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Concise Communication

Hospital-acquired infections among adult patients admitted for coronavirus disease 2019 (COVID-19)

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Abstract

In a multicenter cohort of 963 adults hospitalized due to coronavirus disease 2019 (COVID-19), 5% had a proven hospital-acquired infection (HAI) and 21% had a proven, probable, or possible HAI. Risk factors for proven or probable HAIs included intensive care unit admission, dexamethasone use, severe COVID-19, heart failure, and antibiotic exposure upon admission.

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Between 4% and 14% of hospitalized coronavirus disease 2019 (COVID-19) patients may develop a secondary bacterial, viral, or fungal infection.[1,2] Little is known about risk factors for these infections. In this study, we aimed to characterize infections that develop after 48 hours of hospitalization (ie, hospital-acquired infections, HAIs) in COVID-19 patients including both microbiologic confirmed cases and clinically suspected cases and to investigate risk factors for acquiring them.

Methods

Study population

Retrospective study of patients aged ≥18 years admitted to the Johns Hopkins Health System (JHHS) with a positive molecular severe acute respiratory coronavirus virus 2 (SARS-CoV-2) test between March 1, 2020, and May 30, 2020. Patients were excluded if they were identified as positive for SARS-CoV-2 on routine admission screening when admitted for other unrelated conditions, if they had a hospital stay outside the JHHS for >24 hours before presentation, and/or if they were discharged or died within 48 hours of admission.

Setting

The JHHS is composed of 5 hospitals including teaching and nonteaching hospitals in the Washington–Baltimore region.

Definitions

Consensus HAI definitions were developed for hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), viral pneumonia, fungal infection, bloodstream infection (BSI), urinary tract infection (UTI), skin and soft-tissue infection (SSTI), and *Clostridioides difficile* infection (CDI) by a multidisciplinary expert panel consisting of antimicrobial stewardship, general and transplant or oncology infectious disease, critical care and infectious disease pharmacy experts (Supplementary Table 1 online). Definitions included proven, probable, and possible categories based on clinical, laboratory, and radiographic criteria. These consensus definitions were retrospectively applied by manual chart review. Only the first episode of infection for each category was included. Demographic and laboratory data were obtained from a Hopkins COVID-19 registry.[3] Antibiotic exposure at presentation was defined as any antibiotic started within the first 48 hours of admission irrespective of duration and indication.

COVID-19 disease severity was assessed using the World Health Organization (WHO) scale.[4] The study was approved by the Johns Hopkins Medicine Institutional Review Board.

Statistical analysis

Categorical and continuous variables were compared using χ^2 and Wilcoxon rank-sum tests, respectively. Variables that were significantly associated with developing a secondary infection on univariable logistic regression analysis were used to build a multivariable regression model. Multicollinearity was assessed and was not present. A 2-sided P value <.05 was considered statistically significant for all tests. Statistical analysis was completed using STATA version 16.0 software (StataCorp, College Station, TX).

Results

Of 963 patients that met inclusion criteria, 5% (49 of 963) developed at least 1 proven HAI, most commonly bacteremia (22 of 963, 2%), UTI (19 of 963, 2%), or bacterial pneumonia (15 of 963, 1.5%; VAP 9 of 963, HAP 6 of 963). Furthermore, 7% (72 of 963) developed at least 1 proven or probable HAI, and a total of 21% (206 of

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Table 1. Cohort characteristics of patients admitted due to COVID-19 who developed a proven or probable infection after 48 hours of hospitalization (i.e., hospital-acquired infection [HAI]) compared to COVID-19 individuals who did not develop an infection

Characteristic	Total N=829	No infection N=757 (91%)	Proven/probable HAI N=72 (9%)	*P* value
Age, median (IQR)	62 (49, 74)	62 (47, 74)	65 (49, 71)	0.89
Female, n (%)	391 (47)	360 (48)	31 (43)	0.46
Race, n (%)				0.63
White	248 (30)	230 (30)	18 (25)	
Black	292 (35)	265 (35)	27 (37.5)	
Other	289 (35)	262 (35)	27 (37.5)	
Hispanic ethnicity, n (%)	248 (30)	223 (30)	25 (35)	**0.04**
Long-term care resident, n (%)	151 (18)	134 (18)	17 (24)	0.21
Charlson comorbidity index, mean ±SD	0.8 ±1.80	0.7 ±1.68	1.1 ±2.03	**<0.01**
Congestive heart failure, n (%)	91 (11)	72 (10)	19 (26)	**<0.01**
Diabetes, n (%)	74 (9)	67 (9)	7 (10)	0.80
Chronic obstructive pulmonary disease, n (%)	34 (4)	30 (4)	4 (6)	0.51
Body mass index, median (IQR)	29 (25.1, 34.3)	28.9 (25, 34)	30.8 (26.2, 36.3)	**0.04**
Immunocompromising condition*, n (%)	61 (7)	55 (7)	6 (8)	0.74
Admission to intensive care, n (%)	80 (10)	45 (6)	35 (49)	**<0.01**
WHO severity score¥, n (%)				**<0.01**
Mild disease	663 (80)	638 (84)	25 (35)	
Severe disease	166 (20)	119 (16)	47 (65)	
Maximum CRP (mg/dl), median (IQR)	13.5 (5.9, 34.0)	11.8 (5.6, 28.2)	20.7 (8.4, 40.1)	**<0.01**
Maximum ferritin* (ng/ml), median (IQR)	648 (314, 1197)	626 (299, 1171)	966 (277, 1354)	0.12
Initial procalcitonin* (ng/ml), median (IQR)	0.19 (0.09, 0.52)	0.16 (0.09, 0.36)	0.41 (0.16, 1.04)	**<0.01**
Receipt of any antibiotic within 48 hours of admission, n (%)	631 (76)	560 (74)	71 (99)	**<0.01**
Dexamethasone, n (%)	22 (2.1)	15 (2)	7 (10)	**<0.01**
Remdesivir, n (%)	64 (8)	55 (7)	9 (12.5)	0.11
Length of stay (days), median (IQR)	7.6 (4.4, 13.2)	6.2 (4.0, 10.1)	25.1 (15.4- 39.9)	**<0.01**

IQR: interquartile range, SD: standard deviation, CRP: C reactive protein. *Immunocompromising condition: Immunocompromising conditions includes HIV/AIDS, receipt of biologics, prednisone 20mg daily for > 2 weeks, chemotherapy within 6 months, and solid organ or hematopoietic stem cell transplant. WHO: World Health Organization. The WHO scale is an 8-point ordinal severity scale, mild includes WHO score of 3 (not on oxygen) or 4 (on nasal cannula or facemask oxygen) while severe disease includes WHO score 5 (high-flow nasal cannula or noninvasive positive pressure ventilation), 6 (intubation and mechanical ventilation), and 7 (intubated; mechanical ventilation; and other signs of organ failure, including use of extracorporeal membrane oxygen, hemodialysis, or vasopressors).

963) had at least 1 proven, probable, or possible infection. There were 62 proven infections, 27 probable infections, and 180 possible infections (Supplementary Table 2 online).

Among respiratory infections, 133 patients (14%) met any criteria for bacterial HAP, although only 16 (12%) of 133 were adjudicated as proven or probable; the remaining 117 cases (88%) were classified as possible HAP. Also, 73 patients (8%) met criteria for VAP; 16 (22%) of 73 were considered proven or probable, and 57 (88%) of 73 were possible cases. was 4.3 days (IQR, 2.4–8.1), and the median time from admission to developing VAP was 9.5 days (IQR, 6.1–15.2). HAP cases were more frequently caused by gram-positive bacteria, specifically *Staphylococcus aureus*; gram-negative bacteria were more commonly seen in VAP cases, with *Klebsiella* spp being the most common (Supplementary Table 3 online). BSIs were most commonly caused by methicillin-susceptible *Staphylococcus aureus* (MSSA) and *Klebsiella* spp, and the most common sources were pneumonia and vascular catheters. Of the 22 BSIs, 4 (18%) were National Healthcare Safety Network (NHSN)–defined central-line–associated bloodstream infections (CLABSIs). SSTIs and CDIs were less frequent: 9 of 963, (1%) and 5 of 963 (0.5%), respectively. There were 2 cases of probable pulmonary aspergillosis and 6 cases of possible pulmonary aspergillosis, and most of these patients were in the ICU at the time of diagnosis. There were no cases of pneumonia due to other respiratory viruses.

Characteristics of patients who met criteria for proven or probable infection and those who did not meet criteria for any infection category are shown in Table 1. Risk factors associated with proven or probable HAI on univariable logistic regression analysis included ICU admission prior to HAI, World Health Organization (WHO) severe disease on admission, dexamethasone therapy during hospitalization, and antibiotic exposure at admission (Table 2). On multivariable logistic regression analysis, independent risk factors for development of proven or probable HAI included history of congestive heart failure (aOR, 2.45; 95% CI, 1.21–4.93), dexamethasone during hospitalization (aOR, 4.32; 95% CI, 1.56–11.95), ICU admission prior to HAI (aOR, 5.03; 95% CI, 2.60–9.70), receipt of antibiotics within first 48 hours of hospitalization (aOR, 11.43; 95% CI, 1.53–85.04), and severe disease on admission (aOR, 3.83; 95% CI, 2.05–7.14). The median

Table 2. Factors associated with development of proven/probable infections after 48 hours of hospitalization for COVID-19 **(N=829)**

Variable	Unadjusted Odds Ratio (95% CI)	*P* value	Adjusted Odds Ratio (95% CI)	*P* value
Female sex	1.19 (0.73- 1.95)	0.46	0.92 (0.52 – 1.63)	0.79
≥65 years	1.01 (0.79 – 1.30)	0.88	0.95 (0.71 – 1.26)	0.73
Black race	1.30 (0.69 – 2.42)	0.40	–	
Hispanic ethnicity	1.27 (0.76 – 2.12)	0.35	–	
Long term care resident	1.43 (0.80 – 2.55)	0.21	–	
History of congestive heart failure	3.41 (0.94 – 2.53)	0.08	2.45 (1.21 – 4.93)	**0.01**
Obesity (BMI ≥30)	1.55 (0.86 – 1.36)	0.30	–	
Immunocompromising condition	1.16 (0.48 – 2.79)	0.74	–	
Admission to the intensive care unit	13.17 (7.06 – 24.53)	**<0.01**	5.03 (2.60 – 9.70)	**<0.01**
Severe disease*on admission	10.07 (5.97 – 17.00)	**<0.01**	3.83 (2.05 – 7.14)	**<0.01**
Receipt of antibiotics in first 48 hours of admission	24.97 (3.44 – 180.97)	**<0.01**	11.43 (1.53 – 85.04)	**<0.01**
Dexamethasone	5.32 (2.09 –13.53)	<0.01	4.32 (1.56 – 11.95)	**<0.01**

*Severe disease includes WHO score 5 (high-flow nasal cannula or noninvasive positive pressure ventilation), 6 (intubation and mechanical ventilation), and 7 (intubated; mechanical ventilation; and other signs of organ failure, including use of extracorporeal membrane oxygen, hemodialysis, or vasopressors).

LOS was significantly longer among patients who developed a proven or probable HAI compared to patients who did not develop an HAI (median, 25.1 days vs 6.2 days; $P < .01$).

Discussion

In this retrospective cohort of hospitalized adults with COVID-19 between March and May 2020, 5% had a proven HAI; 7% had a proven or probable HAI; and 21% had a proven, probable, or possible infection. Antibiotic exposure within 48 hours of admission, severe disease, dexamethasone therapy during hospitalization and ICU admission prior to infection were independent risk factors for developing an HAI.

The prevalence of HAIs in patients with COVID-19 in our and others' studies[1] is higher than that reported for non–COVID-19 patients which has been ∼ 3% in recent years.[5] These findings may be due to more severe illness in COVID-19 patients, and higher device utilization and mechanical ventilation, and/or disruption of regular infection prevention activities by the pandemic (eg, measures to prevent CLABSI and VAP such as frequent assessment of central lines, spontaneous breathing trials, and interruption of sedation became more challenging).[6] Additional factors that may have contributed include redeployment of staff who were unfamiliar with usual infection prevention practices and a shift toward virtual rounds.

Previous studies have shown that most antibiotics prescribed to COVID-19 patients on admission are unnecessary,[7] although the role of antibiotics in immunocompromised patients remains to be elucidated.[8] In our cohort, ∼80% of patients received antibiotics on admission. Although our study does not prove causality between receipt of antibiotics on admission and later development of HAI, prior antibiotic use was an independent risk factor for HAI after adjustment for illness severity; this finding supports enhanced antibiotic stewardship in COVID-19 patients.

Our lower rate of pulmonary aspergillosis (0.8%) compared to recent studies could be due to the definitions used (other studies have used a modified probable definition that did not require host risk factors), the lack of microbiological testing, and/or a smaller ICU population.[9,10]

Our study has several limitations. Expectorated sputum and bronchoalveolar lavage were discouraged early in the pandemic due to the risk of aerosolization of infectious respiratory particles and may have limited our ability to detect proven respiratory infection cases. However, we included probable and possible categories that did not require microbiologic culture. Several authors performed adjudication of cases and definitions may have been applied differently; however, the authors met several times to review cases to ensure uniform use of the definitions, minimizing this risk.

In summary, receipt of antibiotics at the time of admission, which in most cases may be unnecessary,[7] may lead to subsequent secondary infections during hospitalization. Infection prevention efforts should focus in ICU patients.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2021.148

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Conflicts of interest. All authors report no conflicts of interest.

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