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Predictors and outcomes of healthcare-associated infections in COVID-19 patients

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ABSTRACT

Introduction: Healthcare-associated infections (HAI) after viral illnesses are important sources of morbidity and mortality. This has not been extensively studied in hospitalized COVID-19 patients.
Methods: This study included all COVID-19-positive adult patients (≥18 years) hospitalized between 01 March and 05 August 2020 at the current institution. The Centers for Disease Control and Prevention definition of HAI in the acute care setting was used. The outcomes that were studied were rates and types of infections and in-hospital mortality. Several multivariable logistic regression models were constructed to examine characteristics associated with development of HAI.
Results: Fifty-nine (3.7%) of 1565 patients developed 140 separate HAIs from 73 different organisms: 23 were Gram-positive, 39 were Gram-negative and 11 were fungal. Patients who developed HAI did not have higher odds of death (OR 0.85, 95% CI 0.40–1.81, $p = 0.69$). HAIs were associated with the use of tocilizumab (OR 5.04, 95% CI 2.4–10.6, $p < 0.001$), steroids (OR 3.8, 95% CI 1.4–10, $p = 0.007$), hydroxychloroquine (OR 3.0, 95% CI 1.0–8.8, $p = 0.05$), and acute kidney injury requiring hemodialysis (OR 3.7, 95% CI 1.1–12.8, $p = 0.04$).
Conclusions: HAI were common in hospitalized Covid-19 patients. Tocilizumab and steroids were associated with increased risk of HAIs.

Introduction

Secondary infections after viral illnesses occur frequently and may lead to adverse outcomes. In previous influenza epidemics, for example, many deaths were the direct result of secondary bacterial pneumonia (Morens et al., 2008). Although seemingly common, these infections remain poorly characterized. In a few small studies during the 2009 H1N1 pandemic (Dhanoa et al., 2011), approximately 19% of cases were reported to have secondary bacterial infections, of which *Streptococcus pneumoniae* was the most common isolate (MacIntyre et al., 2018). Reports describing the epidemiology of secondary infections associated with COVID-19 pneumonia are limited and have small sample sizes. Zhou et al. reported a 50% rate of secondary infection in people who died compared with 1% in survivors (Zhou et al., 2020). Chen et al. reported 4% rates of fungal infection (Chen et al., 2020).

Although management strategies for COVID-19 have evolved through the pandemic, use of therapies with immune-modulating properties such as IL-6 receptor antagonists and corticosteroids is common (Geleris et al., 2020, Jordan et al., 2020, Morena et al., 2020, Selvaraj et al., 2020, Valk et al., 2020). These medications are used in attempts to quell the hyperactive host immune response that appears to play a key role in clinical deterioration (Wiersinga et al., 2020). Many patients are also likely to be exposed to antibiotics secondary to ongoing fever, which may not necessarily

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represent superimposed infections. Further, in patients who are critically ill, central venous and urinary catheter use is common (O'Grady et al., 2011). These factors combined likely raise susceptibility to the acquisition of secondary infections in COVID-19.

This study aimed to describe the epidemiology of secondary infections after hospitalization for COVID-19. Since these are acquired while patients are hospitalized, the Centers for Disease Control and Prevention (CDC) surveillance definition of healthcare-associated infection (HAI) was used to study these infections (Horan et al., 2008). As an exploratory aim it also attempted to discern risk factors for acquiring such infections.

Methods

Study design and data source

A retrospective analysis was performed of adult COVID-19 patients (age ≥18 years) admitted to a large community hospital in a rural setting in Northeast Georgia between 01 March and 10 June 2020. COVID-19 patients were identified from the Epic® electronic medical record system using International classification of disease 10th Clinical Modification (ICD10CM) and/or Current Procedural Terminology (CPT) codes for COVID-19 and/or positive for SARS CoV-2- PCR. Clinical and demographical details were obtained from Epic® Caboodle data warehouse and Cerner APACHE® outcomes. Systems integration was provided by IPC Global by leveraging their in-Process Data Factory innovation running on Amazon Web Services® VPC. COVID-19 patients who required readmission to the hospital after initial discharge were excluded. The study was reviewed and found exempt by Northeast Georgia Health System IRB board.

General management of COVID-19 patients

Patients were admitted to the Intensive Care Unit (ICU) if their fraction of inspired oxygen (FiO2) requirement was >50% (>10 L/min on nasal cannula or >50% on high-flow oxygen). All patients received therapeutic anticoagulation if they had D-dimer >2 and a sepsis-induced coagulopathy (SIC) score >3 (Ding et al., 2018). Initially, all admitted patients received hydroxychloroquine until data regarding efficacy were released; thereafter, patients did not receive this medication (Shah et al., 2020, Tang et al., 2020). Tocilizumab was administered if patients met laboratory parameters supportive of cytokine storm, which included three or more of the following: 1) ferritin >300 ng/mL with doubling within 24 h; 2) ferritin >600 ng/mL; 3) lactate dehydrogenase (LDH) >250 U/L; 4) elevated D-dimer (> 2 mcg/mL FEU); 5) high-sensitivity C-reactive protein (CRP) >7 mg/L; or 6) HScore >110. Convalescent plasma was used if patients had dyspnea, RR ≥ 30, PF ratio ≤300 or had the treating clinician adjudicated life-threatening disease. Standard Center for Medicare and Medicaid Services (CMS) guideline-based management was provided for prevention of ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CAUTI) and central line-associated blood stream infection (CLABSI).

Definitions

Culture data were reviewed to ascertain the presence of infection. Infections were classified as respiratory (tracheal aspirate, bronchoalveolar lavage), blood, urine, and other (body fluids such as pleural cavity, abdominal cavity). The CDC definition of HAIs in the acute care setting was used (Horan et al., 2008). It was deemed that an HAI was present if cultures were positive and obtained after 3 days of hospital admission. Days to positive cultures was defined as time from day of admission to the day the culture was collected. Since cultures can be negative, 'possible infection' was defined if the patient developed a fever >100.4 OF after the third day of admission and there were blood cultures drawn and antibiotics started within 24 h of this fever. Also included within this definition was if the white cell blood count (WBC) count rose to >15,000 after the third day of admission and there were blood cultures drawn and antibiotics started within 24 h of this elevation in WBC. Possible infection was not included in HAI.

Outcomes

The primary outcome of interest was rate of HAIs. Secondary outcomes included in-hospital mortality.

Table 1
Healthcare-associated infections: organisms and source and time to infection.

	Number of patients	Source				Median time to infection
		Blood	Respiratory	Urine	others	
Gram-positive infections						
MRSA	7	5	7	0	1	14
MSSA	6	5	6	1	0	13
Staphylococcus hominis	1	1	1	0	0	14
Staphylococcus epidermidis	4	4	4	0	0	15
Group D *Streptococcus*	5	5	4	1	0	12.5
Gram-negative infections						
Escherichia coli	7	5	4	4	0	19
Klebsiella	7	2	7	1	0	21
Pseudomonas	10	7	10	3	1	15.5
Serratia	3	2	3	1	0	28
Enterobacter	6	3	6	1	0	19.5
Proteus	2	2	2	1	0	21.5
Citrobacter	1	0	1	0	0	24
Acinetobacter	2	0	2	0	0	26
Stenotrophomonas	1	1	1	0	0	8
Fungal infections						
Candida albicans	6	6	5	2	1	13
Non-*Candida albicans*	5	5	4	2	0	15
Clostridium difficile	14					

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

Statistics

All statistical analysis was preformed using STATA MC 16.0 (Stata-Corp, College Station, Tx). Categorical data were described using frequency count and percentages. Medians and interquartile ranges were used for continuous variables as they were not normally distributed. Demographic and clinical characteristics of patients who had HAIs were compared with those who did not using Chi-square and Wilcoxon rank tests for categorical and continuous variables, respectively. Statistical significance of $p < 0.05$ was set for all analyses. Multivariable logistic regression models were used to determine factors associated with the development of HAIs in COVID-19. A single predictor logistic regression was used to identify significant associations between putative risk factors and development of secondary infections. Variables found significant at $p < 0.10$ were candidates for inclusion in the primary model. Regardless of significance, variables known to be associated with outcomes in COVID-19 and those previously identified as risk factors for developing secondary infections were included. The backward elimination method was used to remove other variables from the final model. The final model was bootstrapped using 2000 bootstrap replicates and case resampling with replacement from the original dataset.

Multivariable logistic regression analysis was used to examine the association of HAIs with in-hospital mortality. Since patients who developed HAIs were sicker and had higher inflammatory markers, propensity scores were used to adjust for these differences. A propensity score was used to identify the probability that a patient would develop an HAI; this was calculated for every patient. The propensity score was computed using multivariable logistic regression model, with HAIs as the dependent variable and incorporating multiple independent variables, which included demographic and clinical characteristics along with laboratory markers. Therefore, the propensity score that was obtained was used as a continuous variable to further adjust the above regression.

Results

There were 1565 patients with COVID-19 within the study period. Of these, 140 separate HAIs from 73 different organisms developed in 59 (3.7%) patients. Of 140 HAIs, 53 were bacteremia, 67 were pneumonia and 17 were UTI. Thirty-eight patients had bacteremia from a single organism and 15 patients had bacteremia from more than one organism. Seventy-three separate organisms constituted 140 HAIs; of these, 23 (31.5%) were Gram-positive

Table 2
Demographic and clinical characteristics of COVID-19 patients with and without healthcare-associated infection (HAI).

Total	No HAI 1514	HAI 59	*p*
Age	62 (48–75)	61 (52–69)	0.45
Male (%)	51.1	64.7	0.06
Race (%)			0.009
White	60.8	45.1	
Black	9.4	17.7	
Hispanic	26.0	25.5	
Asians/Pacific Islander	1	3.9	
Others	3.0	7.8	
Comorbidities (%)			
Hypertension	63.2	70.6	0.28
Congestive heart failure	23.3	27.5	0.48
Diabetes mellitus	38.6	56.8	0.009
COPD	29.7	21.6	0.3
ESRD	3.4	7.8	0.09
Cirrhosis	9.9	5.9	0.34
Cancer	11.5	9.8	0.69
Rheumatological diseases	3.3	3.9	0.80
Home medications (%)			
Anticoagulation	10.4	7.8	0.55
Anti-platelets	17.4	11.7	0.30
ACE/ARB	25.8	35.3	0.13
Immunosuppressants	0.07	0.00	0.82
COVID-19 medications (%)			
Vitamin C	70.1	90.2	0.002
Zinc	69.7	88.2	0.004
Hydroxychloroquine	13.6	27.4	0.005
Tocilizumab	11.6	66.7	< 0.001
Steroids	40.2	78.4	< 0.001
Convalescent plasma	14.1	50.9	< 0.001
Remedesivir	28.2	50.9	< 0.001
Therapeutic anticoagulation	73.3	96.1	< 0.001
Antibiotics started at time of admission (%)			
Azithromycin	48.8	64.7	0.025
Doxycycline	8.1	11.7	0.34
Levofloxacin/ciprofloxacin	6.1	3.9	0.52
Clindamycin	1.1	1.9	0.58
Ceftriaxone	55.0	62.7	0.27
Cefepime	11.7	23.5	0.01
Piperacillin/tazobactam	11.5	13.7	0.63
Vancomycin	22.2	43.1	0.001

Abbreviations: COPDchronic obstructive pulmonary disease; ESRDend-stage renal disease; ACE/ARBangiotensin-converting enzyme/angiotensin receptor blocker.

infections, 39 (53.4%) were Gram-negative and 11 (15%) were fungal infections. Among the Gram-negatives, *Pseudomonas* (n = 10), *Escherichia coli* (n = 7) and *Klebsiella* (n = 7) were the most common bacterial organisms. *Staphylococcus aureus* (n = 13) and *Enterococcus* (n = 5) were the most common bacterial organisms in the Gram-positives. Five of 11 *Candida* infections were non-albicans species. Table 1 provides details of organisms, sources and median time to development of HAI. Fourteen patients developed *Clostridium difficile* infections. There were 118 instances that qualified as possible infections; of these, 48 (40.7%) qualified as culture-positive secondary infections.

Demographics and clinical characteristics

Men and black race had higher rates of HAIs. Rates of HAIs were higher in comorbidities such as diabetes mellitus and end-stage renal disease (Table 2). HAIs were observed to be higher in patients receiving treatment for COVID-19 such as hydroxychloroquine (27.4% vs 13.6%, $p < 0.001$), convalescent plasma (50.9% vs 14.1%, $p < 0.001$), tocilizumab (66.7% vs 11.6%, $p < 0.001$), and steroids (78.4% vs 40.2%, $p < 0.001$). Patients who received cefepime and vancomycin on admission developed higher rates of secondary infection.

Sicker patients on admission with higher Sequential Organ Failure Assessment (SOFA) scores and higher inflammatory markers (such as ferritin, CRP and D-dimer) developed higher rates of secondary infection (Table 3). Patients who developed secondary infections were more often on mechanical ventilation (42.4% vs 10.0%, $p < 0.001$) and had central venous lines (45.8% vs 8.1%, $p < 0.001$).

Multivariable analysis of HAIs

HAIs were associated with the use of tocilizumab (OR 5.04, 95% CI 2.4–10.6, $p < 0.001$), steroids (OR 3.8, 95% CI 1.4–10, $p = 0.007$), hydroxychloroquine (OR 3.0, 95% CI 1.0–8.8, $p = 0.05$) and acute kidney injury requiring hemodialysis (OR 3.7, 95% CI 1.1–12.8, $p = 0.04$). Other medications, convalescent plasma and remdesivir were not associated with increased rates of HAIs (Table 4).

Outcomes

Patients developing secondary infection had significantly higher in-hospital mortality when compared with those who did not develop secondary infection (40.7% vs 11.8%, $p < 0.001$) (Table 5). However, secondary infections were not associated with increased risk of death on multivariable analysis (OR 0.85, 95% CI 0.40–1.80, $p = 0.67$) (Appendix 1). The length of hospital stay was significantly longer in patients who developed secondary infections. Disposition in patients with secondary infections was significantly higher in skilled nursing facilities and long-term acute care (SNF/LTAC) when compared with those who did not have secondary infections (35.3% vs 13.6%, $p < 0.001$).

Table 3
Clinical features and inflammatory markers in COVID-19 patients: comparison of patients with healthcare-associated infection (HAI) and those without.

	No HAI	HAI	*p*
Total	1506	59	
SOFA score on admission[a]	0 (0–1), 1506	1 (0–2), 59	0.001
Initial laboratory studies[a]			
WBC	8.1 (5.9–11.4), 1501	10.3 (7.3–14.2), 58	0.004
Lymphocyte count	1.06 (0.73–1.51), 1431	0.85 (0.63–1.26), 59	0.048
Hemoglobin	13 (11.5–14.4), 1501	13.8 (12.7–15), 58	0.012
Platelets	212 (164–275), 1499	228 (161–317), 58	0.35
Troponin	0.02 (0.02–0.02), 1234	0.02 (0.02–0.05), 54	0.21
Lactate	1.1 (0.8–1.5), 846	1.5 (1.1–2.1), 56	0.001
BUN	16 (11–25), 1446	20 (14–33), 58	0.008
Creatinine	1.02 (0.82–1.35), 1447	1.24 (0.96–1.59), 58	0.001
ALT	32 (22–54), 1436	42 (28–67), 57	0.03
Bilirubin	0.5 (0.4–0.7), 1405	0.6 (0.4–0.9), 57	0.046
INR	1.15 (1.07–1.27), 1275	1.15 (1.09–1.35), 59	0.38
aPTT	29.7 (27.1–32.8), 897	28.3 (26.2–31.4), 52	0.24
Ferritin	373 (158–805), 1083	743 (442–1450), 57	0.001
CRP	7.4 (2.9–12.8), 1101	12 (8.9–21.2), 58	0.001
D-dimer	0.79 (0.48–1.45), 1066	0.92 (0.60–2.02), 56	0.001
ICU admissions	422 (28.0%)	58 (98.3%)	0.001
SOFA score on ICU admission[a]	1 (0–3), 400	1 (0–3), 52	0.75
Use of mechanical ventilation (%)	191 (12.7%)	56 (94.9%)	< 0.001
Mechanical ventilation before HAI	150 (10.0%)	25 (42.4%)	< 0.001
Length of mechanical ventilation (days)[a]	6 (1–12), 188	18 (12–29), 55	< 0.001
Required proning if on ventilator (%)	14.6	30.4	0.007
Required paralytic if on ventilator (%)	23.5	51.8	0.001
Required inhaled vasodilators if on ventilator (%)	6.3	17.8	0.007
Required tracheostomy if on ventilator (%)	6.8	25.0	0.001
Use of vasopressors			
Required norepinephrine (%)	11.9	83.0	< 0.001
Required vasopressin (%)	5.5	52.5	< 0.001
Required epinephrine (%)	2.1	13.7	< 0.001
Required angiotensin 2(%)	0.5	1.7	0.24
CVL before HAI (%)	8.1	45.8	< 0.001
Acute renal failure requiring hemodialysis (%)	1.5	22.0	< 0.001
Acute DVT/PE (%)	4.2	22.0	< 0.001

Abbreviations: CVL, central venous line; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell count; BUN, blood urea nitrogen; ALT, alanine aminotransferase; INR, international normalized ratio: CRP, C-reactive protein; DVT/PE, deep venous thrombosis/pulmonary embolism.
[a] median (interquartile range), number of samples.

Table 4
Factors associated with development of healthcare-associated infections.

	Odds ratio	95% CI	*p*
Age	0.99	0.96–1.01	0.58
Male gender	0.76	0.37–1.53	0.45
DM	1.29	0.62–2.69	0.48
ESRD	1.05	0.24–4.55	0.94
COPD	0.82	0.38–1.77	0.62
Cancer	1.36	0.37–4.98	0.63
Hydroxychloroquine*	2.96	1.00–8.86	0.05
Steroids*	3.79	1.44–10.01	0.007
Tocilizumab*	5.04	2.39–10.65	< 0.001
Convalescent plasma	1.86	0.88–3.92	0.10
Central venous catheter	2.47	0.87–6.97	0.088
Mechanical ventilation	1.11	0.34–3.54	0.86
AKI requiring hemodialysis*	3.67	1.05–12.80	0.04
Antibiotics on admission	1.02	0.31–3.32	0.96
SOFA score >2 on admission	1.21	0.52–2.76	0.65

Abbreviations: DM, diabetes mellitus; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; AKI, acute kidney injury; SOFA, Sequential Organ Failure Assessment.

Discussion

The COVID-19 pandemic has seen the use of immunomodulating medications to help prevent dysregulated immune responses, also called cytokine storm (Wiersinga et al., 2020). This study reports experience of all COVID-19 patients who were admitted to the current hospital until 05 August 2020. There were more than 1500 patients, of which 250 required intubation for severe COVID-19. The number of patients who developed HAIs was observed to be about 3.7%.

Multiple host and environmental factors determine the development of HAI in any hospitalized patient. Secondary infections in post-viral infection emanate from increased immune susceptibility, increasing the risk of co-infections and HAIs (Hendaus et al., 2015, Smith and McCullers, 2014). In patients with the influenza virus there is increased susceptibility to bacterial adhesion by bacteria such as *Streptococcus* and *Pseudomonas* (Pittet et al., 2010). Antibiotics used for bacterial infections can result in changes in normal flora of the host (Haak and Wiersinga, 2017). Patients with prolonged hospital stays are also at risk of nosocomial infections.

However, modifiable factors such as protocols for mitigation of infection, staff education and practices and hospital policies for lines and catheters also play a role. Before the COVID-19 pandemic, various CMS measures were in place at the current hospital to prevent VAP, CLABSI and CAUTI. With immense surges of COVID-19, various systems in place have been under stress and unable to be utilized at their normal capacity. At the current center, the number of COVID-19 patients in the ICU in the peak times ranged from 30–45. The hospital system supported the COVID-19 crisis with an additional 50 beds during the surge in capacity. Both doctors and nursing capacity were increased to cope with the increase in patient volumes. Due to this extra support, CMS core measures were still performed to a reasonable extent. For this reason, the rates of HAI may be difficult to compare to other hospital systems.

Similar to previous studies on HAIs, central venous line use was associated with higher rates of both bacterial and fungal infections (Muskett et al., 2011, Zhao et al., 2016). Using antibiotics was associated with risk of fungal infections: all 11 patients who developed fungal infections received antibiotics on admission. Since most of the COVID-19 patients presented with fever, cough and chest X-ray findings of pneumonia, many received empiric antibiotics for community-acquired pneumonia. However, patients receiving cefepime and vancomycin on admission had higher rates of HAIs.

Tocilizumab has regularly been used in COVID-19, due to concerns about cytokine storm from the deregulated IL6 pathway being the underlying problem causing severe disease (Morena et al., 2020). This drug has been used for MAS-HLH-induced cytokine storm in diseases like rheumatoid arthritis (Grom et al., 2016). Its use in the ICU has not been studied and is likely not risk-free as it blocks IL6R, which is an important regulator of the immune system. Tocilizumab was studied in 16,074 rheumatoid arthritis patients and was associated with increased risks bacterial infections: diverticulitis, pneumonia and bacteremia (Pawar et al., 2019). Tocilizumab was given to 210 patients with severe COVID-19 at the current center, of which 42 (20%) developed HAI. It was observed that tocilizumab was associated with increased risk of HAIs. In COVID-19 patients receiving tocilizumab, HAI has been reported to be around 27–32% (Morena et al., 2020, Rossotti et al., 2020).

In the initial phase of the pandemic, hydroxychloroquine was also extensively used at the current center and 220 patients received this medication. Hydroxychloroquine destabilizes lysosomal membranes and promotes the release of lysosomal enzymes inside cells, which can inhibit the function of lymphocytes and thus has immunomodulatory and anti-inflammatory effects (Schrezenmeier and Dorner, 2020). An association with HAIs was found, although the lower limit of confidence interval was one.

Although this study focused on culture-positive organisms, there were significant numbers of patients who may have had HAI but were culture-negative. Both timing of culture and use of antibiotics can affect the positivity of culture rates, with up to 50% of infections in ICU being culture-negative (Gupta et al., 2016). To study these patients, any fever/leukocytosis along with blood cultures and initiation of empiric antibiotics was defined as possible infection. Only 40% culture-positive rates were observed when a patient qualified as 'possible infection'.

Although this study reported experience with >1500 COVID-19 patients, it had certain limitations. It was a single-center study and it would be difficult to extrapolate the results to other centers, which may have different support systems, protocols for prevention of infections and use of COVID-19 medications. The

Table 5
Outcomes of patients with healthcare-associated infections (HAI).

Total	No HAI	HAI	*p*
Died (%)	11.8	40.7	< 0.001
Length of hospital stay in survivors, median (IQR)	5 (3–9)	32 (26–41)	< 0.001
Time to death, median (IQR)	8 (3–15)	25.5 (20.5–30.5)	< 0.001
Disposition (%)			< 0.001
Home	70.8	26.5	
Home with health care	12.9	17.6	
Rehab/SNF/LTAC/acute care	13.6	35.3	
Others	2.6	20.6	

Abbreviations: SNF/LTAC, skilled nursing facility/long-term acute care.

retrospective nature of the study prevented any causative risk factors to be found. There may be other unknow underlying factors that would affect development of HAI in COVID-19 patients. Lastly, there were missing values with respect to the inflammatory markers; they were therefore unable to be used in the regression models, which may have improved the model for this disease. Despite these limitations, this study provided insight into rates of HAIs in this group of patients and assessed risk factors. Cautious use of hydroxychloroquine and tocilizumab is advised, as these drugs can lead to higher rates of HAIs and have not been shown to be beneficial (Kiley, 2020, Relations, 2020). CMS guidelines for prevention of healthcare-acquired infections are vital.

Conflict of interest

The authors declare no competing financial interests.

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None.

Ethical approval

The study was reviewed and found exempt by Northeast Georgia Health System IRB board.

CRediT authorship contribution statement

Gagan Kumar: Conceptualization, Data curation, Investigation, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Alex Adams:** Data curation, Writing - original draft, Writing - review & editing. **Martin Hererra:** Data curation, Writing - original draft, Writing - review & editing. **Erine Raybon Rojas:** Writing - original draft, Writing - review & editing. **Vartika Singh:** Writing - original draft, Writing - review & editing. **Ankit Sakhuja:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Mark Meersman:** Resources, Software, Supervision, Validation. **Drew Dalton:** Resources, Software, Supervision, Validation. **Shravan Kethireddy:** Conceptualization, Data curation, Methodology, Writing - original draft, Writing - review & editing. **Rahul Nanchal:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Achuta Kumar Guddati:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.11.135.

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