Antibiotic Resistant Infections among COVID-19 Inpatients in U.S. Hospitals

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Abstract:

We described bacterial/fungal co-infections and antibiotic resistant infections among inpatients diagnosed with COVID-19 and compared findings with inpatients diagnosed with influenza-like-illness. Less than 10% of COVID-19 inpatients had bacterial/fungal co-infection. Longer lengths of stay, critical care stay, and mechanical ventilation contribute to increased incidence of hospital-onset infections among COVID-19 inpatients.

Keywords: COVID-19, Antibiotic Resistance, Epidemiology

Introduction:

Bacterial co-infections are commonly identified among patients with influenza and other viral respiratory infections [1]. However, estimated rates of bacterial co-infections and secondary bacterial infections among inpatients with Novel Coronavirus Disease 2019 (COVID-19) are low, despite findings of frequent antibiotic use among inpatients with COVID-19 [1-5]. Given the frequent use of antibiotics and reports of increases in antibiotic resistant infections among COVID-19 inpatients and during surges of COVID-19 hospitalizations, our objective was to determine the rate of bacterial or fungal co-infections and certain antibiotic resistant infections among inpatients with COVID-19 [6, 7]. Further, we compared these findings with a cohort of inpatients diagnosed with influenza-like-illness (ILI) discharged during 2019.

Methods:

We conducted a retrospective study using adult and pediatric inpatient discharge and microbiology data from U.S. hospitals included in the Premier Healthcare Database Special COVID-19 Release (PHD-SR, release date 10/12/2021) [8]. The PHD-SR contains discharge records for all inpatients discharged from participating acute care, general, non-Federal US hospitals. Inpatient visit records included diagnostic and procedure codes, demographic information, admission and discharge dates, and facility characteristics [9]. Hospitals were limited to those with available microbiology data. Microbiology data included detailed information such as genus and species of bacterial isolates, day and time stamp of specimens, and associated antimicrobial sensitivity testing results [8].

We described demographic and clinical characteristics of inpatients diagnosed with COVID-19 in 2020–2021 or ILI in 2019. To define the cohort of COVID-19 diagnosed inpatients we selected discharges with an *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) primary or secondary diagnosis code of B97.29 (other coronavirus as the cause of diseases classified elsewhere) discharged during March–April 2020 and admitted during February–April 2020 or

discharges with a primary or secondary ICD-10-CM code of U07.1 (COVID-19; introduced April 2020) discharged during April 2020–June 2021 [3]. The cohort of inpatients with ILI was defined as inpatients discharged during January–June 2019 with any primary or secondary ICD-10-CM diagnosis code consistent with ILI (Supplemental Appendix Table A1, see https://www.health.mil/Reference-Center/Publications/2015/10/01/Influenza-Like-Illness).

To identify co-infections among the COVID-19 and ILI cohorts, we first identified patients with at least one microbiology specimen collected between 3 days prior to admission and 3 days post discharge. Specimens with a test result of "bacteria identified", "fungus identified", or with an antimicrobial sensitivity result were considered positive bacterial or fungal cultures. We retrospectively calculated proportions of inpatients with a positive bacterial or fungal culture among inpatients with ILI and COVID-19. Organisms identified among specimens with a sensitivity result taken from ILI and COVID-19 inpatients were described with frequencies.

In order to examine antibiotic resistance, we further limited specimens to those that yielded an organism of interest and had susceptibility testing results to determine whether the isolate had the resistance phenotype of interest: methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamases (ESBLs), carbapenem-resistant Enterobacteriaceae (CRE), vancomycin resistant Enterococcus (VRE), carbapenem-resistant Acinetobacter spp. (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) [9]. Specimens categorized as surveillance (i.e., cultures labeled as rectal, perirectal, or nasal) and non-incident cases (defined below) were excluded. Specimens collected from blood, bone, cerebrospinal fluid, peritoneal fluid, pleural fluid, and lymph nodes were considered from sterile body sites. Non-sterile specimen body site specimens included urine, sputum, and wounds. Only the first positive specimen for each phenotype was included. Cultures were defined as incident if the inpatient had no prior inpatient culture of the same phenotype in the previous 14 days. For inpatients with more than one positive clinical culture, cultures from a sterile body site were prioritized over those with non-sterile body site specimen sources within 14 days. Clinical cultures were defined as

community-onset (CO) when the culture was taken between the 3 days preceding admission and the first 3 days after admission. Clinical cultures taken on day 4 or later after admission were considered hospital-onset (HO).

We calculated the rates of resistant infections as the number of positive specimens with the resistance phenotype of interest per 10,000 discharges stratified by epidemiology classification (HO/CO). In addition, we compared the rates of infections for each phenotype and epidemiology classification using a multivariable logistic model and adjusting for age group, gender, race/ethnicity for both CO and HO infections. To evaluate whether differences in HO AR infections between ILI and COVID-19 inpatients were driven by higher severity of illness, we further adjusted for length of stay, critical care stay (yes or no), and mechanical ventilation (yes or no) in secondary models. Models account for inter-facility correlation using generalized estimating equations.

This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy (See e.g., 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 the 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). A value of $p<0.01$ was considered significant.

Results:

A cohort of 142,426 inpatients diagnosed with ILI were identified in 275 hospitals during January–June 2019 and a cohort of 206,465 COVID-19 diagnosed inpatients were identified in 280 hospitals during January 2020–June 2021 (Supplemental Appendix Table A2). On average, inpatients with COVID-19 had longer lengths of stay (LOS) than inpatients with ILI (mean: 8.3 vs. 6.1 days). The proportion of inpatients who spent at least one day in a critical care unit among those diagnosed with COVID-19 was 48.3% compared with 46.4% among inpatients with ILI. Among inpatients with

COVID-19, 13.0% had at least one day of invasive mechanical ventilation compared with 10.2% of inpatients diagnosed with ILI.

The proportion of inpatients with a bacterial or fungal culture obtained was similar for COVID-19 and ILI (56.2% and 60.4%, respectively). The percent of discharges with a positive culture categorized as CO was lower among inpatients with COVID-19 compared with inpatients with ILI (7.0% vs. 10.4%). However, the percent of discharges with a positive culture categorized as HO was higher among inpatients with COVID-19 (4.1% vs. 2.4%). The most common organisms identified among inpatients diagnosed with ILI and COVID-19 were similar while HO sterile specimen sources for inpatients with COVID-19 were more common (Supplemental Appendix Table A3 and Table A4). CO infection rates of MRSA, ESBL, CRE, VRE, CRAB, and CRPA tended to be lower, but HO infection rates were higher among COVID-19 inpatients compared with those diagnosed with ILI across all pathogens (Table 1).

Multivariable logistic models showed significantly lower odds of CO MRSA, CRPA, and CRAB among inpatients diagnosed with COVID-19 compared with inpatients with ILI (Table 1). There was a significantly higher odds of HO MRSA, ESBL, CRE, and CRPA among COVID-19 inpatients compared with ILI. HO models further adjusted for length of stay, critical care stay, and invasive mechanical ventilation did not show an increase in the odds of HO infections (Supplemental Appendix Table A5).

Discussion:

Based on our findings, the incidence of CO bacterial and fungal co-infection, including with antibiotic resistant pathogens, among patients admitted with COVID-19 was less than 10% of patients, indicating that empiric antibiotic therapy should not be used to treat COVID-19 patients [10]. Our findings show that COVID-19 inpatients have a higher risk of HO antibiotic resistant infections compared with inpatients diagnosed with ILI. However, when adjusting for LOS, critical care stay, and

receipt of invasive mechanical ventilation during hospitalization, the differences were less marked, suggesting that these risk factors contribute to higher HO infection rates among COVID-19 inpatients, consistent with other studies [4, 5]. Increases in HO-ESBL and other HO infections among COVID-19 inpatients may be due to longer hospital stays associated with COVID-19 and high rates of antibiotic exposure among inpatients with COVID-19 [3]. A small multi-center study found infections caused by gram-negative organisms increased in frequency with longer hospital stays among inpatients diagnosed with COVID-19 [4].

We used a large administrative dataset representing information from a diverse sample of hospital sizes, teaching status, urban/rural locations, and geographic divisions. However, our study had several limitations: the study did not include hospitals located in the Mountain U.S. census division; administrative data are collected primarily for billing purposes and adapted for research resulting in possible misclassification in clinical and facility information, which is most likely non-differential; and the study did not include molecular diagnostics for identification of potential infections. However, we defined antibiotic resistant pathogens using previously validated methods for identifying these infections among electronic healthcare databases [9]. Prior research on the prevalence of antibiotic resistant infections among inpatients during the COVID-19 pandemic in the U.S. has consisted mostly of single center or smaller multi-center studies [4, 11].

The pandemic has changed healthcare delivery, antibiotic prescribing patterns, and infection control practices within U.S. hospitals and community settings [2, 3, 11, 12]. Longer LOS, critical care stay, and receipt of invasive mechanical ventilation contribute to incidence of HO antibiotic resistant infections among inpatients with COVID-19. Hospitals should continue to focus on infection control and antibiotic stewardship measures for patients with COVID-19 to prevent healthcare-associated infections, including antibiotic resistant pathogens.

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Citations:

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1 **Tables:**

2 Table 1. Antibiotic Resistant Infections among Inpatients diagnosed with COVID-19 Compared with Inpatients diagnosed with ILI.

	ILI[1] (N=142,426)		COVID-19[2] (N=206,456)		COVID-19 Compared with ILI		
	Frequency (N)	Rate per 10,000 discharges	Frequency (N)	Rate per 10,000 discharges	Odds Ratio[3]	99% Confidence Interval	P-value
Hospital-Onset							
MRSA	451	31.7	1,056	51.2	1.54	(1.23, 1.94)	<.0001
ESBL	186	13.1	633	30.7	2.34	(1.70, 3.23)	<.0001
CRE	18	1.3	88	4.3	2.99	(1.35, 6.62)	0.0005
VRE	151	10.6	265	12.8	1.24	(0.95, 1.62)	0.0391
CRPA	86	6.0	264	12.8	2.03	(1.23, 3.33)	0.0003
CRAB	24	1.7	41	2.0	1.02	(0.52, 2.00)	0.9455
Community-Onset							
MRSA	1,395	98.0	960	46.5	0.55	(0.48, 0.63)	<.0001
ESBL	829	58.2	1,059	51.3	0.99	(0.83, 1.19)	0.9385
CRE	41	2.9	31	1.5	0.57	(0.27, 1.18)	0.0681
VRE	204	14.3	204	9.9	0.77	(0.53, 1.12)	0.0666
CRPA	173	12.1	86	4.2	0.31	(0.20, 0.48)	<.0001
CRAB	40	2.8	27	1.3	0.45	(0.23, 0.86)	0.0013

[1]ILI discharges were defined as a hospitalization with a discharge during January–June 2019 and any of the following primary or

secondary ICD-10-CM codes: B97.89, H66.9, H66.90, H66.91, H66.92, H66.93, J00, J01.9, J01.90, J06.9, J09.X, J10.X, J11.X, J12.89, J12.9, J18, J18.1, J18.8, J18.9, J20.9, J40, R05, R50.9.

[2]COVID-19 discharges were defined as hospitalizations with a primary or secondary ICD-10-CM code of U07.1 discharged during April 2020–June 2021 or a primary or secondary ICD-10-CM code of B97.29 discharged during March–April 2020 and admitted during February–April 2020.

[3]Multivariable logistic models adjusted for gender, age group, race, and ethnicity.