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Clinical Studies

Predictors of respiratory bacterial co-infection in hospitalized COVID-19 patients

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ABSTRACT

The primary objectives were to determine the prevalence of and identify variables associated with respiratory bacterial co-infection in COVID-19 inpatients. Secondary outcomes included length of stay and in-hospital mortality. Eighty-two (11.2%) of 735 COVID-19 inpatients had respiratory bacterial co-infection. Fifty-seven patients met inclusion criteria and were matched to three patients lacking co-infection (N = 228 patients). Patients with co-infection were more likely to receive antibiotics [57 (100%) vs 130 (76%), $P < 0.0001$] and for a longer duration [19 (13-33) vs 8 (4-13) days, $P < 0.0001$]. The multi-variable logistic regression model revealed risk factors of respiratory bacterial co-infection to be admission from SNF/LTAC/NH (AOR 6.8, 95% CI 2.6-18.2), severe COVID-19 (AOR 3.03, 95% CI 0.78-11.9), and leukocytosis (AOR 3.03, 95% CI 0.99-1.16). Although respiratory bacterial co-infection is rare in COVID-19 inpatients, antibiotic use is common. Early recognition of respiratory bacterial coinfection predictors in COVID-19 inpatients may improve empiric antibiotic prescribing.

1. Introduction

COVID-19, caused by the novel SARS-CoV-2 virus, was first identified in Wuhan, China, in December 2019 and declared a worldwide pandemic by the World Health Organization (WHO) in March 2020. SARS-CoV-2 infects cells that express angiotensin-converting enzyme (ACE)2 receptors. A variety of organ systems may therefore be impacted, but patients predominantly present with respiratory symptoms including shortness of breath, cough, and fever (Mclachlan, 2020). Due to the lack of distinguishing characteristics of COVID-19 pneumonia from other infectious respiratory etiologies, providers are challenged with deciding whether empiric anti bacterials are warranted (Use of chest imaging, 2020). One argument against standard prescribing of empiric antibiotics in hospitalized COVID-19 patients is the low rate of bacterial co-infection. Previously published literature has demonstrated COVID-19 co-infection rates with bacteria or fungi to be less than 10%, yet the majority of patients have received antimicrobial therapy (Rawson et al., 2020, Langford *et al.*, 2020, Vaughn *et al.*, 2021, Wang *et al.*, 2021, Hughes *et al.*, 2020).

In order to best steward antibiotics in the setting of COVID-19, predictors of bacterial co-infection must be identified. Only one large study to date identified the presence of invasive devices, diabetes, and combination antibiotics as predictors of nosocomial infections in COVID-19 patients (Langford *et al.*, 2020). However, this study failed to evaluate predictors of community-acquired bacterial co-infections in the setting of COVID-19 and was not specific to respiratory co-infections. Another study found that patients who were older, presented with more severe illness, or were admitted to a for-profit hospital were more likely to receive early empiric antimicrobial therapy (Vaughn *et al.*, 2021). This study aim was to evaluate variables associated with respiratory bacterial co-infections, community or hospital-acquired, in hospitalized patients with COVID-19.

2. Materials and methods

2.1. Study design and participants

This retrospective cohort study included hospitalized patients with COVID-19 at The Ohio State University Wexner Medical Center (OSUWMC) from February 1, 2020 to September 30, 2020. Inpatients

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with a positive SARS-CoV-2 antigen or PCR were identified by the OSUWMC Information Warehouse and screened for inclusion. Patients with respiratory bacterial co-infection were matched with three hospitalized COVID-19 patients lacking respiratory co-infection who were admitted within 7 days of each other. Patients were included once during the study timeframe based on their first (index) admission for COVID-19. Protected populations including inmates, pregnant patients, and patients < 18 or > 89 years of age were excluded as well as patients with respiratory bacterial colonization.

2.2. Study objectives and definitions

2.2.1. Study objectives

The primary objectives of this study were to determine the prevalence of and identify potential variables associated with respiratory bacterial co-infection in hospitalized COVID-19 patients. Secondary outcomes included length of stay and in-hospital mortality.

2.2.2. Study definitions

Respiratory bacterial co-infection was defined as a positive bacterial respiratory culture or a positive bacterial antigen test (e.g., *Legionella* or *Streptococcus pneumoniae* urine antigen) identified in the presence of a positive COVID-19 PCR or antigen test during the same admission. Cultures and/or antigen tests were obtained at the discretion of the provider on a case by case basis. Community-acquired respiratory bacterial co-infection was defined as an infection identified within 48 hours of hospital admission, while hospital-acquired respiratory bacterial co-infection was defined as an infection occurring in a patient more than 48 hours after admission that was not documented on initial presentation and for which antibiotic treatment was administered. Mild to moderate COVID-19 was defined as inpatients with SpO2 > 94% on room air not progressing to severe COVID-19 within 24 hours of admission while severe COVID-19 was defined as inpatients with SpO2 < 94% on room air or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Cumulative mechanical ventilator days were defined as the aggregate number of days a patient was intubated on mechanical ventilation throughout the index admission. Antibiotic days were defined as the aggregate number of calendar days for which any amount of antibiotic agents were administered to a patient. Narrow spectrum agents included metronidazole, dicloxacillin, cefazolin, cephalexin, amoxicillin, penicillin G, and ampicillin. Broad spectrum agents included ceftriaxone, ertapenem, ampicillin/sulbactam, amoxicillin/clavulanate and cefdinir. MRSA agents included vancomycin, ceftaroline, sulfamethoxazole-trimethoprim, linezolid, and clindamycin. Anti-Pseudomonal beta-lactams included cefepime, piperacillin-tazobactam, meropenem, and ceftolozane-tazobactam. Non-beta-lactam anti-Pseudomonal agents included ciprofloxacin, levofloxacin, tobramycin, and aztreonam. Atypical agents included doxycycline, minocycline, and azithromycin.

2.3. Data collection

Data collected included patient demographics such as age, sex, residence type [e.g., personal residence, nursing home (NH), skilled nursing facility (SNF), long-term care acute care facility (LTAC), etc.], Charlson Comorbidity Index, and pertinent co-morbidities including chronic lung disease (i.e., COPD, asthma, interstitial lung disease, and cystic fibrosis), cardiac disease (i.e., coronary artery disease, congestive heart failure, and implanted cardiac devices), diabetes mellitus, and immunocompromise (i.e., active chemotherapy, >20 mg of prednisone equivalents for > 2 weeks, bone marrow or organ transplantation, immune deficiency, or CD4 count < 200 cells/mm^3).

Clinical characteristics included the presence and hospital day of positive respiratory bacterial cultures with pathogens identified and susceptibilities as well as Streptococcus or Legionella urinary antigens, antibiotic(s) administered and duration, maximum inflammatory markers within 72 hours of admission (i.e., procalcitonin, WBC, CRP, IL-6, and ferritin), glucocorticoid administration during admission, tocilizumab administration during admission, maximum temperature within 24 hours of admission, and severity of COVID-19.

Clinical outcomes collected included intensive care unit (ICU) admission, length of stay (hospital and ICU), in-hospital mortality, need for mechanical ventilation, and cumulative mechanical ventilator days.

2.4. Statistical analysis

Hospitalized COVID-19 patients with and without respiratory bacterial co-infection were compared. Demographic and clinical information was analyzed using descriptive statistics. Continuous variables are presented as median (interquartile range) and analyzed using Wilcoxon rank sum test. Categorical variables are presented as frequency (percent) and compared using the Chi-Square or Fishers Exact Test as appropriate.

A multivariable logistic regression (MLR) model was conducted to identify covariates associated with respiratory bacterial co-infection. Adjusted Odds Ratios (AOR) and 95% confidence intervals (95% CI) were used to assess the strength of covariate association with respiratory bacterial co-infection in hospitalized COVID-19 patients. Variables were included in the model via a forward selection method if they were highly significant ($P \leq 0.05$), met Akaike information criterion (AIC) likelihood ratio, and met Receiver Operating Characteristics (ROC) considerations. All statistical tests were conducted utilizing SAS software version 9.3 (SAS Institute, Cary, NC).

3. Results

Seven hundred thirty-five patients were hospitalized with COVID-19 during the study period. Of these, 82 (11.2%) had a respiratory bacterial co-infection. Twenty-five patients with respiratory bacterial co-infection were excluded for the following reasons: colonization (n = 8), non-index COVID-19 admission (n = 8), inmate (n = 6), pregnancy (n = 1), and other (n = 2). Each of the 57 included patients with respiratory bacterial co-infection was matched with three patients lacking respiratory bacterial co-infection (n = 171), resulting in a total sample size of 228 patients. Baseline characteristics are summarized in Table 1.

Among the patients with respiratory bacterial co-infection, the incidence of community- and hospital-acquired infection was fairly evenly split [29 (51%) vs 28 (49%), respectively]. The median hospital day of positive culture was 8.5 [2.75-11] in patients with hospital-acquired respiratory bacterial co-infection. Pathogens identified from respiratory culture included *Staphylococcus aureus* [28 (49%)], Enterobacterales [18 (32%)], non-fermenting Gram negatives [12 (21%)], and other Gram positives [12 (21%)].

More patients with respiratory bacterial co-infection were prescribed at least one antibiotic than those without respiratory bacterial co-infection [57 (100%) vs 130 (76%), $P < 0.0001$]. Furthermore, patients with a respiratory bacterial co-infection received a longer cumulative duration of antibiotic days [19 (13-33)] vs. 8 [(4-13, ,), P <0.0001]. Antimicrobial classes prescribed are depicted in Fig. 1. Clinical outcomes are shown in Table 2.

Variables considered for inclusion in the MLR model based on univariate analyses included age, residence in or admission from a SNF/LTAC/nursing home, COVID-19 severity, procalcitonin, WBC count, and Charlson Comorbidity Index Score. The MLR model revealed potential risk factors of respiratory bacterial co-infection to be admission from SNF/LTAC/NH (AOR 6.8, 95% CI 2.6-18.2), presentation with severe COVID-19 (AOR 3.03, 95% CI 0.78-11.9), and leukocytosis (AOR 3.03, 95% CI 0.99-1.16).

Table 1
Baseline characteristics of hospitalized COVID-19 patients with and without respiratory bacterial co-infection.

N = 228	Respiratory bacterial co-infection (*n* = 57)	No respiratory bacterial co-infection (*n* = 171)	*P*-Value
Age, years	68 [60-76]	58 [43-71]	0.0003
Male	36 (63%)	92 (54%)	0.22
Admission from SNF/LTAC/NH	27 (47%)	26 (15%)	<0.0001
Charlson Comorbidity Index	3 [1-4]	2 [0-4]	0.08
COPD	14 (25%)	14 (8%)	0.001
Asthma	7 (12%)	17 (10%)	0.62
Interstitial Lung Disease	5 (9%)	0 (0%)	<0.0001
Cardiac Disease	15 (26%)	31 (18%)	0.18
Diabetes Mellitus	24 (42%)	67 (39%)	0.7
Immunocompromised	7 (12%)	33 (19%)	0.23
COVID-19 Severity			
Mild to Moderate	4 (7%)	73 (43%)	<0.0001
Severe	53 (93%)	98 (57%)	
Procalcitonin (*n* = 116)	0.31 [0.16-0.95]	0.15 [0.07-0.67]	0.01
WBC	11.7 [7.2-15.6]	8.0 [5.7-11.5]	0.0001
CRP (*n* = 190)	139.7 [85.4-249.2]	105.6 [30.7-161.3]	0.003
Ferritin (*n* = 186)	927.2 [513.5-2,264.3]	666.7 [251.1-1,231.3]	0.02
IL-6 (*n* = 81)	99.4 [26.6-302.5]	44.2 [20.5-107]	0.1
Temperature (F)	100.6 [99.3-102.3]	100.1 [98.9-101.4]	0.04
Glucocorticoids	34 (60%)	62 (36%)	0.002
Tocilizumab	5 (9%)	8 (5%)	0.25

SNF = skilled nursing facility; NH = Nursing Home; LTAC = long term acute care; WBC = white blood cell; IL-6 = interleukin-6; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein.
Maximum WBC, ferritin, IL-6, CRP were collected within 72 hours of admission. Temperature was collected within 24 hours of admission.
Data are presented as median [IQR] or number (%) as appropriate.

4. Discussion

This study reports a rate of respiratory bacterial co-infection of 11.2% among hospitalized patients with COVID-19. This is slightly higher than previously reported rates (Rawson et al., 2020, Langford *et al.*, 2020, Vaughn *et al.*, 2021, Wang *et al.*, 2021, Hughes *et al.*, 2020). Admission from a SNF/LTAC/NH, presentation with severe COVID-19, and leukocytosis were predictors of respiratory bacterial co-infection based on a MLR analysis. To our knowledge, this is the first study evaluating predictors of community- or hospital-acquired respiratory bacterial co-infection in hospitalized COVID-19 patients.

The Infectious Diseases Society of America (IDSA) Guidelines for the Diagnosis and Treatment of Adults with Community-acquired Pneumonia (CAP) suggest CAP risk factors include age over 65 years; comorbidities including chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; asplenia; and smoking

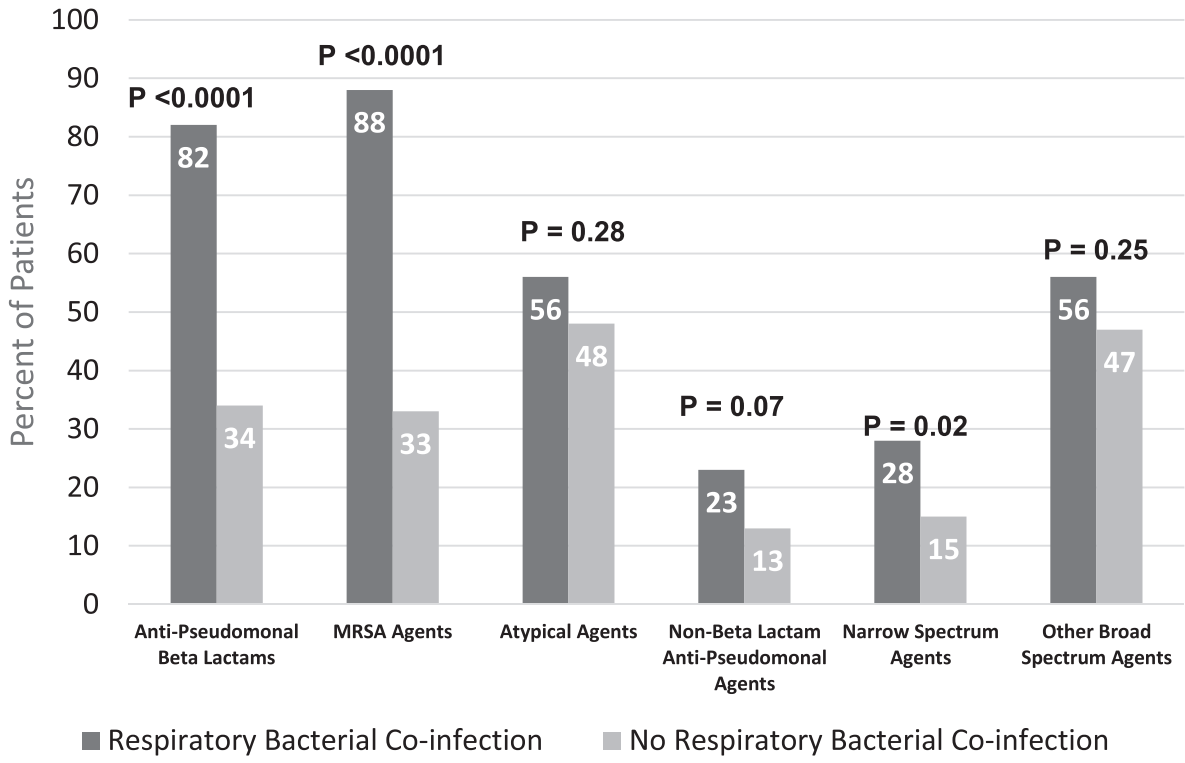

Fig. 1. Antimicrobial agents prescribed to hospitalized COVID-19 patients with and without respiratory bacterial co-infection. MRSA = methicillin-resistant *Staphylococcus aureus*.

Table 2
Clinical outcomes of hospitalized COVID-19 patients with and without respiratory bacterial co-infection.

	Respiratory bacterial co-infection (*n* = 57)	No respiratory bacterial co-infection (*n* = 171)	*P*-Value
ICU Admission	49 (86%)	43 (25%)	<0.0001
ICU LOS, Days	16 [8-22] (*n* = 49)	7 [4-15] (*n* = 43)	0.0003
Hospital LOS, Days	19 [14-26]	8 [5-13]	<0.0001
Mechanical Ventilation	45 (79%)	27 (16%)	0.002
Cumulative Mechanical Ventilator Days	11 [5-18] (*n* = 45)	8 [3-14] (*n* = 27)	0.08
Mortality	19 (33%)	17 (10%)	<0.0001
Hospital Day of Mortality	22 [8-25] (*n* = 19)	13 [6-15] (*n* = 17)	0.08

ICU = intensive care unit; LOS = length of stay

(Metlay et al., 2019). In contrast, risk factors for hospital-acquired pneumonia (HAP) include mechanical ventilation greater than 48 hours, ICU admission, duration of ICU or hospital stay, severity of underlying illness, and presence of comorbidities (Kalil et al., 2016). Although not identical, risk factors for respiratory bacterial co-infection in this study were similar to those outlined in the aforementioned CAP and HAP IDSA guidelines. That is, SNF/LTAC/NH residence likely correlates with the presence of comorbidities and severe COVID-19 represents severe underlying illness.

He, Wang, and colleagues identified the presence of invasive devices, diabetes, and combination antibiotics as predictors of nosocomial infections in COVID-19 patients, but did not evaluate patients with community-acquired co-infection or those specific to the respiratory tract (He *et al.*, 2020). The inclusion of patients with community-acquired co-infection may allow for selective empiric antibiotic prescribing in newly admitted COVID-19 patients. This represents a critical opportunity for antimicrobial stewardship programs given that unnecessary antibiotic use promotes the development of antibiotic resistance, *C. difficile* infections, adverse drug events, as well as increased healthcare costs (Ventola, 2015, Mullish and Williams, 2018, Dadgostar, 2019).

The present study found a slightly higher incidence of bacterial co-infection (11.2%) than previously reported rates (Rawson et al., 2020, Langford *et al.*, 2020, Vaughn *et al.*, 2021, Wang *et al.*, 2021, Hughes *et al.*, 2020). A systematic review of 18 studies encompassing 806 COVID-19 patients found that only 62 (8%) patients had a bacterial or fungal co-infection of any type (Rawson et al., 2020). A similar study consisting of 836 COVID-19 patients found 6.1% of patients had a bacterial or fungal co-infection of any type (Hughes *et al.*, 2020). Additionally, a recent meta-analysis of 24 studies included 3506 COVID-19 patients but identified only 3.5% of patients as having a bacterial co-infection (Langford *et al.*, 2020). Another cohort study of 1705 COVID-19 patients identified a community-onset bacterial infection in 3.5% of patients (Vaughn *et al.*, 2021). Lastly, an additional cohort study observed 1396 COVID-19 patients and found bacterial co-infection in 2.7% of patients (Wang *et al.*, 2021). Differences in rates of co-infection could be attributed to the types and sources of infection evaluated. The previous studies reported rates of co-infection from any site and of any type, while the present study was limited to respiratory bacterial co-infection of community- or hospital-onset. The findings of our study, combined with those of these previous studies, suggest that bacterial co-infections, although occurring, are a relatively infrequent complication.

In addition to antibiotic days, this study reports a breakdown of antibiotic classes used, adding to the existing literature which reported cumulative antibiotic exposure. The majority of patients in the co-infected group received anti-Pseudomonal beta-lactams and anti-MRSA agents, which suggests that prescribing was both empiric and culture-directed based on the organism distribution observed. The proportion of patients receiving therapy for atypical agents of pneumonia and other broad spectrum agents was lower and similar between the two groups. This is an expected finding given these categories include commonly prescribed empiric therapies for community-acquired pneumonia (e.g., ceftriaxone and respiratory quinolones).

There are several limitations worth noting. First, this was a retrospective, single center study with a small sample size limited by the observed population of patients with respiratory bacterial co-infection. Second, it is possible that misclassification of patients with culture-negative pneumonia occurred in which patients had respiratory bacterial co-infection but lacked a positive culture or antigen test. Also, this study did not assess non-respiratory bacterial co-infections so antibiotic prescribing in some patients may have been driven by bacterial co-infections outside of the respiratory tract. Next, the research team did not have access to all outside hospital records for transferred patients due to limitations in the electronic health record. Also, laboratory values and vitals were assessed upon admission which may not have reflected severity of illness at the time of respiratory bacterial co-infection onset in patients with hospital-acquired or ventilator-associated pneumonia. Finally, COVID-19 treatments changed greatly over the study timeframe, so clinical outcomes may have varied over time due in part to evolving COVID-19 management strategies. Variations in clinical outcomes at different times in the pandemic were not specifically assessed; however, an attempt was made to overcome this by matching co-infected and non-co-infected patients within 7 days of admission.

Future studies should include a larger sample size and utilize power calculations to assure statistical and clinical significance.

5. Conclusion

Although respiratory bacterial co-infection is rare in hospitalized COVID-19 patients, antibiotic use is common. Hospitalized COVID-19 patients may be more likely to have respiratory bacterial co-infection if they are admitted from a nursing home/SNF/LTAC, have severe COVID-19, or present with leukocytosis. Prompt recognition of predictors of respiratory bacterial co-infection in hospitalized COVID-19 patients may facilitate more prompt initiation of appropriate antimicrobial therapy, thus mitigating the risk of less favorable outcomes while also improving antimicrobial stewardship among patients at low risk for co-infection.

Authors' contributions

Austin Bolker: Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization. Kelci Coe: Methodology, Formal Analysis, Writing – Review & Editing. Jessica Smith: Methodology, Writing – Review & Editing. Kurt Stevenson: Conceptualization, Methodology, Writing – Review & Editing, Funding Acquisition. Shu-Hua Wang: Methodology, Writing – Review &

Editing. Erica Reed: Conceptualization, Validation, Methodology, Investigation, Writing – Review & Editing, Supervision, Project Administration.

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Ethical approval

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Declaration of competing interest

None to declare.

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