





Original Article

Healthcare-associated infections on the intensive care unit in 21 Brazilian hospitals during the early months of the coronavirus disease 2019 (COVID-19) pandemic: An ecological study

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Abstract

Objective: The coronavirus disease 2019 (COVID-19) pandemic has caused a global health crisis and may have affected healthcare-associated infection (HAI) prevention strategies. We evaluated the impact of the COVID-19 pandemic on HAI incidence in Brazilian intensive care units (ICUs).

Methods: In this ecological study, we compared adult patients admitted to the ICU from April through June 2020 (pandemic period) with the same period in 2019 (prepandemic period) in 21 Brazilian hospitals. We used the Wilcoxon signed rank-sum test in a pairwise analysis to compare the following differences between the pandemic and the prepandemic periods: microbiologically confirmed central-line-associated bloodstream infection (CLABSI) and ventilator-associated pneumonia (VAP) incidence density (cases per 1,000 central line and ventilator days, respectively), the proportion of organisms that caused HAI, and antibiotic consumption (DDD).

Results: We detected a significant increase in median CLABSI incidence during the pandemic: 1.60 (IQR, 0.44–4.20) vs 2.81 (IQR, 1.35–6.89) ($P = .002$). We did not detect a significant difference in VAP incidence between the 2 periods. In addition, we detected a significant increase in the proportion of CLABSI caused by *Enterococcus faecalis* and *Candida* spp during the pandemic, although only the latter retained statistical significance after correction for multiple comparisons. We did not detect a significant change in ceftriaxone, piperacillin–tazobactam, meropenem, or vancomycin consumption between the studied periods.

Conclusions: There was an increase in CLABSI incidence in Brazilian ICUs during the first months of COVID-19 pandemic. Additionally, we detected an increase in the proportion of CLABSI caused by *E. faecalis* and *Candida* spp during this period. CLABSI prevention strategies must be reinforced in ICUs during the COVID-19 pandemic.

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The coronavirus disease 2019 (COVID-19) pandemic has caused a health crisis around the globe. Resources routinely used to prevent healthcare-associated infection (HAI) have been redirected toward the management of the pandemic. An informal query conducted in April 2020 found that infection prevention and control (IPC)

workers spent >75% of their time responding to the pandemic. The diversion of traditional HAI prevention duties may have compromised HAI monitoring and prevention.¹ Another challenge was the shortage of personal protective equipment (PPE), leading to the need for rationing its use, which in turn may have affected the spread of multidrug-resistant organisms.² In addition, the high rates of empirical antibiotic use in COVID-19 cases and the reduced time dedicated to antimicrobial stewardship during the pandemic may have had an effect on antimicrobial resistance.³

Since Brazil's first case of COVID-19 was reported on February 26, 2020, Brazil rapidly became the epicenter of the disease in Latin America and figured among the most affected countries in the world.⁴ The high rates of HAI before the pandemic as well as the high rate of antimicrobial resistance in Brazil have posed additional challenges to this scenario because the high number of COVID-19 cases can be aggravated by healthcare-associated complications.⁵

In this study, we evaluated the impact of the COVID-19 pandemic on the incidence of central-line-associated bloodstream infection (CLABSI) and ventilator-associated pneumonia (VAP) in Brazilian intensive care units (ICUs).

Methods

Data sources

In this ecological study, we evaluated adult patients admitted to intensive care units (ICUs) from April through June 2020 (during the COVID-19 pandemic) compared to the same period in 2019 (before the pandemic). We collected data from 21 Brazilian hospitals from 6 different states (São Paulo, Espírito Santo, Paraná, Ceará, Pernambuco, and Maranhão) that comprise the 3 most populated Brazilian regions. The IPC team of each hospital collected clinical and laboratory data.

We collected the following data: the number of COVID-19 patients admitted to the ICUs (suspected or laboratory-confirmed cases), the total number of ward and ICU beds of each hospital, and the total number of patients admitted to adult ICUs. We also collected data on the number of patient days, central-line days, ventilator days, CLABSI, VAP, and antibiotic consumption in all adult ICUs. We classified the participating hospitals as public or private. The study protocol (no. 77243517.8) was approved by the ethics committee of each participating hospital. No patient identifiers were recorded to ensure anonymity. There was no contact with patients, and patient consent was not required.

Outcomes

The primary end points were the incidence density of CLABSI and of VAP in each hospital. The definition of these infections is shown in Supplementary Table S1 (online); they were based on the National Health Surveillance Agency (ANVISA) surveillance that was adapted from the CDC/NHSN surveillance definitions and criteria for HAI.⁶

Statistical analysis

Overall, data from April through June 2019 (prepandemic period) were compared with data from April through June 2020 (pandemic period). A single incidence density measurement of CLABSI (cases per 1,000 central-line days) or VAP (cases per 1,000 ventilator days) was made in the 3-month periods before the pandemic and after the pandemic started. Categorical variables are presented as absolute numbers and percentages; continuous variables are

presented as median (interquartile range, IQR) due to their non-normal distributions. The comparison of the number of patients admitted to the ICU, patient days, central-line days, total CLABSI, CLABSI incidence density, ventilator days, total VAP, and VAP incidence density of each period were compared in a pairwise analysis using the Wilcoxon signed rank-sum test. The pairwise comparisons of the CLABSI and VAP incidence densities were also stratified by public and private hospitals. The effect of total number of patient days in April–June 2020 and proportion of ICU admissions by COVID-19 patients in April–June 2020 on the change of the incidence density of HAI between the prepandemic and the pandemic periods was evaluated by entering each of these 2 independent variables separately in a linear regression model with the change in incidence density of CLABSI or VAP as the dependent variable. The organisms that caused CLABSI and VAP from the 2 periods were compared using the Wilcoxon signed rank-sum test. Because the total number of CLABSIs and VAP cases might differ from one year to another, the proportions of each organism causing HAI in each hospital in each period were compared. Because several causative organisms were evaluated, we adjusted this analysis for multiple comparisons according to the Hochberg procedure.⁷ We also compared the proportion of drug-resistant bacteria between the prepandemic and pandemic periods in a pairwise analysis using the Wilcoxon signed rank-sum test. We evaluated the proportion of carbapenem-resistance among Enterobacteriaceae, carbapenem-resistance among *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (nonfermentative gram-negative bacilli), methicillin-resistance among *Staphylococcus aureus*, and vancomycin-resistance among *Enterococcus faecalis* and *Enterococcus faecium*. The association of antibiotic consumption (estimated by the defined daily doses (DDDs) per 1,000 patient days of selected antimicrobials) with the proportion of specific organisms causing HAI in each hospital was compared using a linear regression model. The change in the proportion of specific organisms causing HAI between the pandemic and the prepandemic periods was the dependent variable, and the changes in DDD between the 2 periods were compared as the independent variable. The linear regression models used to evaluate factors associated with changes in the proportion of organisms causing HAI and to evaluate changes in incidence density of HAI presented residuals that were approximately normally distributed and the data showed homoscedasticity. Statistical tests were 2-tailed with a significance level of .05. The SPSS version 17.0 software (IBM, Armonk, NY) and R version 4.1.0 software (R Foundation for Statistical Computing, Vienna, Austria) were used for the analyses.

Results

The 21 hospitals had a median of 164 beds (IQR, 127–275) in patient wards and 50 ICU beds (IQR, 32–85). Among them, 11 hospitals (52%) were private (Supplementary Table S2 online). Although the first hospitalizations for COVID-19 were recorded in February 2020, the number of COVID-19 hospitalizations showed a substantial increase in April 2020 and stabilized between April and June 2020 (Fig. 1). Therefore, the analyses in our study are centered on the period of April through June. We evaluated 118,704 patient days from April through June in 2019 and 2020. We could not obtain data regarding the number of COVID-19 admissions from one of the hospitals. Thus, during the study period, 4,563 patients with COVID-19 were admitted to an ICU

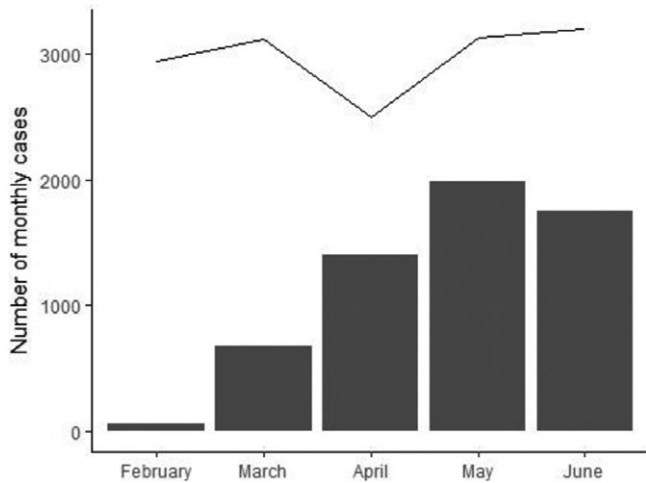


Fig. 1. Total number of admissions (line) and number of COVID-19 admissions (bars) to the intensive care unit of 20 Brazilian hospitals from February 2020 through June 2020.

in 1 of 20 hospitals from April through June 2020. All other analyses evaluated data from the 21 hospitals unless stated otherwise.

During the pandemic compared to the pre-pandemic period, the overall number of ICU admissions decreased and the number of patient days remained stable in the ICUs. In contrast, central-line days, CLABSIs, ventilator days, and VAPs all increased during the pandemic (Fig. 2 and Table 1).

Compared to the pre-pandemic period, there was an increase in CLABSI incidence density during the pandemic in 18 hospitals, whereas 2 hospitals showed a decrease in CLABSI and 1 hospital did not report any CLABSI in either period (Fig. 3 and Supplementary Table S2 online). We detected an overall increase in CLABSI incidence density during the pandemic compared to the pre-pandemic period: 2.81 (IQR, 1.35–6.89) versus 1.60 (IQR, 0.44–4.20; $P = .002$ in the pairwise comparison) (Table 1). The stratified analyses showed that the increase in CLABSI reached statistical significance among public hospitals but not private hospitals (Table 1). A sensitivity analysis excluding one outlier (ie, a public hospital with an important increase in CLABSI incidence) confirmed that there was a significant increase in CLABSI incidence overall (2.75 [IQR, 1.31–6.71] vs 1.46 [IQR, 0.22–4.27]; $P = .003$) and among public hospitals (2.81 [IQR, 1.35–7.23] vs 1.20 [IQR, 0–4.20]; $P = .012$) during the pandemic compared to the pre-pandemic period. There was no significant effect of total number of patient days ($\beta = 0.001$; $P = .635$) or the proportion of ICU admissions by COVID-19 patients ($\beta = 1.844$; $P = .558$) on the change in CLABSI incidence density between the 2 periods.

We detected an increase in VAP incidence density in 15 hospitals during the pandemic compared to the pre-pandemic period. However, 5 hospitals demonstrated a decrease and 1 hospital did not have any VAP in either period (Fig. 3 and Supplementary Table S2 online). Overall, the pairwise comparison showed no significant change in VAP incidence density during the pandemic compared to the pre-pandemic period: 3.65 (IQR, 1.38–6.46) versus 2.99 (IQR, 0.72–4.80; $P = .167$) (Table 1). Private hospitals showed a significant increase in VAP incidence density, while there was no significant change in VAP incidence among public hospitals (Table 1). A sensitivity analysis excluding 2 outliers (ie, 1 private hospital and 1 public hospital with major increases in VAP incidence) between the pandemic and

pre-pandemic periods showed no significant change in VAP incidence overall (3.64 [IQR, 1.34–6.05] vs 2.99 [IQR, 0–4.45]; $P = .446$) nor among private hospitals (3.14 [IQR, 1.25–6.41] vs 2.25 [IQR, 0–4.04]; $P = .059$) nor public hospitals (3.64 [IQR, 0.94–5.32] vs 4.14 [IQR, 1.99–6.60]; $P = .327$). We did not detect a significant effect of total number of patient days ($\beta = 0.001$; $P = .879$) nor the proportion of ICU admissions by COVID-19 patients ($\beta = -3.618$; $P = .417$) on the change in VAP incidence density between the 2 periods.

During the pandemic, the most frequent causes of CLABSI were *Candida* spp ($n = 38$) and coagulase negative *Staphylococcus* ($n = 38$). During the pre-pandemic period, *Klebsiella pneumoniae* ($n = 16$) and *Candida* spp ($n = 10$) were the most frequent causes of CLABSI (Tables 2 and Supplementary Table S3 online). We detected an increase in the proportion of CLABSI caused by *E. faecalis* and *Candida* spp as well as a decrease in the proportion of CLABSI caused by *S. aureus* during the pandemic. However, after adjusting for multiple comparisons in the pairwise analysis, the only significant change was the increase in *E. faecalis*: 0% (IQR, 0–0) versus 8% (IQR, 0–15%; $P = .028$).

The most frequent causative agents of VAP were *P. aeruginosa* ($n = 44$) and *Acinetobacter baumannii* ($n = 24$) during the pandemic, and *P. aeruginosa* ($n = 21$) and *S. aureus* ($n = 11$) in the pre-pandemic period. We did not detect significant changes in the frequency of VAP causative agents between the 2 periods (Tables 2 and Supplementary Table S3 online).

Among the causative agents of CLABSI and VAP evaluated together, there was a non-statistically significant increase in the rate of carbapenem resistance among *Enterobacteriaceae* isolates and methicillin resistance among *Staphylococcus aureus* isolates between the 2 periods (Table 3).

We had data on antimicrobial consumption from 16 hospitals. Although we detected an increase in median ceftriaxone and meropenem DDD during the pandemic, there was no significant change in median ceftriaxone, piperacillin–tazobactam, meropenem, or vancomycin DDD between the pre-pandemic and the pandemic periods (Supplementary Table S4 online). We did not detect an association between the change in ceftriaxone consumption and the difference in the proportion of CLABSI caused by *Enterococcus faecalis* between the 2 periods ($\beta = 0.001$; $P = .726$). Similarly, we did not detect an association between the change in piperacillin–tazobactam ($\beta = 0.001$; $P = .942$), meropenem ($\beta = -0.002$; $P = .260$), or vancomycin ($\beta = .001$; $P = .704$) consumption, nor for the difference in the proportion of CLABSI caused by *Candida* spp between the 2 periods.

Discussion

Our study demonstrated that there was a substantial increase in CLABSI incidence in Brazilian ICUs during the early months of the COVID-19 pandemic. On the other hand, we did not detect significant variation in VAP incidence. We also observed an increase in the proportion of CLABSI caused by *Enterococcus faecalis* and *Candida* spp during this period.

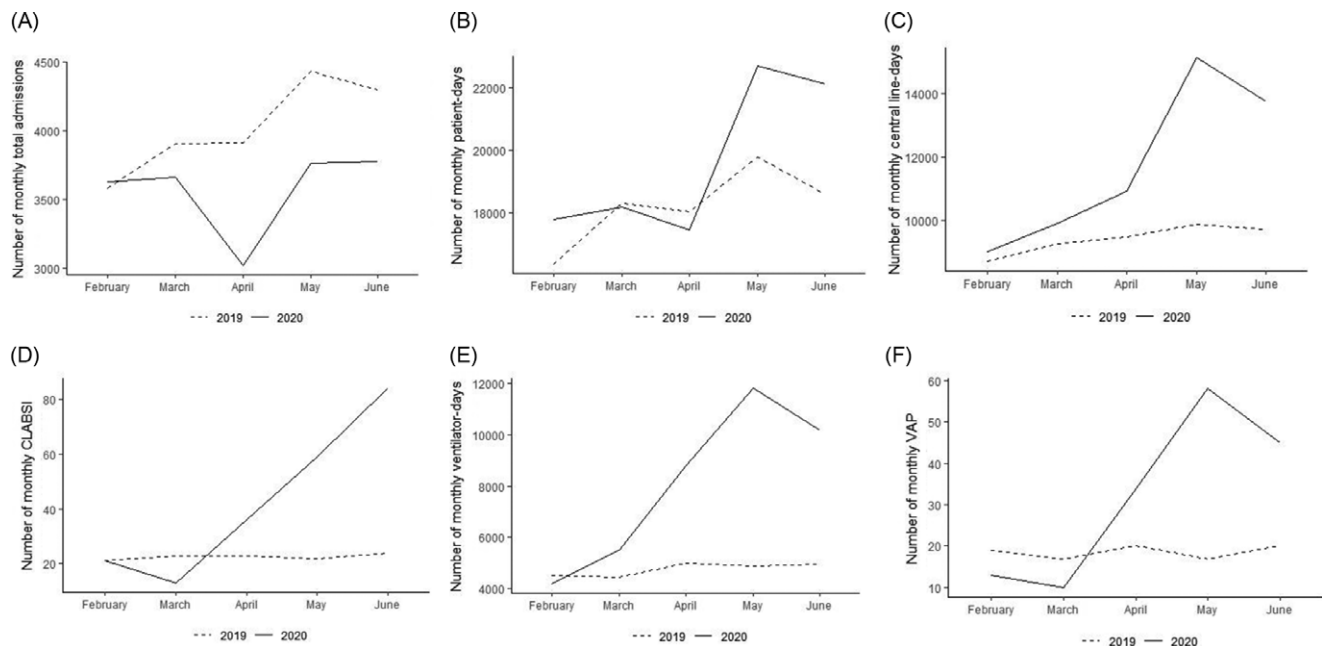
The increase in CLABSI in Brazilian ICUs during the pandemic in our study corroborates the increase in CLABSI demonstrated in a multicenter study evaluating 78 ICUs in the United States during the pandemic compared to the pre-pandemic period.⁸ Additionally, COVID-19 patients are at higher risk of CLABSI acquisition than non-COVID-19 patients.⁸ In contrast, another study did not find a significant variation in CLABSI incidence in the ICU during the COVID-19 pandemic compared to the 2 preceding years.⁹ This

Table 1. Comparison of ICU Admissions, Patient Days, CLABSIs, and VAP Cases in the ICUs of 21 Brazilian Hospitals Between the Prepandemic and Early Pandemic Periods

Variable	Median (IQR)		P Value ^a
	Apr–Jun 2019	Apr–Jun 2020	
No. of patients admitted to the ICU	531 (243–889)	357 (238–716)	.012
Patient days	2,199 (1,339–3,629)	2,114 (1,432–3,772)	.297
Central-line days	1,137 (631–1,992)	1,424 (934–2,311)	.001
CLABSIs, no.	2 (1–6)	4 (2–14)	.001
CLABSI incidence density (per 1,000 central-line days)			
Overall (n=21)	1.60 (0.44–4.20)	2.81 (1.35–6.89)	.002
Public hospitals (n=10)	1.69 (0–4.14)	4.67 (1.39–7.54)	.008
Private hospitals (n=11)	1.60 (0.99–4.60)	2.69 (0.98–5.21)	.075
Ventilator days	674 (361–1,057)	1,078 (725–1,881)	<.001
VAP cases, no.	2 (1–5)	4 (1–10)	.002
VAP incidence density (per 1,000 ventilator days)			
Overall (n=21)	2.99 (0.72–4.80)	3.65 (1.38–6.46)	.167
Public hospitals (n=10)	4.65 (2.27–7.25)	3.65 (1.14–6.43)	.767
Private hospitals (n=11)	2.54 (0–3.98)	3.65 (1.42–6.57)	.033

Note. ICU, intensive care unit; IQR, interquartile range; CLABSI, central-line-associated bloodstream infection; VAP, ventilator-associated pneumonia.

^aPairwise comparison of medians by the Wilcoxon signed rank-sum test.

**Fig. 2.** Total number of patients admitted (A), patient days (B), central-line days (C), CLABSIs (D), ventilator days (E), and VAP cases (F) in the intensive care units of 21 Brazilian hospitals between February–June 2019 and February–June 2020.

difference might be related to distinct impacts of the pandemic on HAI prevention strategies in different hospitals.

The absence of significant variation in VAP incidence during the pandemic in our study corroborates the finding of another investigation.⁹ However, other studies have already demonstrated an increase in VAP incidence during the pandemic, suggesting a higher risk of VAP in COVID-19 patients compared to

non-COVID-19 patients on invasive mechanical ventilation.^{10–12} The contrast between the findings of those studies and our study might be related to differences in IPC practices among the different hospitals.

Several factors could explain the increase in HAIs during the pandemic. The increase in central-line days and ventilator days during the pandemic in our study suggest an increased need of

Table 2. Comparison of the Most Important Causative Organisms of CLABSI and VAP in the ICUs of 21 Brazilian Hospitals Between the Prepandemic and Early Pandemic Periods^a

Organism	Total Among All Hospitals, No. (%) ^b		Proportion of Cases Identified in Each Hospital, Mean % (SD)		Proportion of Cases Identified in Each Hospital Median % (IQR)		P Value ^c	Adjusted. P Value ^d
	Apr–Jun 2019	Apr–Jun 2020	Apr–Jun 2019	Apr–Jun 2020	Apr–Jun 2019	Apr–Jun 2020		
CLABSI causative organism								
<i>Candida</i> spp	10 (15) ^e	38 (21) ^f	6 (12)	27 (33)	0 (0–7)	14 (0–50)	.017	.221
<i>Enterococcus faecalis</i>	2 (3)	21 (12)	1 (4)	14 (17)	0 (0–0)	8 (0–15)	.002	.028
<i>Klebsiella pneumoniae</i>	16 (24)	26 (15)	15 (21)	12 (23)	0 (0–33)	0 (0–20)	.209	1.000
<i>Staphylococcus aureus</i>	8 (12)	10 (6)	7 (13)	2 (4)	0 (0–13)	0 (0–4)	.046	.552
Coagulase negative <i>Staphylococcus</i>	10 (15)	38 (21)	20 (37)	19 (26)	0 (0–35)	13 (0–29)	.865	1.000
VAP causative organism								
<i>Acinetobacter baumannii</i>	7 (12)	24 (18)	6 (13)	16 (30)	0 (0–0)	0 (0–25)	.155	1.000
<i>Pseudomonas aeruginosa</i>	21 (37)	44 (32)	29 (36)	33 (33)	11 (0–50)	27 (0–44)	.983	1.000
<i>Staphylococcus aureus</i>	11 (19)	21 (15)	19 (31)	10 (15)	0 (0–24)	0 (0–20)	.650	1.000

Note. ICU, intensive care unit; IQR, interquartile range; CLABSI, central-line-associated bloodstream infection; VAP, ventilator-associated pneumonia.

^aThe complete list of causative organisms of CLABSI and VAP (see Supplementary Table S3 online).

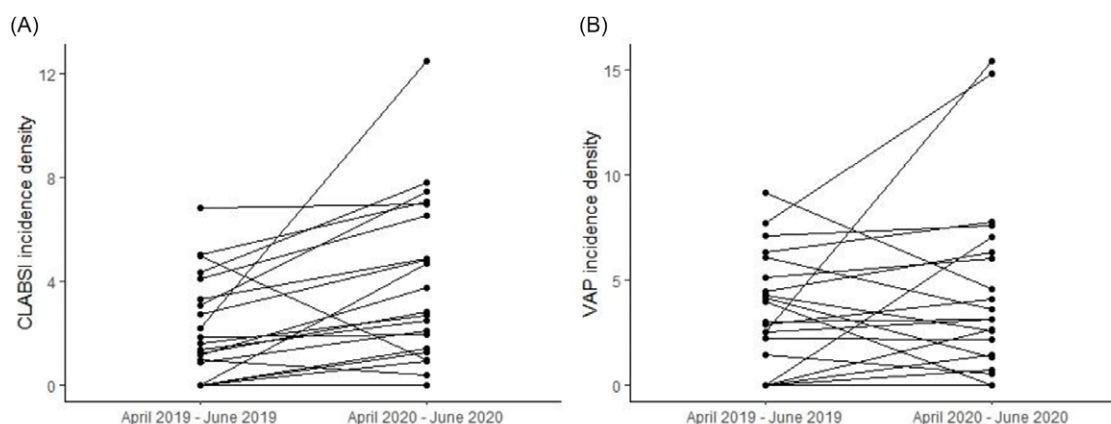
^bSome healthcare-associated infections had >1 causative organism.

^cPairwise comparison of medians by the Wilcoxon signed rank-sum test (*P* value unadjusted for multiple comparisons).

^d*P* values adjusted for multiple comparisons according to the Hochberg procedure.

^e*Candida* spp: 2 *C. albicans*, 2 *C. glabrata*, 1 *C. krusei*, 4 *C. parapsilosis*, and 1 *C. tropicalis*.

^f*Candida* spp: 13 *C. albicans*, 8 *C. glabrata*, 8 *C. parapsilosis*, 8 *C. tropicalis* and 1 non-*albicans Candida* spp.

**Fig. 3.** Variation in CLABSI incidence density (A) and in VAP incidence density (B) in the ICUs of 21 Brazilian hospitals between April–June 2019 and April–June 2020.

invasive procedures and an increased severity of ICU patients during this period. The increased severity of ICU patients could explain at least in part the higher risk of HAI during the pandemic.¹³ The increase in healthcare workers workload has also been demonstrated to increase the risk for HAI in ICUs.¹⁴ Therefore, the high workload of healthcare workers during the pandemic might also have influenced the incidence of HAI. However, the number of patient days and the proportion of COVID-19 patients admitted to the ICU, which could be considered proxies of workload during the pandemic, did not show a significant association with HAI incidence in our study. In addition to these factors, we hypothesize that the IPC teams from different hospitals might have been overwhelmed with the increased workload during the pandemic, and this may have negatively influenced

basic infection control measures and favored the occurrence of HAI. Nevertheless, the confirmation of the association between IPC team workload and HAI incidence needs to be explored in future studies.

Our study results also demonstrated changes in the causative agents of CLABSI during the pandemic. We detected an increase in the proportion of CLABSI caused by *E. faecalis* and *Candida* spp, although the increase in the latter did not retain statistical significance after correction for multiple comparisons. The increase in hospital infection caused by these 2 microorganisms during the pandemic have been demonstrated in several studies.^{8,15,16} Prolonged use of central lines might have contributed to the increase in CLABSI caused by *Candida* spp.¹⁷ We had hypothesized that the use of antimicrobials could have contributed to

Table 3. Comparison of the Rate of Drug-Resistant Organisms Causing HAIs in the ICUs of 21 Brazilian Hospitals Between the Prepandemic and Early Pandemic Periods

HAI Causative Organism	Total Isolates With Antimicrobial Resistance Among All Hospitals, No. (%) ^{a,b}		Proportion of Isolates with Antimicrobial Resistance in Each Hospital, Mean % (SD) ^b		Proportion of Isolates with Antimicrobial Resistance in Each Hospital, Median % (IQR) ^b		P Value ^c
	Apr–Jun 2019	Apr–Jun 2020	Apr–Jun 2019	Apr–Jun 2020	Apr–Jun 2019	Apr–Jun 2020	
Carbapenem-resistant <i>Enterobacteriaceae</i>	15 (32)	34 (44)	18 (36)	22 (35)	0 (0–13)	0 (0–46)	.878
Carbapenem-resistant nonfermentative gram-negative bacilli	28 (68)	67 (67)	26 (44)	35 (44)	0 (0–75)	0 (0–88)	.397
Oxacillin-resistant <i>Staphylococcus aureus</i>	10 (53)	21 (68)	14 (32)	17 (34)	0 (0–0)	0 (0–25)	.450
Vancomycin-resistant <i>Enterococcus</i>	1 (33)	7 (23)	5 (22)	15 (32)	0 (0–0)	0 (0–10)	.066

Note. HAI, healthcare-associated infection; ICU, intensive care unit; SD, standard deviation; IQR, interquartile range.

^aSome healthcare-associated infections had >1 causative organism.

^bProportions were calculated among each group of organisms (eg, proportion of oxacillin-resistant *Staphylococcus aureus* was calculated dividing the number of oxacillin-resistant *Staphylococcus aureus* by the number of *Staphylococcus aureus* identified).

^cPairwise comparison of medians by the Wilcoxon signed rank-sum test.

the increase in CLABSI caused by *E. faecalis*¹⁸ and *Candida* spp.^{19,20} However, we did not find an association between ceftriaxone use and enterococcal CLABSI or between broad-spectrum antibiotic use and CLABSI caused by *Candida* spp in our study.

Although there was no significant variation in the proportion of HAI caused by carbapenem-resistant gram-negative bacilli infection and methicillin-resistant *S. aureus* on the comparison between the pandemic and prepandemic periods in our study, we observed a trend toward the increase in HAI caused by drug-resistant organisms during the pandemic. A single-center study also demonstrated an increase in hospital infections caused by drug-resistant organisms during the pandemic.¹⁶ On the other hand, other studies have shown stability or decreases in HAIs caused by multidrug-resistant organisms during the pandemic.^{9,21,22} The differences in the rates of multidrug-resistant HAI among distinct hospitals during the pandemic may be due to differences in empiric antimicrobial treatments practices and in preexisting drug-resistant microorganisms colonization patterns.

Our study had several limitations. Data from a longer period and from hospitals of other Brazilian regions, would have better represented the pandemic across the country. In addition, it was not possible to evaluate the use of immunosuppressant medications, which could have influenced HAIs. However, we evaluated the early months of the pandemic, when the use of immunosuppressant medications was not standard of care for COVID-19 management in Brazil. Thus, we did not expect a marked increase in immunosuppressant use during the pandemic period evaluated.

In conclusion, our study showed an important increase in CLABSI incidence in Brazilian ICUs during the early months of COVID-19 pandemic. However, there was no significant change in VAP incidence in the same period. Additionally, during the first months of the pandemic, we detected an increase in the proportion of CLABSI caused by *E. faecalis* and *Candida* spp. Therefore, HAI prevention strategies, especially regarding prevention of CLABSI, must be reinforced in adult ICUs during the COVID-19 pandemic.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/ice.2022.65>

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