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Original Article

Increased rates of secondary bacterial infections, including *Enterococcus* bacteremia, in patients hospitalized with coronavirus disease 2019 (COVID-19)

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Abstract

Objective: We compared the rates of hospital-onset secondary bacterial infections in patients with coronavirus disease 2019 (COVID-19) with rates in patients with influenza and controls, and we investigated reports of increased incidence of *Enterococcus* infections in patients with COVID-19.

Design: Retrospective cohort study.

Setting: An academic quaternary-care hospital in San Francisco, California.

Patients: Patients admitted between October 1, 2019, and October 1, 2020, with a positive SARS-CoV-2 PCR (N = 314) or influenza PCR (N = 82) within 2 weeks of admission were compared with inpatients without positive SARS-CoV-2 or influenza tests during the study period (N = 14,332).

Methods: National Healthcare Safety Network definitions were used to identify infection-related ventilator-associated complications (IVACs), probable ventilator-associated pneumonia (PVAP), bloodstream infections (BSIs), and catheter-associated urinary tract infections (CAUTIs). A multiple logistic regression model was used to control for likely confounders.

Results: COVID-19 patients had significantly higher rates of IVAC and PVAP compared to controls, with adjusted odds ratios of 4.7 (95% confidence interval [CI], 1.7–13.9) and 10.4 (95% CI, 2.1–52.1), respectively. COVID-19 patients had higher incidence of BSI due to *Enterococcus* but not BSI generally, and whole-genome sequencing of *Enterococcus* isolates demonstrated that nosocomial transmission did not explain the increased rate. Subanalyses of patients admitted to the intensive care unit and patients who required mechanical ventilation revealed similar findings.

Conclusions: COVID-19 is associated with an increased risk of IVAC, PVAP, and *Enterococcus* BSI compared with hospitalized controls, which is not fully explained by factors such as immunosuppressive treatments and duration of mechanical ventilation. The mechanism underlying increased rates of *Enterococcus* BSI in COVID-19 patients requires further investigation.

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Secondary bacterial infections contribute to excess morbidity and mortality in patients with influenza and other viral lower respiratory tract infections.¹ At the time of hospital admission, bacterial coinfection in patients with coronavirus disease 2019 (COVID-19) is

uncommon, with most studies reporting rates of 3%–8%.^{2–7} In contrast, hospital-onset secondary bacterial infections in COVID-19 patients appear to be a more significant problem, with incidence estimates as high as 87% for ventilator-associated pneumonia (VAP).^{3,4,6,8,9} Given reported associations between secondary bacterial infections and adverse outcomes including increased mortality, further investigation of incidence in COVID-19 patients is needed.^{3,10}

Studies of secondary infections performed to date have used varying VAP definitions, making comparisons of rates, and interpretation of results, challenging. Studies of bloodstream infection

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Table 1A. Baseline Characteristics of Full Study Cohort

Variable	COVID-19 (n = 314)	Influenza (n = 82)	Control (n = 14,332)	P Value ^a
Age, mean y (SD)	57.9 (18.6)	58.6 (21.4)	55.8 (18.6)	.12
Male, no. (%)	176 (56.0)	39 (47.6)	6,479 (45.2)	<.01
Race, no. (%)				
White	100 (31.8)	33 (40.2)	7,760 (54.1)	<.01
Black	23 (7.3)	10 (12.2)	1,453 (10.1)	.21
Asian	57 (18.1)	24 (29.3)	2,587 (18.0)	.03
Other	127 (40.4)	16 (19.5)	2,752 (19.2)	<.01
Unknown	14 (4.5)	2 (2.4)	184 (1.3)	<.01
Ethnicity, no. (%)				
Hispanic/Latino	120 (38.2)	17 (20.7)	2,305 (16.1)	<.01
Immunocompromised, no (%)	100 (31.8)	30 (36.6)	5,129 (35.8)	.35
Immunosuppressive medications in hospital, no. (%)	144 (45.9)	37 (45.1)	5,963 (41.6)	.26
ANC<500, no. (%)	4 (1.3)	4 (4.9)	502 (3.5)	.08
ALC<500, no. (%)	71 (22.6)	36 (43.9)	2,466 (17.2)	<.01
LOS, mean d (SD)	13.6 (14.1)	8.4 (9.9)	6.9 (9.7)	<.01
ICU admission, no. (%)	126 (40.1)	26 (31.7)	2,702 (18.8)	<.01
Central-line days, mean d (SD)	6.8 (19.1)	5.3 (17.4)	2.7 (9.2)	.02
Vent days, mean d (SD)	3.7 (9.5)	2.0 (5.8)	0.3 (2.7)	<.01
Urinary catheter days, mean d (SD)	4.8 (11.0)	2.5 (6.2)	1.4 (4.1)	.37
Blood cultures, mean no. (SD)	3.4 (5.0)	3.1 (3.6)	1.0 (2.4)	<.01
Cultures per patient day, mean no. (SD)	0.3 (0.2)	0.4 (0.4)	0.1 (0.3)	<.01
Admit SOFA ⁷ score, mean (SD)	3.6 (2.9)	4.1 (3.1)	2.4 (2.3)	<.01

(BSI) in COVID-19 patients have reported incidences as high as 40%–68%,^{11,12} but few studies have included a control group, and those that did have variously reported that rates in COVID-19 patients are lower¹³ or higher¹⁴ than in controls, or the same as in influenza patients.⁵ Moreover, many have not adjusted for potential confounders including baseline immunosuppression, receipt of immunosuppressive treatments, and duration of mechanical ventilation, leaving uncertainty about the relative contribution of these factors to secondary infection risk in COVID-19 patients.

Several surveillance studies have reported elevated rates of *Enterococcus* BSI in COVID-19 patients, but it remains unclear why *Enterococcus* spp are often among the most frequent BSI pathogens identified.^{12,14–16} In the 2 prior reports to address this question, nosocomial transmission was either suspected¹¹ or proven.¹⁷ Therefore, whether risk of *Enterococcus* infection is truly elevated in COVID-19 or simply the result of regional infection control practices remains unclear. Furthermore, most secondary bacterial infection surveillance studies in COVID-19 patients have been performed outside of North America, where treatment protocols and antibiotic prescribing patterns may differ, resulting in unclear applicability to settings within the United States.

To address these gaps and advance understanding of hospital-onset secondary bacterial infection risk among patients with COVID-19, we used standardized US Centers for Disease Control and National Healthcare Safety Network (NHSN) definitions to evaluate the incidence of infection-related ventilator-associated complications (IVACs), possible ventilator-associated

pneumonia (PVAP), BSIs, BSIs with *Enterococcus*, and catheter-associated urinary tract infections (CAUTIs) in patients hospitalized for COVID-19, compared to patients with influenza or to a hospitalized control group.

Methods

We performed a retrospective cohort study of adults admitted to the University of California, San Francisco Medical Center (UCSF) between October 1, 2019, and October 1, 2020, by evaluating hospital electronic health records under institutional review board protocol 17-24056 (Table 1). COVID-19 and influenza diagnoses were identified based on SARS-CoV-2 or influenza virus RT-PCR positivity within 2 weeks before or after the day of hospital admission. Controls included patients who were admitted to UCSF Medical Center and who did not have a positive severe acute respiratory coronavirus virus 2 (SARS-CoV-2) or influenza test during the study period. Patients with length of stay <2 days were excluded. Notably, it became institutional practice to test all patients for COVID-19 upon admission in April 2020.

We extracted information on baseline patient characteristics, admissions, treatments, and outcomes directly from the electronic medical record. Sequential Organ Failure Assessment (SOFA) score,¹⁸ included as a measure of severity of illness, was defined as the maximum SOFA score within the first 24 hours of admission. Immunocompromising conditions were identified using a preselected list of ICD-10 codes (Supplementary Table S1 online), and immunosuppressive medications were defined as listed in

Table 1B. Baseline Characteristics of the ICU Cohort

Variable	COVID-19 (n = 126)	Influenza (n = 26)	Control (n = 2,702)	P Value ^a
Age, mean y (SD)	58.1 (17.9)	59.8 (18.8)	60.0 (16.4)	.22
Male, no. (%)	85 (67.5)	12 (46.1)	1,493 (55.3)	.02
Race, no. (%)				
White	30 (23.8)	10 (38.5)	1,528 (56.5)	<.01
Black	6 (4.8)	5 (19.2)	233 (8.6)	.05
Asian	26 (20.6)	7 (26.9)	455 (16.8)	.22
Other	59 (46.8)	3 (11.5)	505 (18.7)	<.01
Unknown	8 (6.4)	2 (7.7)	36 (1.33)	<.01
Ethnicity, no. (%)				
Hispanic/Latino	50 (39.7)	3 (11.5)	416 (15.4)	<.01
Immunocompromised, no. (%)	29 (23.0)	5 (19.2)	908 (33.6)	.02
Immunosuppressive medications in hospital, no. (%)	86 (68.2)	10 (38.5)	2,702 (55.1)	<.01
ANC<500, no. (%)	0 (0.0)	1 (3.8)	83 (3.1)	.13
ALC<500, no. (%)	45 (35.7)	12 (46.2)	617 (22.8)	<.01
LOS, mean d (SD)	22.1 (15.5)	14.7 (14.0)	12.2 (13.7)	<.01
Central-line days, mean d (SD)	13.6 (19.9)	14.8 (28.7)	7.3 (16.8)	<.01
Vent days, mean d (SD)	9.3 (13.2)	6.3 (9.1)	1.7 (6.0)	<.01
Foley days, mean d (SD)	10.8 (13.8)	7.9 (9.1)	4.1 (7.7)	<.01
Blood cultures, mean no. (SD)	6.4 (6.5)	5.7 (5.1)	2.2 (3.9)	<.01
Cultures per patient day, mean d (SD)	0.3 (0.2)	0.4 (0.3)	0.2 (0.3)	<.01
Admit SOFA score, mean (SD)	5.2 (3.4)	6.3 (3.6)	4.0 (3.4)	<.01

Note. ICU, intensive care unit; ANC<500, absolute neutrophil count <500 cells/ μ L at least once during encounter; ALC<500, absolute lymphocyte count <500 cells/ μ L at least once during encounter; LOS, length of stay; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

^aSignificant P values in bold.

Supplementary Table S2 (online). We evaluated the incidence of IVAC, PVAP (a subcategory of IVAC), and CAUTI using the NHSN definitions.¹⁹ We identified BSIs using the NHSN Bloodstream Event definitions,²⁰ and we included both primary and secondary BSIs. Multiple logistic regression was employed to analyze differences in IVAC, PVAP, BSI, and CAUTI between groups. We performed subgroup analyses in patients who were admitted to the intensive care unit (ICU) and in patients who required mechanical ventilation.

Covariates were chosen a priori based on known predisposing factors for bacterial infections, and included age, sex, race or ethnicity, admission SOFA score, underlying immunocompromising conditions, presence of neutropenia and/or lymphopenia, and receipt of immunosuppressive medications while hospitalized. Length of stay, duration of mechanical ventilation, central-line days, and (for CAUTI) urinary catheter days were also included. The number of blood cultures collected during admission was included as a covariate to account for possible differences in sampling frequency between groups. Days of therapy with IV antibiotics was included to account for a possible impact of differences in empiric antibiotic coverage at admission. Baseline differences between groups were evaluated using the χ^2 test for categorical variables or the Kruskal-Wallis test for continuous variables. Logistic regression modeling was performed with R software (R Foundation for Statistical Computing, Vienna, Austria).

Given that COVID-19 patients in our hospital were placed in cohorts on a small number of designated units, we further

investigated whether BSIs with *Enterococcus* spp had a common nosocomial source by performing whole-genome sequencing (WGS) of blood isolates. Illumina WGS was carried out on a MiSeq instrument following previously described methods.²¹ Raw sequences were adapter trimmed and quality controlled with fastp version 0.20.0 software and were analyzed using the SNP Pipeline for Infectious Disease (SPID) software.²² SPID aligned samples against reference genome *Enterococcus faecalis* strain OG1RF using minimap2, followed by Samtools to perform an mpileup.^{21,23} Julia code was then run to call a consensus allele at each position, and the SNP instances were computed between every pair of samples. Phylogenetic analysis was performed using Randomized Axelerated Maximum Likelihood (RAXML).²⁴ Phylogenetic trees were further visualized with ETE Python API.²⁵

Results

In total, 14,728 admissions, including 314 for COVID-19, 82 for influenza, and 14,332 control patient admissions, were evaluated. Given falling rates of influenza hospitalizations during the pandemic, the influenza admissions were concentrated from October 2019 through March 2020. Clinical and demographic characteristics are summarized in Table 1. World Health Organization (WHO) COVID-19 Ordinal Scale for Clinical Improvement scores²⁶ were available for 126 (40.1%) of the COVID-19 patients. The median score was 5 (range, 3–8), corresponding to need for noninvasive ventilation or high-flow oxygen.

Table 2. Rates of Infectious Outcomes in the Full Study Cohort and in the ICU Subgroup

Group	Total	IVAC, No. (%)	PVAP, No. (%)	BSI, No. (%)	<i>Enterococcus</i> BSI, No. (%)	CAUTI, No. (%)
Full cohort						
COVID-19	314	11 (3.5)	4 (1.3)	24 (7.6)	8 (2.6)	3 (1.0)
Influenza	82	3 (3.7)	1 (1.2)	3 (3.7)	0 (0.0)	0 (0.0)
Control	14,332	30 (0.2)	5 (<0.03)	430 (3.0)	48 (0.3)	43 (0.3)
ICU subgroup						
COVID	126	11 (8.7)	4 (3.2)	20 (15.9)	8 (6.4)	3 (2.4)
Flu	26	3 (11.5)	1 (3.8)	3 (11.5)	0 (0.0)	0 (0.0)
Control	2,702	30 (1.1)	5 (0.2)	160 (5.9)	18 (0.7)	25 (0.9)

Note. ICU, intensive care unit; IVAC, infection-related ventilator-associated complications; PVAP, probable ventilator-associated pneumonia; BSI, bloodstream infection; CAUTI, catheter-associated urinary tract infection.

Table 3. Adjusted Odds Ratios (95% CI) for Secondary Bacterial Infections in (3a) COVID-19 versus controls and in (3b) COVID-19 Versus Influenza**Table 3a.** COVID-19 Versus Controls

Independent Variable	IVAC, aOR (95% CI)	PVAP, aOR (95% CI)	BSI, aOR (95% CI)	<i>Enterococcus</i> BSI, aOR (95% CI)	CAUTI, aOR (95% CI) ^a
COVID-19	4.73 (1.70–13.86)^b	10.40 (2.08–52.09)	1.01 (0.56–1.81)	3.75 (1.49–9.41)	0.85 (0.18–3.94)
Age, per year	1.00 (0.98–1.02)	1.00 (0.96–1.05)	1.02 (1.01–1.03)	1.01 (0.99–1.03)	1.01 (0.99–1.03)
Sex, male	1.10 (0.51–2.36)	1.23 (0.27–5.62)	1.33 (1.07–1.67)	1.01 (0.56–1.81)	0.28 (0.14–0.59)
Race or ethnicity					
Black	1.50 (0.45–4.97)	2.25 (0.20–24.88)	0.96 (0.65–1.43)	1.44 (0.57–3.59)	1.57 (0.52–4.71)
Asian	1.53 (0.62–3.79)	1.81 (0.28–11.61)	0.86 (0.65–1.14)	0.73 (0.31–1.73)	1.31 (0.57–2.98)
Hispanic/Latino	0.66 (0.23–1.92)	1.30 (0.21–8.29)	0.87 (0.63–1.21)	1.23 (0.58–2.60)	1.52 (0.66–3.47)
Baseline IC	0.54 (0.23–1.92)	0.14 (0.01–1.42)	0.92 (0.73–1.17)	1.30 (0.71–2.41)	1.90 (0.98–3.69)
IS meds	1.27 (0.57–2.81)	1.36 (0.31–5.99)	0.65 (0.50–0.83)	0.65 (0.34–1.22)	3.45 (1.53–7.79)
ALC<500	1.26 (0.52–3.02)	1.97 (0.41–9.53)	2.01 (1.56–2.58)	1.61 (0.81–3.18)	0.90 (0.41–1.99)
LOS, per day	1.00 (0.98–1.04)	1.01 (0.95–1.07)	0.99 (0.97–1.00)	1.01 (0.99–1.03)	1.03 (1.01–1.04)
Central-line days, per day	0.98 (0.95–1.00)	0.98 (0.94–1.03)	0.97 (0.95–0.98)	0.95 (0.93–0.97)	0.97 (0.95–0.99)
Ventilator days, per day	1.09 (1.05–1.13)	1.04 (0.97–1.12)	0.91 (0.88–0.93)	0.98 (0.94–1.02)	1.01 (0.97–1.06)
No. of blood cultures	1.04 (0.96–1.12)	1.03 (0.87–1.22)	1.58 (1.51–1.66)	1.27 (1.18–1.37)	1.06 (0.98–1.16)
Antibiotic days, per day	1.03 (1.01–1.04)	1.01 (0.98–1.05)	1.02 (1.01–1.03)	1.02 (1.00–1.03)	1.00 (0.98–1.03)
SOFA	1.19 (1.08–1.32)	1.33 (1.11–1.60)	1.07 (1.03–1.11)	1.09 (1.00–1.20)	1.00 (0.90–1.11)

Note. CI, confidence interval; IVAC, infection-related ventilator-associated complications; PVAP, probable ventilator-associated pneumonia; BSI, bloodstream infection; CAUTI, catheter-associated urinary tract infection; IC, immunocompromised; IS meds, immunosuppressive medications; ALC<500, absolute lymphocyte count <500 cells/ μ L at least once during encounter; LOS, length of stay; SOFA, Sequential Organ Failure Assessment score.

^aUrinary catheter days were included as a covariate for the CAUTI outcome only; aOR, 1.06 (1.03–1.09).

^bCovariates significant in the model are in bold.

Rates of IVAC, PVAP, BSI, BSI with *Enterococcus* spp, and CAUTI are provided in Table 2. The median WHO ordinal scale in COVID-19 patients with secondary infection was 7, corresponding to need for mechanical ventilation and additional organ support, suggesting that secondary infections were associated with critical illness.

Compared with controls, the unadjusted odds ratios (OR) for COVID-19 patients were 17.3 (95% confidence interval [CI], 8.6–34.9) for IVAC, 37.0 (95% CI, 9.9–138.3.0) for PVAP, 2.7 (95% CI, 1.8–4.1) for BSI, 7.8 (95% CI, 3.6–16.6) for BSI with *Enterococcus*, and 4.4 (95% CI, 1.4–14.6) for CAUTI. Compared with influenza, unadjusted ORs for COVID-19 patients were 1.0 (95% CI, 0.3–3.5) for IVAC, 1.1 (95% CI, 0.1–9.5) for PVAP,

and 2.2 (95% CI, 0.6–7.4) for BSI. Odds ratios could not be calculated for *Enterococcus* BSI or CAUTI because there were no events in the influenza group.

Adjusted ORs based on logistic regression incorporating multiple covariates for COVID-19 patients versus controls (covariates listed in Table 1) remained significantly increased: 4.7 (95% CI, 1.7–13.2) for IVAC, 10.4 (95% CI, 2.1–52.1) for PVAP, and 3.8 (95% CI, 1.5–9.4) for *Enterococcus* BSI (Table 3A). The adjusted ORs were 1.0 (95% CI, 0.6–1.8) for BSI and 0.9 (95% CI, 0.2–3.9) for CAUTI. The adjusted ORs for COVID-19 compared with influenza were not significant for any infectious outcome (Table 3B).

The ICU subgroup analysis included 126 COVID-19 patients, 26 influenza patients, and 2,702 control patients; characteristics are

Table 3b. COVID-19 Versus Influenza

Independent Variable	IVAC,aOR (95% CI)	PVAP,aOR (95% CI)	BSI,aOR (95% CI)	<i>Enterococcus</i> BSI,aOR (95% CI) ^a	CAUTI,aOR (95% CI) ^a
COVID-19 positive	0.37 (0.05–2.65)	1.06 (0.07–16.64)	2.04 (0.41–10.04)
Age, per year	0.97 (0.91–1.03)	0.98 (0.91–1.05)	1.05 (1.01–1.09)^b
Male sex	4.59 (0.61–34.68)	4.16 (0.25–70.14)	1.24 (0.41–3.80)
Race or ethnicity					
Black	0.92 (0.16–5.35)
Asian	0.84 (0.06–10.93)	4.68 (0.16–139.55)	0.29 (0.06–1.42)
Hispanic/Latino	1.09 (0.17–7.13)	3.65 (0.24–56.35)	0.47 (0.12–1.85)
Baseline IC	1.11 (0.18–6.96)	0.80 (0.04–14.82)	0.61 (0.18–2.07)
IS meds	2.98 (0.48–18.69)	0.24 (0.02–2.58)	1.20 (0.38–3.75)
ALC<500	1.28 (0.19–8.77)	4.98 (0.32–79.58)	0.66 (0.19–2.25)
LOS, per day	0.97 (0.88–1.08)	0.94 (0.78–1.14)	1.02 (0.94–1.11)
Central-line days, per day	0.99 (0.93–1.05)	0.95 (0.86–1.05)	0.96 (0.92–1.00)
Ventilator days, per day	1.18 (1.06–1.32)	1.05 (0.88–1.24)	0.85 (0.78–0.94)
No. of blood cultures	0.87 (0.71–1.07)	1.14 (0.81–1.63)	1.55 (1.26–1.91)
Antibiotic days, per day	1.06 (0.99–1.13)	1.05 (0.94–1.17)	1.05 (0.99–1.11)
SOFA	1.05 (0.84–1.31)	1.34 (0.96–1.87)	1.19 (1.01–1.41)

Note. CI, confidence interval; IVAC, infection-related ventilator-associated complications; PVAP, probable ventilator-associated pneumonia; BSI, bloodstream infection; CAUTI, catheter-associated urinary tract infection; IC, immunocompromised; IS meds, immunosuppressive medications; ALC<500, absolute lymphocyte count <500 cells/ μ L at least once during encounter; LOS, length of stay; SOFA, Sequential Organ Failure Assessment score.

^aUnable to evaluate given no events in the influenza group.

^bCovariates significant in the model are in bold.

shown in Table 1B and outcomes are shown in Table 2. Logistic regression analysis revealed similar findings to those in the entire cohort (Table 4).

The analyses were repeated on the subgroup of patients who required mechanical ventilation, and findings were again similar (characteristics, outcome rates, and logistic regression analyses in Supplementary Tables S3–S5 online).

The 8 *Enterococcus* infections in the COVID-19 group comprised 6 vancomycin-susceptible *Enterococcus faecalis*, 1 vancomycin-susceptible *Enterococcus faecium*, and 1 vancomycin-resistant *Enterococcus faecium*. The patients had a mean age of 60.6 \pm 15.8, similar to the COVID-19 patients as a whole. Notable comorbidities included diabetes mellitus (50%) and history of renal transplant (25%). All 8 patients were in the ICU with central lines in place at the time of bacteremia: 1 patient was on extracorporeal membrane oxygenation. Also, 4 patients received immunosuppressive medications in the hospital, and 6 patients had received broad-spectrum antibiotics prior to BSI onset. In 2 patients, a central line was suspected as the source; in 1 of these patients, the source was a lower-extremity abscess; and in the other 5 cases, the source of bacteremia was unclear. *Enterococcus* BSIs occurred, on average, 13.1 days (SD, \pm 15.1) into the hospital stays. The WGS of *Enterococcus* isolates from the primary COVID-19 ICU revealed that isolates were genetically distinct, thus ruling out a nosocomial outbreak (Supplementary Fig. S1 online).

We further characterized the microbiology of the bloodstream infections in COVID-19 and control patients (Fig. 1). The 3 bloodstream infections in the influenza patients were *Staphylococcus aureus*, group A streptococcus, and viridans group *Streptococcus*. In the COVID-19 group, the 5 PVAPs included 5 distinct organisms: 2 methicillin-susceptible *Staphylococcus aureus* and 1 each

of methicillin-resistant *Staphylococcus aureus*, *Pseudomonas fluorescens*, *Haemophilus influenzae*, and *Burkholderia gladioli*.

Discussion

We report markedly increased rates of IVAC and PVAP in the setting of SARS-CoV-2 infection compared to controls, even after adjusting for potential confounders. Our findings are concordant with 3 recent reports of increased VAP in mechanically ventilated COVID-19 patients compared to controls.^{27–29} Rates of IVAC and PVAP did not differ significantly between COVID-19 and influenza admissions, emphasizing that although influenza patients have a higher rate of bacterial coinfection at the time of admission,² there may be a similarly high risk of secondary bacterial pulmonary infections in both diseases. In patients with influenza, animal models have suggested that increased susceptibility to bacterial infections is due in part to viral induction of type I interferon signaling resulting in suppressed antibacterial immune responses.³⁰ Whether SARS-CoV-2, which has also been demonstrated to cause significant immune dysregulation,³¹ leads to increased VAP via a similar mechanism will require further study.

The incidence of IVAC and PVAP that we report in our critically ill COVID-19 cohort, 8.7% and 3.2%, respectively, are markedly lower than the 38.5%–62% incidence previously reported in the literature.^{2,3,27,28,32,33} We suspect that this difference is related to the use of strict NHSN definitions rather than clinical pneumonia definitions, combined with our study setting in a center where resources, including both personnel and personal protective equipment, were readily available. However, another small study that also used NHSN surveillance definitions reported a PVAP rate of 54% in patients with COVID-19.³⁴ Given the significant overlap

Table 4. ICU Subgroup Analysis: Adjusted Odds Ratios (95% CI) for Secondary Bacterial Infections in COVID-19 Versus Controls (a) and in COVID-19 Versus Influenza (b).
Table 4a. COVID-19 Versus Controls (ICU subgroup)

Independent Variable	IVAC,aOR (95% CI)	PVAP,aOR (95% CI)	BSI,aOR (95% CI)	<i>Enterococcus</i> BSI,aOR (95% CI)	CAUTI,aOR (95% CI) ^a
COVID-19	4.27 (1.61–11.31)^b	8.04 (1.59–40.64)	1.22 (0.60–2.46)	7.91 (2.53–24.76)	0.48 (0.09–2.66)
Age, per year	1.00 (0.97–1.02)	1.00 (0.96–1.05)	1.02 (1.01–1.03)	1.01 (0.98–1.04)	1.01 (0.99–1.04)
Male sex	0.91 (0.43–1.90)	1.03 (0.23–4.56)	1.30 (0.90–1.89)	0.91 (0.36–2.29)	0.26 (0.10–0.66)
Race Black	1.83 (0.56–6.03)	2.61 (0.25–27.64)	1.18 (0.63–2.22)	1.63 (0.33–8.12)	1.37 (0.27–6.86)
Race Asian	1.72 (0.70–4.21)	1.75 (0.27–11.31)	0.88 (0.55–1.41)	0.45 (0.10–2.11)	0.74 (0.18–2.93)
Hispanic/Latino	0.92 (0.33–2.55)	1.55 (0.24–9.94)	0.96 (0.57–1.62)	1.28 (0.42–3.94)	3.53 (1.33–9.36)
Baseline IC	0.60 (0.25–1.42)	0.21 (0.02–1.95)	0.84 (0.56–1.24)	0.87 (0.31–2.44)	1.16 (0.48–2.78)
IS meds	0.81 (0.37–1.78)	0.97 (0.22–4.27)	0.66 (0.45–0.97)	0.44 (0.16–1.21)	4.09 (1.20–13.99)
ALC<500	1.11 (0.48–2.58)	1.79 (0.38–8.45)	1.89 (1.28–2.79)	1.82 (0.65–5.11)	0.82 (0.29–2.35)
LOS, per day	0.99 (0.95–1.03)	0.99 (0.92–1.08)	0.99 (0.98–1.01)	1.02 (1.00–1.05)	1.04 (1.01–1.06)
Central line days, per day	0.98 (0.96–1.01)	0.99 (0.94–1.04)	0.97 (0.95–0.99)	0.95 (0.92–0.98)	0.98 (0.95–1.00)
Ventilator days, per day	1.07 (1.04–1.11)	1.04 (0.96–1.12)	0.94 (0.91–0.97)	0.96 (0.91–1.01)	1.05 (1.00–1.10)
No. of blood cultures	1.01 (0.94–1.09)	1.02 (0.87–1.20)	1.41 (1.33–1.50)	1.20 (1.09–1.33)	1.00 (0.90–1.10)
Antibiotic-days, per day	1.04 (1.02–1.06)	1.01 (0.97–1.06)	1.02 (1.00–1.03)	1.03 (1.01–1.06)	0.98 (0.95–1.02)
SOFA	1.06 (0.96–1.17)	1.18 (0.98–1.43)	1.06 (1.01–1.11)	1.11 (0.98–1.26)	0.99 (0.87–1.12)

Note. ICU, intensive care unit; CI, confidence interval; IVAC, infection-related ventilator-associated complications; PVAP, probable ventilator-associated pneumonia; BSI, bloodstream infection; CAUTI, catheter-associated urinary tract infection; IC, immunocompromised; IS meds, immunosuppressive medications; ALC<500, absolute lymphocyte count <500 cells/ μ L at least once during encounter; LOS, length of stay; SOFA, Sequential Organ Failure Assessment score.

^aUrinary catheter days were included as a covariate for the CAUTI outcome only; aOR, 1.05 (1.01–1.08).

^bCovariates significant in the model are in bold.

Table 4b. COVID-19 Versus Influenza (ICU Subgroup)

Independent Variable	IVAC,aOR (95% CI)	PVAP,aOR (95% CI)	BSI,aOR (95% CI)	<i>Enterococcus</i> BSI,aOR (95% CI) ^a	CAUTI,aOR (95% CI) ^a
COVID-19	0.25 (0.03–2.19)	0.67 (0.03–17.27)	0.74 (0.13–4.15)
Age, per year	0.97 (0.91–1.03)	0.98 (0.91–1.06)	1.06 (1.01–1.10)^b
Sex, male	5.43 (0.66–44.62)	5.42 (0.21–139.57)	1.89 (0.51–6.99)
Race or ethnicity					
Asian	1.00 (0.08–12.93)	4.42 (0.14–140.28)	0.27 (0.05–1.41)
Hispanic/Latino	1.42 (0.22–9.33)	7.30 (0.31–174.41)	0.60 (0.14–2.62)
Baseline IC	1.60 (0.21–12.05)	1.02 (0.04–29.04)	0.36 (0.08–1.71)
IS meds	2.60 (0.37–18.17)	0.17 (0.01–2.08)	1.03 (0.29–3.64)
ALC<500	0.99 (0.12–8.17)	5.68 (0.24–137.05)	1.12 (0.30–4.12)
LOS, per day	0.96 (0.87–1.08)	0.94 (0.77–1.14)	1.02 (0.93–1.11)
Central-line days, per day	1.00 (0.94–1.06)	0.96 (0.86–1.07)	0.97 (0.92–1.02)
Ventilator days, per day	1.17 (1.05–1.31)	1.06 (0.89–1.26)	0.89 (0.81–0.98)
No. of blood cultures	0.87 (0.71–1.05)	1.09 (0.78–1.51)	1.40 (1.16–1.70)
Antibiotic days, per day	1.05 (0.98–1.11)	1.03 (0.93–1.14)	1.04 (0.98–1.10)
SOFA	1.00 (0.79–1.26)	1.19 (0.83–1.70)	1.12 (0.94–1.34)

Note. ICU, intensive care unit; CI, confidence interval; IVAC, infection-related ventilator-associated complications; PVAP, probable ventilator-associated pneumonia; BSI, bloodstream infection; CAUTI, catheter-associated urinary tract infection; IC, immunocompromised; IS meds, immunosuppressive medications; ALC<500, absolute lymphocyte count <500 cells/ μ L at least once during encounter; LOS, length of stay; SOFA, Sequential Organ Failure Assessment score.

^aUnable to evaluate given no events in the influenza group.

^bCovariates significant in the model are in bold.

between the clinical presentations of severe COVID-19 pneumonia and bacterial VAP, further investigation into the true rates of VAP in these patients is needed.

The BSI rates in our COVID-19 cohort were 7.6% overall and 15.9% in the ICU subgroup, with no significant difference in the multi-variable model compared to either controls or influenza patients.

These results are in line with published reports of BSI rates in COVID-19 patients, which have ranged from 3% to 68%^{3,5,11–16} depending on the cohort studied. We also found no difference between groups in rates of CAUTI, concordant with other published data.³⁵

Enterococcus BSI was markedly higher in COVID-19 patients compared to controls and was the most common organism in these

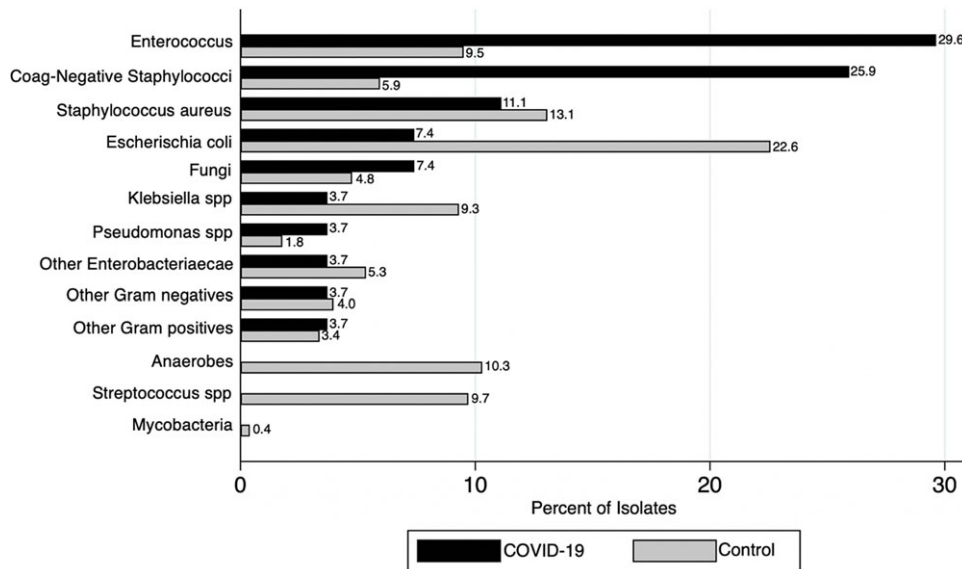


Fig. 1. Organisms isolated from blood culture in patients with COVID-19 patients versus controls.

patients, a finding in line with 2 prior studies that reported *Enterococcus* to be the most frequently identified BSI organism isolated from COVID-19 patients.^{15,16} A third report also identified higher-than-expected incidence of *Enterococcus* BSI in COVID-19 patients compared to controls, although in that study the patients had an epidemiologic link and the possibility that the increased incidence was due to a nosocomial outbreak could not be excluded.¹¹ We, in contrast, found that *Enterococcal* BSI events had no clear epidemiologic association, and further WGS analysis demonstrated genetically distinct isolates, ruling out a common nosocomial source. Whether our finding is the result of SARS-CoV-2 enterocyte tropism³⁶ or systemic inflammatory responses leading to gut translocation, or the result of other factors, needs further investigation.

Our study has several limitations. The study groups had baseline differences in severity of illness, duration of mechanical ventilation, and other factors. Although we attempted to control for these by including them as covariates in the regression analysis, there may have been unmeasured differences between the groups that remained unaccounted for, and this may have affected the magnitude of the effects we observed. Additionally, we used NHSN surveillance definitions for IVAC, PVAP, BSI, and CAUTI, which may have missed some clinician-suspected infections. However, given that these definitions are the standard used across the United States, they enable a consistent comparison across health-care centers; furthermore, many studies have highlighted the low reliability of provider-based VAP diagnoses.^{37–39} The influenza and COVID-19 cohorts were hospitalized during different periods, a necessity given the low rates of influenza virus infection during the COVID-19 pandemic. Finally, this was a single-center study, conducted in a setting where personal protective equipment was sufficient and hospital infection prevention practices closely enforced, and findings may not be generalizable to other settings.

In summary, we report that COVID-19, similar to influenza virus infection, confers a significantly increased risk of hospital-onset secondary bacterial infections, a finding with important implications for infection prevention and clinical management during the ongoing COVID-19 pandemic.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/ice.2021.391>

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