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Risk of Subsequent Sepsis Within 90 Days After a Hospital Stay by Type of Antibiotic Exposure

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Background. We examined the risk of sepsis within 90 days after discharge from a previous hospital stay by type of antibiotic received during the previous stay.

Methods. We retrospectively identified a cohort of hospitalized patients from the Truven Health MarketScan Hospital Drug Database. We examined the association between the use of certain antibiotics during the initial hospital stay, determined a priori, and the risk of postdischarge sepsis controlling for potential confounding factors in a multivariable logistic regression model. Our primary exposure was receipt of antibiotics more strongly associated with clinically important microbiome disruption. Our primary outcome was a hospital stay within 90 days of the index stay that included an *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) discharge diagnosis of severe sepsis (*ICD-9-CM* code 995.92) or septic shock (785.52).

Results. Among 516 hospitals, we randomly selected a single stay for eligible patients. In 0.17% of these patients, severe sepsis/septic shock developed within 90 days after discharge. The risk of sepsis associated with exposure to our high-risk antibiotics was 65% higher than in those without antibiotic exposure.

Conclusions. Our study identified an increased risk of sepsis within 90 days of discharge among patients with exposure to high-risk antibiotics or increased quantities of antibiotics during hospitalization. Given that a significant proportion of inpatient antimicrobial use may be unnecessary, this study builds on previous evidence suggesting that increased stewardship efforts in hospitals may not only prevent antimicrobial resistance, *Clostridium difficile* infection, and other adverse effects, but may also reduce unwanted outcomes potentially related to disruption of the microbiota, including sepsis.

Keywords. sepsis; septic shock; anti-bacterial agents; administrative data; health-care associated infections.

Sepsis is a life-threatening clinical syndrome characterized by acute organ dysfunction resulting from infection and a major contributor to excess morbidity, mortality, and healthcare costs [1]. Nearly one-quarter of sepsis cases have suspected gastrointestinal or an unknown source of infection [2–4]. In addition, there is a long-recognized role for the middle and lower gastrointestinal tract microbiota in the regulation of the immune response, specifically in sepsis [5–7]. Emerging evidence shows that major disruptive forces, such as antibiotics, can lead to shifts in the microbiota that have greater pathogenic potential [8, 9], possibly leading to bacterial translocation [10, 11], a dysregulated immune response [5], or both.

Antibiotics are essential treatments for many hospitalized patients. More than half of hospitalized patients receive an antibiotic [12, 13], but an estimated 30%–50% of antibiotic use in hospitals is inappropriate [13, 14]. Widespread use of antibiotics not only leads to selection for drug resistance and increases risk for *Clostridium difficile* infection (CDI) but also may increase a patient's risk for later development of sepsis [15]. Prescott et al [16] observed an increase in sepsis after hospital discharge for patients with either an infection-related hospitalization or hospitalization with CDI, which they suggested may be due to a distortion of the microbiota, at least partially by antibiotics. It is important to understand the association between antibiotic administration and sepsis and, if a causal association exists, accurately estimate the effect size of antibiotics in precipitating sepsis.

In the current study, our objective was to examine the risk of sepsis within 90 days after discharge among a cohort of US hospitalized patients, according to receipt during a previous hospitalization of antibiotics categorized a priori based on their propensity to disrupt the microbiome in a clinically important way.

METHODS

Data Sources

Adult hospital discharge and drug use data was obtained from the Truven Health MarketScan Hospital Drug Database (HDD), which contains individual billing records for all patients from approximately 500 hospitals. The use of this database to estimate US antimicrobial usage has been described elsewhere and been shown to be representative of acute care hospitals in the

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United States [12, 13, 17]. Because the information required to follow up individuals longitudinally changed from 2010 to 2011, we included hospital admissions for all patients discharged during 2 time periods, from 1 January 2007 through 30 September 2010 and from 1 January 2011 through 30 September 2014. Similar to the procedure used in a previous study [12], for each hospitalization we identified patient demographic and clinical information from the discharge billing data and antibiotic doses administered from the drug utilization data. We also categorized antibiotic doses into 14 classes: aminoglycoside, first- or second-generation cephalosporin, third- or fourth-generation cephalosporin, lincosamide, fluoroquinolone, macrolide, vancomycin, sulfa, β-lactam/β-lactamase inhibitor combinations, carbapenem, penicillin, tetracycline, metronidazole, and miscellaneous. We excluded drugs with nonoral, nonparental routes of administration.

Study Settings and Patients

Patients aged ≥18 years with an inpatient stay were included. For patients with multiple hospital stays within the study period, one stay was randomly selected as the index stay for each patient. Patients with previously documented sepsis or sepsis documented during the index stay and who died during the index stay or in the hospital within the 90 days after a nonsepsis outcome were excluded. We excluded childbirth-related inpatient stays (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes V30-V39).

Exposures

Antibiotic exposures were identified from the selected index hospital stay and stratified into 3 groups of a priori risk based on published epidemiologic strength of association with CDI, which was considered a marker for intestinal microbiota disruption with demonstrated clinical importance [18, 19]. Because the intrinsic activity of an antibiotic against *C. difficile* may reduce this association by suppressing *C. difficile* while the patient is receiving the antibiotic, oral vancomycin was moved to a higher category of risk than would be suggested by its association with CDI, reflecting recent data demonstrating its profound microbiota-disruption potential [20]. High-risk exposures included receipt of third- or fourth-generation cephalosporins, fluoroquinolones, lincosamides, β-lactam/β-lactamase inhibitor combinations, oral vancomycin, and carbapenems [21, 22]. Low-risk exposures included receipt of first- or second-generation cephalosporins, macrolide, tetracycline, metronidazole, and sulfa without receipt of a high-risk antibiotic. Control exposures included receipt of an aminoglycoside, penicillin or intravenous vancomycin (antibiotics that minimally disrupt gastrointestinal flora), without receipt of intermediate- or high-risk antibiotics. Finally, we compared the risk of sepsis in exposed patients to patients without exposure to any antibiotic, our reference group.

Outcome

Our primary outcome (severe sepsis) was a hospital stay within 90 days of the index stay that included an *ICD-9-CM* discharge diagnosis of severe sepsis (*ICD-9-CM* code 995.92) or septic shock (785.52), identified in any position on the hospital discharge bill. We evaluated a secondary outcome (sepsis), using a published definition for hospital administrative data [23], which requires *ICD-9-CM* codes for both infection and acute organ dysfunction within the same hospitalization or a sepsis specific diagnosis [23]. This definition was previously validated against chart review with high specificity and sensitivity [24]. For 1 data source within the HDD, admission dates are masked; therefore, instead of within 90 days, stays within the 2 months after the discharge month were identified.

Statistical Analysis

Univariate comparisons of exposure and outcome groups were conducted using a χ^2 test for categorical variables. To evaluate the risk of sepsis by exposure group, we conducted a multivariable logistic regression model comparing the odds of sepsis for those with high- and low-risk antibiotic exposures to control antibiotic exposures and those without any antibiotic agent exposures. In addition, we evaluated the dose-response relationship in multivariable logistic models, which included either the total duration of antibiotic therapy (in days) or the number of antibiotic classes the patient received during the index stay as dose-response variables. All models included patient demographic and clinical characteristics from their index stay, including sex, age category, length of stay, primary payer, previous hospitalization, comorbidity score [25], certain chronic conditions, as determined through *ICD-9-CM* codes (Table 1), diagnosis-related group type, admission from the emergency room, critical care admission, index stay month and year, and hospital characteristics (bed size, urban or rural location, teaching status, and census division). We also conducted a similar analysis that used any readmission within 90 days as the outcome rather than either of the sepsis outcomes.

Because both facility-level and patient-level data in the HDD are nonidentifiable, it was determined this work did not constitute research involving human subjects. All data were analyzed using SAS software, version 9.3 (SAS Institute).

RESULTS

Among 516 hospitals, we identified 14 120 553 randomly selected index stays among adults. Of those patients, 1 205 226 (8.5%) experienced sepsis either during or before the index stay, and 305 428 (2.2%) died during the index stay or within 90 days of discharge; these patients were excluded. Of the remaining 12 746 135 patients with index stays, 21 247 (0.17%) had severe sepsis or septic shock identified within 90 days of their index stay using our primary outcome, and 92 467 (0.7%) had sepsis identified within 90 days using our secondary outcome (Table 1).

Table 1. Demographic and Clinical Characteristics of Patients by Antibacterial Risk Group[a]

Characteristic	Patients, No. (%)			
	No Antibacterial	High-Risk Antibacterial	Low-Risk Antibacterial	Control Antibacterial
All patients	5 443 331 (42.8)	3 571 964 (28.1)	3 037 618 (23.9)	653 610 (5.1)
Severe sepsis/septic shock[b]	6220 (0.1)	11 510 (0.3)	2863 (0.1)	517 (0.1)
Sepsis[c]	30 114 (0.6)	46 509 (1.3)	12 884 (0.4)	2381 (0.4)
Sex[d]				
Male	2 200 860 (40.4)	1 513 291 (42.4)	1 079 404 (35.5)	125 154 (19.1)
Female	3 242 471 (59.6)	2 058 673 (57.6)	1 958 214 (64.5)	528 456 (80.9)
Age, y[d]				
18–45	2 124 939 (39.0)	962 866 (27.0)	1 150 774 (37.9)	436 453 (66.8)
45–55	804 304 (14.8)	540 402 (15.1)	441 473 (14.5)	44 241 (6.8)
55–65	792 920 (14.6)	585 951 (16.4)	493 663 (16.3)	54 316 (8.3)
65–75	708 661 (13.0)	577 380 (16.2)	485 401 (16.0)	55 991 (8.6)
75–85	654 360 (12.0)	558 486 (15.6)	343 580 (11.3)	45 671 (7.0)
≥85	358 147 (6.6)	346 879 (9.7)	122 727 (4.0)	16 938 (2.6)
Length of stay, d[d]				
1–3	3 962 918 (72.8)	1 680 801 (47.1)	2 010 098 (66.2)	513 705 (78.6)
4–6	980 109 (18.0)	1 032 770 (28.9)	697 238 (23.0)	93 555 (14.3)
7–10	317 700 (5.8)	489 645 (13.7)	221 196 (7.3)	30 099 (4.6)
≥11	182 604 (3.4)	368 748 (10.3)	109 086 (3.6)	16 251 (2.5)
Duration of therapy, d[d]				
0	5 443 331 (100)	0	0	0
1–2	0	818 936 (22.9)	1 999 401 (65.8)	490 392 (75.0)
3–6	0	1 421 841 (39.8)	891 584 (29.4)	141 357 (21.6)
7–13	0	914 789 (25.6)	123 828 (4.1)	18 606 (2.9)
≥14	0	416 398 (11.7)	22 805 (0.8)	3255 (0.5)
Comorbidity score[d]				
Missing	1 646 636 (30.3)	795 458 (22.3)	1 203 561 (39.6)	397 237 (60.8)
0	629 472 (11.6)	423 018 (11.8)	338 376 (11.1)	38 112 (5.8)
1	1 142 711 (21.0)	757 460 (21.2)	533 573 (17.6)	92 480 (14.2)
2	561 470 (10.3)	433 523 (12.1)	200 985 (6.6)	30 276 (4.6)
3	307 751 (5.7)	280 385 (7.9)	108 209 (3.6)	17 547 (2.7)
4	177 527 (3.3)	180 496 (5.1)	62 073 (2.0)	10 377 (1.6)
≥5	309 425 (5.7)	338 113 (9.4)	121 260 (4.0)	17 126 (2.6)
<0	668 339 (12.3)	363 511 (10.2)	469 581 (15.5)	50 455 (7.7)
Critical care duration, d[d]				
0	5 143 787 (94.5)	3 234 679 (90.6)	2 804 869 (92.3)	626 966 (95.9)
1–4	283 559 (5.2)	248 025 (6.9)	207 910 (6.8)	23 888 (3.7)
5–8	13 039 (0.2)	50 361 (1.4)	19 604 (0.7)	2133 (0.3)
≥9	2946 (0.1)	38 899 (1.1)	5235 (0.2)	623 (0.1)
Previous visits in past 90 d, No.[d]				
0	5 043 450 (92.7)	3 251 389 (91.0)	2 889 772 (95.1)	621 829 (95.1)
1	335 442 (6.2)	268 041 (7.5)	130 638 (4.3)	27 486 (4.2)
≥2	64 439 (1.2)	52 534 (1.5)	17 208 (0.6)	4295 (0.7)
Chronic conditions[d]				
Metastatic disease	97 138 (1.8)	122 258 (3.4)	60 398 (2.0)	4643 (0.7)
Congestive heart failure	525 770 (9.7)	435 818 (12.2)	171 177 (5.6)	31 166 (4.8)
Dementia	98 348 (1.8)	95 488 (2.7)	24 452 (0.8)	3303 (0.5)
Renal failure	363 606 (6.7)	275 064 (7.7)	124 797 (4.1)	23 734 (3.6)
Weight loss	60 871 (1.1)	136 950 (3.8)	24 924 (0.8)	3951 (0.6)
Hemiplegia	68 670 (1.3)	56 366 (1.6)	19 101 (0.6)	3445 (0.5)
Alcohol abuse	110 518 (2.0)	42 127 (1.2)	18 763 (0.6)	2434 (0.4)
Any tumor	74 126 (1.4)	91 766 (2.6)	61 029 (2.0)	4772 (0.7)
Arrhythmia	717 807 (13.2)	489 748 (13.7)	282 338 (9.3)	44 430 (6.8)
Pulmonary disease	673 730 (12.4)	829 731 (23.2)	379 966 (12.5)	56 521 (8.7)
Coagulopathy	125 395 (2.3)	80 564 (2.3)	61 966 (2.0)	10 438 (1.6)
Complicated diabetes	124 829 (2.3)	117 080 (3.3)	46 541 (1.5)	9283 (1.4)

Table 1. Continued.

Characteristic	Patients, No. (%)			
	No Antibacterial	High-Risk Antibacterial	Low-Risk Antibacterial	Control Antibacterial
Anemia	493 951 (9.1)	466 309 (13.1)	283 187 (9.3)	55 380 (8.5)
Fluid and electrolyte disorders	793 661 (14.6)	900 042 (25.2)	255 241 (8.4)	36 739 (5.6)
Liver disease	114 774 (2.1)	107 250 (3.0)	36 770 (1.2)	5577 (0.9)
Peripheral vascular disorder	211 656 (3.9)	184 949 (5.2)	132 250 (4.4)	16 758 (2.6)
Psychosis	585 436 (10.8)	157 763 (4.4)	81 167 (2.7)	14 681 (2.3)
Pulmonary circulatory disorders	95 414 (1.8)	82 525 (2.3)	31 191 (1.0)	5239 (0.8)
HIV/AIDS	10 992 (0.2)	24 722 (0.7)	9170 (0.3)	880 (0.1)
Hypertension	2 079 013 (38.2)	1 462 200 (40.9)	1 122 538 (37.0)	129 930 (19.9)
Obesity	424 144 (7.8)	355 440 (10.0)	316 854 (10.4)	41 423 (6.3)
Hyperlipidemia	1 152 995 (21.2)	642 845 (18.0)	476 396 (15.7)	60 169 (9.2)
Uncomplicated diabetes	762 020 (14.0)	558 242 (15.6)	376 413 (12.4)	49 085 (7.5)
Ischemic heart disease	96 773 (1.8)	50 710 (1.4)	38 531 (1.3)	7209 (1.1)
Atrial fibrillation	474 208 (8.7)	33 160 (9.3)	177 456 (5.8)	28 288 (4.3)
Ventricular fibrillation	7819 (0.1)	5482 (0.2)	3957 (0.1)	854 (0.1)
DRG type				
Medical	4 312 907 (79.2)	2 234 137 (62.6)	644 113 (21.2)	445 452 (68.2)
Surgical	778 517 (14.3)	1 153 118 (32.3)	2 258 226 (74.3)	188 693 (28.9)
Other	351 907 (6.5)	184 709 (5.2)	135 279 (4.5)	19 465 (3.0)
Admission through emergency room[d]	2 337 488 (42.9)	1 769 377 (49.5)	532 129 (17.5)	85 763 (13.1)
Primary payer[d]				
Medicare	1 677 801 (30.8)	1 437 289 (40.2)	888 556 (29.3)	119 557 (18.3)
Medicaid	761 141 (14.0)	356 802 (10.0)	348 551 (11.5)	160 066 (24.5)
Blue Cross	757 561 (13.9)	455 286 (12.8)	550 557 (18.1)	107 452 (16.4)
Other Insurance	1 104 014 (20.3)	586 823 (16.4)	590 583 (19.4)	128 696 (19.7)
HMO	649 407 (11.9)	416 726 (11.7)	426 392 (14.0)	94 544 (14.5)
Other	493 407 (9.1)	319 038 (8.9)	232 979 (7.7)	43 295 (6.6)

Abbreviations: DRG, diagnosis-related group; HIV, human immunodeficiency virus; HMO, health maintenance organization.

[a]Table 1 does not include 39 576 (0.3%) patients whose antibiotic exposure did not meet the criteria for the predefined exposure groups.

[b]Severe sepsis/septic shock was defined as a hospital stay within 90 days of the index stay that included an *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) discharge diagnosis of severe sepsis (*ICD-9-CM* code 995.92) or septic shock (785.52), identified in any position on the hospital discharge bill.

[c]Secondary outcome, sepsis used a published definition for hospital administrative data, the "Angus definition," which requires *ICD-9-CM* codes for both infection and acute organ dysfunction within the same hospitalization or a sepsis-specific diagnosis [23].

[d]Characteristic based on information in the record for the index stay.

Patients with severe sepsis within 90 days of an index stay had a mean length of stay of 13.1 days for their sepsis stay, 38% died during their hospitalization for sepsis, and unspecified septicemia (038.9) was the most common primary diagnosis code listed for that stay (Table 2). Pneumonia was the most common primary *ICD-9-CM* diagnosis code listed for the index stay.

For patients with an infection or CDI diagnosis for the index stay, the unadjusted proportion of patients with subsequent severe sepsis was higher than that of patients without infection or a CDI diagnosis (0.3% vs 0.13% for infection and 1.0% vs 0.16% for CDI; both $P < .001$). Among patients with exposure to a high-risk antibiotic agent during the index stay, the proportion of patients with severe sepsis after discharge was 0.3%, compared with just 0.1% for patients without any antibiotic exposure ($P < .001$). Exposure to low-risk or control antibiotic agents was not associated with an increased risk of sepsis compared with patients not exposed to any antibiotics in the unadjusted analysis (Table 1).

In the multivariable logistic model, exposure to a high-risk antibiotic was associated with a higher risk of severe sepsis within 90 days of discharge than in our referent group (odds ratio [OR], 1.65; 95% confidence interval [CI], 1.59–1.70). Exposure to low-risk and control antibiotic agents was not as strongly associated with severe sepsis (OR, 1.07 [95% CI, 1.02–1.13] and 1.22 [1.12–1.34], respectively) (Table 3). Furthermore, both the number of unique antibiotics classes and total days of antibacterial therapy demonstrated a significant dose-response association with postdischarge severe sepsis. Patients exposed to ≥4 antibiotic classes and those with ≥14 days of antibiotic therapy had more than twice the risk of severe sepsis (OR, 2.23 [95% CI, 2.12–2.36] and 2.17 [2.06–2.29], respectively) than those without antibiotic exposure. Similar results were found for our secondary outcome (Table 3). In contrast, when using any readmission within 90 days as the outcome, the association between a high-risk antibiotic and readmission was close to 1 (OR, 1.03; 95% CI, 1.03–1.04) (Table 3).

Table 2. Demographic and Clinical Characteristics of Patients With Severe Sepsis/Septic Shock Within 90 Days After Discharge

Characteristic	Patients With Postdischarge Severe Sepsis/Septic Shock, No. (%)[a] (n = 21 247)
Characteristics of severe sepsis/septic shock stay	
Length of stay, mean, d	13.1
Death during stay	8019 (37.7)
Index stay characteristics	
Sex	
Male	10 810 (50.9)
Female	10 437 (49.1)
Age, y	
18–45	1408 (6.6)
45–55	2135 (10.1)
55–65	3642 (17.1)
65–75	4818 (22.7)
75–85	5668 (26.7)
≥85	3567 (16.8)
Length of stay, d	
1–3	6357 (29.9)
4–6	6398 (30.1))
7–10	4392 (20.7)
≥11	4100 (19.3)
Mean length of stay, d	7.4
Duration of therapy, d	
0	6220 (29.3)
1–2	3135 (14.8)
3–6	4618 (21.7)
7–13	4044 (19.0)
≥14	3230 (15.2)
Critical care duration, d	
0	18 589 (87.5)
1–4	1892 (8.9)
5–8	449 (2.1)
≥9	317 (1.5)
10 Most frequent primary diagnosis codes	
486: Pneumonia, organism unspecified	690 (3.3)
428.0: Congestive heart failure, unspecified	460 (2.2)
038.9: Unspecified septicemia	455 (2.1)
599.0: Urinary tract infection, site not specified	427 (2.0)
491.21: Obstructive chronic bronchitis with acute exacerbation	416 (2.0)
584.9: Acute kidney failure, unspecified	398 (1.9)
507.0: Pneumonitis due to inhalation of food or vomitus	349 (1.6)
434.91: Cerebral artery occlusion, unspecified with cerebral infarction	322 (1.5)
410.71: Subendocardial infarction, initial episode of care	306 (1.4)
518.81: Acute respiratory failure	304 (1.4)

[a]Data represent No. (%) of patients unless otherwise specified. Severe sepsis/septic shock was defined as a hospital stay within 90 days of the index stay that included an *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) discharge diagnosis of severe sepsis (*ICD-9-CM* code 995.92) or septic shock (785.52), identified in any position on the hospital discharge bill.

Because most patients exposed to ≥4 classes of antibiotics were also in the high-risk antibiotic group, we further evaluated the dose response within the high-risk group alone. We also limited the analysis to those with an infection-related primary discharge code during the index stay. Dose responses were observed when our analysis was limited to one of these groups (Table 3).

DISCUSSION

We found a significant association between antibiotic exposure in the hospital and severe sepsis and septic shock either as the cause of or occurring during a subsequent hospitalization within 90 days of discharge. Exposure to antibiotics such as third- or fourth-generation cephalosporin, lincosamide, fluoroquinolone, β-lactam/β-lactamase inhibitor combinations, oral vancomycin, and carbapenem were associated with an increased risk of sepsis. Furthermore, significant dose-response effects were observed for the number of antibiotic classes a patient received during the index hospitalization as well as the total duration of therapy. In contrast, the risk of postdischarge sepsis for exposure to low-risk antibiotics was diminished.

Our findings support, but do not prove, the hypothesis that microbiota disruption is associated with an increased risk of severe sepsis and septic shock within 90 days of discharge from a hospital stay. Prescott et al [16] previously demonstrated that the rate of sepsis 90 days after hospitalization was 3-fold greater than during other observation periods; they also found that hospital events, such as infection or CDI, further increased this rate. Presumably these events, infection and CDI, would disrupt the patient's microbiota, in part because of antibacterial agents. Our study further supports this hypothesis by showing that increased antibiotic exposure or exposure to specific antibacterial agents more likely to disrupt the microbiota is associated with an increased risk in severe sepsis in the 90 days after hospital discharge. We were able to study a large population of >500 hospitals during a 7-year period. Unlike Prescott et al [16], we were able to include hospital pharmacy data, which was previously shown to be consistent with other estimates of hospital antibiotic usage and a representative sample of hospitals in the US [12].

In addition, we determined a priori the antibiotic exposure categories based on their epidemiologic association with clinically important microbiome disruption (ie, CDI risk). Although the types of antibiotic-mediated disruptions that predispose to sepsis may ultimately be determined to be different from those that predispose to CDI, hypothesis-driven a priori analyses based on a theoretical framework may lessen the risk for unmeasured bias or spurious associations based on chance alone. Our study only identified a significantly large association between sepsis and those antibiotics most likely to disrupt the patient's microbiota [18–20], whereas low-risk and control antibiotics showed much smaller increases in the risk of sepsis.

Table 3. Adjusted Odds Ratios for the Association Between Defined Exposures and Severe Sepsis or Septic Shock Within 90 Days After Hospital Discharge in a Cohort of US Hospitals[a]

Antibacterial Exposure	OR (95% CI)	
	Primary Outcome: Severe Sepsis/Septic Shock[b]	Secondary Outcome: Sepsis[c]
High-risk antibacterial agents[d]	1.65 (1.59–1.70)	1.49 (1.47–1.52)
Low-risk antibacterial agents[e]	1.07 (1.02–1.13)	1.04 (1.02–1.06)
Control antibacterial agents[f]	1.22 (1.12–1.34)	1.20 (1.15–1.25)
No exposure to antibacterial agents	Reference	Reference
Antibiotic classes exposed to during stay, No.		
≥4	2.23 (2.12–2.36)	1.92 (1.86–1.97)
3	1.80 (1.72–1.89)	1.57 (1.53–1.61)
2	1.49 (1.43–1.56)	1.36 (1.34–1.39)
1	1.30 (1.25–1.35)	1.26 (1.24–1.28)
0	Reference	Reference
Duration of antibacterial therapy, d		
≥14	2.17 (2.06–2.29)	1.89 (1.84–1.94)
7–13	1.68 (1.61–1.75)	1.52 (1.49–1.55)
3–6	1.41 (1.36–1.47)	1.34 (1.32–1.37)
1–2	1.23 (1.18–1.29)	1.16 (1.13–1.18)
0	Reference	Reference
Patients receiving high-risk antibacterial agents		
Antibiotic classes exposed to during stay, No.		
≥4	1.53 (1.44–1.63)	1.36 (1.32–1.40)
3	1.27 (1.20–1.34)	1.14 (1.11–1.17)
2	1.08 (1.03–1.14)	1.02 (1.00–1.05)
1	Reference	Reference
Duration of antibacterial therapy, d		
≥14	1.61 (1.49–1.74)	1.47 (1.41–1.52)
7–13	1.28 (1.19–1.37)	1.20 (1.16–1.24)
3–6	1.15 (1.08–1.23)	1.10 (1.07–1.13)
1–2	Reference	Reference
Patients receiving low-risk or control antibacterial agents		
Antibiotic classes exposed to during stay, No.		
≥4	1.20 (.83–1.74)	1.72 (1.48–2.01)
3	1.13 (.96–1.33)	1.08 (1.00–1.17)
2	1.03 (.95–1.12)	0.99 (.95–1.03)
1	Reference	Reference
Duration of antibacterial therapy, d		
≥14	1.21 (.98–1.50)	1.43 (1.29–1.59)
7–13	1.11 (.99–1.26)	1.20 (1.14–1.28)
3–6	0.92 (.85–.99)	1.02 (.98–1.06)
1–2	Reference	Reference
Patients with primary infectious diagnosis code		
High-risk antibacterial agents	1.53 (1.43–1.64)	1.41 (1.37–1.46)
Low-risk antibacterial agents	1.00 (.91–1.11)	1.04 (.99–1.09)
Control antibacterial agents	1.07 (.92–1.26)	1.06 (.98–1.15)
No exposure to antibacterial agents	Reference	Reference
Antibiotic classes exposed to during stay, No.		
≥4	2.06 (1.90–2.24)	1.79 (1.71–1.86)
3	1.65 (1.52–1.79)	1.49 (1.43–1.55)
2	1.36 (1.26–1.47)	1.33 (1.27–1.37)
1	1.20 (1.11–1.30)	1.17 (1.13–1.22)
0	Reference	Reference
Duration of antibacterial therapy, d		
≥14	1.95 (1.79–2.12)	1.76 (1.68–1.83)
7–13	1.56 (1.45–1.68)	1.44 (1.39–1.50)
3–6	1.35 (1.25–1.46)	1.30 (1.25–1.35)
1–2	1.06 (.96–1.17)	1.04 (.99–1.09)
0	Reference	Reference
Model using any readmission within 90 d as model outcome (instead of sepsis)[g]		
High-risk antibacterial agents	1.03 (1.03–1.04)	…
Low-risk antibacterial agents	0.88 (.88–.89)	…
Control antibacterial agents	0.90 (.89–.92)	…
No exposure to antibacterial agents	Reference	…

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Multivariable logistic model adjusted for sex, age, primary payer, previous hospitalizations within 90 days, length of stay, comorbidity score, surgical or medical diagnosis-related group, emergency room visit, critical care stays during index visit, month and year of index visit, hospital size (No. of beds), hospital urban/rural location, hospital teaching status, hospital census division, and various chronic conditions based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) discharge codes including: metastatic disease, congestive heart failure, dementia, renal failure, weight loss, hemiplegia, alcohol abuse, any tumor, arrhythmia, pulmonary disease, coagulopathy, complicated diabetes, anemia, fluid and electrolyte disorders, liver disease, peripheral vascular disorder, psychosis, pulmonary circulatory disorders, human immunodeficiency virus/AIDS, hypertension, obesity, hyperlipidemia, uncomplicated diabetes, ischemic heart disease, atrial fibrillation, and ventricular fibrillation.

[b]Severe sepsis/septic shock was defined as a hospital stay within 90 days of the index stay that included an *ICD-9-CM* discharge diagnosis of severe sepsis (*ICD-9-CM* code 995.92) or septic shock (785.52), identified in any position on the hospital discharge bill.

[c]The secondary outcome of sepsis used a published definition for hospital administrative data, the "Angus definition," which requires *ICD-9-CM* codes for both infection and acute organ dysfunction within the same hospitalization or a sepsis-specific diagnosis [23].

[d]High-risk antibacterial exposures included any receipt of third- or fourth-generation cephalosporins, fluoroquinolones, lincosamides, β-lactam/β-lactamase inhibitor combinations, oral vancomycin, or carbapenems.

[e]Low-risk antibacterial exposures included receipt of first- or second-generation cephalosporins, macrolide, tetracycline, metronidazole, or sulfa without receipt of a high-risk antibiotic.

[f]Control antibacterial exposures included any receipt of an aminoglycoside, penicillin, or intravenous vancomycin (antibiotics that minimally disrupt gastrointestinal flora) without receipt of intermediate- or high-risk antibiotics.

[g]We also used a similar model with the same exposures that used any readmission within 90 days as the outcome, rather than either of the sepsis outcomes.

In addition, both dose-response variables showed significant trends with increasing amounts of antibiotics, further supporting our hypothesis that disruption of the patient's microbiota leads to an increased risk of postdischarge sepsis. We were also able to control for a number of demographic and clinical characteristics, including certain chronic conditions likely to be associated

with antibiotic use and hospital readmission in our multivariable models. In sensitivity analyses, we found estimates similar to those of Prescott et al [16], comparing infection-related or CDI-related hospitalizations with non–infection-related hospitalizations without adjustment for our antimicrobial exposures. We also eliminated patients with an *ICD-9-CM* code for CDI during either the index visit or the postdischarge sepsis visit and found consistent results with our primary model, suggesting that our association was not confounded by the well-described relationship between antibiotics and CDI. However, additional epidemiologic and biologic studies may further explore this hypothesis.

Antibiotic-mediated gut microbiota disruptions may increase the risk of sepsis via any one or a combination of 3 broad pathways. The first of these is loss of direct inhibition and competitive nutrient utilization, leading to loss of colonization resistance against more virulent and potentially pathogenic microbiota members [9]. Another pathway emphasizes the loss of immune-regulatory dampening functions of the gut microbiota itself, whereby, at least theoretically, antibiotic effects on the gut microbiota may contribute to a more pronounced septic response from even a non–gut-related site of primary infection [5]. A third pathway is loss of integrity of the gut mucosal barrier function, largely due to loss of short-chain fatty acids normally produced by a healthy microbiota that serve as the main nutrient source for large intestinal enterocytes [26].

Direct adverse drug events, such as allergic reactions and toxic effects like tendon rupture or renal toxicity, as well as the microbiota-mediated effects of antibiotic-associated diarrhea and especially CDI, are long-recognized forms of patient harm resulting from antibiotics [13, 21, 27]. Although the exact mechanisms remain under investigation, there is now a small but increasing body of human observational evidence and animal data suggesting broader detrimental effects on patient outcomes rooted in microbiota disruptions that result from antibiotic use, among other environmental insults [28, 8, 11]. Taur et al [29] showed that, even after controlling for confounders, 3-year mortality rates in bone marrow transplant recipients were associated with gut microbiota diversity at engraftment. Mai et al [30] found that antibiotic-mediated changes in microbiota composition, especially the loss of potentially protective members and "bloom" of proteobacteria, leading up to onset, were associated with late-onset sepsis in human neonates. In adult patients, the population evaluated in our study, poorer outcomes in patients with the systemic inflammatory response are associated with greater microbiota disruption [31].

One hope from our findings is that future innovations focused on restoring or protecting the lower intestinal microbiota from antibiotic-mediated disruption might become a possible approach for preventing sepsis [32]. Recent studies have established fecal microbiota transplantation as a front-line therapy for multiply recurrent CDI [33]. Despite at least 2 case reports of fecal microbiota transplantation apparently used successfully to treat sepsis [34, 35], this remains highly experimental and carries unknown risk. Although animal data suggest that a defined probiotic consortia could be developed to restore the barrier function of the gut and thereby possibly prevent antibiotic-mediated sepsis on that account [36], there are examples where probiotics administered in the throes of severe illness, specifically acute pancreatitis, have increased mortality risk [37]. Recently, a large, randomized, double-blind, placebo-controlled trial of an oral synbiotic preparation given to infants in rural India, observed a 40% reduction in sepsis outcomes [38]. Protecting the lower intestinal microbiota from antibiotic-mediated disruption may be another strategy available soon. Although still under development, methods to inactivate antibiotics that reach the lower intestine, via either enzymatic deactivation (eg, an orally administered β-lactamase [39]) or binding with an absorbent [40], appear promising.

However, another currently available prevention strategy is improved antibiotic stewardship. Although early antibiotic administration is critical for the management of sepsis [41–43], there are many other conditions for which antibiotics are unnecessary and yet often prescribed, thereby needlessly increasing patients' risk of complications, including future sepsis [13]; for example, treatment of asymptomatic bacteriuria or positive cultures from nonsterile body sites where colonization is likely. In addition, recent studies suggest that certain common, serious infections may not need to be treated with broad-spectrum agents or with as many agents [44] or for as long a duration as previously thought [45].

The current study has several limitations. First, administrative data such as the HDD are not collected for research purposes, and misclassification in the pharmacy, clinical, and facility data, including the use of *ICD-9-CM* diagnostic codes, can lead to bias. However, this bias is probably nondifferential and would typically bias the results toward null values. Moreover, this type of pharmacy charge data was previously validated in small samples, with excellent agreement [46, 47]. In addition, our outcome was based on *ICD-9-CM* diagnostic codes, but this definition of sepsis was previously validated [24]. Although we controlled for several demographic and clinical characteristics in the multivariable analysis, residual confounding from unknown factors could affect our findings, particularly the presence of underlying conditions or characteristics that increase antibiotic use in the index hospitalization and the risk of subsequent infection. However, in an analysis restricted to patients with no discharge diagnosis codes indicating an infection during the index hospitalization, our findings were similar, suggesting that an underlying predisposition to infection is less likely to confound our observed association.

Furthermore, when we included any readmission within 90 days as our outcome, instead of sepsis, we observed that the OR for our high-risk antibiotic group was reduced to nearly 1, providing additional support for our hypothesis, rather than

underlying disease as the explanation for the association. In addition, we could include only postdischarge cases of sepsis in which patients returned to the same hospital, because patients in the HDD cannot be followed longitudinally across different hospitals. As such, our estimate of the proportion of sepsis cases after hospitalization was smaller than that in the previous study, and death outside the same hospital was not detectable [16]. Finally, our study did not include any exposure data from healthcare encounters outside the hospital or antibiotics prescribed at discharge.

In conclusion, our study observed a significant increase in severe sepsis and septic shock within 90 days of discharge for patients exposed in the hospital to antibiotics likely to disrupt the patient's microbiota. Given that a significant proportion of inpatient antimicrobial use may be unnecessary [14, 48], this study builds on a growing evidence base suggesting that increased stewardship efforts in hospitals may not only prevent antimicrobial resistance, CDI, and other adverse effects, but may also reduce other unwanted outcomes potentially related to disruption of the microbiota, including sepsis.

Notes

Disclaimer. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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