, our findings underscore the importance of judicious antibiotic prescribing to reduce the harm that can result from antibiotic-associated ADEs.

JAMA Intern Med. doi:10.1001/jamainternmed.2017.1938
Published online June 12, 2017

Author Affiliations: Division of Pediatric Infectious Diseases, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland (Tamma); Department of Pharmacy, Johns Hopkins Hospital, Baltimore, Maryland (Avdic, Dzintars); Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland (Li, Cosgrove).

Corresponding Author: Pranita D. Tamma, MD, MHS, Division of Pediatric Infectious Diseases, Department of Pediatrics, Johns Hopkins University School of Medicine, 200 N Wolfe St, Ste 3149, Baltimore, MD 21287 (ptamma1@jhmi.edu).

Antibiotic use is common in the inpatient setting. Approximately 50% of hospitalized patients receive at least 1 antibiotic during their hospital stay,[1] with an estimated 20% to 30% of inpatient days of antibiotic therapy considered unnecessary.[2-4] The reasons for antibiotic overuse are myriad, including administration of antibiotics for nonbacterial or noninfectious syndromes, treatment of conditions caused by colonizing or contaminating organisms, and durations of therapy that are longer than indicated. Unnecessary use of antibiotics is particularly concerning because antibiotics may be associated with a number of adverse drug events (ADEs), including allergic reactions, end-organ toxic effects, subsequent infection with antibiotic-resistant organisms, and *Clostridium difficile* infections (CDIs).[5-12]

Estimates of the incidence of antibiotic-associated ADEs in hospitalized patients are generally unavailable. Previously, Shehab and colleagues[11] conducted a retrospective analysis of ADEs among patients presenting to emergency departments and found that antibiotics were implicated in 19% of all emergency department visits for ADEs. It is unclear whether these data are generalizable to hospitalized patients for a number of reasons: (1) acutely ill hospitalized patients may be predisposed to certain ADEs, such as antibiotic-associated nephrotoxic effects, particularly those admitted with acute renal

failure for non–antibiotic-related reasons; (2) hospitalized patients are frequently administered intravenous antibiotic therapy, often at high doses, which may have different adverse event profiles than the oral regimens more commonly prescribed in the outpatient setting[14]; (3) hospitalized patients are commonly administered multiple medications concurrently, causing a potentially synergistic increase in the risk of ADE development[15]; and (4) hospitalized patients are more likely to be elderly or have multiple medical conditions, resulting in impaired drug elimination and an increased risk of ADE development.[16,17] Previous studies evaluating antibiotic-associated ADEs in the inpatient setting have used administrative databases and have not accounted for antibiotic-associated ADEs that occurred after hospital discharge.[18,19] Additionally, they have limited their evaluation of ADEs to single antibiotic classes or single infectious syndromes.[18-21] A comparative analysis of the incidence of ADEs across all classes of antibiotics has yet to be performed. Therefore, in the present study, we sought to describe the incidence of antibiotic-associated ADEs for adult inpatients receiving systemic antibiotic therapy while hospitalized in general medicine wards.

Key Points

Question What is the likelihood of developing antibiotic-associated adverse drug events (ADEs) for hospitalized patients receiving antibiotic therapy?

Findings In this cohort study, medical records of 1488 adult inpatients were examined for 30 days after antibiotic initiation for the development of the following antibiotic-associated ADEs: gastrointestinal, dermatologic, musculoskeletal, hematologic, hepatobiliary, renal, cardiac, and neurologic; and 90 days for the development of *Clostridium difficile* infection or incident multidrug-resistant organism infection. Twenty percent of patients experienced at least 1 antibiotic-associated ADE.

Meaning These findings underscore the importance of judicious antibiotic prescribing to reduce the harm that can result from antibiotic-associated ADEs.

Methods

Setting and Patients

This study was conducted at the Johns Hopkins Hospital, a 1194-bed tertiary care facility in Baltimore, Maryland. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board, with a waiver of informed consent due to the retrospective nature of the study. The data were retrospectively collected on patients 18 years and older admitted to 4 general medicine services between September 2013 and June 2014.[6] All patients who received antibiotics for at least 24 hours were included. Exclusion criteria included prophylactic antibiotic use with no clear stop dates, antibiotics used for noninfectious indications (eg, rifaximin for hepatic encephalopathy, erythromycin for intestinal motility), topical or inhaled antibiotics, and antituberculosis regimens.

Data Collection and Definitions

Demographic data, preexisting medical conditions, antibiotic regimens, and ADEs were collected via patient medical record review. Both inpatient and outpatient medical records were reviewed to obtain follow-up data for patients in the Johns Hopkins Health System. In addition, the Epic Care Everywhere Network, a secure health information exchange, was accessed to view patient data from a large number of health care facilities throughout the United States.[22] This enabled the identification of patients presenting to outside emergency departments, hospitals, or primary care clinics with antibiotic-associated ADEs, if these facilities were in the Epic system.

All antibiotic regimens were adjudicated for appropriateness and associated ADEs by at least 2 infectious diseases physicians or pharmacists (P.D.T., E.A., K.D., and S.E.C.). Days of therapy (DOTs) were defined as the number of days from antibiotic initiation until the completion of antibiotic courses. A single DOT was recorded for each individual antibiotic administered to a patient on a given calendar day. Unnecessary antibiotic days were defined as DOTs that were not clinically indicated based on recommendations in the Johns Hopkins Hospital Antibiotic Guidelines.[23] For calculations of overall rates of ADEs, the denominator included all patients receiving antibiotics (n = 1488). For calculations involving a single antibiotic, the denominator included only patients receiving that particular antibiotic.

Avoidable ADEs were defined as the proportion of overall ADEs that occurred in patients for whom antibiotic therapy was considered not indicated. Nonindicated antibiotic regimens did not include patients with prolonged durations of therapy because our goal was to determine the incidence of adverse reactions for patients for whom no antibiotic therapy was necessary. For example, if a patient received ciprofloxacin for 15 days for pyelonephritis when 7 days would have been sufficient and the patient developed tendinitis on day 16, one would be unable to attribute the adverse event to the 7 indicated days of ciprofloxacin use or the additional 8 days of unnecessary ciprofloxacin use. We also did not consider overly broad spectrum antibiotic therapy prescribed for valid indications as not indicated because of the impossibility of knowing whether the patient would or would not have developed an ADE with a narrower choice, particularly in the same class of antibiotics.

Criteria used to define antibiotic-associated ADEs are summarized in Table 1. These definitions were derived from available literature, package inserts, and/or consensus opinions prior to any data collection related to the present work. Patients were observed for 30 days from the date of antibiotic initiation for most ADEs (gastrointestinal, dermatologic, musculoskeletal, hematologic, hepatobiliary, renal, cardiac, and neurologic events) and for 90 days from the date of antibiotic initiation for CDI and the development of multidrug-resistant organism (MDRO) infections not previously identified. All ADEs other than CDI or incident MDRO infections were censored at 30 days due to concerns for underestimating the incidence if a longer evaluation period was used because these ADEs generally occur during exposure to particular antibiotics or shortly thereafter. In contrast, data suggest that CDI and the emergence of

Table 1. Criteria Used for Antibiotic-Associated Adverse Drug Events

Adverse Drug Event	Definition
Within 30 d of Antibiotic Initiation	
Non-*Clostridium difficile*-associated diarrhea	>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. Patients with a positive *C difficile* PCR test result were excluded from this category
Nausea and vomiting	Nausea and vomiting associated with antibiotic administration, in the absence of an alternate explanation
Hematologic	Anemia (hemoglobin level <10 g/dL), leukopenia (white blood cell count <4500 cells/μL), or thrombocytopenia (platelet count <150 × 10^3/μL) with levels below patient's baseline and in the absence of bleeding or myelosuppressive therapies
Hepatobiliary	Cholestasis (total bilirubin level >3 mg/dL) or transaminitis (aspartate transaminase or alanine transaminase level >3 times patient's baseline) in the absence of existing hepatobiliary disease or recent biliary instrumentation
Renal	Increase in serum creatinine level >1.5 times patient's baseline in the absence of precipitating factors for acute kidney injury such as sepsis or the receipt of intravenous contrast or other nephrotoxic agents[24]
Neurologic	Altered mental status, peripheral neuropathy, or seizures in the absence of preexisting neurologic conditions, substance-related toxic effects, or infectious syndromes
Dermatologic	Rash, including hives, nonhives rashes, and red man syndrome, temporally associated with antibiotic administration with resolution on antibiotic discontinuation; excluding vancomycin-associated red man syndrome
Cardiac	QTc >440 ms in males or >460 ms in females in the absence of preexisting arrhythmias, based on ≥2 electrocardiograms
Anaphylaxis	Acute onset of respiratory compromise, hypotension, or end-organ dysfunction within minutes after initiation of antibiotic administration, in the absence of an alternative explanation
Myositis	Increase in creatine phosphokinase level >5 times patient's baseline, in the absence of existing myopathy or statin use
Within 90 d of Antibiotic Initiation	
C difficile infection	Clinical signs and symptoms consistent with *C difficile* infection in the setting of a positive *C difficile* PCR test result and the absence of laxative use
Infection with MDR organism[25]	Infection with any of the following organisms, in a patient without a history of colonization or infection with the same organism: methicillin-resistant *Staphylococcus aureus*; vancomycin-resistant enterococci; carbapenem-resistant Enterobacteriaceae; MDR *Acinetobacter*; MDR *Pseudomonas*; or a gram-negative organism with a greater than 2-fold increase in the minimum inhibitory concentration of an antibiotic compared with the initial infection

Abbreviations: MDR, multidrug-resistant; PCR, polymerase chain reaction.

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10.0; to convert white blood cell count to ×10^9 per liter, multiply by 0.001; to convert platelet count to ×10^9 per liter, multiply by 1.0; to convert bilirubin to micromoles per liter, multiply by 17.104.

MDRO infections can become clinically apparent several weeks to months after discontinuing antibiotic therapy.[26,27]

All potential ADEs were adjudicated in the context of the patient's medical history and clinical course to ensure that each event was likely to have been antibiotic associated, both to rule out alternative explanations and to appropriately categorize ADEs. Each ADE was then attributed to a single antibiotic, based on the likelihood of that antibiotic causing the specific ADE and the temporal relationship of the antibiotic's administration to the ADE. For example, acute kidney injury in a patient receiving vancomycin and cefepime would have been attributed to vancomycin use only. This step was performed to avoid overestimating the incidence of ADEs because most patients in our cohort received multiple antibiotics during their hospital stays. However, because virtually all antibiotics can cause CDI or the emergence of MDRO infections, the development of either of these 90-day ADEs was attributed to all preceding antibiotic used.

Statistical Analysis

Rates per 10 000 person-days and 95% confidence intervals were calculated for each ADE and antibiotic class. For 30-day ADEs, the numerator was the number of ADEs attributed to each antibiotic or class of antibiotics. The denominator was the person-time at risk for all patients who received that particular antibiotic or class of antibiotics, computed as the time, in days, from antibiotic initiation to the ADE for patients who experienced the ADE, with censoring at 30 days for patients who did not experience the ADE. The proportion of 30-day antibiotic-associated ADEs per antibiotic or antibiotic class and the proportion of patients receiving a particular antibiotic or antibiotic class who developed a 30-day ADE were also calculated. For 90-day ADEs, the numerator accounted for all preceding antibiotics rather than only a single antibiotic. The denominator was the person-time at risk for all patients who received antibiotics, computed as the time, in days, from antibiotic initiation to ADE onset, with censoring at 90 days. Hazard ratios were calculated to identify the incremental risk of an ADE conferred by each additional day of antibiotic use. All analyses were performed using Stata 13 (StataCorp).

Results

Antibiotic Regimens

Of the 5579 patients admitted to the 4 included medicine wards during the study period, 1488 (27%) patients received antibiotics for at least 24 hours and were included in the analysis. Previous work describes the demographic data, preexisting medical conditions, sources of infection, and "appropriateness" of antibiotic use of the included population in more detail.[6] In brief, the median age was 59 years (interquartile range [IQR], 49-69 years) and 758 (51%) participants were female. The most common underlying medical conditions were diabetes (491 [33%]), structural lung disease (327 [22%]), and congestive heart failure with an ejection fraction of less than 40% (178 [12%]). The median length of hospital stay was 4 days (IQR, 2-9 days). The most common indications for antibiotic

therapy were urinary tract infections (179 [12%]), skin and soft-tissue infections (119 [8%]), and community-acquired pneumonia (104 [7%]).

The most frequently prescribed antibiotics were third-generation cephalosporins (607 [41%] regimens), parenteral vancomycin (544 [37%] regimens), and cefepime (414 [28%] regimens) (Table 2). The majority of patients (1176 [79%]) received more than 1 antibiotic during the hospitalization. The median DOTs per patient was 7 days (IQR, 4-14 days). A total of 324 unique ADEs occurred; 298 (20%) patients experienced at least 1 antibiotic-associated ADE. The overall rate of antibiotic-associated ADEs was 22.9 per 10 000 person-days.

Every additional 10 antibiotic DOTs conferred a 3% increased risk of an ADE. A total of 236 (73%) antibiotic-associated ADEs occurred during hospitalization and the remaining 88 (27%) occurred after hospital discharge including 33 (18%) 30-day ADEs, 11 (20%) CDIs, and 44 (52%) MDRO infections. The study investigators determined that 287 (19%) of antibiotic regimens were not clinically indicated, most commonly because of treatment of asymptomatic bacteriuria or treatment of noninfectious lower respiratory tract conditions (eg, aspiration pneumonitis, congestive heart failure).[6] Of the 287 nonindicated antibiotic regimens, 56 (20%) were associated with an ADE.

30-Day ADEs

Of the 324 overall ADEs, 186 (57%) were 30-day ADEs. The median time to development of a 30-day ADE was 5 days (IQR, 3-8 days). The median times to 30-day ADEs for the various organ systems were as follows: cardiac, 11 days (IQR, 4-18 days); gastrointestinal, 5 days (IQR, 2-9 days); hematologic, 12 days (IQR, 6-24 days); hepatobiliary, 8 days (IQR, 4-12 days); renal, 5 days (IQR, 2-10 days); and neurologic, 3 days (IQR, 2-4 days). The most common ADEs were gastrointestinal, renal, and hematologic abnormalities, accounting for 78 (42%), 45 (24%), and 28 (15%) 30-day ADEs, respectively (Table 2). Tables 3 and 4 outline the proportions of 30-day ADEs attributable to specific antibiotics or antibiotic classes and the proportion of patients receiving a specific antibiotic or antibiotic class who developed 30-day ADEs, respectively.

Aminoglycosides, parenteral vancomycin, and trimethoprim-sulfamethoxazole were associated with the highest rates of nephrotoxic effects at 21.2 (95% CI, 12.5-66.0), 12.1 (95% CI, 7.7-19.0), and 13.2 (95% CI, 5.9-29.3) episodes per 10 000 person-days, respectively (Table 2). Two patients experienced QTc prolongation—1 receiving azithromycin and 1 receiving ciprofloxacin after 4 and 18 days of therapy, respectively. Seven patients (6.7 [95% CI, 2.7-12.0] episodes per 10 000 person-days) receiving cefepime developed neurotoxic effects, including encephalopathy or seizures. Less frequent 30-day ADEs, all occurring in single patients, included cefepime-associated anaphylaxis, piperacillin-tazobactam-associated drug fever, daptomycin-associated myositis, ciprofloxacin-associated tendinitis, trimethoprim-sulfamethoxazole-associated pancreatitis, linezolid-associated peripheral neuropathy, vancomycin-associated hives, and a trimethoprim-sulfamethoxazole-associated nonhives rash.

90-Day ADEs

There were 138 ADEs occurring within 90 days, accounting for 43% of all ADEs. Of these 138 ADEs, 54 (39%) were CDI and 84 (61%) were MDRO infections. The median time to development of a 90-day ADE was 15 days (IQR, 4-34 days). The rate of CDI was 3.9 (95% CI, 3.0-5.2) per 10 000 person-days for patients receiving antibiotics, corresponding to 54 (4%) study patients developing CDI within 90 days of antibiotic initiation. The antibiotics most frequently associated with CDI were third-generation cephalosporins (present in 28 [52%] regimens preceding CDI), cefepime (26 [48%] regimens), and fluoroquinolones (19 [35%] regimens).

The rate of emergence of incident MDRO infections was 6.1 (95% CI, 4.9-7.6) per 10 000 person-days, corresponding to 84 [6%] study patients developing an infection with a new MDRO within 90 days of antibiotic initiation. Subsequent gram-positive resistance was observed in 60 (4%) patients, at a rate of 4.8 (95% CI, 3.7-6.1) cases per 10 000 person-days. Forty (67%) of the MDRO cases were related to vancomycin-resistant enterococci infections. Gram-negative resistance occurred less frequently at a rate of 1.7 (95% CI, 1.2-2.6) cases per 10 000 person-days, or in 30 (2%) patients, with extended-spectrum β-lactamase production being the most common resistance mechanism identified.

Clinically Significant ADEs

Antibiotic-associated ADEs were then categorized into clinically significant and non-clinically significant categories. Only 1 category was selected per patient, with the more severe category selected when multiple categories were met. A total of 314 (97%) of the 324 antibiotic-associated ADEs were considered clinically significant because of the following reasons: new hospitalization(s) (n = 10 [3%]), prolonged hospitalization (n = 77 [24%]), additional clinic or emergency department visits (n = 29 [9%]), and additional laboratory tests, electrocardiograms, or imaging (n = 198 [61%]). There were no deaths attributable to any antibiotic-associated ADE.

Discussion

We found that 20% of hospitalized patients receiving at least 24 hours of antibiotic therapy developed an antibiotic-associated ADE. Moreover, 20% of ADEs were attributable to antibiotics prescribed for conditions for which antibiotics were not indicated. Every 10 DOTs conferred an additional 3% risk of an ADE. Our findings underscore the importance of avoiding unnecessary antibiotic prescribing to reduce the harm that can result from antibiotic-associated ADEs.

Previous studies on antibiotic-associated ADEs in the inpatient setting have largely been limited to single infectious syndromes or single antibiotic classes.[18-21,28] For example, Lin and colleagues[18] evaluated the incidence of antibiotic-associated ADEs using an administrative database of hospitalized patients with pneumonia. They found that even though less than 1% of patients developed ADEs, the presence of an antibiotic-associated ADE was an independent predictor of prolonged hospital lengths of stay and total hospital charges.

Table 2. Rates of 30-Day Antibiotic-Associated Adverse Drug Events in 1488 Hospitalized Patients Receiving Antibiotics per 10 000 Person-days (PD)[a]

Antibiotic Agent	No. of Patients Receiving Agent	Cardiac		Gastrointestinal[b]		Hematologic		Hepatobiliary		Renal		Neurologic		Other Events[c]	
		No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)	No.	Rate per 10 000 PD (95% CI)
β-Lactam[d]	1187	0	...	59	17.4 (13.5-22.4)	27	8.7 (5.3-11.3)	6	3.4 (3.1-7.9)	17	6.9 (3.1-12.9)	10	3.8 (1.5-5.3)	2	0.6 (0.1-2.2)
Ampicillin	63	0	...	2	11.6 (2.9-46.2)	1	5.6 (0.8-39.6)	0	...	1	5.6 (0.8-39.6)	0	...	0	...
Amoxicillin-clavulanate	102	0	...	3	12.6 (4.5-25.2)	0	...	0	...	0	...	0	...	0	...
Ampicillin-sulbactam	52	0	...	1	7.2 (1.0-51.2)	0	...	0	...	2	14.2 (13.9-49.6)	0	...	0	...
Oxacillin	33	0	...	4	37.1 (12.0-105.0)	1	10.8 (1.5-76.4)	2	21.6 (5.4-86.6)	0	...	0	...	0	...
Piperacillin-tazobactam	315	0	...	16	14.8 (13.1-23.0)	4	4.3 (1.6-11.4)	1	1.1 (0.2-7.9)	1	1.1 (0.2-7.9)	1	1.1 (0.2-7.9)	1	1.1 (0.2-7.9)
Cefazolin	79	0	...	0	...	1	4.4 (0.6-31.4)	0	...	2	8.2 (1.6-24.8)	0	...	0	...
Ceftriaxone	607	0	...	14	8.0 (4.7-13.5)	11	6.2 (3.4-11.3)	3	2.1 (1.4-12.3)	5	2.8 (1.2-6.8)	1	0.6 (0.1-3.9)	0	...
Cefpodoxime	89	0	...	2	7.7 (1.9-30.9)	0	...	0	...	0	...	0	...	0	...
Cefepime	414	0	...	10	8.5 (4.6-15.8)	6	5.0 (2.2-11.1)	0	...	6	5.0 (2.2-11.1)	7	6.7 (2.7-12.0)	1	0.8 (0.1-5.8)
Ertapenem	85	0	...	3	12.1 (3.9-37.6)	0	...	0	...	0	...	0	...	0	...
Meropenem	80	0	...	4	18.0 (6.8-48.0)	3	12.9 (4.2-40.1)	0	...	0	...	1	4.4 (0.8-29.4)	0	...
Non-β-lactams															
Aminoglycosides	32	0	...	0	...	0	...	0	...	2	21.2 (12.5-66.0)	0	...	0	...
Azithromycin	400	1	0.8 (0.1-5.9)	1	0.8 (0.1-5.9)	0	...	4	3.4 (1.3-9.0)	0	...	0	...	0	...
Clindamycin	193	0	...	3	5.4 (1.8-16.8)	0	...	0	...	0	...	0	...	0	...
Daptomycin	8	0	...	0	...	0	...	0	...	0	...	0	...	1	44.8 (6.3-318.3)
Doxycycline	57	0	...	2	12.4 (3.1-49.7)	0	...	0	...	0	...	0	...	0	...
Fluoroquinolones	394	1	0.9 (0.1-6.2)	5	4.4 (1.8-10.6)	1	0.9 (0.1-6.2)	3	2.6 (0.8-8.0)	1	0.9 (0.1-6.2)	1	0.9 (0.1-6.2)	1	0.9 (0.1-6.2)
Linezolid	23	0	...	0	...	0	...	0	...	0	...	1	15.8 (2.2-112.3)	0	...
Metronidazole	175	0	...	1	2.0 (0.3-14.2)	0	...	0	...	0	...	1	2.0 (0.3-14.2)	0	...
Trimethoprim-sulfamethoxazole	155	0	...	5	11.2 (4.7-26.9)	0	...	0	...	6	13.2 (5.9-29.3)	0	...	1	2.1 (0.3-15.1)
Intravenous vancomycin	544	0	...	2	1.3 (0.3-5.2)	0	...	0	...	19	12.1 (7.7-19.0)	0	...	2	1.3 (0.3-5.2)
Overall rates	1488[e]	2	0.4 (0.1-1.8)	78	18.2 (14.6-22.8)	28	6.4 (4.4-9.2)	13	2.9 (1.7-5.0)	45	10.6 (7.9-14.2)	13	2.9 (1.7-5.0)	7	1.6 (0.8-3.3)

[a] The following regimens are included in the overall rates and resulted in no 30-d adverse drug events: penicillin (21), amoxicillin (47), dicloxacillin (1), cephalexin (44), second-generation cephalosporins (38), ceftazidime (6), ceftaroline (8), aztreonam (22), fosfomycin (10), nitrofurantoin (26), tigecycline (3), oral vancomycin (84).

[b] Includes nausea, emesis, non-*Clostridium difficile*–associated diarrhea.

[c] Other adverse drug events include cefepime-associated anaphylaxis (1), piperacillin-tazobactam–associated drug fever (1), ciprofloxacin-associated tendinitis (1), daptomycin-associated myositis (1), trimethoprim-sulfamethoxazole–associated pancreatitis (1), vancomycin-associated hives (1), and trimethoprim-sulfamethoxazole-related nonhives rash (1).

[d] Some patients received more than 1 β-lactam antibiotic.

[e] Most patients (1176 [79%]) received more than 1 antibiotic.

Table 3. Proportion of 30-Day Antibiotic-Associated Adverse Drug Events in 1488 Hospitalized Patients Receiving Systemic Antibiotic Therapy[a]

Antibiotic Agent	No. of Patients Receiving Agent	No. (%)						
		Cardiac	Gastrointestinal[b]	Hematologic	Hepatobiliary	Renal	Neurologic	Other Events[c]
β-Lactams[d]	1187	0	59 (5.0)	27 (2.3)	6 (0.5)	17 (1.4)	10 (0.8)	2 (0.2)
Ampicillin	63	0	2 (3.2)	1 (1.6)	1 (1.6)	1 (1.6)	0	0
Amoxicillin-clavulanate	102	0	3 (2.9)	0	0	0	0	0
Ampicillin-sulbactam	52	0	1 (1.9)	0	0	2 (3.8)	0	0
Oxacillin	33	0	4 (12.1)	1 (3.0)	2 (6.0)	0	0	0
Piperacillin-tazobactam	315	0	16 (5.1)	4 (1.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Cefazolin	79	0	0	1 (1.3)	0	2 (2.5)	0	0
Ceftriaxone	607	0	14 (2.3)	11 (1.8)	3 (0.5)	5 (0.8)	1 (0.2)	0
Cefpodoxime	89	0	2 (2.2)	0	0	0	0	0
Cefepime	414	0	10 (2.4)	6 (1.4)	0	6 (1.4)	7 (1.7)	1 (0.2)
Ertapenem	85	0	3 (3.5)	0	0	0	0	0
Meropenem	80	0	4 (5.0)	3 (3.8)	0	0	1 (1.3)	0
Non-β-lactams								
Aminoglycosides	32	0	0	0	0	2 (6.3)	0	0
Azithromycin	400	1 (0.3)	1 (0.3)	0	4 (1.0)	0	0	0
Clindamycin	193	0	3 (1.6)	0	0	0	0	0
Daptomycin	8	0	0	0	0	0	0	1 (12.5)
Doxycycline	57	0	2 (3.5)	0	0	0	0	0
Fluoroquinolones	394	1 (0.3)	5 (1.3)	1 (0.3)	3 (0.8)	1 (0.3)	1 (0.3)	1 (0.3)
Linezolid	23	0	0	0	0	0	1 (4.3)	0
Metronidazole	175	0	1 (0.6)	0	0	0	1 (0.6)	0
Trimethoprim-sulfamethoxazole	155	0	5 (3.2)	0	0	6 (3.9)	0	1 (0.6)
Intravenous vancomycin	544	0	2 (0.4)	0	0	19 (3.5)	0	2 (0.4)
Any antibiotics	1488[e]	2 (0.1)	78 (5.2)	28 (1.9)	13 (0.9)	45 (3.0)	13 (0.9)	7 (0.5)

[a] The following regimens are included in the overall rates and resulted in no 30-d adverse drug events: penicillin (21), amoxicillin (47), dicloxacillin (1), cephalexin (44), second-generation cephalosporins (38), ceftazidime (6), ceftaroline (8), aztreonam (22), fosfomycin (10), nitrofurantoin (26), tigecycline (3), oral vancomycin (84).

[b] Includes nausea, emesis, non-*Clostridium difficile*–associated diarrhea.

[c] Other adverse drug events include cefepime-associated anaphylaxis (1), piperacillin-tazobactam–associated drug fever (1), ciprofloxacin-associated tendinitis (1), daptomycin-associated myositis (1), trimethoprim-sulfamethoxazole–associated pancreatitis (1), vancomycin-associated hives (1), and trimethoprim-sulfamethoxazole-associated nonhives rash (1).

[d] Some patients received more than 1 β-lactam antibiotic.

[e] Most patients (1176 [79%]) received more than 1 antibiotic.

Werner et al[20] evaluated the frequency of adverse events related to unnecessary fluoroquinolone use in hospitalized patients based on medical record review. They found that approximately 40% of days of fluoroquinolone therapy were unnecessary and 27% of regimens were associated with adverse events including gastrointestinal events (14%), MDRO colonization (8%), and CDI (4%). Finally, Macy and Contreras[19] evaluated the incidence of cephalosporin-associated ADEs using an administrative database and found that the most frequently reported serious ADEs were CDI, occurring in approximately 1% of patients.

We believe that our study enhances these investigations in a number of ways. First, unlike previous studies, we evaluated antibiotic-associated ADEs that occurred in both the inpatient setting as well as the outpatient setting after hospital discharge, enabling us to produce a more global picture of the overall incidence of antibiotic-associated ADEs.[13,18,19,20] Our previous work suggests that approximately 40% of antibiotics prescribed for hospitalized patients represent antibiotics prescribed at the time of hospital discharge that are to be continued after leaving the hospital.[6] We believe that it is important to include these antibiotic days in estimates of antibiotic-associated adverse events for hospitalized patients. Second, in our cohort, infectious diseases physicians and pharmacists reviewed all patient medical records to identify ADEs and to determine whether they were most likely attributable to recent or current antibiotic use using strict, predefined criteria. In contrast, previous studies have generally used administrative databases, in which relevant events are commonly miscoded and through which attributable risk cannot always be assigned.[13,18] Furthermore, we did not limit our evaluation to specific antibiotic classes but, rather, included all antibiotic classes.

Limitations

Our study has a number of limitations. This was a single-center study at an academic hospital with a medically complex patient population. Replication of our results at other in-

Table 4. Proportion of 1488 Patients Receiving Systemic Antibiotic Therapy Who Developed Adverse Drug Events (ADEs) Within 30 Days[a]

Antibiotic Agents	No. (%) Total ADEs	Cardiac	Gastrointestinal[b]	Hematologic	Hepatobiliary	Renal	Neurologic	Other Events[c]
Any β-lactam[d]	121 (65.1)	0	59 (75.6)	27 (96.4)	6 (46.2)	17 (37.8)	10 (76.9)	2 (28.6)
Ampicillin	4 (2.2)	0	2 (2.6)	1 (3.6)	0	1 (2.2)	0	0
Amoxicillin-clavulanate	3 (1.6)	0	3 (3.8)	0	0	0	0	0
Ampicillin-sulbactam	3 (1.6)	0	1 (1.3)	0	0	2 (4.4)	0	0
Oxacillin	7 (3.8)	0	4 (5.1)	1 (3.6)	2 (15.4)	0	0	0
Piperacillin-tazobactam	24 (12.9)	0	16 (20.5)	4 (14.3)	1 (7.7)	1 (2.2)	1 (7.7)	1 (14.3)
Cefazolin	3 (1.6)	0	0	1 (3.6)	0	2 (4.4)	0	0
Ceftriaxone	34 (18.3)	0	14 (17.9)	11 (39.3)	3 (23.1)	5 (11.1)	1 (7.7)	0
Cefpodoxime	2 (1.1)	0	2 (2.6)	0	0	0	0	0
Cefepime	30 (16.1)	0	10 (12.8)	6 (21.4)	0	6 (13.3)	7 (53.8)	1 (14.3)
Ertapenem	3 (1.6)	0	3 (3.8)	0	0	0	0	0
Meropenem	8 (4.3)	0	4 (5.1)	3 (10.7)	0	0	1 (7.7)	0
Non-β-lactams								
Aminoglycosides	2 (1.1)	0	0	0	0	2 (4.4)	0	0
Azithromycin	6 (3.2)	1 (50.0)	1 (1.3)	0	4 (30.8)	0	0	0
Clindamycin	3 (1.6)	0	3 (3.8)	0	0	0	0	0
Daptomycin	1 (0.5)	0	0	0	0	0	0	1 (14.3)
Doxycycline	2 (1.1)	0	2 (2.6)	0	0	0	0	0
Fluoroquinolones	13 (7.0)	1 (50.0)	5 (6.4)	1 (3.6)	3 (23.1)	1 (2.2)	1 (7.7)	1 (14.3)
Linezolid	1 (0.5)	0	0	0	0	0	1 (7.7)	0
Metronidazole	2 (1.1)	0	1 (1.3)	0	0	0	1 (7.7)	0
Trimethoprim-sulfamethoxazole	12 (6.5)	0	5 (6.4)	0	0	6 (13.3)	0	1 (14.3)
Intravenous vancomycin	23 (12.4)	0	2 (2.6)	0	0	19 (42.2)	0	2 (28.6)
All antibiotics*	186 (100)	2 (100)	78 (100)	28 (100)	13 (100)	45 (100)	13 (100)	7 (100)

[a] The following regimens are included in the overall rates and resulted in no 30-d adverse drug events: penicillin (21), amoxicillin (47), dicloxacillin (1), cephalexin (44), second-generation cephalosporins (38), ceftazidime (6), ceftaroline (8), aztreonam (22), fosfomycin (10), nitrofurantoin (26), tigecycline (3), oral vancomycin (84).

[b] Includes nausea, emesis, non-*Clostridium difficile*–associated diarrhea.

[c] Other ADEs include cefepime-associated anaphylaxis (1), piperacillin-tazobactam–associated drug fever (1), ciprofloxacin-associated tendinitis (1), daptomycin-associated myositis (1), trimethoprim-sulfamethoxazole–associated pancreatitis (1), vancomycin-associated hives (1), and vancomycin-associated nonhives, non–red man syndrome rash (1).

[d] Some patients received more than 1 β-lactam antibiotic.

* Most patients (1176 [79%]) received more than 1 antibiotic.

stitutions and in other patient populations is necessary to enhance the generalizability of our findings. This would also allow for ADE estimates for antibiotic agents not included on our hospital formulary. Furthermore, because prescriptions of some antibiotics were so infrequent (eg, penicillin, ceftaroline fosamil, tigecycline), accurate estimates of some drug-specific ADEs could not be calculated. Our approximations of antibiotic-associated ADEs are likely underestimations for a number of reasons. First, our hospital has had a robust antibiotic stewardship program since 2002 that remained active during the study period, likely reducing overall antibiotic prescriptions, durations of antibiotic therapy, and consequently antibiotic-associated ADEs. Second, we were unable to evaluate data from patients who had follow-up medical care outside the Epic Care Everywhere network, for example those who presented to primary care clinicians, emergency departments, or urgent care centers not using the Epic electronic medical record system.[22] Of note, only 119 (8%) patients were considered lost to follow-up with no subsequent inpatient or outpatient visits documented in the Epic Care Everywhere network. Additionally, it is plausible that a portion of patients in this cohort may have previously experienced serious antibiotic-associated ADEs, leading to future avoidance of these agents (eg, hives from penicillin use as a child), also potentially underestimating the incidence of antibiotic-associated ADEs. Finally, we did not include excessively prolonged durations of antibiotic therapy or inappropriately broad antibiotic use toward our calculation of avoidable antibiotic-associated ADEs, likely underestimating this value.

Conclusions

In summary, antibiotic-associated ADEs are common among inpatients receiving antibiotics, some of which may be avoid-

able with more judicious use of antibiotics. The frequency of antibiotic-associated ADEs may not be recognized by clinicians because ADEs have varied manifestations, clinicians may be unaware of the risks associated with specific antibiotic agents, or because they may occur after patients are discharged from the hospital. Our findings provide quantitative data about the risk of ADEs that clinicians should consider when weighing decisions to initiate or discontinue antibiotic therapy and lend further credence to the importance of antibiotic stewardship to optimize patient safety.

ARTICLE INFORMATION

Accepted for Publication: April 6, 2017.

Published Online: June 12, 2017. doi:10.1001/jamainternmed.2017.1938

Author Contributions: Dr Tamma had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Tamma, Avdic, Li, Cosgrove.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Tamma, Avdic, Li, Dzintars.
Critical revision of the manuscript for important intellectual content: Avdic, Li, Dzintars, Cosgrove.
Statistical analysis: Tamma, Li.
Obtained funding: Tamma, Avdic, Cosgrove.
Administrative, technical, or material support: Avdic, Dzintars.
Supervision: Dzintars, Cosgrove.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was made possible by an investigator-initiated grant from Pfizer Independent Grants for Learning and Change and The Joint Commission.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Yuan Zhao, MPH, Johns Hopkins University, and John Keenan, MD, Johns Hopkins University, for their assistance with data collection. Dr Keenan received a portion of his salary from Pfizer/The Joint Commission.

REFERENCES

1. Magill SS, Edwards JR, Beldavs ZG, et al; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Prevalence of antimicrobial use in US acute care hospitals, May-September 2011. *JAMA*. 2014;312(14):1438-1446.

2. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. *Arch Intern Med*. 2003;163(8):972-978.

3. Camins BC, King MD, Wells JB, et al. Impact of an antimicrobial utilization program on antimicrobial use at a large teaching hospital: a randomized controlled trial. *Infect Control Hosp Epidemiol*. 2009;30(10):931-938.

4. Ingram PR, Seet JM, Budgeon CA, Murray R. Point-prevalence study of inappropriate antibiotic use at a tertiary Australian hospital. *Intern Med J*. 2012;42(6):719-721.

5. Cosgrove SE, Seo SK, Bolon MK, et al; CDC Prevention Epicenter Program. Evaluation of postprescription review and feedback as a method of promoting rational antimicrobial use: a multicenter intervention. *Infect Control Hosp Epidemiol*. 2012;33(4):374-380.

6. Tamma PD, Avdic E, Keenan JF, et al. What is the more effective antibiotic stewardship intervention: pre-prescription authorization or post-prescription review with feedback? *Clin Infect Dis*. 2017;64(5):537-543.

7. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis*. 2014;14:13.

8. Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for *Clostridium difficile* infection after exposure to antibiotics. *J Antimicrob Chemother*. 2012;67(3):742-748.

9. Liu NW, Shatagopam K, Monn MF, et al. Risk for *Clostridium difficile* infection after radical cystectomy for bladder cancer: analysis of a contemporary series. *Urol Oncol*. 2015;33(12):503.e17-503.e22.

10. Kuster SP, Rudnick W, Shigayeva A, et al; Toronto Invasive Bacterial Diseases Network. Previous antibiotic exposure and antimicrobial resistance in invasive pneumococcal disease: results from prospective surveillance. *Clin Infect Dis*. 2014;59(7):944-952.

11. Alshammari TM, Larrat EP, Morrill HJ, Caffrey AR, Quilliam BJ, LaPlante KL. Risk of hepatotoxicity associated with fluoroquinolones: a national case-control safety study. *Am J Health Syst Pharm*. 2014;71(1):37-43.

12. Torres MJ, Blanca M, Fernandez J, et al; ENDA; EAACI Interest Group on Drug Hypersensitivity. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy*. 2003;58(10):961-972.

13. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis*. 2008;47(6):735-743.

14. File TM Jr, Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. *Antimicrob Agents Chemother*. 1997;41(9):1965-1972.

15. Hammond DA, Smith MN, Li C, Hayes SM, Lusardi K, Bookstaver PB. Systematic review and meta-analysis of acute kidney injury associated with concomitant vancomycin and piperacillin/tazobactam. *Clin Infect Dis*. 2017;64(5):666-674.

16. Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. *Br J Clin Pharmacol*. 1998;46(5):505-511.

17. Pretorius RW, Gataric G, Swedlund SK, Miller JR. Reducing the risk of adverse drug events in older adults. *Am Fam Physician*. 2013;87(5):331-336.

18. Lin RY, Nuruzzaman F, Shah SN. Incidence and impact of adverse effects to antibiotics in hospitalized adults with pneumonia. *J Hosp Med*. 2009;4(2):E7-E15.

19. Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: a retrospective population-based analysis. *J Allergy Clin Immunol*. 2015;135(3):745-52.e5.

20. Werner NL, Hecker MT, Sethi AK, Donskey CJ. Unnecessary use of fluoroquinolone antibiotics in hospitalized patients. *BMC Infect Dis*. 2011;11:187.

21. Blumenthal KG, Kuhlen JL Jr, Weil AA, et al. Adverse drug reactions associated with ceftaroline use: a 2-center retrospective cohort. *J Allergy Clin Immunol Pract*. 2016;4(4):740-746.

22. Epic Care Everywhere Network. https://www.epic.com/CareEverywhere/. Accessed December 6, 2016.

23. Johns Hopkins Medicine Antibiotic Guidelines 2015-2016. http://www.hopkinsmedicine.org/amp. Accessed February 5, 2017.

24. Goldstein SL, Kirkendall E, Nguyen H, et al. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. *Pediatrics*. 2013;132(3):e756-e767.

25. Centers for Disease Control and Prevention. Antimicrobial resistant phenotype definitions. https://www.cdc.gov/nhsn/pdfs/ps-analysis-resources/phenotype_definitions.pdf. Accessed January 26, 2017.

26. Anand A, Bashey B, Mir T, Glatt AE. Epidemiology, clinical manifestations, and outcome of *Clostridium difficile*-associated diarrhea. *Am J Gastroenterol*. 1994;89(4):519-523.

27. Gerding DN, Olson MM, Peterson LR, et al. *Clostridium difficile*-associated diarrhea and colitis in adults: a prospective case-controlled epidemiologic study. *Arch Intern Med*. 1986;146(1):95-100.

28. Johannes CB, Ziyadeh N, Seeger JD, Tucker E, Reiter C, Faich G. Incidence of allergic reactions associated with antibacterial use in a large, managed care organisation. *Drug Saf*. 2007;30(8):705-713.

29. Meropol SB, Localio AR, Metlay JP. Risks and benefits associated with antibiotic use for acute respiratory infections: a cohort study. *Ann Fam Med*. 2013;11(2):165-172.