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Risk of Subsequent Sepsis within 90 Days of a Previous Hospital Stay by Type of Antibiotic Exposure

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Abstract

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, determined *a priori*, during the initial hospital stay and risk of post-discharge 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 ICD-9-CM discharge diagnosis of severe sepsis (995.92) or septic shock (785.52).

Results: Among 516 hospitals, we randomly selected a single stay for eligible patients. Of those, 0.17% developed severe sepsis/septic shock within 90 days after discharge. The risk of sepsis associated with exposure to our high risk antibiotics was 65% higher compared to 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 or increased quantities of antibiotics during hospitalization. Given 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, CDI and other adverse effects, but 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

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Background:

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 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. While over half of hospitalized patients receive an antibiotic, [12, 13] 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. 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.[16] Understanding the association between antibiotic administration and accurately estimating the potential effect size of antibiotics in precipitating sepsis is important.

Our objective was to examine, among a cohort of US hospitalized patients, the risk of sepsis within 90 days after discharge according to receipt during a previous hospitalization of antibiotics categorized *a priori* on the basis of 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 previously and been shown to be representative of acute care hospitals in the US [12, 13, 17]. Since the information required to follow individuals longitudinally changed from 2010 to 2011, we included hospital admissions for all patients discharged during two time periods, January 1, 2007 through September 30, 2010 and January 1, 2011 through September 30, 2014. Similar to 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. Further, we categorized antibiotic doses into fourteen classes: aminoglycoside, $1^{st}/2^{nd}$ generation cephalosporin, $3^{rd}/4^{th}$ generation cephalosporin, lincosamide, fluoroquinolone, macrolide, vancomycin, sulfa, beta-lactam/beta-lactamase inhibitor combinations, carbapenem, penicillin, tetracycline, metronidazole, and miscellaneous. We excluded drugs with non-oral, non-parental routes of administration.

Study Settings and Patients:

Patients 18 years of age or older with an inpatient stay were included. For patients with multiple hospital stays within the study period, one stay was randomly selected to be the index stay for each patient. Patients with previously documented sepsis, sepsis documented during the index stay, who died during the index stay, or died in the hospital within the 90 days following a non-sepsis outcome were excluded. Further we excluded childbirth-related inpatient stays (ICD-9-CM codes: V30-V39).

Exposures:

Antibiotic exposures were identified from the selected index hospital stay and stratified into three 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 $3^{rd}/4^{th}$ generation cephalosporins, fluoroquinolones, lincosamides, beta-lactam/beta-lactamase inhibitor combinations, oral vancomycin, and carbapenems. [21, 22] Low risk exposures included receipt of $1^{st}/2^{nd}$ 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 GI 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 (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 one data source within the HDD, admission dates are masked; therefore, instead of within 90 days, stays within the two months following the discharge month were identified.

Statistical Analysis:

Univariate comparisons of exposure and outcome groups were conducted using a chi-square 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 to those without any antibiotic agent exposures. In addition, we evaluated the dose-response relationship in multivariable logistic models, which included either total days of antibiotic therapy 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 (LOS), primary payer, previous hospitalization, co-morbidity score[25], certain chronic conditions as determined through ICD-9-CM codes (Table 1), diagnosis-related group (DRG) type, admission from the emergency room, critical care admission, index stay month and year, and hospital characteristics (bed size, urban/rural location, teaching status, census division). In addition, we conducted a similar analysis that used any readmission within 90 days as the outcome rather than either of the sepsis outcomes.

As both facility- and patient-level data in the HDD are non-identifiable, it was determined this work did not constitute research involving human subjects. All data were analyzed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results:

Among 516 hospitals, we identified 14,120,553 randomly selected index stays among adults. Of those, 1,205,226 (8.5%) either experienced sepsis during or prior to 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 index stays, there were 21,247 (0.17%) who had severe sepsis or septic shock identified within 90 days of their index stay using our primary outcome while 92,467 (0.7%) had sepsis identified within 90 days using our secondary outcome, Table 1.

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

For those with an infection or CDI diagnosis in the index stay, the unadjusted proportion of patients with subsequent severe sepsis was higher compared to those without infection or CDI diagnosis, (0.3% vs 0.13%, $p<0.0001$) and (1.0% vs 0.16%, $p<0.0001$), respectively. Among patients with exposure to a high risk antibiotic agent during the index stay, the proportion of patients with severe sepsis post-discharge was 0.3%, $p<0.0001$, compared to just 0.1% of patients without any antibiotic exposures. Exposure to low risk or control antibiotic agents was not associated with an increased risk of sepsis compared to 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 compared to our referent group, OR=1.65 95% CI:1.59–1.70. Exposure to low risk and control antibiotic agents were not as strongly associated with severe sepsis (OR=1.07, 95% CI: 1.02–1.13, OR=1.22, 95% CI:1.12–1.34 respectively), Table 3. Further, both the number of unique antibiotics classes and total days of antibacterial therapy demonstrated significant dose-response association with post-discharge severe sepsis. Patients exposed to four or more antibiotic classes or those with 14 or more days of antibiotic therapy had over twice the risk of severe sepsis

(OR=2.23, 95% CI:2.12–2.36, OR=2.17, 95% CI:2.06–2.29, respectively), compared to those without antibiotic exposure. Similar results were found for our secondary outcome, Table 3. In contrast, when using any readmission within 90 days, the association between a high risk antibiotic and readmission was close to one (OR=1.03, 95% CI:1.03–1.04), Table 3.

Since most patients exposed to four or more different 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 3rd/4th generation cephalosporin, lincosamide, fluoroquinolone, beta-lactam/beta-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 days of therapy. In contrast, the risk of post-discharge 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. previously demonstrated that the rate of sepsis 90 days post-hospitalization was 3-fold greater than other observation periods.[16] They also found that hospital events, such as infection or CDI further increased this rate.[16] Presumably these events, infection and CDI, would disrupt the patient's microbiota in part due to anti-bacterial agents. Our study further supports this hypothesis by showing that increased antibiotic exposure, or exposure to specific anti-bacterial agents more likely to disrupt the microbiota are associated with an increased risk in severe sepsis in the 90 days following hospital discharge. We were able to study a large population of over 500 hospitals over a seven year period. Unlike the study by Prescott, et al, 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 upon their epidemiologic association with clinically important microbiome disruption (i.e., CDI risk). While 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 upon a theoretical framework may lessen the risk for unmeasured bias or spurious associations based upon 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] while low risk and control antibiotics showed much smaller increases in

the risk of sepsis. 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 post-discharge sepsis. Furthermore, we were able to control for a number of demographic and clinical characteristics including certain chronic conditions likely associated with antibiotic use and hospital readmission in our multivariable models. In sensitivity analyses, we found similar estimates to those by Prescott comparing infection-related or CDI-related hospitalizations to non-infection-related hospitalizations without our antimicrobial exposures [26]. We also eliminated patients with an ICD-9-CM code for CDI either in their index visit or during the post-discharge 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 three 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 area 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.[27]

Direct adverse drug events, such as allergic reactions and toxicities 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, 28] While 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, among other environmental insults,[29] antibiotic use.[8, 11] Taur et al. showed that, even after controlling for confounders, 3-year mortality in bone marrow transplant recipients was associated with gut microbiota diversity at engraftment.[30] Mai et al. 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.[31] In adult patients, the population evaluated here, poorer outcomes in patients with the systemic inflammatory response (SIRS) are associated with greater microbiota disruption. [32]

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.[33] Recent studies have established fecal microbiota transplantation (FMT) as a front-line therapy for multiply recurrent *C. difficile* infection.[34] Despite at least two case reports of FMT apparently used successfully to treat sepsis [35, 36], 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 [37], there are examples where probiotics administered in the throes of severe illness, specifically acute pancreatitis, have increased mortality.[38] 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.[39] Protecting the lower intestinal microbiota from antibiotic-mediated disruption may be another strategy available soon. Though still under development, methods to inactivate antibiotics that reach the lower intestine via either enzymatic deactivation, (e.g., an orally administered beta-lactamase[40]), or by binding with an absorbent [41], appear promising.

However, another currently available prevention strategy is improved antibiotic stewardship. Although early antibiotic administration is critical for the management of sepsis, [42–44] there are many other conditions for which antibiotics are unnecessary and yet often prescribed, thereby needlessly increasing patients' risk for complications including future sepsis;[13] for example, treatment of asymptomatic bacteruria or positive cultures from non-sterile 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 or as many agents [45] or for as long duration as previously thought.[46]

This 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 likely non-differential and would typically bias the results towards null values. Also, this type of pharmacy charge data was previously validated in small samples with excellent agreement.[47, 48] 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. Further, when we included any readmission within 90 days as our outcome instead of sepsis, we observed that the odds ratio for our high risk antibiotic group was reduced to nearly one, providing additional support for our hypothesis, rather than underlying disease, explaining the association. In addition, we could only include post-discharge cases of sepsis in which patients returned to the same hospital, as patients in the HDD cannot be followed longitudinally across different hospitals. As such, our estimate of the proportion of sepsis cases following hospitalization was smaller than the previous study and death outside the same hospital was not detectable.[26] Finally, our study did not include any exposure data from health care encounters outside of 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 to antibiotics in the hospital likely to disrupt the patient's microbiota. Given that a significant proportion of inpatient

antimicrobial use may be unnecessary [14, 49], 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 also reduce other unwanted outcomes potentially related to disruption of the microbiota, including sepsis.

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Key Points

Among a retrospective cohort of patients, the risk of sepsis was 65% higher for patients exposed to antibiotics more likely to disrupt the gut microbiota compared to those without any antibiotic exposure.

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Table 1:

Demographic and Clinical Characteristics of Patients by Anti-bacterial Risk Group

Characteristic	No anti-bacterial	%	High Risk Anti-bacterial	%	Low Risk Anti-bacterial	%	Control Anti-bacterial	%
All	5443331	42.8	3571964	28.1	3037618	23.9	653610	5.1
Severe Sepsis/Septic Shock[1]	6220	0.1	11510	0.3	2863	0.1	517	0.1
Sepsis[2]	30114	0.6	46509	1.3	12884	0.4	2381	0.4
Sex[3]								
Male	2200860	40.4	1513291	42.4	1079404	35.5	125154	19.1
Female	3242471	59.6	2058673	57.6	1958214	64.5	528456	80.9
Age[3]								
18-45	2124939	39.0	962866	27.0	1150774	37.9	436453	66.8
45-55	804304	14.8	540402	15.1	441473	14.5	44241	6.8
55-65	792920	14.6	585951	16.4	493663	16.3	54316	8.3
65-75	708661	13.0	577380	16.2	485401	16.0	55991	8.6
75-85	654360	12.0	558486	15.6	343580	11.3	45671	7.0
85+	358147	6.6	346879	9.7	122727	4.0	16938	2.6
Length of Stay[3]								
1-3	3962918	72.8	1680801	47.1	2010098	66.2	513705	78.6
4-6	980109	18.0	1032770	28.9	697238	23.0	93555	14.3
7-10	317700	5.8	489645	13.7	221196	7.3	30099	4.6
11+	182604	3.4	368748	10.3	109086	3.6	16251	2.5
Days of Therapy[3]								

Characteristic	No anti-bacterial	%	High Risk Anti-bacterial	%	Low Risk Anti-bacterial	%	Control Anti-bacterial	%
0 DOT	5443331	100	0		0		0	
1-2 DOT	0		818936	22.9	1999401	65.8	490392	75.0
3-6 DOT	0		1421841	39.8	891584	29.4	141357	21.6
7-13 DOT	0		914789	25.6	123828	4.1	18606	2.9
14+ DOT	0		416398	11.7	22805	0.8	3255	0.5
Co-morbidity score[3]								
Missing	1646636	30.3	795458	22.3	1203561	39.6	397237	60.8
0	629472	11.6	423018	11.8	338376	11.1	38112	5.8
1	1142711	21.0	757460	21.2	533573	17.6	92480	14.2
2	561470	10.3	433523	12.1	200985	6.6	30276	4.6
3	307751	5.7	280385	7.9	108209	3.6	17547	2.7
4	177527	3.3	180496	5.1	62073	2.0	10377	1.6
5+	309425	5.7	338113	9.4	121260	4.0	17126	2.6
NA	668339	12.3	363511	10.2	469581	15.5	50455	7.7
Critical Care Days[3]								
0 days	5143787	94.5	3234679	90.6	2804869	92.3	626966	95.9
1-4 days	283559	5.2	248025	6.9	207910	6.8	23888	3.7
5-8 days	13039	0.2	50361	1.4	19604	0.7	2133	0.3
9+ days	2946	0.1	38899	1.1	5235	0.2	623	0.1
Previous Visits in last 90 Days[3]								
0	5043450	92.7	3251389	91.0	2889772	95.1	621829	95.1
1	335442	6.2	268041	7.5	130638	4.3	27486	4.2
2+	64439	1.2	52534	1.5	17208	0.6	4295	0.7
Chronic Conditions[3]								

Characteristic	No anti-bacterial	%	High Risk Anti-bacterial	%	Low Risk Anti-bacterial	%	Control Anti-bacterial	%
Metastatic Disease	97138	1.8	122258	3.4	60398	2.0	4643	0.7
Congestive Heart Failure	525770	9.7	435818	12.2	171177	5.6	31166	4.8
Dementia	98348	1.8	95488	2.7	24452	0.8	3303	0.5
Renal Failure	363606	6.7	275064	7.7	124797	4.1	23734	3.6
Weight Loss	60871	1.1	136950	3.8	24924	0.8	3951	0.6
Hemiplegia	68670	1.3	56366	1.6	19101	0.6	3445	0.5
Alcohol	110518	2.0	42127	1.2	18763	0.6	2434	0.4
Any Tumor	74126	1.4	91766	2.6	61029	2.0	4772	0.7
Arrhythmia	717807	13.2	489748	13.7	282338	9.3	44430	6.8
Pulmonary Disease	673730	12.4	829731	23.2	379966	12.5	56521	8.7
Coagulopathy	125395	2.3	80564	2.3	61966	2.0	10438	1.6
Complicated Diabetes	124829	2.3	117080	3.3	46541	1.5	9283	1.4
Anemia	493951	9.1	466309	13.1	283187	9.3	55380	8.5
Electrolytes	793661	14.6	900042	25.2	255241	8.4	36739	5.6
Liver Disease	114774	2.1	107250	3.0	36770	1.2	5577	0.9
Peripheral Vascular Disorder	211656	3.9	184949	5.2	132250	4.4	16758	2.6
Psychosis	585436	10.8	157763	4.4	81167	2.7	14681	2.3
Pulmonary Circulatory Disorders	95414	1.8	82525	2.3	31191	1.0	5239	0.8
HIV/AIDS	10992	0.2	24722	0.7	9170	0.3	880	0.1
Hypertension	2079013	38.2	1462200	40.9	1122538	37.0	129930	19.9
Obesity	424144	7.8	355440	10.0	316854	10.4	41423	6.3
Hyperlipidemia	1152995	21.2	642845	18.0	476396	15.7	60169	9.2
Uncomplicated Diabetes	762020	14.0	558242	15.6	376413	12.4	49085	7.5
Ischemic Heart Disease	96773	1.8	50710	1.4	38531	1.3	7209	1.1
Atrial Fib	474208	8.7	33160	9.3	177456	5.8	28288	4.3
Ventricular Fib	7819	0.1	5482	0.2	3957	0.1	854	0.1
DRG Type[3]								

Characteristic	No anti-bacterial	%	High Risk Anti-bacterial	%	Low Risk Anti-bacterial	%	Control Anti-bacterial	%
Med	4312907	79.2	2234137	62.6	644113	21.2	445452	68.2
Surgical	778517	14.3	1153118	32.3	2258226	74.3	188693	28.9
Other	351907	6.5	184709	5.2	135279	4.5	19465	3.0
Emergency Room[3]	2337488	42.9	1769377	49.5	532129	17.5	85763	13.1
Primary Payer[3]								
Medicare	1677801	30.8	1437289	40.2	888556	29.3	119557	18.3
Medicaid	761141	14.0	356802	10.0	348551	11.5	160066	24.5
Blue Cross	757561	13.9	455286	12.8	550557	18.1	107452	16.4
Other Insurance	1104014	20.3	586823	16.4	590583	19.4	128696	19.7
HMO	649407	11.9	416726	11.7	426392	14.0	94544	14.5
Other	493407	9.1	319038	8.9	232979	7.7	43295	6.6

*Footnote: Table does not include 39576 (0.3%) whose antibiotic exposure did not meet the criteria for the pre-defined exposure groups.

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

2 -Secondary outcome, sepsis used a published definition for hospital administrative data, “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]

3 –Characteristic based on information in the index stay.

Table 2:

Demographic and Clinical Characteristics of Patients with Severe Sepsis/Septic Shock within 90 Days Post-Discharge

Characteristic	Post Discharge Severe Sepsis/Septic Shock[1]	%
All	21247	
Characteristics of the Severe Sepsis/Septic Shock Stay		
Mean Length of Stay (days)	13.1	
Died	8019	37.7
Index Stay Characteristics		
Sex		
Male	10810	50.9
Female	10437	49.1
Age		
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
Index Length of Stay		
1-3	6357	29.9
4-6	6398	30.1
7-10	4392	20.7
11+	4100	19.3
Mean (days)	7.4	
Days of Therapy		
0 DOT	6220	29.3
1-2 DOT	3135	14.8
3-6 DOT	4618	21.7
7-13 DOT	4044	19.0
14+ DOT	3230	15.2

Characteristic	Post Discharge Severe Sepsis/Septic Shock[1]	%
Critical Care Days		
0 days	18589	87.5
1-4 days	1892	8.9
5-8 days	449	2.1
9+ days	317	1.5
Ten 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

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

Table 3:

Adjusted Odds Ratio Describing the Association between Defined Exposures and Severe Sepsis and Septic Shock within 90 Days of Hospital Discharge in a Cohort of US Hospitals*

	Primary Outcome: Severe Sepsis/Septic Shock[1]			Secondary Outcome: Sepsis[2]		
	OR	Lower CI	Upper CI	OR	Lower CI	Upper CI
High Risk Anti-bacterial agents[3]	1.65	1.59	1.70	1.49	1.47	1.52
Low Risk Anti-bacterial agents[4]	1.07	1.02	1.13	1.04	1.02	1.06
Control Anti-bacterial agents[5]	1.22	1.12	1.34	1.20	1.15	1.25
No Exposure to Anti-bacterial agents	Ref			Ref		
# Antibiotic Classes Exposed to during Stay						
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	Ref			Ref		
# Days of Anti-bacterial Therapy						
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	Ref			Ref		
For Patients Receiving High Risk Anti-bacterial Agents						
# Antibiotic Classes Exposed to during Stay						
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	Ref			Ref		
# Days of Anti-bacterial Therapy						
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	Ref			Ref		

	Primary Outcome: Severe Sepsis/Septic Shock[1]			Secondary Outcome: Sepsis[2]		
	OR	Lower CI	Upper CI	OR	Lower CI	Upper CI
For Patients Receiving Low Risk or Control Anti-bacterial Agents						
# Antibiotic Classes Exposed to during Stay						
4+	1.20	0.83	1.74	1.72	1.48	2.01
3	1.13	0.96	1.33	1.08	1.00	1.17
2	1.03	0.95	1.12	0.99	0.95	1.03
1	Ref			Ref		
# Days of Anti-bacterial Therapy						
14+	1.21	0.98	1.50	1.43	1.29	1.59
7-13	1.11	0.99	1.26	1.20	1.14	1.28
3-6	0.92	0.85	0.99	1.02	0.98	1.06
1-2	Ref			Ref		
Patients with Primary Infectious Diagnosis Code						
High Risk Anti-bacterial agents	1.53	1.43	1.64	1.41	1.37	1.46
Low Risk Anti-bacterial agents	1.00	0.91	1.11	1.04	0.99	1.09
Control Anti-bacterial agents	1.07	0.92	1.26	1.06	0.98	1.15
No Exposure to Anti-bacterial agents	Ref			Ref		
# Antibiotic Classes Exposed to during Stay						
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	Ref			Ref		
# Days of Anti-bacterial Therapy						
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	0.96	1.17	1.04	0.99	1.09
0	Ref			Ref		
Model using any readmission within 90 days as outcome instead of sepsis[6]						
High Risk Anti-bacterial agents	1.03	1.03	1.04			
Low Risk Anti-bacterial agents	0.88	0.88	0.89			

	Primary Outcome: Severe Sepsis/Septic Shock[1]			Secondary Outcome: Sepsis[2]		
	OR	**Lower CI**	**Upper CI**	**OR**	**Lower CI**	**Upper CI**
Control Anti-bacterial agents	0.90	0.89	0.92			
No Exposure to Anti-bacterial agents	Ref					

*Multivariable Logistic Model adjusted for sex, age, primary payer, previous hospitalizations within 90 days, length of stay, co-morbidity score, surgical or medical DRG, emergency room visit, critical care stays during the index visit, month and year of the index visit, hospital bed size, hospital urban/rural location, hospital teaching status, hospital census division, and various chronic conditions based on ICD-9-CM discharge codes including: metastatic disease, congestive heart failure, dementia, renal failure, weight loss, hemiplegia, alcohol, any tumor, arrhythmia, pulmonary disease, coagulopathy, complicated diabetes, anemia, electrolytes, liver disease, peripheral vascular disorder, psychosis, pulmonary circulatory disorders, HIV/AIDS, hypertension, obesity, hyperlipidemia, uncomplicated diabetes, ischemic heart disease, atrial fib, and ventricular fib.

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

2 - Secondary outcome, sepsis used a published definition for hospital administrative data, “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]

3 - High risk anti-bacterial exposures included any receipt of $3^{rd}/4^{th}$ generation cephalosporins, fluoroquinolones, lincosamides, beta-lactam/beta-lactamase inhibitor combinations, oral vancomycin, and carbapenems.

4 - Low risk anti-bacterial exposures included receipt of $1^{st}/2^{nd}$ generation cephalosporins, macrolide, tetracycline, metronidazole, and sulfa without receipt of a high risk antibiotic.

5 - Control anti-bacterial exposures included any receipt of an aminoglycoside, penicillin or intravenous vancomycin (antibiotics that minimally disrupt GI flora) without receipt of intermediate or high-risk antibiotics.

6 - In addition, we conducted a similar model with the same exposures that used any readmission within 90 days as the outcome rather than either of the sepsis outcomes.