






Bacterial Pneumonia and Respiratory Culture Utilization among Hospitalized Patients with and without COVID-19 in a New York City Hospital

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ABSTRACT COVID-19 is associated with prolonged hospitalization and a high risk of intubation, which raises concern for bacterial coinfection and antimicrobial resistance. Previous research has shown a wide range of bacterial pneumonia rates for COVID-19 patients in a variety of clinical and demographic settings, but none have compared hospitalized COVID-19 patients to patients testing negative for severe acute respiratory syndrome coronavirus (SARS-CoV-2) in similar care settings. We performed a retrospective cohort study on hospitalized patients with COVID-19 testing from March 10th, 2020 to December 31st, 2020. A total of 19,219 patients were included, of which 3,796 tested positive for SARS-CoV-2. We found a 2.6-fold increase ($P < 0.001$) in respiratory culture ordering in COVID-19 patients. On a per-patient basis, COVID-19 patients were 1.5-fold more likely than non-COVID patients to have positive respiratory cultures (46.8% versus 30.9%, $P < 0.001$), which was primarily driven by patients requiring intubation. Among patients with pneumonia, a significantly higher proportion of COVID-19 patients had ventilator-associated pneumonia (VAP) relative to non-COVID patients (86.3% versus 70.8%, $P < 0.001$), but a lower proportion had community-acquired (11.2% vs 25.5%, $P < 0.01$) pneumonia. There was also a significantly higher proportion of respiratory cultures positive for methicillin-resistant *Staphylococcus aureus*, *Klebsiella pneumoniae*, and antibiotic-resistant organisms in COVID-19 patients. Increased rates of respiratory culture ordering for COVID-19 patients therefore appear to be clinically justified for patients requiring intubation, but further research is needed to understand how SARS-CoV-2 increases the risk of VAP.

KEYWORDS COVID-19, SARS-CoV-2, pneumonia, coinfection, respiratory culture, respiratory infection

Concern for bacterial coinfection among COVID-19 patients resulted in empirical antimicrobial therapy given to a large proportion of patients hospitalized at our medical center during 2020 (1). While a relatively high rate of bacterial and influenza coinfection has characterized hospitalized influenza patients, with estimates ranging from 11% to 35% (2, 3), less is known about the rate of bacterial pneumonia in hospitalized COVID-19 patients. Furthermore, in influenza, bacterial coinfection has been found to be more frequently of community origin, with one study of hospitalized adults in the United States finding that more than 54% of coinfections in adults were diagnosed within the first 48 h of hospitalization (3). Several studies have examined bacterial coinfection for COVID-19 patients in inpatient and intensive care unit (ICU) settings, generally finding lower rates than for influenza patients (4–7). Of the two largest such studies, one found very low rates of community-acquired pneumonia (CAP) (1.5%) (7), while the other found an overall bacterial pneumonia rate of 2.1%, with the overwhelming majority being hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) (6, 8). One study among ICU patients found much higher rates of patients with positive respiratory cultures (28%); however, 90% of these

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patients required mechanical ventilation (9). One study directly comparing rates of CAP among patients with influenza, respiratory syncytial virus (RSV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from 2011 to 2020 found that CAP coinfection rates were 27% and 29% for influenza and RSV, respectively, but only 4% for SARS-CoV-2 (10). While this study did not assess rates of HAP or VAP in these patients, another study by this group looked specifically at lower respiratory tract infections (LRTI) in ventilated patients, finding significantly higher rates of LRTI in COVID-19 patients and a 2-fold higher risk of bacterial pneumonia compared to non-COVID patients (11).

Therefore, when all hospitalized patients are considered together, rates of bacterial pneumonia appear lower in COVID-19 patients relative to hospitalized influenza and RSV patients but greater for intubated COVID-19 relative to non-COVID patients. In contrast to influenza, few of these infections are community acquired, but none of these studies have assessed the concurrent rate of bacterial CAP, HAP, and VAP rates compared to non-COVID patients for whom respiratory cultures were ordered during the same period. In addition, no previous studies have assessed whether respiratory culture ordering was appropriate based on rates of positivity in the setting of COVID-19 for these groups. This lack of a direct comparison between COVID-19 and non-COVID-19-infected patients makes it difficult to determine whether the highly disparate reported rates of bacterial coinfection represent the heterogeneity of the patient populations studied or a truly elevated risk of bacterial pneumonia associated with SARS-CoV-2 infection.

Additionally, respiratory culture utilization among COVID-19 patients has not been previously studied. Understanding the rates of respiratory culture ordering and positivity among COVID-19 patients is needed to determine whether culture ordering is appropriate among hospitalized COVID-19 patients, and to understand the risk of HAP and VAP in this population. To study this further, we compared rates of bacterial pneumonia, respiratory culture ordering, bacterial etiologies, and antibiotic resistance between patients testing positive and negative for COVID-19 in the same hospital setting.

MATERIALS AND METHODS

A retrospective cohort study was conducted on all hospitalized patients with SARS-CoV-2 testing performed at Columbia University Irving Medical Center (CUIMC) located in New York City from March 10th to December 31st, 2020. SARS-CoV-2 RT-PCR testing was performed in-house using the following assays: Cobas SARS-CoV-2 (Roche Molecular Systems, Inc., Branchburg, NJ), Xpert Xpress SARS-CoV-2 (Cepheid, Sunnyvale, CA), and a laboratory-developed test from the Wadsworth Center at the New York State Department of Health. After March 23rd, 2020, all patients admitted CUIMC hospitals were tested for SARS-CoV-2 upon admission, and between March 10th and 23rd, testing was performed by clinical suspicion due to limited testing capacity. Complete data for intubation status were only available from March 10th to September 31st, 2020; therefore, analysis of intubated versus nonintubated patients and VAP was limited to patients with testing performed between these dates.

Data were extracted from medical records to compare respiratory culture utilization and culture results between COVID-19 and non-COVID patients; these data included time of SARS-CoV-2 testing, SARS-CoV-2 test results, dates of admission and discharge, intubation status, number of respiratory cultures performed, time of respiratory culture orders, and results of respiratory culture testing, including time of culture results, bacterial species recovered, and antimicrobial susceptibility.

Rates of respiratory culture utilization and culture positivity were compared between COVID-19 and non-COVID patients, as was the distribution of recovered species, antimicrobial susceptibility profiles, intubation status, and ordering time of positive cultures during hospital admission to stratify pneumonia cases into community acquired (≤ 2 days) versus hospital acquired (> 2 days) versus ventilator associated (> 2 days after intubation) (8). A positive respiratory culture was defined as any potential respiratory pathogen recovered from culture, whereas a negative result was defined as either no growth, when cultures were resulted as "mixed commensal microbiota," or when only yeast were isolated. Respiratory cultures were excluded if SARS-CoV-2 testing was performed after respiratory cultures were ordered to ensure that all culture results analyzed were from patients of known COVID-19 status at time of testing.

Chi-squared testing was used to identify statistically significant differences in rates of respiratory culture ordering, positivity, antibiotic resistance, and CAP, HAP, or VAP in COVID-19-positive and -negative patients. A two-tailed Student's *t* test was used to assess statistical significance in time to respiratory culture positivity (when results of continuous variables were being compared). Data analysis was initially performed using Microsoft Excel, with statistical tests performed using R and R-Studio for reproducibility.

RESULTS

Demographics of SARS-CoV-2-positive and -negative populations. A total of 19,275 participants were initially included: 3,805 (19.7%) tested positive for SARS-CoV-2 and 15,470

TABLE 1 Demographics of SARS-CoV-2-positive and -negative patient population^a

Category/Subcategory	SARS-CoV-2 positive	SARS-CoV-2 negative	P value
Age (yr)			
Mean (±SD)	62.0 ± 21.0	48.7 ± 26.4	<i>P</i> < 1e-15
Sex			
Male	54.0%	43.2%	<i>P</i> < 1e-15
Female	46.0%	56.8%	
Race			
White	11.8%	19.0%	<i>P</i> < 1e-15
Black	12.8%	13.1%	
Hispanic/Latino	51.9%	39.6%	
Other	23.5%	28.3%	
Care setting			
ED	<0.1%	<0.1%	<i>P</i> < 0.00001
Admitted	79.9%	83.1%	
ICU	20.0%	16.9%	
Mortality	16.9%	3.0%	<i>P</i> < 1e-15
Intubation ^b	16.9%	7.9%	<i>P</i> < 1e-15

^aED, emergency department; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus.

^bData included are from March-September 2020.

(80.3%) tested negative. Fifty-six patients were excluded due to respiratory cultures ordered prior to SARS-CoV-2 testing, leaving 19,219 participants for study analysis. SARS-CoV-2 positivity rates varied widely over the study period, from a peak of nearly 60% in April 2020 to a low of just over 3% in September 2020. Demographic characteristics of included patients are shown in Table 1. Compared to non-COVID patients, COVID-19 patients were older ($P < 0.001$), more likely to be male ($P < 0.001$), more likely to be Hispanic/Latino, less likely to be white, and were more likely to receive care in the ICU ($P < 0.001$). The mortality rate was also 5.6-fold higher (16.9% versus 3.0%, $P < 0.001$) and intubation rate 2.9-fold higher (16.9 versus 7.9, $P < 0.001$) for COVID-19 patients.

Increased rates of respiratory culture ordering in COVID-19 patients. COVID-19 patients were 2.6 times as likely to have respiratory cultures ordered compared to non-COVID patients (16.0% vs 6.2%, $P < 0.001$, Table 2). Although the rate of respiratory culture ordering varied by month (Fig. 1A), significantly higher ordering was seen among COVID-19 patients across all months except July 2020. Increased ordering was also reflected in a higher number of cultures ordered per patient for COVID-19 patients relative to non-COVID patients (4.3 versus 2.7 per patient, $P < 0.001$), and significantly increased rates of culture ordering per COVID-19 patient were seen both early and late in the study period (March, April, August, and December, Fig. 1B).

A much higher rate of respiratory culture ordering was seen overall among intubated patients (55.9%) vs nonintubated patients (3.6%). Among intubated patients, however, the proportion of with respiratory cultures ordered was still significantly higher for those with COVID-19 compared to non-COVID patients (69.9% versus 47.0%, $P < 0.001$), as was the number of cultures ordered per patient (4.9 versus 3.4, $P < 0.001$) (Table 2; Fig. 2D). Among patients who did not require intubation, there was also a significantly higher rate of respiratory culture ordering for COVID-19 relative to non-COVID patients (5.6 vs 3.1%, $P < 0.001$); however, there was no significant difference in the number of respiratory cultures ordered per patient (Table 2; Fig. 2D).

Higher likelihood of respiratory culture positivity among intubated COVID-19 patients. Overall, 7.6% of COVID-19 patients had positive respiratory cultures versus 1.8% for non-COVID patients (Table 3). Among patients who had respiratory cultures ordered, COVID-19 patients were also more likely than non-COVID patients to have a positive culture (46.8% vs 30.9%, $P < 0.001$; Fig. 3A; Table 3). Even accounting for the higher rate of respiratory culture ordering among COVID-19 patients, on a per culture basis, COVID-19 patients still had a higher percentage of positive cultures (33.4% vs 26.9%, $P < 0.001$; Table 3).

The higher rate of positive cultures among COVID-19 patients was primarily driven

TABLE 2 Respiratory culture ordering

Metric	Total	SARS-CoV-2 positive	SARS-CoV-2 negative	P value
Total patients	19,219	3,796	15,423	
Total cultures ordered	5,152	2,587	2,565	
Patients with respiratory cultures ordered	1,569 (8.2%)	607 (16.0%)	962 (6.2%)	$P < 1e-15$
Cultures ordered per patient	3.3	4.3	2.7	$P < 1e-14$
Total patients (March to September)	14,172	3,273	10,899	
Intubated patients ^a	1,425 (10.0%)	555 (16.9%)	870 (7.9%)	$P < 1e-15$
Intubated patients with respiratory cultures ordered ^a	797 (55.9%)	388 (69.9%)	409 (47.0%)	$P < 1e-15$
Cultures ordered per intubated patient ^a	4.1	4.9	3.4	$P < 1e-5$
Nonintubated patients with respiratory cultures ordered ^a	465 (3.6%)	156 (5.6%)	309 (3.1%)	$P < 1e-5$
Cultures ordered per nonintubated patient ^a	1.4	1.4	1.4	$P = 0.94$

^aData included are from March to September 2020.

by patients requiring intubation. A total of 26.0% of all intubated patients had positive respiratory cultures collected more than 48 h after intubation, qualifying as VAP. Among intubated patients, VAP was more than twice as likely in COVID-19 patients relative to non-COVID patients (38.7% versus 17.8%, $P < 0.001$; Fig. 2E; Table 3). When looking at only intubated patients who had respiratory cultures ordered, there remained a significantly higher proportion of COVID-19 positive patients with VAP compared to non-COVID patients (62.5% versus

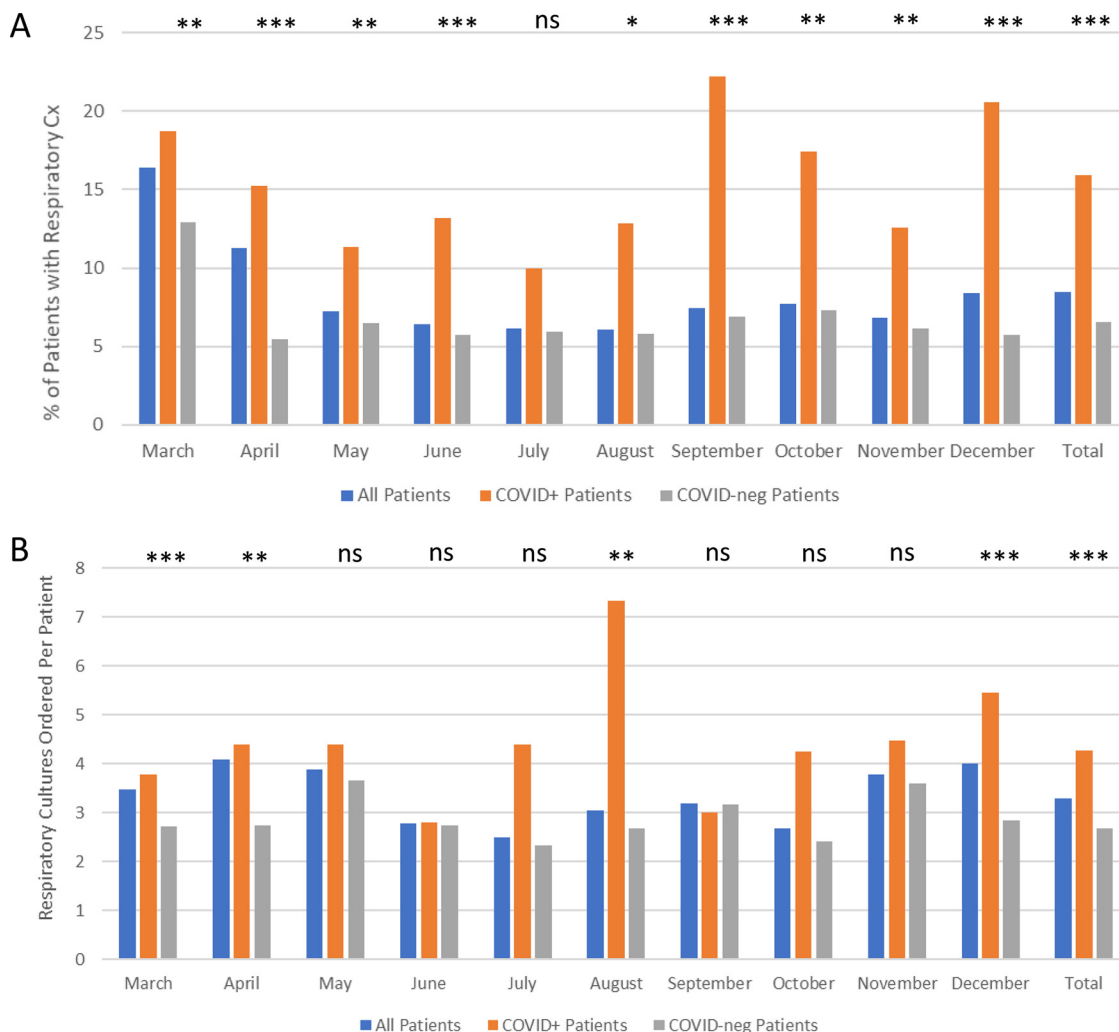


FIG 1 Respiratory culture (Cx) ordering by COVID-19 status. (A) Percentage of patients with respiratory cultures ordered, by month and total. (B) Average number of respiratory cultures ordered per patient, by month and total. *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$; ns, not significant.

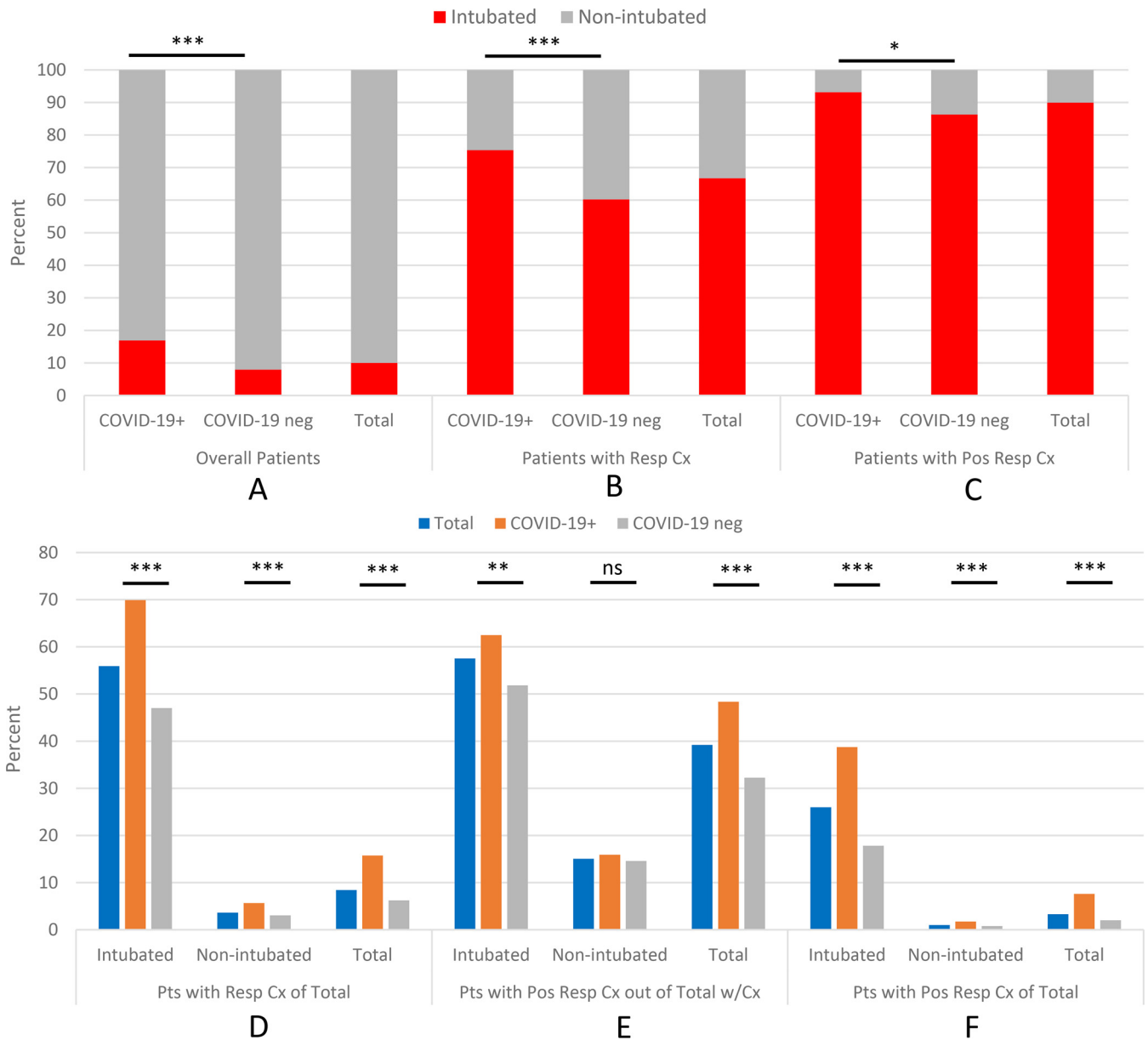


FIG 2 Rates of respiratory culture ordering and positivity in intubated patients. (A) Percentage of overall patients by COVID-19 status who are intubated. (B) Percent of patients with respiratory cultures (Resp Cx) ordered who are intubated or nonintubated by COVID-19 status. (C) Percent of patients with positive respiratory culture results who are intubated or nonintubated by COVID-19 status. (D) Percentage of intubated, nonintubated or overall hospitalized patients who have respiratory cultures ordered by COVID-19 status. (E) Percent of intubated, nonintubated, or overall hospitalized patients with positive respiratory culture results out of the total number with cultures ordered by COVID-19 status. For intubated patients, only those respiratory cultures collected more than 48 h after intubation were included. (F) Percent of intubated or overall hospitalized patients with positive respiratory cultures out of total patients by COVID-19 status. For intubated patients, only those respiratory cultures collected more than 48 h after intubation were included. *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$; ns, not significant.

51.8%, $P < 0.01$; Fig. 2E; Table 3). However, among nonintubated patients, there were no significant differences by COVID-19 status in the proportion of patients with respiratory cultures ordered that resulted as positive (Fig. 2E and F; Table 3). When comparing rates of respiratory culture positivity on a per-culture basis by intubation status, there was a higher positivity rate for intubated COVID-19 compared to intubated non-COVID patients (39.1% versus 35.1%, $P < 0.05$), but no significant difference by COVID-19 status among nonintubated patients (Table 3). Intubated COVID-19 patients also had a significantly higher rate of respiratory culture ordering prior to the first positive culture (Fig. 3B) yet also had more positive cultures per patient (Fig. 3C).

Among culture-positive patients, COVID-19 patients had a significantly lower rate of CAP,

TABLE 3 Respiratory culture positivity

Metric	Total	SARS-CoV-2 positive	SARS-CoV-2 negative	P value
Total patients (March to December)	19,219	3,796	15,423	
Patients who had positive respiratory cultures	572 (3.0%)	287 (7.6%)	285 (1.8%)	$P < 1e-15$
% of patients with positive cultures among patients with cultures ordered	37.0%	46.8%	30.9%	$P < 1e-9$
Cultures that resulted as positive (% of total)	1,554 (30.2%)	863 (33.4%)	691 (26.9%)	$P < 1e-6$
Total patients (March to September)	14,172	3,273	10,899	
Intubated patients	1,425 (10.0%)	555 (16.9%)	870 (7.9%)	
Intubated patients with ventilator-associated pneumonia (VAP) (%) ^a	370 (26.0%)	215 (38.7%)	155 (17.8%)	$P < 1e-15$
% of intubated patients with respiratory cultures ordered and Ventilator-associated pneumonia (VAP) ^a	57.5%	62.5%	51.8%	$P < 0.01$
Cultures that resulted as positive from intubated patients (% of total) ^a	1,073 (37.5%)	672 (39.1%)	401 (35.1%)	$P < 0.05$
Nonintubated patients who had positive respiratory cultures (%) ^a	133 (1.0%)	51 (1.7%)	81 (0.8%)	$P < 1e-5$
% of nonintubated patients with respiratory cultures ordered that resulted as positive ^a	15.0%	15.9%	14.6%	$P = 0.67$
Cultures that resulted as positive from nonintubated patients (% of total) ^a	373 (13.2%)	85 (15.0%)	288 (12.3%)	$P = 0.25$

^aData included are from March to September 2020.

defined as positive cultures within the first 2 days of admission, compared to non-COVID patients (11.2% vs 25.5%, $P < 0.001$; Fig. 4; Table 4). Conversely, a significantly higher proportion of pneumonia cases also occurred at least 2 days after admission for COVID-19-positive patients relative to non-COVID patients (Fig. 4), and this difference was particularly pronounced in patients with positive cultures at least 10 days after admission (65.5% versus 39.3%, $P < 0.001$). When we specifically assessed HAP, defined as positive respiratory cultures that resulted more than 2 days after admission but not in patients who had been ventilated for more than 2 days, we found no significant difference in COVID-19 patients relative to non-COVID patients (Fig. 4; Table 4). The overwhelming majority (86.3%) of bacterial pneumonia cases among COVID-19 patients were ventilator associated, and this was significantly higher than the rate of VAP in non-COVID patients with bacterial pneumonia (70.8%, $P < 0.001$; Fig. 4; Table 4).

Bacterial etiologies of positive respiratory cultures. Respiratory cultures grew a wide range of bacterial pathogens in our patient population. The most common organism overall was *Pseudomonas aeruginosa* (Fig. 5). For COVID-19 patients, the most common organisms in descending order were *Staphylococcus aureus*, *P. aeruginosa*, and *Klebsiella pneumoniae*. For non-COVID patients, the most common organisms in descending order were *P. aeruginosa*, *S. aureus*, and *K. pneumoniae*. Among patients with positive respiratory cultures, methicillin-resistant *S. aureus* (MRSA) were more common for COVID-19 patients (8.9% versus 5.4%, $P < 0.05$), and there was a significant increase in the proportion of overall COVID-19-positive versus -negative patients with MRSA respiratory infections (1.05% versus 0.15%, $P < 0.001$). There was also a significantly higher proportion of COVID-19 patients whose cultures grew *K. pneumoniae* (26.1% versus 16.3%, $P < 0.01$).

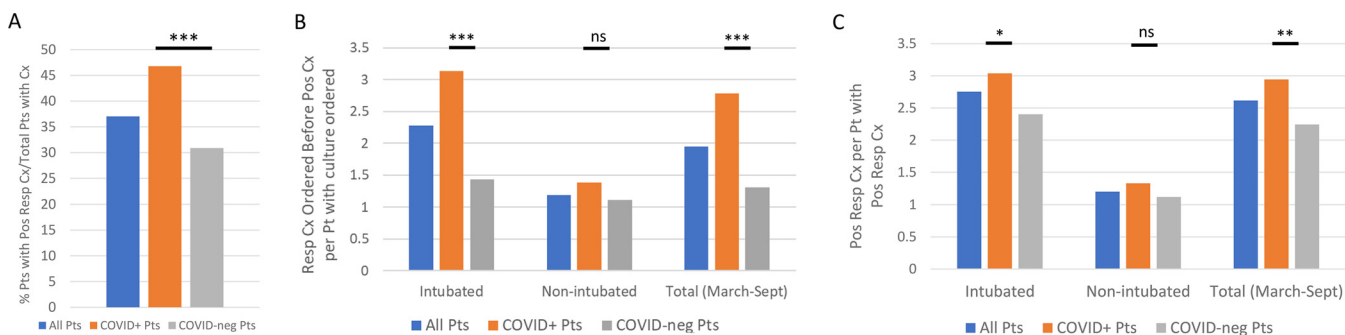


FIG 3 Positive respiratory culture rates by COVID-19 status. (A) Percentage of patients with positive respiratory cultures of those with any respiratory culture ordered. (B) The number of negative respiratory cultures ordered prior to the first positive culture, as well as negative cultures ordered in patients with no positive cultures, per patient with respiratory cultures ordered by intubated and COVID-19 status. (C) Number of positive respiratory cultures per patient with any positive respiratory cultures resulted by intubation and COVID-19 status. *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$; ns, not significant.

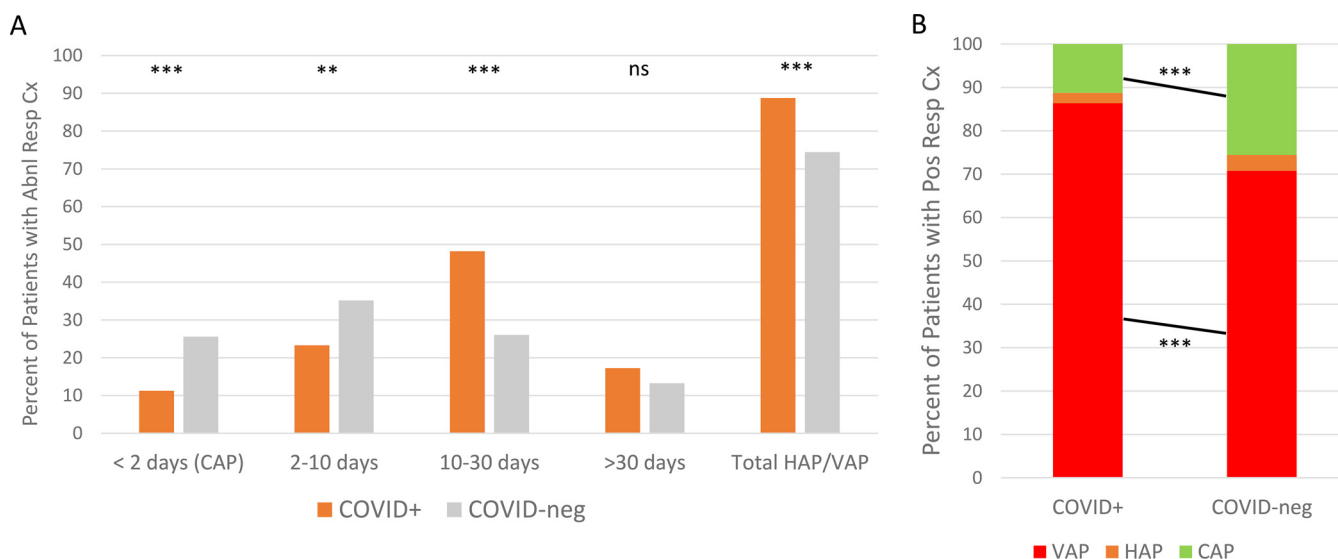


FIG 4 Time from admission to respiratory culture positivity. (A) Percentage of total COVID-19 or non-COVID patients with positive respiratory culture grouped by time interval from admission to respiratory culture ordering comparing community-acquired pneumonia (CAP; <48 h) to hospital-acquired (HAP) or ventilator-associated pneumonia (VAP). (B) Percentage of total COVID-19 or non-COVID patients with positive respiratory culture who fit criteria for CAP, HAP, or VAP (8). **, $P < 0.01$, ***, $P < 0.001$; ns, not significant.

Antibiotic resistance in COVID-19 bacterial pneumonia. In agreement with our finding of increased rates of MRSA-positive respiratory cultures in COVID-19 patients, we found increased rates of resistance to penicillin class antibiotics (penicillin, ampicillin, and oxacillin), 63.4 versus 50.1% of COVID-19-positive versus -negative patients who had a positive culture result ($P < 0.05$). Rates of penicillin-class resistance among Gram-positive organisms were higher among COVID-19 patients (51.8 versus 40.7%), but this difference was not significant. Relative to non-COVID patients, COVID-19 patients showed no significant increases in rates of Enterobacterales resistant to third-generation cephalosporins, carbapenem-resistant Enterobacterales, and carbapenem-resistant *P. aeruginosa* or *Acinetobacter baumannii*.

DISCUSSION

During the first 10 months of the COVID-19 pandemic we found significantly higher utilization of respiratory cultures for COVID-19 patients compared to non-COVID patients at our New York City medical center across both intubated and nonintubated subgroups. Yet despite the increased ordering, intubated COVID-19 patients still had a higher percentage of positive respiratory cultures than intubated non-COVID patients, suggesting that COVID-19 patients have an elevated risk for VAP. However, the nonintubated subgroup showed no such difference in rates of respiratory culture positivity by COVID-19 status when normalized by culture ordering. Bacterial pneumonia in COVID-19 patients was much more likely to be ventilator associated and less likely to be community acquired when compared to non-COVID patients. When excluding intubated patients, rates of hospital-acquired pneumonia were similar among COVID-19 patients relative to non-COVID patients. This study is the first to directly assess respiratory culture ordering and positivity in COVID-19 and non-COVID patients in the same hospital. Given the higher rate of positivity among intubated COVID-19 patients, respiratory culture ordering appears warranted for this

TABLE 4 Bacterial pneumonia categories^a

Metric	Total	SARS-CoV-2 positive	SARS-CoV-2 negative	P value
Total pneumonia patients ^b	468	249	219	
Cases of CAP ^b	84 (17.9%)	28 (11.2%)	56 (25.5%)	$P < 0.0001$
Cases of HAP ^b	14 (3.0%)	6 (2.4%)	8 (3.6%)	$P = 0.61$
Cases of VAP ^b	370 (79.1%)	215 (86.3%)	155 (70.8%)	$P < 0.0001$

^aCAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

^bData included are from March to September 2020.

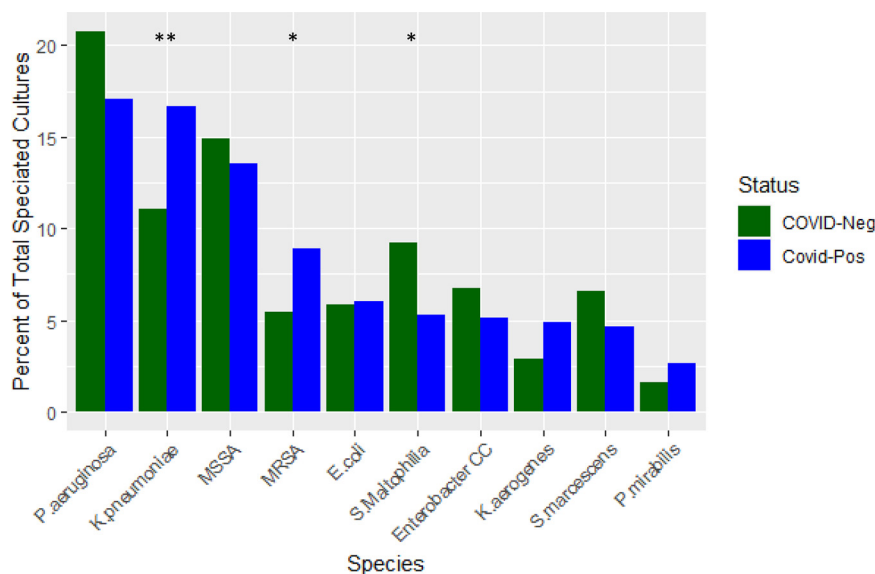


FIG 5 Bacterial species identified in positive respiratory cultures in COVID-19 versus non-COVID patients. Percent of total patients in each category of COVID-19 status with the 10 most common species for COVID-19 patients in descending order. MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*. *, $P < 0.05$, **, $P < 0.01$.

subset of hospitalized COVID-19 patients in whom there is a higher suspicion for bacterial pneumonia.

While more than 80% of respiratory coinfections in COVID-19 patients occurred more than 2 days into hospitalization, and the majority of these occurred well into hospitalization (>10 days), nearly all these cases qualified as VAP and were therefore attributable to intubation rather than other sources of hospital-acquired infection. Only 1.7% of nonintubated COVID-19 patients were found to have bacterial pneumonia, and when this was normalized to respiratory culture ordering, the rate was not significantly different than that for nonintubated non-COVID patients. We also found similarly low rates of CAP in COVID-19 patients compared to what has previously been cited in the literature. A recent study of hospitalized COVID-19 patients looked specifically at rates of bacterial coinfection within the first 3 days of hospitalization and found 1.1% with probable infection and an additional 12.4% with possible coinfection when all types of infection were considered (12). Looking specifically at respiratory bacterial coinfections, our study found 0.9% of COVID-19 patients with positive cultures in the first 3 days of hospitalization, in contrast to 6.8% of COVID-19 patients with positive cultures representing HAP or VAP by this definition. The low rate of community-acquired respiratory infections we found here further supports the conclusions of Coenen et al. (12) that empirical antibiotic therapy for COVID-19 patients is generally not indicated during early hospitalization (13).

From a diagnostic stewardship perspective, nonintubated COVID-19 patients had similarly low rates of bacterial pneumonia as non-COVID patients when normalized by respiratory culture ordering providing evidence against routine respiratory culture ordering for nonintubated COVID-19 patients. However, the relatively high rates of VAP that we found in COVID-19 patients supports a lower threshold for respiratory culture ordering and initiation of antimicrobial therapy for intubated patients. However, intubated COVID-19 patients had a higher number of negative cultures prior to the first positive culture and pneumonia incidence for this group only increased after day 10 of admission, suggesting that routine respiratory culture ordering may not be indicated earlier in the hospital course. Diagnostic stewardship efforts for COVID-19 patients may therefore show the most benefit if directed toward reducing overordering of respiratory cultures during initial hospitalization and reducing overordering for patients not requiring intubation. These efforts may be even more relevant in the setting of 2022 Omicron variants, with fewer hospitalized COVID patients requiring intubation than during the study period.

Positive respiratory cultures of COVID-19 patients were enriched for pathogens associated with hospital-acquired infection with a generally similar proportion non-COVID patients. However, there were significant increases in both *K. pneumoniae* and MRSA respiratory infections, which we interpreted as further corroborating an increased level of hospital-acquired infections for COVID-19-positive patients, particularly relative to the total number of patients testing positive. Overall rates of resistance to penicillin-class antibiotics were significantly higher in respiratory isolates from COVID-19-positive patients, which corroborates data from other studies demonstrating high rates of MRSA and multidrug-resistant bacterial infections in COVID-19 patients (6, 14). One such study also showed that there were significant increases in antibiotic resistance by the duration of hospital stay, including rates of MRSA, vancomycin-resistant enterococci, ceftriaxone-resistant Enterobacterales, and carbapenem-resistant Enterobacterales and carbapenem-resistant *P. aeruginosa* or *A. baumannii* (14). Interestingly, we did not find significant increase in resistance rates between COVID-19-positive and -negative patients for ceftriaxone-resistant Enterobacterales, carbapenem-resistant Enterobacterales, and carbapenem-resistant *P. aeruginosa* or *A. baumannii*. However, further study is necessary to understand the mechanism by which MRSA rates are increased by SARS-CoV-2 infection and whether this is via direct effect of the virus on the host environment or indirectly through affecting host exposure to drug-resistant pathogens.

Some limitations of this study include its representation of data from a single institution only. There were also significant baseline demographic differences in the COVID-19-positive and -negative populations. In addition, a control group of patients with other respiratory viral infections would have been a useful comparison but testing for other respiratory viruses was largely suspended during the study period as the incidence of these viruses was dramatically reduced and limited testing supplies were redirected toward testing for SARS-CoV-2. Nevertheless, by comparing COVID-19 patients to non-COVID patients that had respiratory cultures ordered, the control group was enriched for patients with high clinical suspicion of respiratory illness, demonstrating an elevated risk of VAP in COVID-19 patients even when compared to this higher risk group and allowing for an analysis of culture utilization compared to the baseline group of patients for whom respiratory cultures are normally ordered. Another potential limitation of this study was incomplete data for some of the variables analyzed. Prior to March 23rd, 2020, not all patients admitted to CUIMC were tested for SARS-CoV-2 due to limited testing capacity, and this population of patients with unknown COVID-19 status was therefore not included in our data. Data on intubation status among non-COVID patients from October to December 2020 were also not available, which prevented a complete analysis for this subgroup during those months. However, complete data on intubation status for COVID-19 patients showed that 88% of intubated patients were hospitalized from March to September, and rates of intubation (mean 8.0% \pm 1.7%) were stable during that period. Finally, antimicrobial susceptibility data were not available for several antibiotic classes, such as fluoroquinolones, aminoglycosides and macrolides, which would have been helpful for a more comprehensive characterization of resistance. In addition, the data analyzed here represent one period early in the pandemic, during which time rates of COVID-19 varied by month. The COVID-19 patient population represented here is largely composed of those infected during the initial surge of infections in New York City from March to May of 2020 and may not represent later stages of the pandemic during which different SARS-CoV-2 variants have become dominant.

In summary, the data presented here suggest that patients COVID-19 infection resulted are at higher risk for bacterial pneumonia relative to non-COVID patients, but the overwhelming majority of pneumonia cases were seen in the setting of prolonged hospitalization and intubation, rather than increased rates of CAP as seen with other viruses such as influenza. Possible explanations for these findings include longer periods of hospitalization for COVID-19 patients, inadequate infection control practices during acute phases of the pandemic, or direct effects of SARS-CoV-2 itself on the pathogenesis of bacterial pneumonia during intubation. Based on these findings, respiratory cultures are likely indicated for COVID-19 patients with prolonged hospitalization and ventilator dependence, and diagnostic stewardship efforts should be

focused toward reducing overordering earlier in the hospital course and among nonintubated patients. Further studies are necessary to understand how SARS-CoV-2 increases the risk of VAP among intubated patients.

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