

# Central Line-Associated Bloodstream Infection in Adult Intensive Care Units during the COVID-19 Pandemic in Argentina

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### ABSTRACT

**Objective:** To characterize central line-associated bloodstream infection (CLABSI) occurring in adult Intensive Care Units (ICUs) in Argentina during the COVID-19 pandemic, as reported to the VIHDA Program (VIHDA is the acronym for "Vigilancia de Inspecciones Hospitalarias en Argentina, or "Surveillance of Hospital Infections in Argentina") their associated microorganisms, and resistance profiles.

**Methods:** A descriptive cross-sectional study on CLABSI reported to the VIHDA program during 2020-2021. We described the socio-demographic, clinical, and microbiological characteristics of CLABSI.

**Results:** The study included 2788 patients admitted to the ICU, of which 36.5% of the cases (n=1209) involved COVID-19. The median time between central catheter placement and IPS diagnosis was nine days (p25-p75: 5-14). Among ICU patients who presented with CLABSI, 50.3% died (n=1402); the proportion of deaths among those admitted for COVID-19 was higher compared to other reasons (p<0.05). The most frequently isolated microorganisms were *Klebsiella pneumoniae* (25.0%; n=884), coagulase-negative *Staphylococcus* (CNS) (17.2%; n=609), and *Acinetobacter* sp. (10.5%; n=370). Both *Klebsiella pneumoniae* and *Acinetobacter* sp. showed high percentages of non-susceptibility to third-generation cephalosporins and carbapenems. Thirty percent of *S. aureus* and 66.2% of SCN were methicillin-resistant.

**Conclusions:** In Argentina, during the pandemic, there was an increase in CLABSI in patients hospitalized in the ICU, along with the dynamics of COVID-19 cases. Mortality in patients with CLABSI admitted for COVID-19 was higher. A high proportion of multi-resistant microorganisms was evident.

**Keywords:** Healthcare-Associated Infection (HAI); Central Line-Associated Bloodstream Infection (CLABSI); Antimicrobial Resistance (AMR); COVID-19 Pandemic; Intensive Care Units (ICUs).

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## Infección primaria de la sangre asociada a catéter central en unidades de cuidados intensivos de adultos durante la pandemia de COVID-19 en la Argentina

### RESUMEN

**Objetivo:** caracterizar las infecciones primarias de la sangre asociadas a catéter central (IPS-CC) ocurridas en unidades de cuidados intensivos (UCI) de adultos de la Argentina durante la pandemia de COVID-19 informadas al Programa VIHDA, sus microorganismos asociados y perfil de resistencia.

**Métodos:** estudio descriptivo transversal sobre las IPS-CC informadas al programa VIHDA durante el período 2020-2021. Se describieron características sociodemográficas, clínicas y microbiológicas de las IPS-CC.

**Resultados:** se incluyeron 2788 pacientes internados en UCI, de los cuales en el 36,5% de los casos (n = 1209) el motivo de ingreso fue COVID-19. Entre la colocación del CC y el diagnóstico de IPS, la mediana fue de 9 días (p25-p75: 5-14). El 50,3% de los pacientes en UCI que presentaron una IPS-CC fallecieron (n = 1402); la proporción de fallecidos cuyo motivo de internación fue COVID-19 fue mayor con respecto a otros motivos (p < 0,05). Los microorganismos más frecuentemente aislados fueron: *Klebsiella pneumoniae* (25,0%; n = 884), *Staphylococcus coagulasa negativo* (SCN) (17,2%; n = 609) y especies de *Acinetobacter* (10,5%; n = 370). Tanto *Klebsiella pneumoniae* como las especies de *Acinetobacter* mostraron elevados porcentajes de no sensibilidad (NS) para cefalosporinas de tercera generación y carbapenemes. El 30,0% de *S. aureus* y el 66,2% de SCN fueron resistentes a la meticilina.

**Conclusiones:** en la Argentina, durante la pandemia, aumentó la ocurrencia de IPS-CC en pacientes internados en UCI acompañando la dinámica de casos de COVID-19. La letalidad en pacientes con IPS-CC ingresados por COVID-19 fue mayor. Pudo evidenciarse una alta proporción de microorganismos multirresistentes.

**Palabras clave:** infección asociada al cuidado de la salud (IACS), infección primaria de la sangre asociada a catéter central (IPS-CC), resistencia a los antimicrobianos (RAM), pandemia de COVID-19, Unidad de Cuidados Intensivos (UCI).

### INTRODUCTION

In December 2019, the first case of severe acute respiratory syndrome (SARS) caused by the new variant 2 of coronavirus, SARS-CoV-2, was reported in Wuhan, China<sup>1</sup>. After rapid global spread, on March 11, 2020, the World Health Organization (WHO) declared the COVID-19 pandemic<sup>2</sup>. The first COVID-19 case in Argentina became known on March 3, 2020<sup>3</sup>.

In Argentina and most countries, between 2020 and 2021, the development of the COVID-19 pandemic has been described in waves, referring to the graphical appearance of the temporal distribution of cases<sup>4-6</sup>. These descriptions compare the waves in terms of magnitude, case severity, geographical distribution, the dynamics of introducing people with active SARS-CoV-2 infection into regions, and their relation to the different health policies regarding control and mitigation measures implemented<sup>6</sup>.

During the 2020-2021 period in Argentina, three waves occurred<sup>6</sup>, and by July 15, 2022, a total of 9,426,171 infections and 129,145 deaths related to coronavirus had been reported since the beginning of the pandemic<sup>7</sup>.

The increasing number of COVID-19 cases created a growing workload, one of the main challenges for the health system to address during the pandemic. The focus was on the response capacity of intensive care units

(ICUs) and the need for mechanical respiratory assistance (MRA)<sup>8,9</sup>.

The workload in ICUs came to be regarded as an influential factor in care quality. That was evident in a study conducted in the Buenos Aires province in early 2021, which found that survival rates were lower in ICUs with over 80% occupancy<sup>8</sup>.

Healthcare-associated infections (HAIs) reflect the quality of care provided to patients.

In Argentina, epidemiological surveillance of healthcare-associated infections (HAIs) has been ongoing since 2004 through the National Program for Epidemiology and Control of Hospital Infections (VIHDA: Vigilancia de Infecciones Hospitalarias de Argentina) from the Instituto Nacional de Epidemiología Dr. Juan H. Jara (INE). The program has a virtual platform, VIHDA-WEB, to which affiliated healthcare institutions systematically record data on HAIs events in ICUs and surgical units associated with procedures, subsequently fed into a national database. Specifically, it monitors central line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), ventilator-associated pneumonia (VAP), and surgical site infections (SSI)<sup>10</sup>.

Catheter-related infections are a particularly relevant issue due to their frequency, morbidity, mortality, and the fact that they are potentially preventable clinical conditions.

Since patients treated in ICUs during periods of high demand showed worse clinical outcomes, we hypothesized that the high workload in ICUs during the pandemic could result in more episodes of CLABSI.

## OBJECTIVES

Characterize CLABSI in adult ICUs in Argentina in the context of the COVID-19 pandemic during 2020-2021 reported to the VIHDA Program<sup>10</sup>.

Identify the microorganisms most frequently associated with these infections and their antimicrobial resistance profile.

## MATERIALS & METHODS

We conducted a cross-sectional descriptive study to characterize CLABSI recorded in adult ICUs during 2020-2021 in Argentina.

The population of interest consisted of those episodes of CLABSI reported to the VIHDA-WEB system by healthcare institutions affiliated with the VIHDA program that were in "regimen" status during the study period, which implies that their data had undergone a quality control process.

In 2020, 186 ICUs from all over the country reported episodes, and there were 199 in 2021. Each episode contains information about a healthcare-associated infection associated with a risk factor, in this case, CLABSI. We only included closed episodes, which comprise the official data from the Ministerio de Salud de la Nación (MSAL).

The names of the institutions whose records form part of this publication are confidential, and patient records are encrypted in the system<sup>11</sup>.

We used the database of confirmed COVID-19 cases reported to the National Health Surveillance System (SNVS 2.0) to describe COVID-19 cases corresponding to the period of interest<sup>11</sup>.

The variables considered in this study included the sociodemographic characteristics of the patients, as well as the clinical and microbiological characteristics of CLABSI.

Among the sociodemographic characteristics included were sex (female/male), age group (according to five-year age groups), and region of residence (Northwest Argentina –NOA–, Northeast Argentina –NEA–, Central, Cuyo, South, and Buenos Aires Metropolitan Area –AMBA–, according to the distribution used by MSAL)<sup>12</sup>.

Among the clinical CLABSI characteristics, we included epidemiological week (taking into account the date of diagnosis for CLABSI cases and the opening date for COVID-19 cases), reason for ICU admission, date of ICU admission, date of central line placement, date of CLABSI diagnosis, discharge date, and CLABSI outcome (deceased/not deceased).

As for the microbiological characteristics of the CLABSI, we included identified microorganisms, antimicrobial resistance (sensitive/non-sensitive, showing resistant and intermediate results for each corresponding antibiotic according to the specific organism), and antimicrobial resistance mechanisms (presence/absence

for each corresponding mechanism according to the microorganism).

Regarding data analysis, we described quantitative variables by summary measures and categorical variables by absolute and percentage distribution.

We compared proportions using the Chi-square test. Any differences with  $p < 0.05$  were considered statistically significant.

To gather the data recorded in the VIHDA-WEB system, we used queries on Microsoft SQL Server 2008R2<sup>®</sup> and the R.4.2.1<sup>®</sup> language to consolidate and process the working database.

## RESULTS

### Sociodemographic and clinical characterization of CLABSI

In the distribution by sex and age, there was a predominance of CLABSI in men (65.5%) and in the age group of 61 to 65 years; the age groups between 51 and 70 years accounted for more than 50% of the cases.

Regarding the geographical distribution by region of residence of patients with CLABSI, the highest proportion of patients and reporting units corresponded to the Central region, followed by the AMBA region (Área Metropolitana de Buenos Aires).

When taken together, more than 80% of the cases evaluated came from these two regions. In this context, during the period 2020-2021, 3,206 episodes of CLABSI were reported to the VIHDA-WEB system in 2,788 patients hospitalized in adult ICUs, with a ratio of 1.2 episodes per patient, meaning that for every 100 patients, 20 had two episodes of CLABSI.

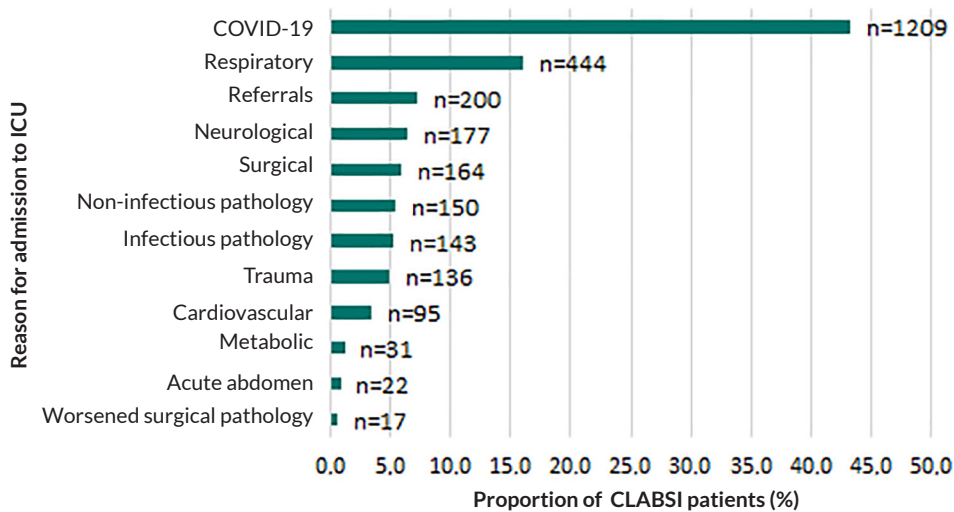
In the distribution by reason for ICU admission, out of the total number of CLABSI cases reported, the main reason was COVID-19 ( $n = 1,209$ ), which was three times higher than the second reason for hospitalization (non-COVID-19 respiratory diseases,  $n = 444$ ) (Fig. 1).

Comparing the temporal curves of the distribution of CLABSI cases with the total number of confirmed COVID-19 cases, we can see that the CLABSI curve followed the peaks of COVID-19 cases during the pandemic waves (Fig. 2), except for the peak seen between week 48 of 2021 and the early weeks of 2022. This particular peak was associated with mild respiratory illnesses, during which a large proportion of the population was on vaccination, and some isolation measures were beginning to phase out.

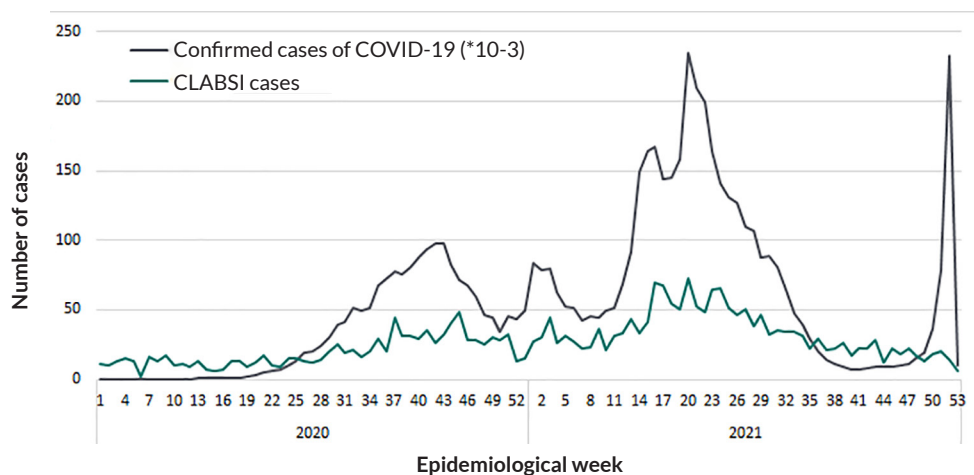
At the national level, the clinical course of CLABSI cases comprised a median of 0 days ( $p_{25}$ - $p_{75}$ : 0-2) between ICU admission and the placement of the central catheter (CC), a median of 9 days ( $p_{25}$ - $p_{75}$ : 5-14) between catheter placement and the diagnosis of CLABSI, and a median of 10 days ( $p_{25}$ - $p_{75}$ : 7-14) between the diagnosis of CLABSI and the discharge date.

50.3% of ICU patients who developed CLABSI died ( $n = 1,402$ ); only 293 due to CLABSI (10.5% of the total), and 725 passed away while undergoing CLABSI (26.0% of the total).

At the national level, the proportion of CLABSI patients whose reason for ICU admission was related to



**Figure 1.** Number of patients with CLABSI by reason for ICU admission. 2020-2021, Argentina. COVID-19: includes confirmed and suspected cases of COVID-19; Respiratory: reasons for respiratory-related hospitalization other than COVID-19 (respiratory distress, exacerbation of chronic obstructive pulmonary disease [COPD], need for mechanical ventilation); Transfers: reasons for hospitalization that include the transfer of the patient from other institutions or units; Neurological: includes cerebrovascular accident [CVA], intracranial hemorrhage, seizure syndrome, severe head trauma; Infectious pathology: infectious reasons for hospitalization other than COVID-19; Trauma: includes accidents, falls from heights, stab or gunshot wounds, polytrauma, burns; Cardiovascular: includes angina, arrhythmia, hypertensive crisis, and acute myocardial infarction; Acute abdomen: includes peritonitis and pancreatitis.



**Figure 2.** Distribution by epidemiological week of patients with CLABSI (based on diagnosis date) and national confirmed COVID-19 cases (based on opening date). 2020-2021, Argentina.

COVID-19 was higher compared to those admitted for other reasons. This difference was statistically significant ( $p < 0.05$ ).

50.3% of the ICU patients who presented with CLABSI died ( $n = 1402$ ); only 293 died as a result of the CLABSI (10.5% of the total), and 725 during ongoing CLABSI (26.0% of the total).

At the national level, the proportion of patients with IPS-CC who died and whose reason for admission was related to COVID-19 was higher than that of those with

other reasons for admission. This difference was statistically significant ( $p < 0.05$ ).

#### Microbiological characterization of CLABSI

It has been stated that the most frequently found etiological agents in CLABSI in ICUs are gram-positive cocci; however, in recent years, gram-negative bacilli and *Candida* species have increased in importance. *Staphylococcus* species are, worldwide, the main etiological agents of CLABSI.

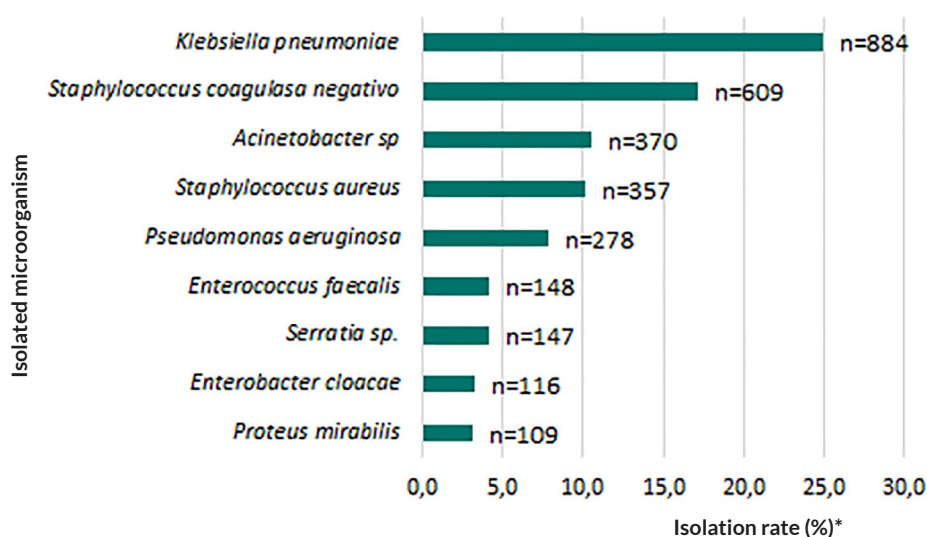
In our study, at the national level, the most frequently isolated microorganism (MO) was *Klebsiella pneumoniae* (*K. pneumoniae*) (24.97%; n = 884), followed by coagulase-negative *Staphylococcus* (CNS) (17.20%; n = 609), *Acinetobacter* species (10.45%; n = 370), *Staphylococcus aureus* (*S. aureus*) (10.08%; n = 357), and *Pseudomonas aeruginosa* (*P. aeruginosa*) (7.85%; n = 278) in fifth place. These results are similar to those obtained in the consolidated reports of the VIHDA Program in 2017, 2018, and 2019 on CLABSI in adults in Argentina, where *K. pneumoniae* was always the most frequently isolated microorganism<sup>10</sup> (Fig. 3).

Table 1 shows the resistance results reported by laboratories for gram-negative bacilli to third-generation cephalosporins and carbapenems, the resistance

mechanisms inferred by the laboratories for these microorganisms, and the methicillin resistance results for *Staphylococcus* species, completing the profile of the five most frequently isolated microorganisms (MO) from CLABSI.

71.9% of *Klebsiella pneumoniae* isolates showed non-susceptibility (NS) to third-generation cephalosporins, but extended-spectrum beta-lactamases (ESBL) were detected in only 29.3%. Meanwhile, 52.1% showed NS to carbapenems, with 40.3% attributed to the presence of carbapenemases (KPC, MBL, OXA-48-like).

In *Pseudomonas aeruginosa*, NS to carbapenems was mainly associated with non-enzymatic mechanisms (83%), followed by metallo-beta-lactamases (14.1%).



**Figure 3.** Distribution of microorganisms identified in patients with CLABSI with at least 100 isolates. 2020-2021, Argentina. The relative frequencies were calculated based on the total number of isolates in patients with CLABSI (n = 3,540).

**Table 1.** Antimicrobial resistance mechanisms of microorganisms isolated in patients with CLABSI. 2020-2021, Argentina

Resistance mechanisms inferred by the laboratories*	<i>Klebsiella pneumoniae</i> (n = 883)	<i>Pseudomonas aeruginosa</i> (n = 277)	<i>Acinetobacter sp.</i> (n = 370)	<i>Staphylococcus aureus</i> (n = 357)	<i>Staphylococcus coagulasa negativos</i> (n = 609)
ESBL*	29.3	3.3	3.0	NA	NA
KPC	17.2	1.1	2.4	NA	NA
MBL	14.7	14.1	5.4	NA	NA
OXA 48-like%	5.2	0.7	3.8	NA	NA
Double carbapenemases (%)	3.2	1.1	1.1	NA	NA
Methicillin resistance (%)	NA	NA	NA	30.0	66.2

\*The results of the isolates with antibiogram results and antibiotic resistance mechanisms are reported. ESBL: Extended-Spectrum Beta-Lactamases; KPC: *Klebsiella pneumoniae* carbapenemases; MBL: Metallo-Beta-Lactamases; OXA 48-like: OXA 48-like oxacillinase. Double carbapenemases: includes isolates with KPC-OXA 48-like, MBL-KPC, and MBL-OXA 48-like. NA: not applicable.

Carbapenem resistance in *Acinetobacter* species exceeds 90% due to the acquisition of class D carbapenemases inherent to this genus; metallo-beta-lactamase presence was detected in 5.4% of the isolates.

Regarding the resistance mechanisms detected in *Staphylococcus* species isolates, 29.9% of *S. aureus* were methicillin-resistant, and 66.0% of coagulase-negative *Staphylococcus*.

Regarding the results of the reported antibiograms and the antimicrobial resistance mechanisms inferred by the laboratories for microorganisms isolated in patients with CLABSI, we found that, of the total *K. pneumoniae* isolates, 71.9% showed non-susceptibility (NS) to third-generation cephalosporins (cefotaxime and ceftazidime); we detected ESBL in only 29.3%. A total of 52.1% of *K. pneumoniae* were non-susceptible to carbapenems; in 40.3%, this was due to the presence of carbapenemases (Klebsiella pneumoniae carbapenemases [KPC], metallo-beta-lactamases [MBL], and oxacillinase OXA 48-like [OXA 48-like]).

In the case of *P. aeruginosa*, 44.6% of the isolates were non-susceptible (NS) to carbapenems, and 14.1% showed the presence of MBL, assuming non-enzymatic mechanisms in the remaining isolates.

Non-susceptibility (NS) to carbapenems in *Acinetobacter* species was 91.5%, which can be associated with acquiring class D carbapenemases typical of this genus. We detected the presence of metallo-beta-lactamase in 5.4% of the isolates.

Regarding the resistance mechanisms detected in the isolates of *Staphylococcus* species, 30.0% of *S. aureus* and 66.2% of coagulase-negative *Staphylococcus* were resistant to methicillin (see Table 1).

## DISCUSSION

Numerous studies have reported that patients admitted to ICUs for COVID-19 more frequently experienced a healthcare-associated infection (HAI) complication than other patients<sup>13,14</sup>; in particular, a higher frequency of CLABSI has been well-established<sup>15-18</sup>. This study aimed to evaluate the problem with a focus on HAIs surveillance and specifically describe the incidence of CLABSI in adult ICUs during the COVID-19 pandemic.

The profile of patients admitted to ICUs during the pandemic changed compared to previous years. That was due, on the one hand, to the characteristics of COVID-19 patients (over 50 years old, with comorbidities and a body mass index over 30) and, on the other hand, to the measures adopted to cope with the emergency, such as the suspension of scheduled surgeries and the reduction in traffic accidents due to population isolation measures<sup>19,20</sup>.

The time intervals between the different milestones in the clinical course of CLABSI suggest, on the one hand, early placement of central catheters (CC), coinciding with the date of ICU admission, and on the other hand, that CLABSI may be more associated with catheter maintenance than with its insertion, given that the median time to diagnosis extends to 9 days.

Regarding the isolated etiological agents, *K. pneumoniae* was the most frequent microorganism, as has been observed since 2017 in ICU CLABSIs in our country, differing from the literature, which describes *Staphylococcus* species as the main etiological agent of ICU CLABSI. This situation could be related to the placement of the CC in the femoral access and the pronation of patients, a common condition in those hospitalized for respiratory conditions. Further studies are necessary to explore the relationship between CC location and the microorganisms found and to determine whether factors such as prone positioning, specific COVID-19 treatments, comorbidities, changes in infection control practices, or a combination of them may be associated with higher rates of CLABSI or other healthcare-associated infections (HAIs).

Both *K. pneumoniae* and *Acinetobacter* species and *P. aeruginosa* showed high percentages of non-susceptibility (NS) to third-generation cephalosporins and carbapenems, which may be due to the antibiotic pressure exerted by the increased use of antimicrobials for the treatment of bacterial co-infections associated with COVID-19.<sup>21</sup>

## CONCLUSIONS

The development of this study highlighted an increase in the occurrence of CLABSI (central line-associated bloodstream infections) in adult patients in Argentina during the 2020-2021 period, which followed the dynamics of COVID-19 cases.

The main reason for hospitalization in these patients was a history of COVID-19, and there were more cases than expected in both years compared to baseline values. Additionally, mortality was significantly higher in these patients compared to those who did not have a history of COVID-19.

The maintenance of the central catheter (CC), rather than its placement, was identified as a probable factor in the development of CLABSI, which suggests future actions to improve management and reduce infection risk.

A high proportion of multidrug-resistant microorganisms was evident.

The relationship between CLABSI and COVID-19 is not yet fully clarified.

Our results underscore the importance of maintaining epidemiological surveillance of healthcare-associated infections (HAIs) despite disruptive events such as the COVID-19 pandemic and providing periodic information on their characteristics and the profile of the microorganisms involved to contribute to better care and safety conditions for ICU patients.

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**Author contributions:** Conceptualization: MG, LDA, BIC, NJT, KL, GFM, IEP, FL. Methodology: MG, FH, LDA, BIC, DA, IEP, FL. Software: MG, FH, DA, LEF, RGL. Validation: MG, FH, DA, LEF, RGL. Formal analysis: MG, FH, LDA, NJT, LEF, RGL, IEP, FL. Investigation: MG, FH, LDA, BIC, NJT, LEF, RGL, IEP, FL. Resources: MG, FH, LDA, BIC,

NJT, CEBV, LEF, RGL, KL, GFM, IEP, FL. Writing – Original Draft: MG, LDA, KL, GFM, IEP, FL. Writing – Review and Editing: MG, LDA, BIC, NJT, CEBV, RGL, KL, GFM, IEP, FL. Data curation: FH, DA, LEF, RGL. Visualization: BIC, CEBV, LEF, RGL, KL, GFM, IEP, FL. Project administration: CEBV, LEF, RGL, IEP, FL. Supervision: IEP, FL.

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