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Characteristics of COVID-19 Patients with Bacterial Co-infection Admitted to the Hospital from the Emergency Department in a Large Regional Healthcare System

Shortened Title: The Rate of Bacteremia With COVID-19

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ABSTRACT

Introduction: The rate of bacterial co-infection with SARS-CoV-2 is poorly defined.

The decision to administer antibiotics early in the course of SARS-CoV-2 infection depends on the likelihood of bacterial co-infection.

Methods: We performed a retrospective chart review of all patients admitted through the emergency department with confirmed SARS-CoV-2 infection over a 6 week period in a

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large healthcare system in the United States. Blood and respiratory culture results were abstracted and adjudicated by multiple authors. The primary outcome was the rate of bacteremia. We secondarily looked to define clinical or laboratory features associated with bacteremia.

Results: There were 542 patients admitted with confirmed SARS-CoV-2 infection, with an average age of 62.8 years. Of these, 395 had blood cultures performed upon admission, with 6 true positive results (1.1% of the total population). An additional 14 patients had positive respiratory cultures treated as true pathogens in the first 72 hours. Low blood pressure and elevated white blood cell count, neutrophil count, blood urea nitrogen, and lactate were statistically significantly associated with bacteremia. Clinical outcomes were not statistically significantly different between patients with and without bacteremia.

Conclusions: We found a low rate of bacteremia in patients admitted with confirmed SARS-CoV-2 infection. In hemodynamically stable patients, routine antibiotics may not be warranted in this population.

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic has already infected over 75 million individuals and caused more than a million deaths.¹ The disease has overwhelmed health care systems and challenged clinicians' ability to provide timely evidence-based care, especially to critically ill patients.² The Surviving Sepsis Campaign (SSC) recently issued 54 statements regarding management of critically ill adults with COVID-19, the disease caused by SARS-CoV-2,³

addressing topics such as fluid resuscitation, mechanical ventilation, steroids, and intravenous immunoglobulins. However, most of these recommendations are based on limited evidence due to the novelty of the disease.

One clinical dilemma raised by the SSC is whether to use antibiotics in patients with COVID-19. Discerning concomitant bacterial sepsis or superinfection among patients with COVID-19 can be very difficult, given the similarity in symptoms (fever, cough, myalgias, etc).⁴ The uncertainty surrounding clinical management is reflected in data from Wuhan, where up to 53% of patients with non-severe disease and >90% of patients admitted to the hospital were given intravenous antibiotics.⁵⁻⁷ A systematic review of 76 studies encompassing over 11,000 patients with COVID-19 found that 64% were treated with antibiotics. Data from other severe respiratory viruses suggest significant rates of bacterial co-infection. Research on the Middle East Respiratory Syndrome demonstrated an 18% bacterial co-infection rate in 330 patients in the ICU,⁸ while the reported bacterial co-infection rate in influenza ranges from 11% to 35%.⁹ Recent systematic reviews have reported bacterial co-infection rates of approximately 7% for hospitalized patients with COVID-19, but are based on a small number of studies, many of which do not discern between bacterial infections present on admission versus those acquired in the hospital.^{10,11} A large multicenter registry reported a 3.5% community-onset bacterial co-infection with COVID-19,¹² and despite frequent use of broad spectrum antibiotics, further data is urgently needed.¹³ Further, patients with suspected bacterial co-infection may have worse outcomes.¹⁴ The most current guidelines from the SSC recommend empiric antimicrobial treatment for mechanically ventilated patients, with early de-

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escalation guided by microbiology and culture results; but acknowledge those recommendations are based on low-quality evidence.³

This study aimed to define the rate of bacteremia or bacterial co-infection in admitted COVID-19 patients and to identify clinical or laboratory risk factors associated with bacteremia to help guide early antimicrobial use.

METHODS

This retrospective chart review was approved as exempt research by the local institutional review board.

Patients and Settings

The study took place across a large integrated health system that includes 14 hospitals across the state of Indiana. Annual emergency department (ED) volume across the hospitals ranges from approximately 6,000 to 90,000, and the system sees over 400,000 combined ED patients annually.

Included patients were adults aged ≥ 18 years, admitted to the hospital from the ED between March 1, 2020, and April 13, 2020, with a positive Polymerase Chain Reaction (PCR) test for SARS-CoV-2 within 3 days of admission. Patients with a PCR test obtained greater than 3 days after hospital admission were excluded because this is the earliest timeframe in which a positive test could be reasonably attributed to an infection occurring during the early part of the hospitalization, rather than being present prior to admission. No further exclusion criteria were applied.

Data Collection

Data was abstracted using a standardized form and was entered into REDCap,¹⁵ a secure data collection instrument. Extracted data included days from symptom onset to ED presentation, basic demographics (age and gender), comorbidities, ED vitals signs, laboratory values (culture results and chest imaging results), and level of care at the time of admission. Level of care was defined based on the computerized order entered by the admitting hospitalist team. Chest imaging results based on final radiologist interpretation were labeled as “clear,” “single lobe infiltrates,” “multi-lobar infiltrates,” or “clear x-ray with involvement on CT only.” Vital signs included initial and final ED blood pressure, heart rate, oxygen saturation, temperature, and respiratory rate. If an ambulatory oxygen saturation was documented in the electronic medical record (EMR), it was extracted and recorded separately. Comorbidities were based on chart review of the ED note, admission note, and any clinic or primary care notes available in the EMR. The presence or absence of the following comorbidities was recorded for each patient: smoking, obesity, hypertension, diabetes, hyperlipidemia, heart failure, previous ischemic heart disease, active cancer, dialysis dependent renal disease, chronic obstructive pulmonary disease (COPD), asthma, active cancer, current chemotherapy, HIV, history of organ transplantation, and current use of oral immunosuppressants.

Outcomes

The primary outcome was the rate of true positive blood cultures performed at admission (within 24 hours of hospital arrival) in patients who tested positive for COVID-19. All blood culture results were initially documented as negative, positive (any bacterial

growth in any bottle), or not done. Since some positive blood cultures can be caused by skin contaminants not causing any infection, all positive cultures were adjudicated by 2 authors as either true positive or contaminants. Criteria to determine “true positive” versus “contaminant” were predefined. Institutional protocol directs collection of 4 bottles (2 from each of 2 different sites) when drawing blood cultures. Any case in which more than 2 of 4 bottles grew bacteria were considered true positives. Any patient with repeat blood cultures that were positive were considered true positive. Growth of bacteria outside of typical skin flora (such as *staphylococcus* or *streptococcus*) was generally considered true positive. If a positive in <3 of 4 bottles was noted to be a “probable contaminant” in the provider notes or infectious disease consultation notes, and if antibiotics were discontinued before 5 days of treatment, growth was classified as a false positive. In cases of disagreement, the discrepancy was resolved through discussion or adjudicated by a third author. Patients in whom no blood cultures were drawn within 72 hours were classified as not bacteremic. Patients with positive culture results were thus divided into “true positive” bacteremia versus “contaminant.” We defined associations between clinical variables and true positive blood cultures and compared clinical outcomes between those with and without true positive blood cultures.

We also assessed respiratory cultures drawn in the first 72 hours. Since it is more difficult to define a true positive respiratory culture versus contaminant or carrier state, all respiratory cultures with bacterial growth were considered true pathogens if the admitting team treated them as such, and incidental (not causing infection) if the care team noted the findings to be likely non-infectious and the patient was successfully treated without antibiotics.

Urine cultures were not included in our analyses, since urinalysis can be performed with immediate results to guide antibiotic treatment related to urine infections, so initially “occult” urine infection is unlikely. Further, asymptomatic bacteriuria is common in some populations.

Statistical Analysis

Mean ages were compared using a two-sided t-test after a test for the ratio between the two standard deviations showed no significant difference. Categorical data were compared based on blood culture results with Fisher’s exact test and p-values were reported when statistically significant. Comparison of means was otherwise accomplished through an analysis of variance between groups if the concurrent Bartlett’s test for equal variances did not refute the validity of the comparison. P-values were not reported if Bartlett’s test demonstrated significant differences. All statistical analyses were performed using Stata/IC 16.1 (StataCorp LLC, College Station, Texas).

RESULTS

We identified 542 adults with a positive COVID-19 PCR test admitted during the study period, and all were included. Table 1 provides demographic information on the cohort. The average patient age was 62.8 years; 49.6% were male. Patients with bacteremia were older than those without (79.8 vs 62.6 years; $p = 0.01$) but were otherwise similar demographically and had similar comorbidities. Among all patients, 395 (73%) had blood cultures performed at admission. Of those, 42 demonstrated growth in any bottle, and 6 demonstrated true positive blood cultures, representing 1.1% (95% CI = 0.4% to 2.3%) of the study population and 14% of all blood cultures with any bacterial growth. Table 2

provides details on the 6 bacteremic patients. There were 12 positive blood cultures drawn after at least 24 hours in the hospital. Only one of the 12 was performed within 72 hours of admission and was a contaminant.

Respiratory cultures were performed on 80 patients in the first 24 hours of hospitalization, of which 16 reported any growth. Of those, 7 (5 staphylococcus aureus) were treated as true pathogens by the admitting teams. There were 12 patients with any growth on respiratory cultures between 24 and 72 hours, 8 of which were treated as true pathogens, for a total of 15 (2.8%, 95% CI = 1.6% to 4.5%) patients with any bacterial respiratory pathogen treated in the first 72 hours of admission. One patient had both a true positive blood culture and a true positive respiratory culture by our definitions, although the cultures were positive for different organisms.

Table 3 displays the initial vital sign, laboratory, and radiographic data stratified by the presence or absence of early bacteremia. Although patients with bacteremia tended to have higher heart rate, higher respiratory rate, and lower oxygen saturation, the only vital sign differences reaching statistical significance were systolic and diastolic blood pressures, which were both lower in patients with bacteremia. Patients with bacteremia had significantly higher white blood cell counts (13.5 vs 7.3), neutrophil counts (12.4 vs 5.7), and lactate (4.1 vs 1.6). C-reactive protein, and procalcitonin values were higher in patients with bacteremia, but these differences did not reach statistical significance.

Table 4 displays vital sign, laboratory, and radiology findings among the 20 patients with any true positive bacterial culture (blood or respiratory) compared to those without any true positive bacterial culture. Vital sign findings were similar to the comparisons in table

3, with lower blood pressure noted in patients with bacterial co-infection, but in the comparison including those with true positive respiratory cultures, co-infected patients were also had statistically significantly lower pulse oximetry readings. Lactate was no longer statistically significantly associated with true positive cultures when including blood and respiratory co-infections, but other laboratory associations were similar to those found in patients with bacteremia.

Mortality for the entire cohort was 14.4%. None of the 6 patients with bacteremia died, but 3 of the 6 were intubated (compared to 29.7% of those without bacteremia). Intensive care admission was 15.9% without, and 50% with bacteremia. None of the differences in clinical outcomes reached statistical significance. Outcomes are presented in Table 5.

DISCUSSION

We found a low rate of early bacteremia or bacterial respiratory co-infection among patients admitted to the hospital from the ED with confirmed COVID-19 infection. The small number of bacteremic patients precluded robust evaluation of associations, but our results suggest that older age, lower blood pressure, and certain laboratory abnormalities are associated with an increased risk of bacteremia. In addition to bacteremia, there were additional patients who were treated for positive respiratory cultures, although this number was also small. Combining all bacteremic patients and those with positive respiratory cultures within 72 hours of admission, 20/542 (3.7%; 95% CI = 2.3% to 5.6%) of all patients had a documented bacterial co-infection.

The initial treatment of patients with COVID-19 is complicated by several factors, including lack of proven therapies, delays in COVID-19 test results, and clinical

presentations that often have significant overlap with bacterial pneumonia or sepsis.⁴ One of the initial treatment decisions for patients admitted with presumed or confirmed COVID-19 is whether or not to cover with antibiotics for bacterial co-infection, or bacterial infection masquerading as COVID-19. Current guidelines reflect the uncertainty in the evidence. The SSC recommends antibiotics in mechanically ventilated patients, but rates this as a weak recommendation based on low quality of evidence.³ The National Institute for Health and Care Exchange (NICE) guidelines state: “If there is confidence that the clinical features are typical for COVID-19, it is reasonable not to start empirical antibiotics,” but generally recommend antibiotics for those with sepsis criteria or those in whom bacterial infection is suspected.¹⁶ Our findings imply that older patients, patients with comorbidities, and those with hypotension are likely higher risk for bacterial co-infection and these factors may reasonably lower a clinician’s threshold to initiate antibiotic therapy for patients admitted to the hospital from the ED with a COVID-like illness.

Additionally, the current study adds to previous work to determine the rate of bacterial co-infection in patients with COVID-19. Recent systematic reviews have found bacterial co-infection rates with COVID-19 of 6.9% and 7.0% overall.^{10,11} One review noted that the rate of co-infection at presentation was 3.5%, with the remainder attributed to hospital acquired infections.¹⁰ Our rate of 3.7% with evidence of bacteremia or pulmonary infection identified within 72 hours of admission further corroborates those previous findings, as well as those of another multicenter registry.¹⁷

While procalcitonin has shown promise in helping differentiate bacterial infections from other types of infection or illness,^{18,19} data related specifically to COVID-19 is sparse,²⁰

and our results did not support a clear association between elevated procalcitonin and bacterial co-infection. While we found some association between certain laboratory values and bacterial co-infection, we had too few cases of co-infection to make recommendations regarding how to interpret these laboratory values in patients with COVID-19.

LIMITATIONS

There are several important limitations to this study. First, only patients with PCR confirmed COVID-19 were included. The overall rate of bacteremia or bacterial infection may be different in “suspected COVID-19” patients than in those who have a confirmed diagnosis. Since PCR results may not be available early in the course of a patient admitted for suspected COVID-19, our results cannot suggest that it is safe to withhold antibiotics from a suspected COVID-19 patient until the PCR result is positive. Once the patient is confirmed to have COVID-19 however, our findings suggest that the rate of concurrent bacterial infection is likely quite low.

We prioritized bacteremia as our primary outcome because of the difficulty in defining a true positive respiratory culture. We found that an additional 2.6% of patients were treated for a bacterial pulmonary pathogen identified within the first 72 hours of admission. While these patients were treated with antibiotics at our institution, it is unclear whether these cultures represented true bacterial pathogens or incidental bacterial flora.

We found a very small number of bacteremic patients. The small number of true positives also limited our ability to find statistical associations between patient characteristics and bacteremia, and there were far too few cases to try to derive a decision instrument.

Although we set objective criteria for true positive cultures vs. contaminants, there is no universally accepted way to adjudicate such cases, and this process may lead to errors resulting in either over- or under-estimation of bacterial infections.

Seasonal variations in bacterial sepsis and influenza may also impact the applicability of these results to different times of the year. Lastly, although the data was taken from 14 different hospitals, they all operate in the same state under the same healthcare system, so our results may not be widely applicable to other healthcare systems or settings.

CONCLUSIONS

We found a low rate of bacteremia or bacterial pulmonary infection among patients admitted to the hospital with confirmed COVID-19 infection. Combined with other studies, our results suggest that physicians may consider treating hemodynamically stable patients with confirmed COVID-19 and without high clinical suspicion for bacterial co-infection without routine antibiotics.

The authors report no conflicts of interest related to this manuscript.

Author Contributions:

Conceptualization: TL, AZW, and BRH

Data Acquisition and Analysis: TL, AZW, AB, AC, NG, DBH, PIM, KDP, RAT, and BRH

Drafting of the Manuscript: TL, AZW, and BRH

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Statistical Analysis: TL

Supervision: BRH

Data Availability Statement:

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Table 1: Patient Demographics and Comorbidities

Mean Age (<i>sd</i> *)	62.8 (16.5)
Female – <i>no.</i> (%)	273 (50.4)
Tobacco Use – <i>no.</i> (%)	43 (8)
Obesity	211 (39.0)
Diabetes	218 (40.3)
Hyperlipidemia	281 (51.7)
Hypertension	368 (67.5)
COPD	68 (12.5)
Asthma	57 (10.4)
Organ Transplant	6 (1.1)
HIV	6 (1.1)

**sd* = standard deviation

Table 2: Characteristics of Patients with True Positive Blood Culture Results

Patient	Blood Culture Findings	Treatment Course	Disposition
1	Aerobic and anaerobic bottles growing Coagulase negative staphylococcus. Positive for Methicillin-resistance Staphylococcus epidermidis. Repeat blood culture- aerobic bottle grew coagulase negative staphylococcus.	Started on Meropenem and Vancomycin and narrowed to vancomycin after 2 days for a total of 5 days prior to discharge to home hospice.	Discharged on home hospice
2	Aerobic bottle growing Enterococcus faecalis and aerococcus species. Anaerobic bottle growing Globicatella. Repeat blood cultures negative.	Treated with IV Vancomycin for 10 days and Cefepime for 6 days.	Discharged home
3	Anaerobic bottle growing Enterococcus faecalis.	Treated with IV ceftriaxone and doxycycline for first 2 days. De-escalated to IV ampicillin for a 8 days.	Discharged home
4	Aerobic and anaerobic bottles growing Methicillin-resistant Staphylococcus epidermidis. Aerobic bottles growing Corynebacterium striatum. Repeat blood cultures (2/2) growing Staphylococcus epidermidis.	Received 8 days of vancomycin.	Discharged home
5	Aerobic bottle (2/2) growing Coagulase negative Staphylococcus (Staph pettenkoferi).	Received 7 days of vancomycin.	Discharged home
6	Aerobic bottle growing Acinetobacter radioresistense. Urine culture positive for Klebsiella and Escherichia coli.	Received 10 days of cefepime for both blood culture and urine culture results.	Discharged home

Table 3: Characteristics of Initial Presentation By Blood Culture Status

	Patients without True Positive Blood Cultures (n = 536)	Patients with True Positive Blood Cultures (n = 6)	P Value
	<i>Mean (sd*)</i>		
Days since symptom onset	7.1 (5.4)	4.3 (5.5)	0.21
Initial vital signs and laboratory values			
Temperature (Celsius)	37.6 (1.1)	37.9 (1.7)	0.39
Heart rate	97.9 (20.7)	111.5 (27.7)	0.11
Respiratory rate	22.6 (6.7)	26.8 (10.8)	0.13
Systolic blood pressure	135.0 (22.7)	104.2 (22.9)	0.001
Diastolic blood pressure	77.9 (17.2)	63.7 (8.4)	0.043
Pulse oximetry reading	91.8 (8.0)	86.2 (14.4)	0.09
White Blood Cell Count	7.3 (3.5)	13.5 (4.0)	< 0.001
Absolute Neutrophil Count	5.7 (3.2)	12.4 (6.2)	<0.001
Lactate	1.6 (1.3)	4.1 (1.9)	< 0.001
CRP	13.4 (18.9)	15.7 (8.6)	0.81

Procalcitonin	1.4 (9.8)	3.2 (5.3)	0.69
Radiology Results	<i>No. (%)</i>		NS**
No radiographic findings	61 (11.6)	1 (16.7)	
Single lobe involvement	55 (10.5)	1 (16.7)	
Multilobe involvement	387 (73.9)	4 (66.7)	
Positive CT without positive radiograph	21 (4.0)	0 (0)	

**sd* = Standard deviation

** Not statistically significant

Table 4: Characteristics of Initial Presentation By Blood or Respiratory Culture Status

	Patients without True Positive Blood or Respiratory Cultures (n = 522)	Patients with True Positive Blood or Respiratory Cultures (n = 20)	P Value
	<i>Mean (sd*)</i>		
Days since symptom onset	7 (5)	6 (7)	NS**
Initial vital signs and			

laboratory values			
Temperature (Celsius)	37.6 (1.0)	37.5 (1.8)	NS
Heart rate	98 (21)	104 (23)	NS
Respiratory rate	23 (7)	25 (11)	NS
Systolic blood pressure	135 (23)	124 (30)	0.042
Diastolic blood pressure	78 (17)	69 (17)	0.021
Pulse oximetry reading	92 (7)	79 (18)	0.0039
White Blood Cell Count	7.3 (3.4)	9.7 (4.7)	0.033
Absolute Neutrophil Count	5.6 (3.2)	8.5 (5.3)	0.027
Lactate	1.6 (1.3)	2.2 (1.9)	NS
CRP	13.1 (19.0)	21.1 (12.7)	NS
Procalcitonin	1.2 (9.1)	7.0 (18.4)	NS
Radiology Results	<i>No. (%)</i>		
No radiographic findings	61 (12)	1 (5)	NS

Single lobe involvement	55 (11)	1 (5)	
Multilobe involvement	373 (73)	18 (90)	
Positive CT without positive radiograph	21 (4)	0 (0)	

**sd* = Standard deviation

** Not statistically significant

Table 5: Comparison of Outcomes by Blood Culture Status

	Patients without True Positive Blood Cultures	Patients with True Positive Blood Cultures
	<i>No. (%)</i>	
Admitted to ICU	83 (15.9)	3 (50.0)
Started on dialysis prior to discharge	24 (4.5)	0 (0)
Intubated prior to discharge	159 (29.7)	3 (50.0)
Died before discharge	78 (14.6)	0 (0)

*All three intubations in the true positive group occurred within 24 hours.

** No findings were statistically significant by Fisher's exact test.