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MAJOR ARTICLE

Prevalence of Co-infection at the Time of Hospital Admission in COVID-19 Patients, A Multicenter Study

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Background. Bacterial infections may complicate viral pneumonias. Recent reports suggest that bacterial co-infection at time of presentation is uncommon in coronavirus disease 2019 (COVID-19); however, estimates were based on microbiology tests alone. We sought to develop and apply consensus definitions, incorporating clinical criteria to better understand the rate of co-infections and antibiotic use in COVID-19.

Methods. A total of 1016 adult patients admitted to 5 hospitals in the Johns Hopkins Health System between March 1, 2020, and May 31, 2020, with COVID-19 were evaluated. Adjudication of co-infection using definitions developed by a multidisciplinary team for this study was performed. Both respiratory and common nonrespiratory co-infections were assessed. The definition of bacterial community-acquired pneumonia (bCAP) included proven (clinical, laboratory, and radiographic criteria plus microbiologic diagnosis), probable (clinical, laboratory, and radiographic criteria without microbiologic diagnosis), and possible (not all clinical, laboratory, and radiographic criteria met) categories. Clinical characteristics and antimicrobial use were assessed in the context of the consensus definitions.

Results. Bacterial respiratory co-infections were infrequent (1.2%); 1 patient had proven bCAP, and 11 (1.1%) had probable bCAP. Two patients (0.2%) had viral respiratory co-infections. Although 69% of patients received antibiotics for pneumonia, the majority were stopped within 48 hours in patients with possible or no evidence of bCAP. The most common nonrespiratory infection was urinary tract infection (present in 3% of the cohort).

Conclusions. Using multidisciplinary consensus definitions, proven or probable bCAP was uncommon in adults hospitalized due to COVID-19, as were other nonrespiratory bacterial infections. Empiric antibiotic use was high, highlighting the need to enhance antibiotic stewardship in the treatment of viral pneumonias.

Keywords. SARS-CoV-2; COVID-19; co-infection; community-acquired pneumonia; antimicrobial use.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), and since its recognition in December 2019, over 33 million people have been infected worldwide [1]. Patients with COVID-19 frequently present with fever and respiratory symptoms, and in severe cases they go on to develop respiratory failure and/or death [2–4]. Distinguishing presenting symptoms of COVID-19 from those of bacterial community-acquired pneumonia (bCAP), for which antibiotics are required, is clinically challenging [5]. Bacterial co-infections for other epidemic coronaviruses such as SARS-CoV-1 and MERS-CoV are relatively low; however, rates as high as 20%–30% have been reported in pandemic influenza [6–8]. Limited data thus far have shown that microbiologic-proven bacterial co-infections appear to be uncommon (<5%) in COVID-19 patients, yet as many as 50%–90% receive antibiotics [9–13]. The lack of a standardized definition of bCAP limits our understanding of the clinical need for antibiotics in this population. The current practice of identifying bacterial co-infections solely based on the presence of positive microbiologic tests (eg, gram stain or culture) without additional clinical correlation [9–14] can lead to both overdiagnosis of infection in patients who are colonized with organisms rather than infected and underdiagnosis of infections, as a microbiologic diagnosis is not always attained in CAP [5]. To address this limitation, a multidisciplinary team developed consensus definitions of co-infections in COVID-19 patients based on microbiologic

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data and clinical criteria, with an emphasis on respiratory co-infections, as COVID-19 is predominantly a respiratory illness. We subsequently applied those definitions through manual chart review and estimated the prevalence of bacterial, viral, and fungal co-infections with COVID-19. We also endeavored to characterize antibiotic use in the context of defined co-infections.

METHODS

Study Population

We included adult patients from 5 acute care hospitals within the Johns Hopkins Health System (JHHS), which serves the metropolitan Baltimore and Washington, DC, areas, admitted between March 1, 2020, and May 31, 2020. Patients with a positive SARS-CoV-2 nucleic acid amplification test (NAAT) at least 10 days before or within 3 days after admission were eligible. Patients were excluded if they were asymptomatic and incidentally found to be positive for COVID-19 on admission screening (began May 13, 2020), transferred from a hospital outside of JHHS after more than 24 hours of an inpatient stay, or died within 12 hours of admission. To perform manual chart review in 70% of all patients included in the study period, we randomly selected 1141 out of 1556 eligible patients. A comparison of clinical characteristics between those included in the study and eligible but not included is shown in Supplementary Table 1. This project was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine.

Adjudication of Co-infection

A multidisciplinary team, including antimicrobial stewardship, hospital epidemiology and infection control, general infectious disease, transplant/oncology infectious disease, pulmonary/critical care, and infectious disease pharmacy, was convened to develop consensus definitions for co-infections and to form an adjudication committee. Co-infections were considered present at the time of admission (initial 48 hours). We included the following co-infections: bacterial community-acquired pneumonia (bCAP), atypical CAP, respiratory virus co-infection, fungal respiratory co-infection, bloodstream infection (BSI), urinary tract infection (UTI), and *Clostridioides difficile* infection (CDI). To better estimate clinically suspected bCAP, we categorized cases as proven (clinical and radiographic criteria consistent with bCAP and positive microbiologic test present), probable (high clinical suspicion based on clinical and radiographic criteria but no positive microbiologic test present), or possible (low clinical suspicion and not all clinical and radiographic criteria of bCAP met). Detailed descriptions of the criteria included in the definitions can be found in Table 1. Possible bCAP was the least strict in terms of criteria; however, we wanted to capture cases where there was ambiguity in diagnosis. Fungal infections and endemic mycosis definitions were adapted from previously published guidance [15]. A random pool of 25 cases was reviewed by the committee to ensure the definitions were being uniformly applied. Charts were randomly assigned to committee members, and each chart was reviewed by a single reviewer. Throughout the course of adjudication, 4 meetings were held with members of the adjudication committee to ensure uniform application of definitions and to clarify any uncertainties or discrepancies that arose. When there was a discrepancy or uncertainty about how to adjudicate a particular case, a consensus was reached among the adjudication committee.

Data Collection

Demographic information, medical history, comorbid conditions, data from a previously validated tool that identifies patients at risk for septic shock (Targeted Real-time Early Warning Score [TREWS]) [16], and medication orders and administration were obtained electronically from the medical records. The following additional data were collected through manual chart review: radiographic findings, vital signs, microbiologic data, and presence of additional infections not included in the co-infections outlined in Table 1. Immunocompromising conditions included HIV/AIDS, receipt of biologic agents, steroid use at an equivalent of prednisone ≥20 mg daily for ≥2 weeks before admission, chemotherapy within 6 months, and solid organ or hematopoietic stem cell transplant. The following antibiotics were considered "CAP antibiotics": ceftriaxone or cefdinir + azithromycin or doxycycline, ampicillin/sulbactam + azithromycin, cefepime + azithromycin or doxycycline, piperacillin/tazobactam + azithromycin or doxycycline, vancomycin + piperacillin/tazobactam, vancomycin + cefepime, or ceftriaxone alone. Patient records were reviewed to adjudicate the indication of the following antibiotic combinations: vancomycin + piperacillin/tazobactam, vancomycin + cefepime, or vancomycin + ceftriaxone. For calculating duration of therapy, 1 antibiotic day was any dose of any number of antibiotics given to a patient on 1 calendar day. Both inpatient antibiotics and those given at the time of discharge were recorded.

Statistical Analysis

The primary outcome was the proportion of respiratory co-infections among SARS-CoV-2-infected individuals. Secondary outcomes included antibiotic use for respiratory tract bacterial co-infections and nonrespiratory co-infections. Patients who died within 5 days of hospitalization were excluded from duration of antibiotic therapy calculations as 5 days is the typical duration of therapy for bCAP treatment. The chi-square test was used to analyze categorical variables, and the Wilcoxon-Mann-Whitney test was used for continuous variables. All statistical tests were 2-sided, with $P < .05$ considered

Table 1. Criteria for Adjudication of Co-infection Considered Present at Time of Admission[a]

Type of Infection	Proven	Probable	Possible
Bloodstream infection	Organism(s) recovered from blood culture and deemed not to be a contaminant[b]	-	-
Viral/atypical respiratory co-infection	• Positive NAAT for other respiratory viruses (other than SARS-CoV-2) • Positive test result for *Mycoplasma* or *Legionella*	-	-
Bacterial respiratory co-infection	Meets clinical and microbiologic criteria Clinical criteria: • Temp >38°C or <36°C AND WBC ≥12 000[c] AND • Chest imaging (x-ray or CT) consistent with bacterial infection (eg, lobar consolidation, air bronchogram) AND • Requiring supplemental oxygen AND • Producing purulent sputum (at least moderate PMNs on sputum gram stain) Microbiologic criteria: • Pathogen identified on respiratory culture AND/OR • Positive *S. pneumoniae* urinary antigen	Meets clinical criteria AND clinical improvement on antibiotics within 48–72 h	1 clinical (but not hypoxia) criterion OR radiographic criteria
Fungal respiratory infection	Microscopic analysis of tissue (including postmortem) consistent with hyphae or yeast AND evidence of associated tissue damage (note: recovery in culture from nonsterile sites such as sputum, BAL is probable)	Presence of host factor,[d] clinical features, AND mycologic evidence present Clinical features: • Lower respiratory tract fungal disease • At least 1 on CT chest: dense well-circumscribed lesions +/- halo sign, air crescent sign, cavity Mycological criteria: • Recovery of a mold in culture or of fungal elements from a respiratory source OR • Indirect test[e]	- Appropriate host factors and clinical features but no mycologic support OR - Evidence of positive fungal indirect test[e] or fungal culture with unclear supporting clinical features
Endemic mycosis	In a host[d] with an illness consistent with endemic mycosis and at least 1 of: • Recovery in culture • Histopathologic (including postmortem) • Direct microscopic demonstration of morphologic forms	In a host[f] with an illness consistent with endemic mycosis with indirect mycologic evidence (eg, *Histoplasma* antigen)	-
Urinary tract infection	Must include all of the following: • Positive urine culture • Pyuria (>10 WBC/HPF) on urinalysis • Signs or symptoms of lower or upper UTI (suprapubic tenderness, costovertebral angle pain or tenderness, dysuria)[f]	-	-
Clostridioides difficile infection	Includes: • Positive *C. difficile* NAAT • Clinical picture compatible with CDI (diarrhea AND abdominal pain or leukocytosis or abnormal CT or megacolon)	-	-
Other	Other infections present at time of admission, but not included in this list	-	-

Abbreviations: BAL, bronchoalveolar lavage; CDI, *Clostridioides difficile* infection; COVID-19, coronavirus disease 2019; CT, computed tomography; HPF, high-power field; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; PMNs, polymorphonuclear cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor; UTI, urinary tract infection; WBC, white blood cell count.

[a]Present or diagnosed on hospital day 1 or 2.

[b]Contamination was determined based on several factors including number of positive cultures, if vascular hardware present, consultant's opinion, and/or documentation of such in the patient's chart.

[c]Leukopenia was not considered, as leukopenia and lymphopenia are commonly seen with COVID-19 infections.

[d]Host factors include recent history of neutropenia (<500 PMN/mm^3) for >10 days temporally related to the onset of fungal disease, hematologic malignancy, receipt of an allogeneic stem cell or solid organ transplant, receipt of a solid organ transplant, prolonged use of corticosteroids with mean minimum dose 0.3 mg/kg/d of prednisone equivalent for >3 weeks, treatment with other recognized T-cell immunosuppressants (such as cyclosporine, TNF-α blockers, specific monoclonal antibodies [such as alemtuzumab], or nucleoside analogs) during the past 90 days, or inherited severe immunodeficiency.

[e]Indirect fungal tests include positive serum or BAL galactomannan ≥0.5, fungal pathogen identified in culture and/or fungal elements identified in microscopic analysis of sterile material, cryptococcal antigen, *Pneumocystis* direct fluorescent antigen, and/or PCR.

[f]If history is unable to be obtained due to mental status and/or intubation/sedation and other criteria are met, this is not required.

significant. All statistical analyses were performed using Stata, version 16.0 (StataCorp, College Station, TX, USA).

RESULTS

Description of Cohort

Of the 1141 randomly selected patients from the study period for manual chart review, 1016 met inclusion criteria (3 excluded for death within 12 hours of hospitalization and 122 excluded due to asymptomatic screening or transfer from another hospital with hospital stay >24 hours). The median age of the cohort (interquartile range [IQR]) was 61 (48–74) years, and 46% (n = 473) were female (Table 2). One hundred eighty-nine patients (19%) were admitted from a long-term care facility (LTCF), the median Charlson comorbidity index (IQR) was 2 (1–3), and 57 (5.7%) had an immunocompromising condition. One hundred eighteen (12%) were admitted to the intensive care unit (ICU), and 310 (30.5%) were identified to be

Table 2. Characteristics of the Cohort and Adjudication of Bacterial Community-Acquired Pneumonia

	Total[a]	Proven/Probable Bacterial CAP	Possible Bacterial CAP	No CAP[b]	*P* Value (Proven/Probable vs No CAP)	*P* Value (Possible vs No CAP)
	n = 1016	n = 12	n = 483	n = 521		
Cohort characteristics, No. (%)						
Age, median (IQR), y	62 (48–74)	63 (48.5–68)	61 (48.5–73.5)	62 (48–75)	.63	.90
Female	473 (46)	4 (0.8)	226 (48)	245 (52)	.36	.96
Race					.40	.63
White	315 (31)	2 (17)	148 (31)	165 (32)		
Black	355 (35)	6 (50)	175 (36)	174 (33)		
Other	349 (34)	4 (33)	161 (33)	184 (35)		
Latino/Hispanic	289 (28)	3 (25)	140 (29)	146 (28)	.82	.68
Long-term care facility resident	189 (19)	4 (33)	89 (18)	96 (18)	.20	1
Charlson comorbidity index, median (IQR)	2 (1–3)	1 (1–2.5)	2 (1–3)	1 (1–3)	.53	.27
Admission to intensive care unit	118 (12)	4 (33)	76 (16)	38 (7)	<.01	<.01
Sepsis criteria[c]	310 (30.5)	7 (58)	172 (36)	131 (25)	<.01	<.01
Maximum CRP value, median (IQR), mg/dL	13.1 (5.8–32.9)	27.7 (15.4–78.5)	15 (6.8–43.9)	10.7 (4.7–24.6)	.04	<.01
Maximum ferritin value, median (IQR), ng/mL	643 (309–1185)	1101 (639–2283)	737 (403–1390)	563 (262–969)	.02	<.01
Diabetes	90 (9)	0	47 (10)	43 (8)	.29	.41
Congestive heart failure	114 (11)	1 (8)	61 (13)	52 (10)	.85	.18
Chronic obstructive pulmonary disease	40 (4)	0	17 (4)	23 (4)	.45	.46
Immunocompromising condition[d]	57 (5.7)	0	32 (7)	25 (5)	.43	.21
Length of stay, median (IQR), d	7.1 (4–12.7)	8.5 (5.2–33)	7.7 (4–13.2)	6.8 (3.9–12.1)	20	.06
Pneumonia criteria, No. (%)						
Fever	577 (57)	10 (83)	316 (65)	251 (49)	.01	<.01
Hypothermia	59 (6)	0	30 (6)	29 (6)	.39	.54
Supplemental oxygen	720 (71)	11 (83)	374 (77)	335 (65)	.05	<.01
Purulent sputum	34 (3)	3 (25)	26 (5)	5 (1)	<.01	<.01
Leukocytosis	148 (15)	6 (50)	118 (24)	24 (5)	<.01	<.01
Chest radiographic findings[e]						
Consolidation/consolidative opacity	184 (18)	5 (42)	149 (31)	30 (6)	<.01	<.01
Ground glass opacity	163 (16)	1 (8.3)	83 (17)	79 (15)	.51	.38
Infiltrate	338 (33)	5 (42)	192 (40)	140 (27)	<.01	<.01
Interstitial opacity	128 (13)	3 (25)	72 (15)	52 (10)	.03	.01
Other/unspecified opacity	167 (16)	1 (2)	106 (22)	60 (11)	<.01	<.01
Antibiotic use, No.[f] (%)						
Receipt of CAP antibiotics	677 (69)	11 (100)	370 (81)	304 (59)	-	<.01
Days of therapy, median (IQR)	1.1 (0–4.4)	4.12 (2.36–10.21)	3.60 (1–5.83)	1 (0–4.05)	<.01	<.01

Abbreviations: CAP, community-acquired pneumonia; CRP, C-reactive protein; CT, computed tomography; IQR, interquartile range.

[a]The number of patients manually reviewed who met inclusion/exclusion criteria.

[b]Includes patients for whom there was no bacterial respiratory infection/community acquired infection, who also did not have either a bloodstream infection and/or urinary tract infection.

[c]As identified by Targeted Real-Time Early Warning Score, which predicts septic shock.

[d]Immunocompromising conditions includes HIV/AIDS, receipt of biologics, prednisone >20 mg daily for ≥2 weeks, chemotherapy within 6 months, and solid organ or hematopoietic stem cell transplant.

[e]Chest x-ray or CT of the chest, findings based upon final read from radiologist; percentages may add up to >100% given that some patients have more than 1 pattern of findings detailed.

[f]n = 977 (after excluding patients who died within 5 days of hospitalization), considers antibiotics prescribed upon discharge.

at high risk of developing septic shock based on the TREWS algorithm [16]. The median hospital length of stay (IQR) was 7.1 (4–12.7) days.

Prevalence of Co-infections on Admission in COVID-19 and Associated Characteristics

A description of the co-infections present at the time of admission is shown in Table 3. Two patients (0.2%) had another viral co-infection (1 with respiratory syncytial virus [RSV] and 1 with both influenza A and RSV), and 1 patient had a proven bacterial respiratory co-infection (methicillin-susceptible *Staphylococcus aureus* [MSSA] cultured from sputum). Eleven patients (1.1%) met criteria for probable bCAP, and 483 (48%) were considered possible bCAP. There were no cases of fungal respiratory infection or endemic mycoses.

Forty-two (4%) had 52 nonrespiratory co-infections. Nonrespiratory infections included BSI in 20 patients (2%), UTI in 30 patients (3%), and CDI in 2 patients (0.2%). The most common blood pathogens included *Staphylococcus aureus* [6], coagulase-negative *Staphylococcus* [5], and *Escherichia coli* [5], and the most common urinary pathogens were *E. coli* [10], *Proteus* spp. [5], and *Klebsiella* spp. [4] (Supplementary Table 2). Compared with those with respiratory co-infection only, patients with respiratory and nonrespiratory co-infections were more likely to be white (45% vs 29%; $P < .01$), to be older in age (median age, 70 vs 61 years; $P < .01$), and to live in an LTCF (56% vs 16%; $P < .01$) (Supplementary Table 3).

Characteristics Associated With Bacterial Community-Acquired Pneumonia Co-infection

There were no differences in baseline demographics including age, sex, race, ethnicity, residence in LTCF, and comorbidities between the CAP categories (Table 2). There was a greater proportion of patients with proven/probable bCAP and possible bCAP admitted to the ICU as compared with patients with no co-infection present (33% vs 16% vs 7%, respectively; $P < .01$).

Table 3. Co-infections Present at Time of Hospitalization due to COVID-19

Type of Infection	No. of Patients (%)
Viral/atypical respiratory infection	2 (0.2)
Bacterial respiratory infection	
By any definition	497 (49)
Proven	1
Probable	11
Possible	483
Fungal infection	
Fungal respiratory infection[a]	0
Endemic mycoses	0
Bloodstream infection	20 (2)
Urinary tract infection	30 (3)
Clostridioides difficile colitis	2 (0.2)

Abbreviation: COVID-19, coronavirus disease 2019.

[a]Includes *Cryptococcus, Pneumocystis jirovecii, Aspergillus* spp., and other molds.

Similarly, more patients in the proven/probable and possible categories were at higher risk of septic shock (per the TREWS algorithm) and had higher maximum CRP and ferritin values as compared with the no respiratory bacterial co-infection group. No patients with an immunocompromising condition were found to have proven or probable bCAP. The median length of hospitalization for the proven/probable bCAP group was 8.5, vs 6.8 days for the no co-infection group ($P = .06$). Among all patients, 636 (63%) had fever and/or hypothermia, 720 (71%) required supplemental oxygen, 148 (15%) had leukocytosis, and 34 (3%) had purulent sputum. Microbiologic tests for the evaluation of bCAP were performed in patients as follows: 637 (63%) had blood cultures, 140 (14%) had a respiratory culture, 291 (29%) had an *S. pneumoniae* urinary antigen test, and 294 (20%) had a *Legionella* urinary antigen test. The most common imaging finding was a nonspecified infiltrate (33%), followed by consolidation/consolidative opacity (18%), ground glass opacity (16%), and interstitial opacity (13%).

Among those with possible bCAP as compared with no bCAP, there were higher proportions with fever (65% vs 49%; $P < .01$), purulent sputum (5% vs 1%; $P < .01$), peripheral leukocytosis (24% vs 5%; $P < .01$), and consolidative opacity (31% vs 6%; $P < .01$) (Table 2).

Antibiotic Use

Overall, 71% (717/1016) of patients received at least 1 dose of a bCAP antibiotic. In the subgroup of patients who survived beyond 5 days of admission (n = 977), 100% of proven/probable cases, 81% of possible bCAP cases, and 59% of patients without co-infection received bCAP antibiotics, respectively ($P < .01$) (Table 2). Most patients (67%) without evidence of bCAP co-infection and 45% of patients with possible bCAP had antibiotics discontinued within 48 hours. The median duration of bCAP therapy (IQR) (including inpatient and outpatient antibiotics) was 4.1 (1.1–10.2) days for proven/probable bCAP, 3.6 (1–5.8) for possible bCAP, and 1 (0–4) for no bacterial co-infection ($P < .01$). Antibiotic use decreased over time; a smaller proportion of patients were started on antibiotics in May compared with March and April (61% vs 77% and 75%, respectively; $P < .01$), and duration of therapy was shorter in May (median duration [IQR], 1 [0–4] day) than in March or April (median duration [IQR], 2.9 [0–5.1] days; $P < .01$).

DISCUSSION

In this multisite retrospective cohort of COVID-19 patients hospitalized between March and May 2020, we found a proven respiratory co-infection in 0.3% of the cohort (1 bacterial co-infection with MSSA and 2 viral co-infections with RSV and influenza). Using a consensus clinical definition, we found that only 1.1% of patients had a probable bacterial respiratory co-infection (ie, had clinical and radiographic criteria consistent with bCAP and responded to antibiotic therapy, but did

not have a microbiologic diagnosis). The proportion of patients with proven respiratory co-infection in our study was lower than in published studies, in which the percentage with proven respiratory co-infection has ranged from 3.1% to 5% [10, 11, 17]. This difference may be explained by the consensus definitions we employed, by the timing of the outbreak in our geographic area (spring vs winter in Europe and China) when non-SARS-CoV-2 respiratory viruses were circulating infrequently, or by the population affected (unknown history of pneumococcal vaccination between populations in different studies).

A strength of this study is that we attempted to recreate some of the diagnostic uncertainties faced in clinical practice by not relying solely on microbiologic criteria (such as respiratory cultures and/or antigen detection), but by creating probable and possible categories of bCAP. We found that 521 (51%) patients had no clear evidence of bacterial respiratory co-infection, while 483 (48%) fell into the possible category. The latter included patients who may have had an isolated sign of bacterial co-infection (eg, leukocytosis or consolidative opacity). These findings suggest that isolated signs of bCAP cannot be relied upon to make antibiotic decisions in patients with COVID-19. Prior studies [9, 10, 14] have found relatively high rates of antibiotic use in COVID-19 patients, raising concerns for the global impact of the pandemic on driving antimicrobial resistance, as was observed with the SARS-CoV-1 outbreak [18, 19]. In our study, most patients without evidence of bCAP and almost half of those with a low suspicion of bCAP had antibiotics discontinued at 48 hours. We speculate that this may be related to antibiotic stewardship programs' focused efforts on assessment of antibiotic needs at 48 hours [20], and increased knowledge regarding the risk of bacterial co-infection with COVID-19 in the literature has continued to emerge. COVID-19 is known to cause a sepsis syndrome [4, 21–23]; in our cohort, 25% of patients adjudicated to not have bCAP met sepsis criteria, highlighting the complexity around antibiotic decision-making in patients with COVID-19. A previous study of COVID-19 patients admitted to the ICU failed to demonstrate a benefit of early antibiotics (ie, antibiotics given before arrival to the ICU) on mortality or development of ventilator-associated infection or bacteremia [24]. This underscores the ongoing need for more accurate ways to identify patients likely to benefit from antibiotics in lower respiratory tract infections.

Respiratory fungal infection, mostly invasive aspergillosis, may develop in up to 25% of patients infected with SARS-CoV-2 according to retrospective and prospective small studies in Europe [25–27]. These infections were seen in critically ill patients after several days of hospital admission. In our study, which included co-infections detected within the first 48 hours, there were no cases of fungal co-infection. More research is needed to better characterize this potential risk, which seems to occur later in the course of disease and in ICU patients [11, 25–28].

Overall, 5% (52/1016) of COVID-19 patients had any proven nonrespiratory co-infection present upon admission to the hospital, with urinary tract co-infections being the most common. As may be expected, patients coming from an LTCF and who were of older age were more likely to present with additional bacterial co-infections. In some cases, it was not possible for clinicians to ascertain symptoms, and thus in attempts to be inclusive of potential infection in otherwise ill patients, these patients were considered to have a UTI if they met specific criteria. Even with this definition possibly encompassing asymptomatic bacteriuria, the rate of co-infection with UTI in patients with COVID-19 was lower in our study (3%) than previously observed (10%) [11]. This difference may be due to differences in culturing practices or to our applying a standard definition of UTI in adjudication.

There are several limitations to this study. It is retrospective and observational in nature, and therefore limited by the diagnostic tests obtained and procedures performed at the time of clinical care. Although we developed standardized definitions of co-infections through a multidisciplinary team, the experts involved in developing the definitions are from a single institution, which may limit the generalizability of these definitions. However, the criteria used by the experts were based on Infectious Diseases Society of America (IDSA) guidelines for CAP [5]. The IDSA/American Thoracic Society CAP guidelines suggest empiric initial antibacterial treatment for those with influenza due to the relatively high rates of bacterial co-infection [5]. However, the low prevalence of bacterial co-infection shown here, as well as in other studies, would suggest that empiric initial antibiotics are not needed, and in fact are not recommended in World Health Organization recommendations [10, 11, 17, 29]. The time period of the study does not cover the peak of respiratory viral season, limiting its generalizability and possibly leading to underestimation of respiratory viral co-infection. However, data from China also indicated a low prevalence (0.4%) of influenza coinfection with SARS-CoV-2. We did not collect data on history of pneumococcal vaccination, which may impact the risk of developing bCAP [30].

In conclusion, in contrast to patients with influenza in whom bacterial co-infection is a common complication [31, 32], bacterial co-infection with SARS-CoV-2 at the time of presentation has so far been rare, and currently the initial routine use of antibiotics in all COVID-19-infected individuals is not indicated [29]. Standardization of bacterial co-infection definitions would strengthen consistency and reproducibility among clinical studies and could enhance antibiotic stewardship strategies by providing a template for guidelines regarding when antibiotics should and should not be considered.

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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Patient consent. Informed consent was not obtained from patients, as this work was retrospective and did not modify care received. The design of the work was approved by our local institutional review board.

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