

## Trends in Antibiotic Use in United States Hospitals During the Coronavirus Disease 2019 Pandemic

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We described antibiotic use among inpatients with coronavirus disease 2019 (COVID-19). Most COVID-19 inpatients received antibiotic therapy. We also described hospital-wide antibiotic use during 2020 compared with 2019, stratified by hospital COVID-19 burden. Although total antibiotic use decreased between years, certain antibiotic use increased with higher COVID-19 burden.

**Keywords.** antibiotic use; antimicrobial stewardship; COVID-19; epidemiology.

Coronavirus disease 2019 (COVID-19) has presented unprecedented challenges for US hospitals. Recent reports estimate that more than 70% of COVID-19 inpatients receive antibiotic therapy despite low prevalence of secondary bacterial infections among inpatients with COVID-19 [1–4]. The objectives of this analysis were to describe antibiotic use among hospitalized inpatients diagnosed with COVID-19 and hospital-wide antibiotic use in a large cohort of US hospitals during 2020 compared with 2019 stratified by COVID-19 burden.

### METHODS

We conducted a retrospective study of adult and pediatric inpatient hospitalizations at US hospitals included in the Premier Healthcare Database Special COVID-19 Release ([PHD-SR] release date January 10, 2021). The PHD-SR contains hospital discharge records for all adult and pediatric inpatients discharged from participating general acute care, non-federal US hospitals [5]. We included hospitals reporting at least 100 antibiotic days of therapy (DOT) per 1000 patient days (PDs) during all months of the study period, and we excluded

hospitals with incomplete reporting of DOT or PDs. One DOT represents the use of a single antibiotic on a given day regardless of the number of doses or dosage strength. A COVID-19 inpatient hospitalization was defined as a primary or secondary *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) diagnosis code of B97.29 (other coronavirus as the cause of disease classified elsewhere) in administrative data for an inpatient admitted during February–April 2020 and discharged during March–April, or a primary or secondary ICD-10-CM diagnosis code of U07.1 (COVID-19; introduced April 2020) for an inpatient discharged during April–October 2020 [6–8].

For each inpatient discharge, we identified antibiotics listed in the US Food and Drug Administration's National Drug Code Directory [9] that the inpatient received during the hospitalization based on hospital charge data. Only antibiotics administered by oral or parenteral routes were included. We calculated antibiotic use as DOT/1000 PDs and defined the proportion of hospital discharges in which an inpatient received at least 1 dose of an antibiotic during their stay.

We described demographic and clinical characteristics for inpatients diagnosed with COVID-19 and stratified by receipt of an antibiotic during their stay. The PHD-SR defines urban settings as areas whose (1) core census blocks have a population density of at least 1000 people per square mile and (2) surrounding census blocks have an overall density of at least 500 people per square mile; areas that did not meet this definition were considered rural [5]. Critical care was defined as admission to an intensive care unit or critical care unit. We described the proportion of antibiotic agents used in inpatients with COVID-19 and stratified by critical care admission and invasive mechanical ventilation. Critical care admission and invasive mechanical ventilation at any time during hospitalization, independent of antibiotic receipt, were determined using inpatient billing records; in-hospital mortality was determined using inpatient discharge status [7].

To assess the impact of COVID-19 burden on hospital-wide antibiotic use, each hospital admission month during March–October 2020 was categorized into quartiles based on the rate of COVID-19 cases per 10 000 discharges. Therefore, a hospital could appear in different quartiles for different months depending on their COVID-19 burden for a given month but would only appear in one quartile during a given month. Hospitals without COVID-19 cases were included. We compared differences in hospital-wide antibiotic use during March–October 2019 and 2020 for hospital months in each quartile to assess the effect of COVID-19 burden on antibiotic DOT/1000 PDs by type of antibiotic.

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Median difference in DOT/1000 PDs was calculated for each COVID-19 burden quartile, and the Wilcoxon signed-rank test was used to evaluate statistical significance;  $P < .01$  was considered significant.

This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy (see the following: 45 C.F.R. part 46; 21 C.F.R. part 56; 42 U.S.C. §241(d), 5 U.S.C. §552a, 44 U.S.C. §3501 et seq.). All data were analyzed using PySpark (Python) on the Data Collation and Integration for Public Health Event Response (DCIPHER) platform and SAS version 9.4 (SAS Institute Inc., Cary, NC).

## RESULTS

Of 716 hospitals, 67.9% were located in urban settings, 69.8% had fewer than 300 beds, and 97.6% reported having inpatients with COVID-19 (Supplemental Appendix Table 1). Overall, 213 338 inpatients had a COVID-19 diagnosis (Table 1). Most (77.3%) inpatients diagnosed with COVID-19 received at least 1 antibiotic day during their stay, and 81.3% of those who received an antibiotic were started on admission. Differences in distribution of race/ethnicity were small, ranging from 0.02% to 3.66% between inpatients with COVID-19 who received antibiotics and those who did not. Comparing inpatients with COVID-19 who received antibiotics with those who did not,

**Table 1. Characteristics of Inpatients With COVID-19<sup>a</sup> Stratified by Antibiotic Receipt**

Inpatient Characteristics	Inpatients With COVID-19		
	Total N = 213 338 (%)	Received Antibiotics N = 164 943 (77.3%)	Did Not Receive Antibiotics N = 48 395 (22.7%)
Sex			
Male	109 818 (51.5)	86 085 (52.2)	23 733 (49.0)
Female	103 380 (48.5)	78 763 (47.8)	24 617 (50.9)
Unknown	140 (<0.1)	95 (<0.1)	45 (<0.1)
Age, mean (IQR), years	61.5 (26.0)	62.4 (25.0)	58.6 (29.0)
Age Group, years			
0–17	2056 (1.0)	1179 (0.7)	877 (1.8)
18–49	50 328 (23.6)	36 552 (22.2)	13 776 (28.5)
50–64	58 057 (27.2)	45 188 (27.4)	12 869 (26.6)
65–84	80 875 (37.9)	64 420 (39.1)	16 455 (34.0)
≥85	22 022 (10.3)	17 604 (10.7)	4418 (9.1)
Race			
White	119 440 (56.0)	92 773 (56.2)	26 667 (55.1)
Black	45 404 (21.3)	34 994 (21.2)	10 410 (21.5)
Asian	5635 (2.6)	4158 (2.5)	1477 (3.1)
Other	30 698 (14.4)	24 268 (14.7)	6430 (13.3)
Unknown	12 161 (5.7)	8750 (5.3)	3411 (7.0)
Ethnicity			
Hispanic	45 503 (21.3)	35 187 (21.3)	10 316 (21.3)
Non-Hispanic	130 596 (61.2)	99 602 (60.4)	30 944 (64.0)
Unknown	37 239 (17.5)	30 154 (18.3)	7085 (14.6)
Location From Which Inpatient Was Admitted			
Nonhealthcare point of origin	173 093 (81.1)	134 859 (81.8)	38 234 (79.0)
Clinic	10 973 (5.1)	8157 (4.9)	2816 (5.8)
Transfer from a different hospital	15 893 (7.4)	11 149 (6.8)	4744 (9.8)
Transfer from skilled nursing or intermediate care facility, or born inside hospital	8336 (3.9)	6927 (4.2)	1409 (2.9)
Antibiotic started on admission <sup>b</sup>	134 071 (62.8)	134 071 (81.3)	-
Length of therapy (LOT) <sup>c</sup> , mean (IQR), days	4.7 (5.0)	6.0 (5.0)	-
Critical care admission <sup>d</sup>	96 218 (45.1)	81 139 (49.2)	15 079 (31.2)
Invasive mechanical ventilation <sup>d</sup>	30 944 (14.5)	29 662 (18.0)	1282 (2.6)
Length of hospital stay, mean (IQR), days	8.4 (7.0)	9.4 (8.0)	5.0 (4.0)
In-hospital mortality	29 082 (13.6)	26 677 (16.2)	2405 (5.0)

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range.

<sup>a</sup>A COVID-19 inpatient hospitalization was defined as a primary or secondary *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) diagnosis code of B9729 (other coronavirus as the cause of disease classified elsewhere) in administrative data for an inpatient admitted during February–April 2020 and discharged during March–April, or a primary or secondary ICD-10-CM diagnosis code of U07.1 (COVID-19) for an inpatient discharged during April–October 2020.

<sup>b</sup>Day 1 of hospitalization or earlier.

<sup>c</sup>One LOT represents the use of any antibiotic on a given day regardless of the number of antibiotics, doses, or dosage strength.

<sup>d</sup>Identified using inpatient billing records, independent of antibiotic receipt.

**Table 2. Median Hospital-Wide Antibiotic Use<sup>a</sup> by Rate of COVID-19 per 10 000 Discharges<sup>b</sup>, March–October 2019 and March–October 2020**

Rate of COVID-19 per 10 000 Discharges <sup>c</sup>		Total (0.00, 7931.03)	Quartile 1 (0.00, 79.58)	Quartile 2 (79.68, 275.33)	Quartile 3 (275.34, 617.41)	Quartile 4 (617.67, 7931.03)
Median Antibiotic Days of Therapy/1000 Patient Days						
All Antibiotics	2019	932	976	892	904	978
	2020	917	940	876	894	967
	Median Difference	-4.29	-19.93	-0.86	4.57	-4.33
	PValue	<.0001	<.0001	.0866	.4945	.0280
Ceftriaxone	2019	135	152	128	127	140
	2020	147	149	134	142	173
	Median Difference	11.76	1.20	7.12	14.14	26.66
	PValue	<.0001	.8071	<.0001	<.0001	<.0001
Vancomycin	2019	137	131	131	137	146
	2020	127	126	126	127	128
	Median Difference	-7.15	-4.52	-4.53	-6.23	-13.51
	PValue	<.0001	.0068	<.0001	<.0001	<.0001
Piperacillin-Tazobactam	2019	116	109	111	116	126
	2020	108	100	104	111	116
	Median Difference	-4.02	-2.13	-2.56	-2.48	-9.21
	PValue	<.0001	.0088	.0009	.0004	<.0001
Cefepime	2019	51	35	53	57	58
	2020	58	36	61	62	67
	Median Difference	4.75	0.00	6.04	5.50	7.83
	PValue	<.0001	.0087	<.0001	<.0001	<.0001
Azithromycin	2019	54	63	50	48	57
	2020	59	50	50	56	89
	Median Difference	3.70	-7.91	0.46	6.30	26.78
	PValue	<.0001	<.0001	.0554	<.0001	<.0001
Meropenem	2019	22	14	21	23	26
	2020	22	11	22	25	27
	Median Difference	0.00	0.00	0.00	0.81	0.67
	PValue	.0002	.2519	.2581	<.0001	.0050
Doxycycline	2019	21	21	21	21	20
	2020	23	19	22	23	25
	Median Difference	0.63	0.00	1.21	1.51	2.02
	PValue	<.0001	.0071	.0002	<.0001	<.0001
Levofloxacin	2019	31	33	26	29	36
	2020	20	19	18	20	23
	Median Difference	-6.88	-6.70	-5.93	-7.07	-8.93
	PValue	<.0001	<.0001	<.0001	<.0001	<.0001

Abbreviations: COVID-19, coronavirus disease 2019.

<sup>a</sup>Hospital-wide antibiotic use rates among all inpatients.

<sup>b</sup>Each hospital admission month during March–October 2020 was categorized into quartiles by COVID-19 burden based on the rate of COVID-19 cases per 10 000 discharges. A hospital could appear in one quartile for 1 month and another quartile for a different month.

<sup>c</sup>Minimum and maximum rate of COVID-19 cases per 10 000 discharges for hospitals in each quartile.

49.2% vs 31.2% were admitted to critical care, 18.0% vs 2.6% required invasive mechanical ventilation, and 16.2% vs 5.0% died, respectively. Inpatients with COVID-19 and on antibiotics had longer lengths of stay (mean 9.4 vs 5.0 days) compared with those without an antibiotic (Table 1).

The antibiotic use rate in inpatients with COVID-19 was 889 DOT/1000 PDs, with a rate of 932 DOT/1000 PDs among inpatients admitted to critical care and 988 DOT/1000 PDs among those requiring invasive mechanical ventilation (Supplemental Appendix Table 2). It is notable that 49.7% of COVID-19

inpatients received at least 1 antibiotic day of ceftriaxone, 44.3% received azithromycin, and 35.6% received a combination of both. Larger proportions of COVID-19 inpatients admitted to critical care or requiring invasive mechanical ventilation received vancomycin, cefepime, piperacillin-tazobactam, and meropenem compared with all inpatients with COVID-19. Among adult inpatients with COVID-19 ( $\geq 18$  years), 77.5% received an antibiotic. In adult COVID-19 inpatients, penicillin and first- or second-generation cephalosporins were rarely used, 1.7% and 5.7%, respectively (Supplemental Appendix

**Table 3).** Among pediatric COVID-19 inpatients (<18 years), 57.3% received an antibiotic, 14.2% received penicillin, and 8.5% received a first- or second-generation cephalosporin. The proportion of inpatients with COVID-19 receiving antibiotics was lower during September–October (71.3%) than during March–May (80.2%); however, the percentage difference in total DOT/1000 PDs ranged from 2.3% to 7.6% across all time periods (March–May, June–August, September–October) (**Supplemental Appendix Table 4**).

During March–October 2020, the median hospital rate of COVID-19 was 275.34 per 10 000 discharges ranging from 0.00 in the first quartile (minimum, 0.00; maximum, 79.58) to 1077.33 in the fourth quartile (minimum, 617.67; maximum, 7931.03). Compared to other quartiles, hospitals in the first quartile were smaller (42.9%, 0–99 beds), more rural (44.2%), and mostly nonteaching hospitals (79.8%) (**Supplemental Appendix Table 1**). Hospital-wide antibiotic use was significantly lower during March–October 2020 compared with March–October 2019, overall and for hospitals with the lowest burden of COVID-19 (**Table 2**). In hospitals with a higher burden of COVID-19, DOT/1000 PDs of ceftriaxone, cefepime, azithromycin, and doxycycline increased, with the largest increases in median difference observed in hospitals with progressively higher COVID-19 burden. The use of vancomycin, piperacillin-tazobactam, and levofloxacin was consistently lower in 2020 compared with 2019 across all hospitals regardless of COVID-19 burden.

## DISCUSSION

Although total antibiotic use was lower during March–October 2020 compared with 2019, almost 80% of inpatients hospitalized with COVID-19 received antibiotics, frequently those used to treat lower respiratory tract infections in hospitalized inpatients [10, 11]. Approximately half of hospitalized inpatients received ceftriaxone, commonly in combination with azithromycin. Although diagnosis date of COVID-19 is unavailable, reassessing empiric antibiotic therapy in inpatients with suspected COVID-19 to stop or tailor treatment when more clinical and diagnostic information is available may optimize inpatient outcomes and prevent adverse events [12]. Higher rates of cefepime and meropenem prescribing were observed (1) in quartiles with the most COVID-19 burden and (2) in critically ill inpatients with COVID-19. In contrast, prescribing of vancomycin and piperacillin-tazobactam decreased in 2020 compared with 2019, which suggests a possible decline in empiric prescribing on admission and throughout hospitalization with preferential use of cefepime for complicated lower respiratory tract infection. Antibiotic stewardship programs can play a critical role in optimizing treatment guidelines and supporting the administration of novel therapeutics for the treatment of inpatients with COVID-19 [13].

Administrative data are collected primarily for billing purposes and adapted for research. There is possible misclassification in pharmacy, clinical, facility information, and unit classification. Similar administrative data have been used to calculate antibiotic use in US hospitals, and our 2019 estimates are similar to previous estimates [14, 15]. Our estimates were limited to acute, non-federal hospitals in the United States and do not adequately represent children's hospitals. As we calculated DOTs/1000 PDs and stratified by admission month, DOTs in our data could represent a 2-month period or more with inpatients that have hospital stays crossing the monthly threshold, potentially impacting monthly calculations.

## CONCLUSIONS

We present antibiotic use data from 716 hospitals, which makes our study one of the largest to date quantifying antibiotic use while accounting for COVID-19 burden and comparing to antibiotic DOT/1000 PDs in the same hospitals in 2019. The majority of inpatients hospitalized with COVID-19 in this dataset received antibiotics on admission. Data show limited reported evidence for secondary bacterial infections [1–4]. Antibiotic stewardship programs can leverage their infrastructure to address challenges that the COVID-19 pandemic has presented to healthcare professionals in the hospital setting [12]. Ensuring resiliency and continuity of hospital stewardship programs is critical to optimize the treatment and outcomes of all inpatients and those with COVID-19 [16, 17].

## Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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