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Secondary Bacterial Pneumonias and Bloodstream Infections in Patients Hospitalized with COVID-19

To the Editor:

Hospitalized patients, particularly those who are critically ill, are at risk for "secondary" infections (1, 2). Initial reports of patients hospitalized with coronavirus disease (COVID-19) indicate that 10–33% develop bacterial pneumonia (3, 4) and 2–6% develop bloodstream infection (BSI) (5, 6). Few studies have reported patient characteristics or the impact of intensive care unit (ICU) admission on secondary infections (3, 6–8). We conducted a descriptive study to identify the prevalence, microbiology, and outcomes of secondary pneumonias and BSIs in patients hospitalized with COVID-19.

Methods

The Emory University Institutional Review Board approved this study. Patients :18 years old with a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) real-time polymerase chain reaction assay admitted to four academic hospitals in Atlanta, Georgia, from February 15 to May 16, 2020, were included. Data were extracted from the electronic medical record (Cerner Millennium) through June 16, 2020, including comorbidities (identified by International Classification of Diseases, 10th revision codes).

Blood cultures were incubated in BACT/ALERT 3D (bioMérieux, Inc.), and respiratory cultures were inoculated on 5% sheep blood, chocolate, and MacConkey agars. Organisms were identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry (bioMérieux, Inc.). Susceptibility testing was performed by Vitek 2 (bioMérieux, Inc.).

We used the U.S. Centers for Disease Control and Prevention (CDC) criteria to determine ventilator-associated events (VAEs), including infection-related ventilator-associated complications (IVACs) and possible ventilator-associated pneumonia (PVAP) (9).

Blood cultures were considered contaminated if one of two sets grew a typically nonpathogenic organism (e.g., coagulase-negative staphylococci) or if the clinical team determined the organism a contaminant. Two of three infectious diseases physicians (M.W.A., D.R.B., and A.B.) reviewed BSIs to determine clinical source and a third (J.T.J.) arbitrated disagreements. Infections were attributed to skin if there was a clinically infected wound or peripheral intravenous line but no central line.

We assessed in-hospital mortality, comparing patients with and without infections using the χ^2 test. SAS University Edition (SAS Institute) was used for data analysis.

Results

Patients. Among 774 patients hospitalized with COVID-19, the median age was 62 years (interquartile range, 50–73), 49.7% were female, and 66.6% were Black (Table 1). Hypertension (75.5%) and diabetes mellitus (45.7%) were the most common comorbidities. Three hundred thirty-five (43.3%) required ICU admission, 238 (30.7%) required mechanical ventilation, and 120 (15.5%) died.

Respiratory infections. Among 238 intubated patients, 201 (84.5%) had at least one respiratory culture sent, and 65 (27.3%) had a positive respiratory culture, with a total of 84 potential pathogens (Table 2). The most common bacteria were *Staphylococcus aureus* (29/84; 34.5%), *Pseudomonas aeruginosa* (16/84; 19.0%), and *Klebsiella* spp. (14/84; 16.7%), with only one *Aspergillus* spp. Mortality did not differ between intubated patients with an identified bacterial respiratory pathogen and those without (41.5% vs. 35.3%, $P = 0.37$).
Forty-six patients (19.3%) had a CDC-defined VAE (15.3 VAEs per 1,000 ventilator-days), 16 (6.7%) had an IVAC (5.3 IVACs per 1,000 ventilator-days), and 5 (2.1%) had a PVAP (1.7 PVAPs per 1,000 ventilator-days). Eleven (23.9%) patients with a VAE required a tracheostomy and 25 (54.3%) died. None of the five patients with PVAP died.

Among 536 (69.3%) nonintubated patients, 186 (34.7%) had *Legionella* urine antigens sent, and two (0.4%) were positive. Sixty-nine (12.9%) had at least one respiratory culture sent, and one was positive

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Table 1. Characteristics of 774 adults hospitalized with COVID-19 in Atlanta, Georgia

Characteristic	Value
Age, median (IQR), yr	62 (50–73)
Female sex, *n* (%)	385 (49.7)
Hispanic ethnicity, *n* (%)	48 (6.2)
Body mass index, median (IQR), kg/m^2 (*n* = 759)	29 (24–34)
Elixhauser comorbidity index, median (IQR) (*n* = 773)	5 (3–8)
Race, *n* (%)	
Black	514 (66.4)
White	156 (20.2)
Unknown	86 (11.1)
Asian	17 (2.2)
American Indian/Alaska Native	1 (0.1)
Comorbidities, *n* (%)	
Hypertension	584 (75.5)
Diabetes mellitus	354 (45.7)
Chronic kidney disease	242 (31.2)
Cancer	130 (16.8)
Liver disease	93 (12.0)
Immunocompromised	56 (7.2)
Laboratory results, median (IQR)	
WBC, ×103/μl	7.7 (5.9–10.8)
Lymphocyte count, ×103/μl (*n* = 673)	1.2 (0.9–1.7)
Hemoglobin, g/dl	12.8 (11.5–14.1)
Platelets, ×103/μl	247 (189–322)
Creatinine, mg/dl (*n* = 773)	1.2 (0.9–1.9)
AST, U/L (*n* = 760)	38 (25–57)
ALT, U/L (*n* = 760)	25 (16–42)
Total bilirubin, mg/dl (*n* = 760)	0.6 (0.4–0.8)
D-dimer, ng/dl (*n* = 579)	1360 (755–3663)
CRP, mg/L (*n* = 590)	131 (70–206)
ESR, mm/h (*n* = 78)	58 (36–85)
LDH, U/L (*n* = 569)	338 (259–452)
Ferritin, ng/ml (*n* = 385)	433 (184–1019)
Troponin-I, ng/ml (*n* = 596)	0.03 (0.03–0.08)
IL-6, pg/ml (*n* = 166)	9 (5–20)
Medications administered, *n* (%)	
Dexamethasone	54 (7.0)
Any steroid	146 (18.9)
Outcomes	
Intensive care unit admission, *n* (%)	335 (43.2)
Mechanical ventilation, *n* (%)	238 (30.7)
Duration of mechanical ventilation, median (IQR), d	10 (5–16)
Died, *n* (%)	120 (15.5)

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = coronavirus disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IL-6 = interleukin-6; IQR = interquartile range; LDH = lactate dehydrogenase; WBC = white blood cells.

Table 2. Characteristics of potential respiratory pathogens (*n* = 84) in 774 patients hospitalized with COVID-19

Characteristic	*n* (%)
Organism	
S. aureus	29 (34.5)
P. aeruginosa	16 (19.1)
Klebsiella species	14 (16.7)
Streptococcus species	4 (4.8)
E. cloacae	3 (3.6)
H. influenzae	2 (2.4)
B. cepacia	2 (2.4)
A. baumannii	1 (1.2)
A. fumigatus	1 (1.2)
Other*	12 (14.3)
Multidrug resistance	
None	60 (71.4)
Methicillin resistance	
S. aureus	14 (16.7)
S. lugdunensis	1 (1.2)
Extended-spectrum β-lactamase	
Klebsiella species	3 (3.6)
Enterobacter cloacae	1 (1.2)
Carbapenem resistance	
P. aeruginosa	3 (3.6)
K. aerogenes	1 (1.2)

Definition of abbreviations: *A. baumannii* = *Acinetobacter baumannii*; *A. fumigatus* = *Aspergillus fumigatus*; *B. cepacia* = *Burkholderia cepacia*; *C. indologenes* = *Chryseobacterium indologenes*; COVID-19 = coronavirus disease; *E. cloacae* = *Enterobacter cloacae*; *H. alvei* = *Hafnia alvei*; *H. influenzae* = *Haemophilus influenzae*; *K. aerogenes* = *Klebsiella aerogenes*; *P. aeruginosa* = *Pseudomonas aeruginosa*; *S. aureus* = *Staphylococcus aureus*; *S. lugdunensis* = *Staphylococcus lugdunensis*; *S. marcescens* = *Serratia marcescens*.
**Corynebacterium* spp. (*n* = 7), *S. lugdunensis* (*n* = 2), *C. indologenes* (*n* = 1), *H. alvei* (*n* = 1), *S. marcescens* (*n* = 1).

(for *S. aureus*). No other bacterial or fungal respiratory pathogens were identified in nonintubated patients.

Bloodstream infections. Of 774 patients, 588 (76.0%) had at least one blood culture sent; 48 (6.2%) had contaminated blood cultures and 36 (4.7%) had BSI, including 5 with polymicrobial BSI (42 isolates total) (Table 3). The majority of BSIs (24/36; 66.7%) had ICU onset. The most common organisms were *S. aureus* (7/42; 16.7%), *Candida* spp. (7/42; 16.7%), and coagulase-negative staphylococci (5/42; 11.9%); 12 (28.6%) were gram negative. The most common source was central line–associated BSI (CLABSI, 17/36; 47.2%), followed by skin (6/36; 16.7%), lungs (5/36; 13.9%), and urine (4/36; 11.1%). Overall, mortality was 50% in patients with BSI versus 13.8% in those without ($P < 0.0001$). Among intubated patients, mortality was 51.9% in patients with BSI versus 35.1% in those without ($P = 0.09$).

Discussion

In this cohort of 774 patients hospitalized with COVID-19, nearly one-third required mechanical ventilation, of whom 27% had positive respiratory cultures and 2% had ventilator-associated pneumonia. Thirty-six patients (5%) developed BSI, of whom 50% died. Secondary infections were associated with traditional risk factors for healthcare-associated infections, including indwelling medical devices, and predominantly in the ICU.

Secondary bacterial pneumonia, commonly due to *S. pneumoniae* and *S. aureus*, complicates 20–30% of influenza (10), and methicillin-resistant *S. aureus* pneumonia has been reported with severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) (11). In our cohort of patients with COVID-19, the risk of secondary bacterial pneumonia was much lower: only three nonintubated patients had microbiologic evidence of bacterial pneumonia. In contrast, intubated patients had a high proportion of cultures positive for *S. aureus*, *P. aeruginosa*, and *Klebsiella* spp., which concurs with a UK multicenter study of patients with

Table 3. Characteristics of bloodstream infections (n = 36) in 774 patients hospitalized with COVID-19

Characteristic	*n* (%)
Source	
Central line	17 (47.2)
Skin	6 (16.7)
Pulmonary	5 (13.9)
Urine	4 (11.1)
Gastrointestinal	3 (8.3)
Unknown	1 (2.8)
Organism (n = 42)*	
S. aureus	7 (16.7)
Candida species	7 (16.7)
Streptococcus species	6 (14.3)
Coagulase negative staphylococci	5 (11.9)
Enterococcus species	5 (11.9)
E. coli	3 (7.1)
Klebsiella species	3 (7.1)
Other gram-negative organisms†	6 (14.3)
Multidrug resistance (n = 42)*	
None	30 (71.4)
Methicillin resistance	
S. aureus	4 (9.5)
Coagulase-negative staphylococci	2 (4.8)
Vancomycin resistance	
Enterococci	3 (7.1)
Carbapenem resistance	
Enterobacterales	2 (4.8)
P. aeruginosa	1 (2.4)
Epidemiologic class‡	
Hospital-onset	26 (72.2)
Healthcare-associated, community-onset	8 (22.2)
Community-onset	2 (5.6)
Collection location	
Intensive care unit	24 (66.7)
Emergency department	10 (27.8)
Ward	2 (5.6)
Outcomes	
Persistent bloodstream infection§	0
Mortality (in-hospital)	18 (50.0)

Definition of abbreviations: COVID-19 = coronavirus disease; *E. cloacae* = *Enterobacter cloacae*; *E. coli* = *Escherichia coli*; *P. aeruginosa* = *Pseudomonas aeruginosa*; *P. melaninogenica* = *Prevotella melaninogenica*; *P. mirabilis* = *Proteus mirabilis*; *S. aureus* = *Staphylococcus aureus*; *S. marcescens* = *Serratia marcescens*.
*Five patients had polymicrobial bacteremia; there were 42 total isolates.
†*Acinetobacter* sp., *E. cloacae*, *P. melaninogenica*, *P. mirabilis*, *P. aeruginosa*, *S. marcescens*.
‡Using U.S. Centers for Disease Control and Prevention guidelines (15).
§Positive blood cultures for the same organism at least 72 hours apart despite appropriate antibiotics.

COVID-19 with suspected ventilator-associated pneumonia (7). Importantly, respiratory bacterial pathogens isolated from patients with COVID-19 are similar to pathogens that cause hospital-acquired pneumonia in patients without COVID-19 (2, 12), with no change from pre–COVID-19 ICU-level resistance rates. These results suggest that hospitalization and intubation are more important than are COVID-19–specific effects in conferring susceptibility to specific pathogens. We did not observe a mortality difference in intubated patients with or without positive respiratory cultures. This may be due to significant empiric antibiotic use and warrants future investigation.

BSIs in our cohort were also largely related to risk factors and pathogens associated with hospitalization. The majority (66.7%) were ICU-onset and nearly half (47.2%) were CLABSIs, which may be related to an increase above the pre–COVID-19 baseline in central line–days among ICU patients (J. Jacob, unpublished results). As with respiratory pathogens, the BSI pathogens (*S. aureus*, *Candida* spp., and coagulase-negative staphylococci) were typical for healthcare-associated BSI in patients without COVID-19 (12). The observed high proportion of contaminants—severalfold higher than the baseline contamination rate of 0.4–1.8% in study hospitals during January and February 2020—may be due to obtaining blood cultures through central lines to minimize exposure for phlebotomists. Importantly, there was no change in observed daily bathing and central line maintenance practices observed by infection prevention teams. Maintaining central access in critically ill patients with COVID-19 can minimize emergent central line placement and potential healthcare worker SARS-CoV-2 exposure. Clinicians should continue to balance the need for central venous access with risk of CLABSI.

Our study has several limitations. First, these results are from academic hospitals in the southeastern United States and may not be generalizable to other settings. Second, we used International Classification of Diseases, 10th revision codes to determine comorbidities, which may be less accurate than reviewer adjudication. Third, we defined ventilator-associated pneumonia using CDC surveillance definitions (9), which may not represent clinical practice and have not been validated for use in patients with COVID-19. To mitigate this limitation, we presented data on all respiratory pathogens to inform empiric antimicrobials for patients with COVID-19 with suspected ventilator-associated pneumonia. Fourth, our study period was before publication of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) dexamethasone trial (13), and corticosteroids were not routinely administered; only 7% of this cohort received any dexamethasone. Future studies should assess the risk of corticosteroids on secondary infections in patients with COVID-19. Finally, results from this descriptive study are not risk-adjusted and therefore should not be used to infer risk associated with different interventions (e.g., risk of BSI in patients with COVID-19 with vs. without central lines).

Overall, few of the 744 patients hospitalized with COVID-19 developed secondary bacterial pneumonia (2%) or BSI (5%). This is consistent with findings from a living meta-analysis reporting a 7% prevalence of bacterial secondary infections in patients with COVID-19 (14). Our analysis adds to this previous literature by demonstrating that the risk factors for these infections (intubation and central lines, respectively) and causative pathogens reflect healthcare delivery and not a COVID-19–specific effect. Our results suggest that clinicians, especially ICU clinicians, should adhere to standard best practices for preventing and empirically treating secondary infections in patients hospitalized with COVID-19. ■

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