Original Article

Early coronavirus disease 2019 (COVID-19) pandemic effects on individual-level risk for healthcare-associated infections in hospitalized patients

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Abstract

Objective: We compared the individual-level risk of hospital-onset infections with multidrug-resistant organisms (MDROs) in hospitalized patients prior to and during the coronavirus disease 2019 (COVID-19) pandemic. We also quantified the effects of COVID-19 diagnoses and intrahospital COVID-19 burden on subsequent MDRO infection risk.

Design: Multicenter, retrospective, cohort study.

Setting: Patient admission and clinical data were collected from 4 hospitals in the St. Louis area.

Patients: Data were collected for patients admitted between January 2017 and August 2020, discharged no later than September 2020, and hospitalized ≥48 hours.

Methods: Mixed-effects logistic regression models were fit to the data to estimate patients’ individual-level risk of infection with MDRO pathogens of interest during hospitalization. Adjusted odds ratios were derived from regression models to quantify the effects of the COVID-19 period, COVID-19 diagnosis, and hospital-level COVID-19 burden on individual-level hospital-onset MDRO infection probabilities.

Results: We calculated adjusted odds ratios for COVID-19-era hospital-onset Acinetobacter spp., P. aeruginosa and Enterobacteriaceae spp infections. Probabilities increased 2.64 (95% confidence interval [CI], 1.22–5.73) times, 1.44 (95% CI, 1.03–2.02) times, and 1.25 (95% CI, 1.00–1.58) times relative to the prepandemic period, respectively. COVID-19 patients were 4.18 (95% CI, 1.98–8.81) times more likely to acquire hospital-onset MDRO S. aureus infections.

Conclusions: Our results support the growing body of evidence indicating that the COVID-19 pandemic has increased hospital-onset MDRO infections.

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44% in methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, and 24% in multidrug-resistant organism (MDRO) bacteremia overall. Similarly, in 2021, Weiner-Lastinger et al reported increases in the national-level standardized infection ratios for central-line-associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated events, and MRSA bacteremia in the 2020 National Healthcare Safety Network. Alternatively, some hospitals have reported reductions in HAIs, possibly due to enhanced infection control practices and heightened awareness of proper personal protective equipment use. Overall, previous research has focused primarily on reporting coinfections and superinfections in COVID-19 hospitalized patients. However, whether non–COVID-19 patients were also at a greater risk of HAIs during the pandemic remains unclear.

We sought to quantify whether COVID-19 pandemic changed the risk for acquiring a multidrug-resistant HAI for both COVID-19 and non–COVID-19 hospitalized patients in a multicenter retrospective cohort. We used admission and clinical data from 4 hospitals to construct mixed-effect logistic regression models and to quantify patient-level risk of acquiring an HAI associated with 1 of 8 multidrug-resistant pathogens: *Acinetobacter* spp, *Clostridioides difficile*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and general MDRO Enterobacteriaceae spp. We estimated the effect of the COVID-19 pandemic period on pathogen-specific HAI acquisition risks for hospitalized patients relative to a prepandemic period. We also quantified the effects of COVID-19 diagnoses preceding HAI onset and intrahospital COVID-19 burden during patients’ hospital stays on individual HAI risk during the pandemic period.

**Methods**

**Study population**

A multicenter retrospective cohort study was conducted in 4 hospitals in the St. Louis area (see Appendix 1 for detailed hospital characteristics). Admission and clinical data were collected for patients admitted between January 2017 and August 2020, discharged no later than September 2020, and hospitalized ≥48 hours. When discharged patients were readmitted to the same hospital <24 hours later, hospitalization data were concatenated into a single record. The data set consists of 260,055 unique admissions associated with 157,120 different patients. We extracted clinical and demographic data for this cohort from the BJC Medical Informatics database, including laboratory and microbiological test results, antibiotic use, and days spent in intensive care units (ICUs). Comorbidity information for this cohort was obtained using *International Classification of Disease, Tenth Revision* (ICD-10) codes with Elixhauser groupings. Cohort members were hospitalized for 6.83 days on average (SD, 8.30 days).

Patients with a positive culture from blood, urine, or respiratory tract specimen for any of 5 MDRO groups previously defined by the Centers for Disease Control and Prevention and described by Burnham et al were identified: MDRO Enterobacteriaceae spp, *S. aureus*, *P. aeruginosa*, *Acinetobacter* spp, and *E. faecium*. See Appendix 2 for MDRO group definitions. *C. difficile* infection was identified by positive toxin enzyme immunoassay from stool. Within the MDRO Enterobacteriaceae spp, we also separately analyzed multidrug-resistant *E. coli* and *K. pneumoniae*. We categorized infections as hospital-onset HAIs if they were first identified ≥48 hours following patient admission. COVID-19 status during admissions were based on results of SARS-CoV-2 PCR testing and/or a diagnosis code for COVID-19 (ICD-10-CM code U07.1). Medical record review was performed for admissions with a COVID-19 ICD-10-CM diagnosis code without a positive laboratory result to confirm a clinical diagnosis. To calculate the infection pressures associated with COVID-19 and HAIs, admissions for the first and last 24 days were removed. The final number of admissions used in the statistical analysis were 250,539.

**Statistical analysis**

We constructed independent mixed-effects logistic regression models to estimate patients’ individual-level risk of infection with the pathogens of interest during hospitalization. Mixed-effects logistic regression models are among methods often used to characterize individual-level infection risk while considering that patients are nested within hospital. All analyses were done using the `lme4` R package version 1.1-27.1 in R Studio version 1.4.1717 running R version 4.0.3 software. We carried out 2 sets of regression analyses, which we refer to as the “full period” and “COVID-19 period” model sets, and we describe predictor variables included in each model set in Table 1. These model sets were intended to answer 2 distinct questions. The former set identified significant ($P \leq 0.05$) differences in patient-level HAI risk associated with the initial 6 months of the COVID-19 pandemic. We used “COVID-19 period” models to determine whether patients with a COVID-19 diagnosis were more or less likely to acquire these HAIs than those not diagnosed with COVID-19, and whether hospital-level COVID-19 burden modulated HAI risk for both COVID-19 and non–COVID-19 admissions. The fixed effects of interest in our models were COVID-19 period, COVID-19 diagnosis, and the hospital-specific COVID-19 burden during a patient stay ($\Delta_{int.}$). The following variables were also included as confounders: time spent in the hospital prior to observed infections, the relative amount of time spent on antibiotics and in intensive care units, and pathogen-specific infection pressures acting on admitted patients. See Appendix 3 for additional information on our model-fitting and model selection procedures.

This study was approved by the Washington University School of Medicine Institutional Review Board (IRB ID no. 202010057) with a waiver of informed consent.

**Results**

The numbers of admissions readily decreased during the early phase of the pandemic, followed by an increase in admissions, to numbers more similar to ranges observed during preceding years (Fig. 1). Figure 2 shows the temporal trends for the estimated infection pressures, calculated as the proportion of patient days contributed by patients with a confirm diagnosis for a given MDRO or COVID-19. There is no clear change in the trends of the MDRO infection pressures in the COVID-19 pandemic period (Fig. 2a). The pandemic period was, however, associated with a notable increase in the proportion of admitted patients presenting with SARS-CoV-2 infection during the hospital stay (Fig. 2b). Adjusted odds ratios associated with COVID-19–period effects on HAI occurrence are given in Table 2. We observed significant COVID-19–period effects for *Acinetobacter* spp, *P. aeruginosa*, and overall Enterobacteriaceae spp HAIs, for which the odds ratios suggest hospital-onset infection probabilities increased by 2.64 (95% confidence interval [CI], 1.22–5.73) times, 1.44 (95% CI,
1.03–2.02) times, and 1.25 (95% CI, 1.00–1.58) times relative to prepandemic time points, respectively. The frequency of respiratory and urine cultures for patients remained unchanged between the prepandemic period and the pandemic period. Also, 5% of patients had a respiratory culture taken regardless of the period.

Rates of urine culture were also very similar between the periods: 16% during the prepandemic period versus 17% during the pandemic period.

Within the pandemic period, COVID-19 patients had both urine and respiratory cultures taken more frequently compared to

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**Table 1. Description of Predictor Variables Included as Fixed Effects in Mixed-Effect Logistic Regression Models**

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Description</th>
<th>Range</th>
<th>Associated Models</th>
<th>Data Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_{j</td>
<td>\pi}$</td>
<td>The HAI pathogen-specific colonization pressure observed in the hospital to which a patient was admitted during their LOS prior to infection diagnosis.</td>
<td>0–1</td>
<td>Full period, COVID-19 period</td>
</tr>
<tr>
<td>$\Delta_{j</td>
<td>\pi}$</td>
<td>The COVID-19 burden observed in the hospital to which a patient was admitted during their LOS prior to infection diagnosis.</td>
<td>0–1</td>
<td>COVID-19 period</td>
</tr>
<tr>
<td>COVID-19_diagnosis$_j$</td>
<td>Binary variable describing whether patients were diagnosed with COVID-19 at admission or following admission but prior to the sample collection date for a positive sample that indicated the infection of interest. Takes the value 1 if patients met this criterion, and 0 if admissions never tested positive for SARS-COV-2 infections, never contracted the HAI of interest, or were only diagnosed with COVID-19 following the HAI diagnosis date.</td>
<td>0–1</td>
<td>COVID-19 period</td>
<td>Discrete</td>
</tr>
<tr>
<td>COVID-19_period</td>
<td>Binary variable describing whether patients were admitted on or following the date of admission for the first COVID-19 patient in the data set. Takes the value 1 if patients met this criteria, and 0 if not.</td>
<td>0–1</td>
<td>Full period</td>
<td>Discrete</td>
</tr>
<tr>
<td>Preceding_Antibiotic_Days$_j$</td>
<td>For admissions with a positive bacterial culture indicating an infection with the pathogen of interest, this is the proportion of days prior to positive sample collection date during which antibiotics were administered to the patient. Defaults to 0 for admissions with no positive test during their hospital stay.</td>
<td>0–1</td>
<td>Full period, COVID-19 period</td>
<td>Proportion</td>
</tr>
<tr>
<td>Preceding_ICU_Days$_j$</td>
<td>For admissions with a positive bacterial culture indicating an infection with the pathogen of interest, this is the proportion of days prior to positive sample collection date during which the patient was in an ICU. Defaults to 0 for admissions with no positive test during their hospital stay.</td>
<td>0–1</td>
<td>Full period, COVID-19 period</td>
<td>Proportion</td>
</tr>
<tr>
<td>Preceding_LOS$_j$</td>
<td>Number of days individuals were hospitalized prior to sample-collection dates for positive samples indicating admissions were positive for an HAI with a pathogen of interest. For admissions that did not produce any positive sample, the value of this variable becomes the patient’s entire LOS.</td>
<td>2–500.125</td>
<td>Full period, COVID-19 period</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

Note HAI, healthcare-associated infection; ICU, intensive care unit; LOS, length of stay.

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**Figure 1.** Sum admissions with lengths of stay ≥2 days admitted to study hospitals each week. Weeks containing or following the first observed COVID-19 patient are highlighted in blue and begin at week 0. Weeks preceding COVID-19 patient admissions are shown were assigned negative IDs.
non–COVID-19 patients. Also, 16% of COVID-19 patients had respiratory cultures versus 4% of non–COVID-19 patients during the pandemic period. Furthermore, 27% of COVID-19 patients had urine cultures versus 16% of non–COVID-19 patients during the pandemic period. Table 3 lists odds ratios associated with effects of COVID-19 diagnoses immediately preceding HAIs and hospital COVID-19 burden ($\Delta_{h_{ix}}$) during patient stays. Overall, a prior COVID-19 diagnosis and the hospital COVID-19 burden were not associated with an increase in patient-level risk for MDRO infection. The only exception was that COVID-19 patients were 4.18 (95% CI, 1.98–8.81) times more likely to acquire a hospital-onset MDRO S. aureus infection. Interestingly, half of our models estimated that COVID-19 burden had protective effects on infection probabilities (ie, odds ratio < 1); however, these effects were not significant at an $\alpha$ level of 0.05. Estimates for all predictors included in all the models are reported in Appendix 3 (online). Overall, number of prior days in the ICU was a significant variable for all HAI risk models, and prior days of antibiotics was also significant for most models.

Discussion

We constructed mixed-effect logistic regression models to estimate COVID-19 effects on the patient-level risk for acquiring 8 MDRO HAIs. Patients admitted to hospitals between March and August 2020 (ie, during the COVID-19 pandemic period) were more likely to become infected with MDRO P. aeruginosa and Enterobacteriaceae spp and Acinetobacter spp infections were associated with the preceding duration of stay in the ICU, suggesting that increased risk to infection may reflect a sicker population during the COVID-19 pandemic period. Prior studies have associated the increased HAI risks with a sicker patient population requiring ICU care, more frequent use of invasive devices, longer courses of antibiotics, and longer stays.22 In our study, patients during the prepandemic period and non–COVID-19 patients in the pandemic period were similar, with comparable lengths of stays, age, comorbidities, and hospital mortality rates. However, there was a slight increase in the percentage of ICU admissions for non–COVID-19 patients in some hospitals during the pandemic period (Table A1-2). Overall, COVID-19 patients were more severely ill, with longer lengths of stay, a higher ICU admission rate, and a higher hospital mortality rate (Table 1). Additionally, we included intrahospital COVID-19 burden during the patient’s hospital stay as a variable to account for the potential indirect effects related to the burden of COVID-19 patients in the facilities, such as staff shortage and burnout or infection control changes (Table 1). Proportion of prior days in the ICU was a significant variable for all the HAI risk models, and proportion of prior days on antibiotics was also significant for most models (Appendices 2 and 3). However, COVID-19 burden was
not significant in any of the HAI models (Table 3). Statistical models by Weiner-Lestinger et al.\textsuperscript{32} and standardized infection ratios by Stephenson et al.\textsuperscript{29} suggest that local COVID-19 burden was positively correlated with hospital-onset infections at the hospital level. These studies did not quantify the effects of COVID-19 burden at the individual level of risk, however. Our findings suggest that the signal observed in previous studies may capture effects of COVID-19–mediated changes in admitted patients’ hospital stay characteristics (eg, length of stay in ICUs) rather than facility-mediated COVID-19 infection effects, such as staff or infection control changes.

Our findings also indicated that having a positive COVID-19 diagnosis increased the probability of subsequently developing a hospital-onset MDRO S. aureus infection, but we could not conclude the same for other HAIs. In general, previous studies have indicated that COVID-19 patients are at increased risk, relative to non–COVID-19 patients, for hospital-onset MDRO HAIs.\textsuperscript{22–28} Superinfection with MDRO S. aureus has been described in previous reports describing HAI incidence in COVID-19 patients.\textsuperscript{8,14} Superinfection with MDRO S. aureus have been directly attributed to the management of COVID-19 patients, which often included use of catheters, intubation, and corticosteroid use.

Although we did not report an increased risk on other HAIs with COVID-19 diagnosis, others have reported increases in other HAIs. Garcia-Vidal et al.\textsuperscript{26} noted that E. coli and P. aeruginosa infections were common in COVID-19 patients. Baskaran et al.\textsuperscript{24} identified E. coli and K. pneumoniae as representing the majority of COVID-19–related HAIs. Study populations in these previous studies were comprised solely of critically ill COVID-19 patients or COVID-19 patients admitted to ICUs.\textsuperscript{24,25,27} Thus, the distribution of HAIs affecting these populations may differ from ours. Our data set contained all 24-hour hospital admissions, and we did not limit our analyses to ICU admissions.

The main strengths of our study are the multisite nature of the study, and that our cohort represented all hospitalized patients, including non–COVID-19 and non-ICU patients. The primary limitation of this study is that the scope of our data were restricted to patient-level post–hospital-admission attributes. Because we were unable to characterize hospital staffing and infection control policy changes, we ultimately lacked the ability to conclusively identify specific causes of COVID-19–related HAI risk modifications. Additionally, we defined the beginning of the COVID-19 period as the time point when the first recorded COVID-19 patient was admitted to one of the hospitals in this study. It is possible that patients infected with SARS-CoV-2 were admitted prior to this date, but their condition went undiscovered due to lack of testing and relative obscurity of the disease.

Our findings suggest that the COVID-19 pandemic has indirectly affected MDRO pathogen transmission in hospitals and that COVID-19 diagnosis may be related to MDRO S. aureus infection risk. These findings can be used to calibrate mechanistic transmission models for simulating HAI incidence, like that presented by Stephenson et al.\textsuperscript{29} and can help to illuminate causative HAI transmission mechanisms in this system. Our work will contribute to the development of effective interventions for preventing HAIs and MDRO transmission in hospitals.

**Supplementary material.** The supplementary material for this article can be found at [https://doi.org/10.1017/ice.2023.83](https://doi.org/10.1017/ice.2023.83)

**Acknowledgments.**

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**Competing interests.** All authors report no conflicts of interest relevant to this article.

### Table 2. Estimated Effects of the “COVID-19_Period” Variable on Individual-Level MDRO HAI Risk

<table>
<thead>
<tr>
<th>HAI Variable of Interest</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 diagnosis</td>
<td>1.29 (0.06–8.97)</td>
</tr>
<tr>
<td>COVID-19 diagnosis</td>
<td>1.07 (0.40–2.83)</td>
</tr>
<tr>
<td>COVID-19 diagnosis</td>
<td>1.08 (0.85–1.37)</td>
</tr>
<tr>
<td>COVID-19 diagnosis</td>
<td>1.40 (0.41–4.95)</td>
</tr>
<tr>
<td>COVID-19 diagnosis</td>
<td>1.33 (0.19–5.15)</td>
</tr>
<tr>
<td>COVID-19 diagnosis</td>
<td>0.97 (0.86–1.08)</td>
</tr>
<tr>
<td>COVID-19 diagnosis</td>
<td>1.74 (0.97–2.98)</td>
</tr>
<tr>
<td>COVID-19 diagnosis</td>
<td>2.22 (0.85–5.14)</td>
</tr>
<tr>
<td>COVID-19 diagnosis</td>
<td>1.03 (0.87–1.21)</td>
</tr>
<tr>
<td>COVID-19 diagnosis</td>
<td>4.18 (1.98–8.81)</td>
</tr>
</tbody>
</table>

*Adjusted ORs denoting the relative risk attributable to 1-unit increases of these variables on pathogen-specific hospital-onset infection probability are given in the Table. ORs for other model variables are not shown. Wald 95% CIs are listed in parentheses.

### Table 3. Estimated Effects of COVID-19 Diagnoses and COVID-19 Burden (Δx) on Individual-Level MDRO HAI Risk

<table>
<thead>
<tr>
<th>HAI Variable of Interest</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter spp</td>
<td>1.12 (0.71–1.72)</td>
</tr>
<tr>
<td>Clostridioides difficile</td>
<td>1.29 (0.06–8.97)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>0.88 (0.73–1.07)</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>1.00 (0.75–1.29)</td>
</tr>
<tr>
<td>Enterobacteriaceae spp</td>
<td>1.33 (0.19–5.15)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>0.97 (0.86–1.08)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>0.86 (0.66–1.09)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2.22 (0.85–5.14)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1.03 (0.87–1.21)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>4.18 (1.98–8.81)</td>
</tr>
</tbody>
</table>

*Adjusted ORs denoting the relative risk attributable to 1-unit increases of these variables on pathogen-specific hospital-onset infection probability are given in the Table. ORs for other model variables are not shown. Wald 95% CIs are listed in parentheses.

Note. MDRO, multidrug-resistant organism; HAI, healthcare-associated infection; OR, odds ratio; CI, confidence interval.

Note. MDRO, multidrug-resistant organism; HAI, healthcare-associated infection; OR, odds ratio; CI, confidence interval.
References


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