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Antibiotic Use and Bacterial Infection among Inpatients in the First Wave of COVID-19: a Retrospective Cohort Study of 64,691 Patients

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ABSTRACT Hospitalized patients with SARS-CoV-2 infection (COVID-19) often receive antibiotics for suspected bacterial coinfection. We estimated the incidence of bacterial coinfection and secondary infection in COVID-19 using clinical diagnoses to determine how frequently antibiotics are administered when bacterial infection is absent. We performed a retrospective cohort study of inpatients with COVID-19 present on admission to hospitals in the Premier Healthcare Database between April and June 2020. Bacterial infections were defined using ICD-10-CM diagnosis codes and associated "present on admission" coding. Coinfections were defined by bacterial infection present on admission, while secondary infections were defined by bacterial infection that developed after admission. Coinfection and secondary infection were not mutually exclusive. A total of 18.5% of 64,961 COVID-19 patients (n = 12,040) presented with bacterial infection at admission, 3.8% (n = 2,506) developed secondary infection after admission, and 0.9% (n = 574) had both; 76.3% (n = 49,551) received an antibiotic while hospitalized, including 71% of patients who had no diagnosis of bacterial infection. Secondary bacterial infection occurred in 5.7% of patients receiving steroids in the first 2 days of hospitalization, 9.9% receiving tocilizumab in the first 2 days of hospitalization, and 10.3% of patients receiving both. After adjusting for patient and hospital characteristics, bacterial coinfection (adjusted relative risk [aRR], 1.15; 95% confidence interval [CI], 1.11 to 1.20) and secondary infection (aRR 1.93; 95% CI, 1.82 to 2.04) were both independently associated with increased mortality. Although 1 in 5 inpatients with COVID-19 presents with bacterial infection, secondary infections in the hospital are uncommon. Most inpatients with COVID-19 receive antibiotic therapy, including 71% of those not diagnosed with bacterial infection.

KEYWORDS COVID-19, antibiotics, bacterial coinfection, secondary infection

Hospitalized patients with SARS-CoV-2 infection (COVID-19) are often suspected of having cooccurring bacterial infection. Thus, 57 to 72% of patients admitted with COVID-19 receive antibiotics (1–4). However, microbiologically confirmed bacterial coinfection only occurs in 1% to 8% of patients presenting with COVID-19 (2–6). Secondary bacterial infection develops after hospital admission in an additional 3 to 14% (1, 5). When present, bacterial coinfection or secondary infection significantly increases morbidity and mortality from COVID-19 (6–8).

Existing studies define bacterial coinfections and secondary infections based on positive microbiologic test results, which likely underestimate the true incidence of

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bacterial infections (9). Sputum culture is an insensitive diagnostic test that relies on the patient's ability to produce a quality specimen (9,10). Blood cultures are infrequently positive in the setting of bacterial pneumonia, and their yield is reduced when collected after the initiation of antibiotics (11). For these reasons and others, guidelines do not recommend routine collection of either sputum or blood cultures among patients with community-acquired pneumonia, including guidelines specifically for the management of COVID-19 pneumonia (12).

The purposes of this study were (i) to estimate the incidence of bacterial coinfection and secondary infection in the setting of COVID-19 based on clinical diagnoses rather than microbiologic testing and (ii) to examine patterns of antibiotic use based on whether bacterial infection was diagnosed at the time of treatment. Previous studies describing the incidence of bacterial infection in COVID-19 based on microbiologic testing primarily took place during the first wave of the pandemic. We focused on data from this period to allow comparison between our results and what has been previously reported.

RESULTS

Among 64,961 patients with COVID-19 present on admission (POA) at 605 hospitals contributing to Premier, 21.7% (n = 14,163) received a diagnosis consistent with bacterial infection. A proportion of 18.5% of patients (n = 12,040) were admitted with bacterial coinfection at admission, 3.9% (n = 2,506) developed secondary bacterial infection after admission, and 0.9% (n = 574) were diagnosed with both. The proportions of patients with bacterial coinfection and secondary infection in demographic and clinical subgroups are shown in Table 1. Risk of bacterial coinfection or secondary infection and patient-level characteristics are listed in Table 2.

The most common subcategories of bacterial coinfection at admission were genitourinary (8.5% of the total sample, n = 5,548), respiratory (6.5%, n = 4,234), other (5.5%, n = 3,598; examples include "other bacterial infections of unspecified site," "abscess of mediastinum"), and bacterial sepsis (1.5%, n = 976) (Fig. 1). The most common subcategories of bacterial secondary infection after admission were respiratory (2.1% of the overall sample, n = 1,372), other (1.3%, n = 827), genitourinary (1.0%, n = 660), and bacterial sepsis (0.5%, n = 315). The most common specific diagnoses associated with bacterial coinfection and secondary infection are listed in Table 3. Risk factors for bacterial coinfection and secondary infection are described in the supplemental material.

A proportion of 22.0% of patients with COVID-19 POA (n = 14,303) died in-hospital or were discharged to hospice. Unadjusted mortality was 19.2% among patients without bacterial infection (n = 9,755 out of 50,903), 30.6% among patients with bacterial coinfection (n = 3,687 out of 12,040), and 44.3% among patients with bacterial secondary infection (n = 1,109 out of 2,506). After adjusting for baseline patient- and hospital-level characteristics, bacterial coinfection (adjusted relative risk [aRR], 1.15; 95% confidence interval [CI], 1.11 to 1.20) and secondary infection (aRR, 1.93; 95% CI, 1.82 to 2.04) were both independently associated with increased adjusted mortality risk.

Antibiotic use among patients with and without bacterial infections. A proportion of 76.3% of patients with COVID-19 POA (n = 49,551) received at least one antibiotic during hospitalization. A proportion of 33.1% (n = 21,475) received an antibiotic with activity against *Pseudomonas aeruginosa*, and 32.7% (n = 21,228) received an antibiotic with activity against methicillin-resistant *Staphylococcus aureus* (MRSA). The most common antibiotics were ceftriaxone (48.5% of the total sample, n = 31,510), azithromycin (46.0%, n = 29,875), and vancomycin (22.9%, n = 14,861). Patients who received an antibiotic were treated for a median of 7 days of therapy (DOT; interquartile range [IQR], 3 to 12). Antipseudomonal agents and anti-MRSA agents were administered for a median of 4 DOT (IQR, 2 to 8) and 3 DOT (IQR, 1 to 6), respectively.

A total of 36,049 patients received an antibiotic without a diagnosis of bacterial infection (70.8% of those without a diagnosis of bacterial infection), including 21,491 who had neither bacterial infection nor a nonspecific pneumonic or septic syndrome (62.9% of

TABLE 1 Characteristics of inpatients with COVID-19 present on admission, by presence or absence of bacterial infection[a]

Characteristic	No. (%) with bacterial infection at admission		No. (%) with bacterial infection after admission	
	Absent (*n* = 52,921)	Present (*n* = 12,040)	Absent (*n* = 62,455)	Present (*n* = 2,506)
Age				
18–30 yr old	2,830 (5.4)	380 (3.2)*	3,154 (5.1)	56 (2.2)*
31–40 yr old	4,243 (8.0)	558 (4.6)*	4,686 (7.5)	115 (4.6)*
41–50 yr old	6,196 (11.7)	958 (8.0)*	6,915 (11.1)	239 (9.5)*
51–60 yr old	9,807 (18.5)	1,627 (13.5)*	10,921 (17.5)	513 (20.5)*
61–70 yr old	11,406 (21.6)	2,533 (21.0)*	13,220 (21.2)	719 (28.7)*
>70 yr old	18,439 (34.8)	5,984 (49.7)*	23,559 (37.7)	864 (34.5)*
Gender				
Male	28,708 (54.3)	5,662 (47.0)*	32,930 (52.7)	1,440 (57.5)*
Female	24,130 (45.6)	6,364 (52.9)*	29,428 (47.1)	1,066 (42.5)*
Race				
Black	12,146 (23.0)	2,725 (22.6)*	14,311 (22.9)	560 (22.4)**
White	22,334 (42.2)	6,032 (50.1)*	27,306 (43.7)	1,060 (42.3)**
Other	13,687 (25.9)	2,575 (21.4)*	15,631 (25.0)	631 (25.2)**
Unknown	4,754 (9.0)	708 (5.9)*	5,207 (8.3)	255 (10.2)**
Hispanic ethnicity	11,074 (20.9)	1,808 (15.0)*	12,375 (19.8)	507 (20.2)
Elixhauser comorbidity index score				
0–2	22,341 (42.2)	2,981 (24.8)*	24,658 (39.5)	664 (26.5)*
3–4	17,945 (33.9)	4,201 (34.9)*	21,267 (34.1)	879 (35.1)*
5–6	9,301 (17.6)	3,262 (27.1)*	11,953 (19.1)	610 (24.3)*
>6	3,334 (6.3)	1,596 (13.3)*	4,577 (7.3)	353 (14.1)*
Source of admission				
Home	41,991 (79.4)	8,608 (71.5)*	48,726 (78.0)	1,873 (74.7)*
Long-term care	2,466 (4.6)	1,242 (10.3)*	3,589 (5.8)	99 (4.0)*
Hospital transfer	3,527 (6.7)	1,032 (8.6)*	4,239 (6.8)	320 (12.8)*
Teaching hospital	34,229 (64.5)	7,658 (63.6)**	40,033 (64.1)	1,854 (74.0)*
Urban hospital	49,206 (93.0)	11,082 (92.0)	57,975 (92.8)	2,313 (92.3)*
Hospital bed size				
0–299 beds	16,136 (30.5)	3,669 (30.5)*	19,241 (30.8)	564 (22.5)*
300–499 beds	15,788 (29.8)	3,989 (33.1)*	19,060 (30.5)	717 (28.6)*
500+ beds	20,997 (39.7)	4,382 (17.3)*	24,154 (38.7)	1,225 (48.9)*
Hospital region				
Midwest	7,946 (15.0)	2,179 (18.1)*	9,731 (15.6)	394 (15.7)**
Northeast	28,456 (53.8)	5,858 (48.7)*	32,925 (52.7)	1,379 (55.0)**
South	13,845 (26.2)	3,350 (27.8)*	16,598 (26.6)	597 (23.8)**
West	2,674 (5.1)	653 (5.4)*	3,191 (5.1)	136 (5.4)**

[a]Values are reported as the frequency, *n*, followed by the column percentage in parentheses. For characteristics with multiple levels, such as age, Elixhauser comorbidity index score, or hospital bed size, an overall chi-square test was performed across all levels rather than a separate comparison at each level. In this study, bacterial infection at admission was used as a proxy for bacterial coinfection. Bacterial infection after admission was used as a proxy for secondary infection. *, significantly different at the level of $P < 0.001$ compared to patients without bacterial infection; **, significantly different at the level of $P < 0.05$ compared to patients without bacterial infection.

patients in this category). Among these patients, the median DOT was 5 (IQR, 2 to 8). A proportion of 16.7% of patients without bacterial infection, sepsis, or pneumonia (*n* = 5,715) received treatment with an antipseudomonal agent (median, 2 DOT; IQR, 1 to 5), and 18.4% (*n* = 6,292) received an anti-MRSA agent (median, 2 DOT; IQR, 1 to 5).

Bacterial secondary infections after immunosuppression. A proportion of 33.2% of patients with COVID-19 POA (*n* = 21,570) received an oral or intravenous steroid, including 19.6% (*n* = 12,709) who received early steroids (i.e., in first 2 calendar days of hospitalization). Among the subset who received early steroids, 5.7% (*n* = 723) developed bacterial secondary infection. After adjusting for patient and hospital characteristics, early steroids were associated with increased risk of bacterial secondary infection (aRR, 1.65; 95% CI, 1.48 to 1.84; see the supplemental material).

A proportion of 6.7% of patients with COVID-19 POA (*n* = 4,364) received

TABLE 2 Absolute risk of bacterial infection at or after admission, by patient characteristics[a]

Characteristic	Bacterial infection at admission	Bacterial infection after admission
Age		
18–30 yr old	14.1 (12.6, 15.6)	2.1 (1.5, 2.8)
31–40 yr old	13.5 (12.4, 14.6)	2.5 (2.0, 3.1)
41–50 yr old	15.1 (14.0, 16.2)	3.2 (2.7, 3.7)
51–60 yr old	15.2 (14.5, 15.9)	4.2 (3.8, 4.6)
61–70 yr old	18.0 (17.3, 18.6)	4.7 (4.3, 5.2)
>70 yr old	21.8 (21.1, 22.4)	3.7 (3.4, 4.0)
Gender		
Male	16.6 (16.2, 17.0)	4.1 (3.8, 4.4)
Female	20.4 (19.9, 21.0)	3.5 (3.2, 3.8)
Race		
Black	17.2 (16.6, 17.9)	3.5 (3.1, 3.8)
White	19.5 (18.9, 20.2)	3.7 (3.4, 4.0)
Other	16.9 (16.1, 17.8)	3.9 (3.5, 4.3)
Unknown	16.7 (15.5, 17.9)	4.3 (3.6, 5.0)
Hispanic ethnicity	16.6 (15.8, 17.4)	4.2 (3.7, 4.6)
Elixhauser index		
0–2	16.0 (15.0, 17.1)	4.4 (3.6, 5.3)
3–4	19.1 (18.5, 19.7)	4.1 (3.7, 4.6)
5–6	20.0 (19.0, 20.9)	3.4 (3.1, 3.8)
>6	18.7 (17.0, 20.3)	3.1 (2.5, 3.8)
Admission source		
Home	18.1 (17.6, 18.7)	3.9 (3.6, 4.2)
Long-term care	21.3 (20.2, 22.5)	6.1 (5.4, 6.8)
Hospital transfer	25.3 (23.9, 26.7)	2.9 (2.3, 3.5)
Immunosuppression by hospital day 2		
Corticosteroids		5.2 (4.7, 5.8)
Tocilizumab		7.8 (6.2, 9.3)
Both		12.2 (9.6, 14.7)
Neither		3.3 (3.1, 3.6)

[a]Cell values represent estimated marginal risk in percentage points predicted by a multivariable log-binomial regression model, assuming the distribution of other covariates was equal to their distribution in the overall sample. Accompanying 95% confidence intervals in parentheses were bootstrapped with 100 repetitions. Multivariable log-binomial regression was adjusted for age, gender, source of admission, race/ethnicity, hospital characteristics, and Elixhauser comorbidities. In this study, bacterial infection at admission was used as a proxy for bacterial coinfection. Bacterial infection after admission was used as a proxy for secondary infection.

tocilizumab, including 2.2% (n = 1,445) who received early tocilizumab. Among the subset who received early tocilizumab, 9.9% (n = 143) developed bacterial secondary infection. After adjusting for patient and hospital characteristics, early tocilizumab was associated with increased risk of bacterial secondary infection (aRR, 2.66; 95% CI, 2.14 to 3.33).

A proportion of 4.9% of patients in the total sample (n = 3,203) received both steroids and tocilizumab, including 1.2% (n = 773) who received both by hospital day 2. Among the subset who received both classes of immunosuppression early in hospitalization, 10.4% (n = 80) developed secondary bacterial infections. When considering both immunosuppressive therapies, early steroids (aRR, 1.60; 95% CI, 1.42 to 1.81) and early tocilizumab (aRR, 2.74; 95% CI, 2.11 to 3.57) were each independently associated with increased risk of bacterial secondary infection, but no interaction effects were detected. After risk adjustment for covariates (and assuming that other covariates are otherwise equal between groups), absolute risk of secondary infection was estimated to be 3.3% (95% CI, 3.1 to 3.6%) among patients not receiving early immunosuppression, 5.2% (95% CI, 4.7 to 5.8%) among patients receiving early steroids, 7.8% (95% CI, 6.2 to 9.3%) among patients receiving early tocilizumab, and 12.2% (95% CI, 9.6

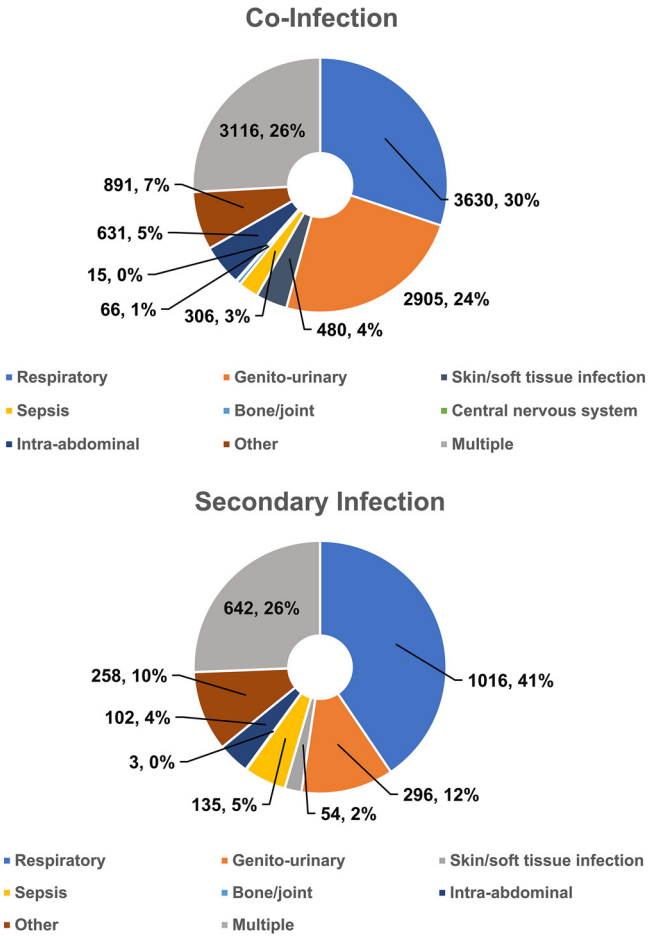

FIG 1 Subcategories of bacterial infection in the setting of COVID-19 present on admission. These figures are intended to represent the source of infection. The category for "multiple" infectious sources includes patients who had infections in >1 nonsepsis categories. A patient with pneumonia and a urinary tract infection would be counted as having multiple infections only. Sepsis was only included as a primary category for patients without another source of infection. A patient with pneumonia and sepsis would be counted as having a respiratory infection only.

to 14.7%) among patients receiving both agents in the first 2 days of hospitalization (see the supplemental material for full models and Fig. 2 for graphical display of absolute risk).

DISCUSSION

In this retrospective cohort study, 18.5% of patients who were hospitalized with COVID-19 POA during the first wave of the COVID-19 pandemic were diagnosed with concurrent bacterial coinfection, and 3.8% were diagnosed with bacterial secondary infection after admission. Antibiotic use was widespread, even in the absence of bacterial infection, pneumonia, or sepsis. This study reflects one of the largest to date to examine bacterial infections and antibiotic use among patients with COVID-19, and the first large study to examine clinical diagnoses of bacterial infection rather than microbiologically confirmed cases.

We observed a higher rate of bacterial coinfections at admission than has been previously reported during the same time period (1–6). This discrepancy between our study and the existing literature is likely explained by our use of diagnosis codes to identify bacterial infections rather than results from microbiologic testing. Studies that define bacterial infections based upon microbiologic test results likely underestimate the true incidence, because cultures are not obtained in every case and may be falsely negative in the setting of

TABLE 3 Most common diagnoses consistent with bacterial infection among patients presenting with COVID-19

ICD 10 code	Description	Frequency[a] [no. (%)]
Bacterial coinfections present on admission		
N39.0	Urinary tract infection, site not specified	4,679 (7.2)
J15.9	Unspecified bacterial pneumonia	2,756 (4.2)
B96.20	Unspecified *Escherichia coli* as the cause of diseases classified elsewhere	1,354 (2.1)
N30.00	Acute cystitis without hematuria	451 (0.7)
J15.6	Pneumonia due to other Gram-negative bacteria	432 (0.7)
B96.1	*Klebsiella pneumoniae* as the cause of diseases classified elsewhere	428 (0.7)
R78.81	Bacteremia	354 (0.5)
B96.89	Other bacterial agents as the cause of diseases classified elsewhere	352 (0.5)
B95.2	*Enterococcus* as the cause of diseases classified elsewhere	342 (0.5)
B96.4	*Proteus* (*mirabilis*) (*morganii*) causing diseases classified elsewhere	310 (0.5)
Bacterial secondary infection not present on admission		
N39.0	Urinary tract infection, site not specified	590 (0.9)
J95.851	Ventilator associated pneumonia	452 (0.7)
J15.9	Unspecified bacterial pneumonia	354 (0.5)
J15.212	Pneumonia due to methicillin-resistant *Staphylococcus aureus*	160 0.2)
B96.20	Unspecified *Escherichia coli* as the cause of diseases classified elsewhere	156 0.2)
B95.2	*Enterococcus* as the cause of diseases classified elsewhere	140 (0.2)
J15.211	Pneumonia due to methicillin-susceptible *Staphylococcus aureus*	140 (0.2)
J15.6	Pneumonia due to other Gram-negative bacteria	133 (0.2)
J15.1	Pneumonia due to *Pseudomonas*	125 (0.2)
R78.81	Bacteremia	125 (0.2)

[a]Reported proportions represent the number of inpatients with a given diagnosis out of the total sample of inpatients with COVID-19 present on admission. For perspective, the total number of patients in our sample with bacterial coinfection was 12,040; 38.9% of inpatients presenting with bacterial coinfection received a diagnosis of N39.0 for urinary tract infection, site not specified. A total of 2,506 patients in our sample developed bacterial secondary infection; 23.5% of inpatients who developed bacterial secondary infection were diagnosed with N39.0 for urinary tract infection, site not specified.

antibiotic use or improper specimen collection. In contrast, though subjective clinician diagnoses have been associated with both overdiagnosis and underdiagnosis (13, 14), discharge diagnoses are relatively accurate. Although an admitting diagnosis of bacterial infection may be incorrect in 27 to 43% of cases (13–15), discharge diagnoses are associated with a positive predictive value for bacterial infection of ≥80% (16, 17). Nonetheless, we suspect that our findings may overestimate the incidence of bacterial infection, given potential financial incentives for hospitals to code severe bacterial illness as POA. The true incidence of bacterial coinfection among COVID-19 inpatients is likely between the rate reported in our study and what has been reported based on microbiologic testing.

As has been widely observed (1–4), we found that antibiotics were commonly pre-

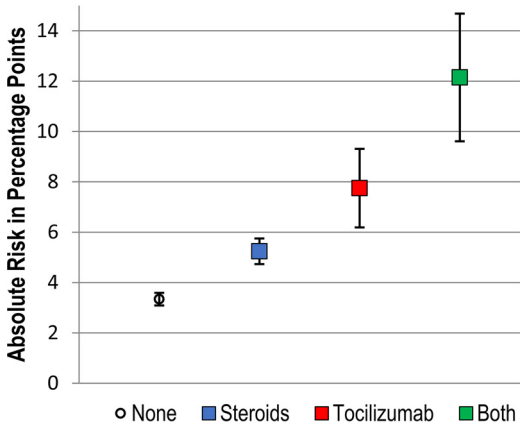

FIG 2 Absolute risk of bacterial secondary infection based on exposure to immunosuppression in the first two days of hospitalization. Percentages represent estimated marginal risk of bacterial infection after admission predicted by a multivariable log-binomial regression model, assuming the distribution of other covariates was equal to their distribution in the overall sample; 95% confidence intervals were bootstrapped with 500 repetitions. Multivariable log-binomial regression was adjusted for age, gender, source of admission, race/ethnicity, hospital characteristics, and Elixhauser comorbidities.

scribed in the context of viral infection due to SARS-CoV-2 during the first wave of the COVID-19 pandemic. Our study builds on the existing literature, however, because of our expansive definition for bacterial infection. After excluding any patient with a possible bacterial infection, including those with undefined sepsis syndromes or unspecified pneumonia, antibiotics were still administered in 3 out of 5 cases. Use of broad-spectrum agents with activity against *Pseudomonas* or MRSA far exceeded the expected prevalence of pneumonia due to these organisms (18). Our study was not designed to evaluate the appropriateness of antibiotic therapy, but we suspect our findings reflect antibiotic overuse driven by fear and uncertainty when the optimal clinical management of COVID-19 was still largely unknown.

Corticosteroids are the cornerstone of evidence-based treatment for hospitalized patients with severe or critical COVID-19 (19). Although the evidence to support use of tocilizumab is evolving, there is likely a role for tocilizumab in the management of hospitalized patients with severe, progressive COVID-19 (20). In our cohort, administration of these agents early in hospitalization either alone or in combination was associated with increased likelihood of bacterial secondary infection. When both agents were used in the first 2 days of hospitalization, the absolute risk of secondary bacterial infection was 12.1%. Although our analysis cannot establish causal relationships and is likely confounded by unobservable factors related to severity of illness, these findings should nonetheless serve to caution providers. Bacterial secondary infections are not uncommon among hospitalized patients with COVID-19 receiving immunosuppression, and careful attention is needed to ensure they are recognized early and managed appropriately.

For this study, we developed a comprehensive list of diagnoses comprising bacterial infections for which patients might be prescribed antibiotics. Although code sets provided by AHRQ in the CCSR were used as the basis of our list, many diagnoses included in relevant CCSR categories were nonspecific and needed to be excluded. Further research is needed to develop and validate standardized code sets to identify bacterial infections from administrative data.

Limitations. The main limitation of this study is that all patients diagnosed with bacterial infection may not actually have bacterial infection, and we were unable to perform chart review to confirm bacterial infection based on clinical criteria. Diagnosis codes reflect clinicians' suspicion for bacterial infection and, thus, likely overestimate the incidence of urinary infections, which are commonly misdiagnosed in the setting of asymptomatic bacteriuria (21). Use of microbiologic data to estimate the incidence of urinary tract infections would be subject to this same bias. Overall, we suspect that diagnosis codes represent a useful approximation when averaged across centers. The next limitation is that classification of bacterial coinfection or secondary infection relied on present on admission coding, which is commonly used in association with health care performance metrics but nonetheless may be influenced by anticipated reimbursement (22, 23). POA coding is accurate in about 70% of cases of community-acquired pneumonia, although differences in accuracy have been reported based on the hospital and diagnosis (24, 25). In cases where POA coding was inaccurate, coinfections may have been misclassified as secondary infections or vice versa. Another limitation is that we were unable to account for medications that patients might have received outside of the hospital encounter, including immunosuppression or antibiotics prescribed prior to admission and antibiotics continued after discharge. Thus, counts of inpatient antibiotic DOT likely underestimate total antibiotic exposures. Additionally, we did not include fungal infections in our analysis and therefore are unable to estimate the incidence of invasive fungal disease among patients receiving immunosuppression. Finally, inclusion in our sample depended on being discharged within the study period. Although the median duration of hospitalization for COVID-19 at that time was about 9 days (26), our study may not have captured severely ill patients who were admitted toward the end of June 2020 or remain hospitalized for a prolonged period. However, estimates of mortality based on Premier data collected during this period are consistent with other published studies and do not demonstrate evidence of bias (27).

Conclusions. Antibiotic treatment was likely overused among patients hospitalized with COVID-19 during the first wave of the pandemic. A proportion of 76% of

inpatients with COVID-19 during this period were prescribed antibiotics, despite only 22% being diagnosed with bacterial infection.

MATERIALS AND METHODS

Data source. We conducted a retrospective observational cohort study of patients who were discharged from hospitals contributing to the Premier Healthcare Database. The data were extracted on 20 July 2020. Contributing hospitals cover highly geographically diverse areas across the United States and capture approximately one of every four U.S. hospital discharges. Premier internally validates all data (28). In addition to research performed by traditional academic institutions, the Premier Healthcare Database has been used by the National Institutes of Health and Centers for Disease Control and Prevention (CDC) to conduct studies related to the clinical epidemiology of COVID-19 (29–31). This study did not include personally identifiable information and was exempt from institutional review board review.

Study sample and COVID-19 case definition. All adult inpatients with COVID-19 present on admission (POA) discharged in April to June 2020 at contributing hospitals were included. COVID-19 POA was defined by the presence of an ICD-10-CM diagnosis code of U07.1, designated POA. The U07.1 code was introduced in April 2020 and represents either a positive test for SARS-CoV-2 or a clinician's statement that a patient has COVID-19 (32). Compared to laboratory data, U07.1 has been validated as highly accurate for identifying hospital admissions related to COVID-19 (33). For patients who arrived by acute care transfer from another hospital, POA refers to a diagnosis that was present at time of admission to the accepting hospital.

Definitions of bacterial coinfection and secondary bacterial infection. Bacterial infections were identified using sets of ICD-10-CM diagnosis codes adapted from relevant categories in the AHRQ Healthcare Utilization Project's Clinical Classification Software Refined (CCSR; see the supplemental material) (34). Final sets of diagnosis codes were reviewed independently by two infectious disease physicians (J. Baghdadi and K. C. Cofey). A third infectious disease physician was available to adjudicate disagreements (A. D. Harris). Diagnosis codes were included if they indicated (i) a specific bacterial pathogen, (ii) bacterial infection generally, or (iii) an infection commonly presumed to be bacterial in origin (e.g., osteomyelitis). Diagnosis codes for chronic infections, mycobacterial infections, and fungal infections were excluded. Several diagnosis codes for acute infection were also excluded on the basis that they may be used in cases of either bacterial or viral illness, such as "other specific sepsis."

Bacterial infections were classified as coinfection or secondary infection relative to the current admission based on whether bacterial diagnoses were marked POA by managing providers. All patients in the study sample had COVID-19 POA. Coinfections were identified by a diagnosis of bacterial infection designated POA, meaning present at the same time as presentation with COVID-19 infection. Secondary infections were identified by bacterial infection that developed during hospitalization but after admission, meaning not present at the time of presentation with COVID-19. Thus, patients who presented to one hospital without bacterial coinfection developed secondary infection and then were transferred to a second hospital would appear from the perspective of the second hospital to have bacterial coinfection. Patients with POA and non-POA bacterial diagnoses were included as having both bacterial coinfection and secondary infection.

Patient and hospital variables. Hospital-level covariates included teaching status, urban versus rural location, and geographic region. To represent the burden of COVID-19 on the admitting hospital, a variable was constructed to capture the percentage of monthly admissions related to COVID-19. To represent intensive care utilization, a variable was constructed to represent the proportion of admitted patients during a given month requiring mechanical ventilation. Patient-level covariates included demographics, source of admission, and POA comorbidities. POA comorbidities were identified by mapping encounter-level diagnosis codes to the Elixhauser comorbidity index (35).

Medication use data. Daily inpatient medication data were extracted from charges for the hospital encounter. Antibiotic use was quantified by days of therapy (DOT). If a patient received two different antibiotics on a single hospital day, 2 DOT were attributed. Specific antibiotic categories of interest included agents with activity against *Pseudomonas aeruginosa* and agents with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (36). Corticosteroids or tocilizumab were defined as "early," meaning likely administered before the development of hospital-acquired infections, if they were administered by hospital day 2. This cutoff was selected to ensure that early immunosuppression clearly preceded hospital-onset infections, which are typically defined as occurring after hospital day three or four (37). Outpatient or discharge medications were not available.

Outcomes. The primary outcome was a composite of in-hospital death, death in hospice, or discharge to hospice. Secondary outcomes included development of bacterial coinfection and bacterial secondary infection.

Statistical methods. Multivariable mixed-effects log-binomial regression models were fit using methodology proposed by Zou et al. to estimate the adjusted relative risk (aRR) (38). Absolute risk of bacterial secondary infection was estimated based on marginal risk predicted by multivariable log-binomial regression modeling, assuming the distribution of other covariates was equal to their distribution in the overall sample. CIs at 95% for absolute risk estimates were bootstrapped with 100 repetitions. Except for use of corticosteroids or tocilizumab in the first 48 h of admission, covariates in multivariable models were limited to characteristics that were present or known at time of admission to the hospital. Stata/IC version 14.1 was used for all analyses.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.6 MB.

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