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ORIGINAL ARTICLE

Health care-associated infections and mortality in critically ill pediatric patients

Infecciones asociadas a la atención de salud y mortalidad en pacientes pediátricos críticamente enfermos

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What do we know about the subject matter of this study?

Healthcare-associated infections (HAIs) are infections acquired in the hospital environment within 48 hours of admission. In pediatric intensive care, they are associated with increased mortality, length of stay, and hospital costs. Many of these infections are potentially preventable and could be a marker of quality of care.

What does this study contribute to what is already known?

This study evaluates the impact of HAIs on a pediatric intensive care unit of reference in a developing country, offering a predictive model of mortality based on demographic, clinical, and microbiological variables of which the presence of multidrug-resistant bacteria stands out.

Abstract

Healthcare-Associated Infections (HAIs) in Pediatric Intensive Care Units (PICUs) are a global problem. Mortality due to HAIs is 10% and may be higher in developing countries. **Objectives:** To determine the association between HAIs and mortality in pediatric patients admitted to the Intensive Care Unit in a tertiary Hospital. **Patients and Method:** Observational retrospective cohort study. Demographic and clinical variables (diagnosis, origin area, length of stay, mortality), as well as infectious variables (type of microorganism, type of HAI, multidrug resistance), were analyzed. The relationship between mortality and the development of HAI was assessed using the Chi-square test. A logistic regression model was used to evaluate other explanatory variables of mortality. **Results:** 363 patients were studied, 23.7% of them were diagnosed with HAIs. The median age was 3 years (IQR: 1-9) and 51.2% were male. The most frequent HAI was ventilator-associated pneumonia (36%). Overall mortality was 10.7%, with a significant difference between groups with and without HAIs (18.4% vs. 8.7%, respectively; p = 0.01). The predictive mortality model concluded an association between mortality and multidrug-resistant (MDR) bacteria (OR: 8.66; 95% CI 2.01-37.21; p = 0.004). This group had a longer stay in the PICU (18 vs. 6 days; p=<0.001). **Conclusions:** For patients admitted to the PICU at *Hospital Baca Ortiz* in 2022, the presence of MDR bacteria was associated with increased mortality and length of stay.

Keywords:
Mortality;
Healthcare-Associated Infections;
Pediatric Intensive Care;
HAIs

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Introduction

Worldwide, healthcare-associated infections (HAIs) in pediatric intensive care units (PICUs) are a problem[1] with implications for costs, hospital resources, and clinical outcomes[2]. The incidence of HAIs varies according to the unit evaluated, ranging from as low as 1.5% to approximately 50% in low-income countries[3]. Local studies in Ecuador have reported a 13.5% prevalence rate[4]. Mortality varies from 10 to 50% depending on the country and the type of PICU analyzed[2,3,5]. The presence of HAIs is a deleterious marker of the evolution of these patients and may determine the need for expensive diagnostic and therapeutic interventions[6].

HAIs are classified according to the source of origin, being the most frequent central venous catheter-associated infection (CVCAI) with a 30% prevalence in the PICU[7,8], followed by ventilator-associated pneumonia (VAP) with 25%[5], catheter-associated urinary tract infections (CAUTI) with 15%[9], and finally surgical site infection (SSI) with 11% prevalence[2].

Several risk factors associated with the development of HAIs have been described, many of which are modifiable depending on the type of infection, the technique used to perform invasive procedures, and the protocols followed during such interventions. In this context, hospitalization stays longer than 10 days, the presence of antibiotic-resistant organisms, and the type of infection developed stand out[3,8,10].

In Ecuador, there are no structured data on the behavior of these infections and their impact on clinical outcomes in pediatric patients, which establishes a knowledge gap on a condition of relevance in the care of critical patients and the quality of services provided. The objective of this study was to determine the association between HAIs and mortality in patients admitted to the PICU of the Hospital Baca Ortiz (HBO) in 2022.

Patients and Method

Study design

Observational, analytical, retrospective cohort study of patients admitted to the PICU of the HBO. This is a tertiary-level institution belonging to the Ministry of Public Health of Ecuador (MSP) that specializes in pediatric patient care and is one of the two national reference hospitals for this age group.

Inclusion criteria

Pediatric patients admitted to the PICU of the HBO in 2022, aged between one month and 15 years.

Exclusion criteria

Patients whose total stay, from hospital admission to ICU discharge, was less than 48 hours, or if their microbiological findings were classified as colonization or contamination (figure 1).

Operational definitions

Healthcare-associated infection (HAI): An infection that developed 48 hours or more after hospital admission, with no evidence that the condition was present or incubating at the time of admission[11]. For this study, HAIs were considered to be CAVCAI, VAP, CAUTI, and SSI.

Colonization: Growth of microorganisms in non-sterile culture samples without clinical evidence of infection[12]. The presence of microorganisms in any sterile specimen was interpreted as infectious, thus initiating appropriate therapy.

Contamination: Applicable to blood and urine cultures. In the case of blood cultures, contamination was defined as the isolation of a contaminant bacterium in patients without risk factors[13]. A blood culture is considered contaminated when only one set out of multiple sets tests positive for a commensal organism, defined as any skin-colonizing bacterium[14]. Regarding urine cultures, any sample with $> 10^5$ CFU/mL of two or more different organisms, or bacterial growth in quantities $< 10^5$ CFU/mL[15], was considered contaminated.

Central venous catheter-associated infection (CVAI)[16]: An infection confirmed by blood culture plus the presence of a central venous catheter (CVC) for more than 2 calendar days.

Ventilator-associated pneumonia (VAP)[17]: An infection that develops in patients who have been on mechanical ventilation for more than two consecutive days, considering the day of ventilator initiation as day one. At the time of diagnosis, the patient must be on mechanical ventilation or have been on it the day before.

Catheter-Associated Urinary Tract Infection (CAUTI)[5]: Indwelling urinary catheter for more than two consecutive days during hospitalization, or within one day after its removal, associated with fever, pain, dysuria, or increased urinary frequency. It also applies when a urine culture shows no more than two microbial species, with at least one present at a concentration of $\geq 10^5$CFU/mL).

Surgical site infection (SSI)[5]: Purulent drainage or isolated organisms at the surgical site (skin, subcuta-

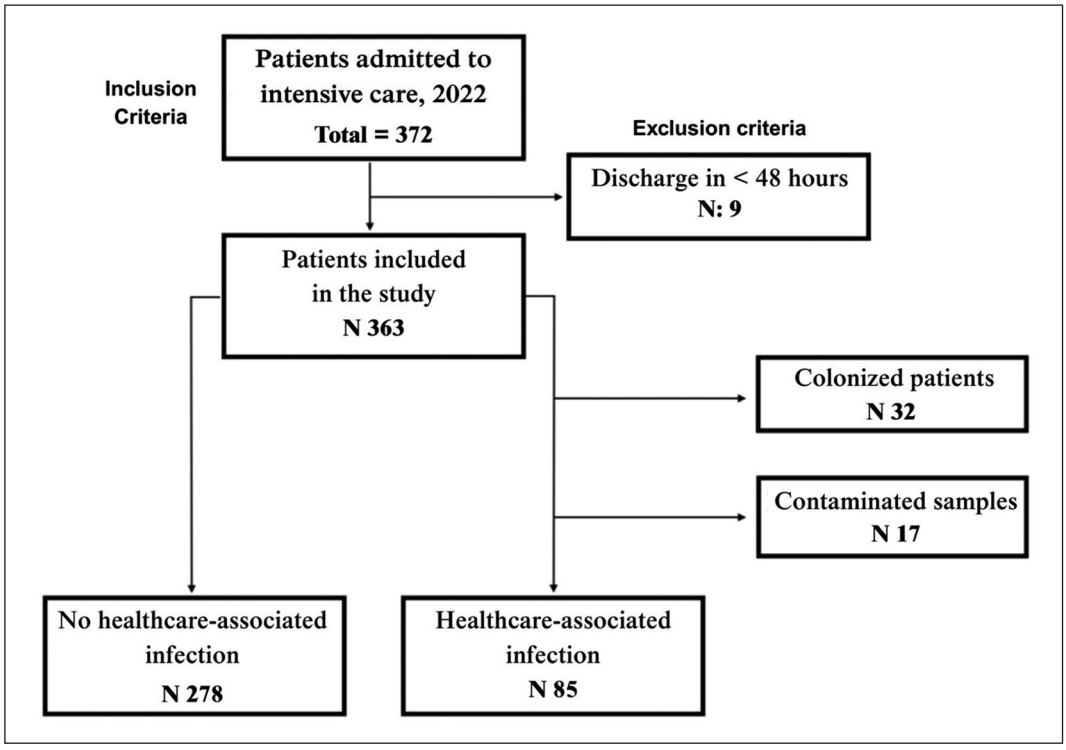

Figure 1. Patient Selection Flowchart.

neous tissue, deep layers, or distant organs) within 30 days following surgery, associated with clinical signs of infection.

Multidrug resistance (MDR)[18]: No susceptibility of a strain to at least one agent from three or more antibiotic classes.

Variable selection

The dependent variable was mortality in intensive care, while the independent variable of interest was the presence of HAIs. The remaining variables were selected to evaluate the demographic profile (age in years, sex, weight in kilograms, and province of origin), clinical characteristics (diagnosis on admission, clinical or surgical type, hospital area of origin, days of stay), and relevant infectious characteristics (type of microorganism isolated, type of HAI, multidrug resistance). The microbiological information was obtained through the HAI registry and passive surveillance sheets from the microbiology laboratory in relation to positive cultures.

Statistical analysis

Univariate analysis included the description of nominal variables in absolute and relative frequencies. Numerical variables were subjected to normality tests to decide the appropriate measure of central tendency and dispersion. For bivariate analysis, chi-square and Student's t-test or their corresponding nonparametric tests were used if necessary. The hypothesis test was established at a significance of < 0.05. Multivariate analysis was performed using binary logistic regression, calculating crude and adjusted odds ratios for clinical, demographic, and infectious disease variables that could modify the relationship between the two variables of interest. Statistical Package for Social Sciences (SPSS) version 24 software was used for the analysis.

The research protocol was approved by the Hospital Ethics Committee, code 003-CEISH-HPBO-PA-2023.

Results

A total of 363 pediatric patients were included, of whom 23.7% (85 patients) were diagnosed with HAIs. The demographic profile showed a median age of 3 years (IQR: 1-9) of which a quarter were younger than 1 year. 188 (51.8%) patients were male. Table 1 describes the demographic and clinical variables when segmenting the population in the presence or absence of HAI.

The most frequent HAI was VAP with 30 cases (35.3%), followed by CVCAI with 27 patients (31.8%), CAUTI with 16 cases (18.8%), and SSI was the least frequent with 12 cases (14.1%). The only HAI associ-

ated with mortality was VAP (p = 0.03) with an OR of 2.73 (95%CI 1.09-6.82).

Overall mortality was 11% (40 patients), with a significant difference between the groups with and without HAIs (18.8%, vs. 8.6%, respectively; p = 0.009). The OR for mortality and HAIs was 2.45 (95%CI 1.23-4.88). PICU length of stay in patients with HAIs was 7 vs. 5.5 (IQR: 5-15 vs. 4-10, respectively) with significant differences between both groups (p: < 0.001). The remaining variables (clinical and demographic) showed no relevant differences.

Table 2 describes the microbiological profile of the infections. *Staphylococcus aureus* and *Candida albicans* were the most common agents in cases of CVCAI. VAP was related to *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in almost half of the cases. *Escherichia coli* was the predominant microorganism in CAUTI. *P. aeruginosa* also led the cases of SSI.

The total percentage of microorganisms reported as resistant to three or more antimicrobials was 6.6% (24 cases), determining in the bivariate analysis association with mortality p < 0.001 with an OR 7.36 (95%CI 3.01-17.96). The most frequent was *S. aureus*, with a frequency of 29.17% (7 cases), followed by *P.*

Table 1. Demographic and clinical data in patients with and without healthcare-associated infections

	HAIs (n: 85)	No HAIs (n: 278)	P-value
Sex			
Female, n (%)	39 (45.9)	136 (48.9)	0.62
Age			
Years, median (IQR)	2 (1-7)	3 (1-9)	0.31
Weight			
Kg, median (IQR)	12 (7-20)	12.9 (7.7-24)	0.39
Origin			
Emergency room, n (%)	45 (52.9)	139 (50)	0.64
Hospitalization, n (%)	11 (12.9)	52 (18.7)	0.22
Surgery, n (%)	28 (32.9)	85 (30.6)	0.68
Outpatient consultation, n (%)	1 (1.2)	1 (0.4)	0.37
City of Origin*			
Pichincha, n (%)	32 (37.6)	117 (42.1)	0.47
Imbabura, n (%)	7 (8.2)	12 (4.3)	0.16
Cotopaxi, n (%)	8 (9.4)	17 (6.1)	0.29
Admission type			
Clinical, n (%)	53 (62.4)	192 (69.1)	0.29
Surgical, n (%)	32 (37.6)	86 (30.9)	0.29
Cancer patient	11 (12.9)	24 (8.6)	0.24
Chronic kidney disease	5 (5.9)	19 (6.8)	0.76
Admission diagnosis**			
Bacterial pneumonia, n (%)	25 (29.4)	99 (35.6)	0.29
Postoperative care, n (%)	31 (36.5)	76 (27.3)	0.11
Viral pneumonia, n (%)	6 (7.1)	25 (9)	0.56
ICU stay			
Days, median (IQR)	7 (5-15)	5.5 (4-10)	< 0.001
Condition at discharge			
Death, n (%)	16 (18.8)	24 (8.6)	0.009

*The three most frequent provinces have been included. **The three most frequent diagnoses have been included. HAI: healthcare-associated infection, IQR: interquartile range

Table 2. Microbial etiologies according to type of nosocomial infection

Microbiological isolates by type of infection		Total cases N = 85
Central venous catheter-associated infection		N = 27
Staphylococcus aureus	n (%)	15 (55.6)
Candida albicans	n (%)	7 (25.9)
Pseudomonas aeruginosa	n (%)	2 (7.41)
Enterococcus faecalis	n (%)	2 (7.41)
Klebsiella pneumoniae	n (%)	1 (3.70)
Ventilator-associated pneumonia		N = 30
Klebsiella pneumoniae	n (%)	8 (26.67)
Pseudomonas aeruginosa	n (%)	8 (26.67)
Stenotrophomonas maltophilia	n (%)	5 (16. 67)
Staphylococcus aureus	n (%)	5 (16.67)
Klebsiella oxytoca	n (%)	2 (6.67)
Acinetobacter baumannii	n (%)	1 (3.33)
Enterobacter cloacae	n (%)	1 (3.33)
Citrobacter coseri	n (%)	1 (3.33)
Urinary tract infection		N = 16
Escherichia coli	n (%)	9 (56.2)
Candida albicans	n (%)	2 (6.25)
Acinetobacter baumannii	n (%)	1 (6.25)
Enterobacter cloacae	n (%)	1 (6.25)
Pseudomonas aeruginosa	n (%)	1 (6.25)
Enterococcus faecalis	n (%)	1 (6.25)
Klebsiella pneumoniae	n (%)	1 (6.25)
Surgical site infection		N = 12
Pseudomonas aeruginosa	n (%)	4 (33.3)
Enterococcus faecalis	n (%)	2 (16.6)
Klebsiella pneumoniae	n (%)	2 (16.6)
Enterobacter cloacae	n (%)	2 (16.6)
Staphylococcus aureus	n (%)	2 (16.6)

aeruginosa, which was reported 5 times, with a relative frequency of 20.83%. *K. pneumoniae* ranked third in frequency, registering 4 occurrences and a relative frequency of 16.67%. Resistance to beta-lactams was 100%. In addition, 14 of the isolates reported production of extended-spectrum beta-lactamases (ESBL). In the test for carbapenem resistance, only two cases were observed (figure 2). Resistance to aminoglycosides and quinolones was 95.7%. No resistance to glycopeptides was reported (table 3).

A binary logistic regression model was created, including the variables that were significant in the bivariate analysis (VAP, HAIs, and the presence of resistant microorganisms). The model also included 2 demographic variables: age in years and age group (less than 1 year, yes/no), and 2 clinical variables: days in the PICU and oncological disease (yes/no). Additionally, the remaining HAIs were included to determine their influence on mortality. The variable selection method was performed using backward steps with likelihood

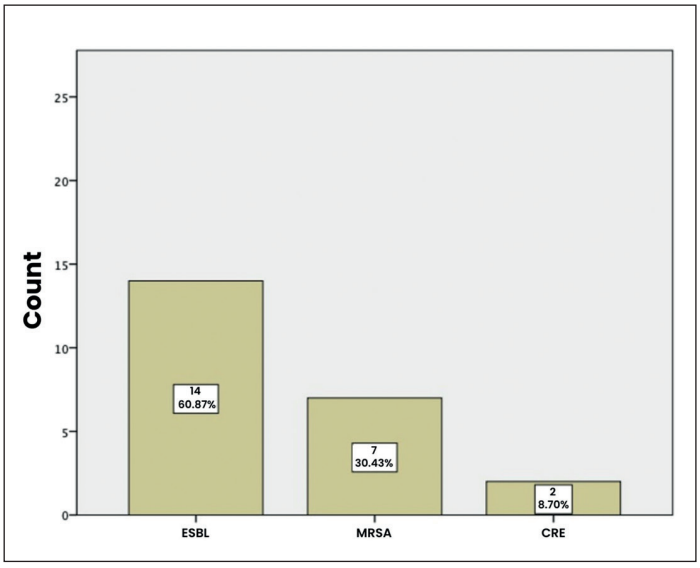

Figure 2. Frequency distribution of bacteria according to resistance profile. ESBL: extended-spectrum beta-lactamases, MRSA: Methicillin-resistant *Staphylococcus aureus*, CRE: carbapenem-resistant enterobacterales.

Table 3. Resistance profile in multidrug-resistant microorganisms

	BL	CP	AG	QN	PM	T	S	GP	M	A	EC	PE
K. pneumoniae	R	S	R	R	S	S	R	N/A	R	N/A	N/A	N/A
P. aeruginosa	R	S	R	R	S	R	S	N/A	R	N/A	N/A	N/A
S. aureus	R	S	R	R	N/A	R	R	S	S	N/A	N/A	N/A
A. baumannii	R	R	R	R	S	R	S	N/A	S	N/A	N/A	N/A
S. aureus	R	S	R	R	N/A	R	R	S	S	N/A	N/A	N/A
K. pneumoniae	R	S	R	R	S	S	R	N/A	R	N/A	N/A	N/A
P. aeruginosa	R	S	R	R	S	R	S	N/A	R	N/A	N/A	N/A
K. pneumoniae	R	S	R	R	S	S	R	N/A	R	N/A	N/A	N/A
C. koseri	R	S	R	R	S	R	R	N/A	R	N/A	N/A	N/A
E. coli	R	S	R	R	S	R	R	N/A	R	N/A	N/A	N/A
A. baumannii	R	R	R	R	S	R	S	N/A	S	N/A	N/A	N/A
S. aureus	R	S	R	R	N/A	R	R	S	S	N/A	N/A	N/A
K. pneumoniae	R	S	R	R	S	S	R	N/A	R	N/A	N/A	N/A
S. aureus	R	S	R	R	N/A	R	R	S	S	N/A	N/A	N/A
P. aeruginosa	R	S	R	R	S	R	S	N/A	R	N/A	N/A	N/A
S. aureus	R	S	R	R	N/A	R	R	S	S	N/A	N/A	N/A
E. cloacae	R	S	R	R	S	R	R	N/A	R	N/A	N/A	N/A
P. aeruginosa	R	S	R	R	R	R	S	N/A	R	N/A	N/A	N/A
S. aureus	R	S	R	R	N/A	R	R	S	S	N/A	N/A	N/A
E. faecalis	R	S	S	S	N/A	S	R	S	S	N/A	N/A	N/A
S. aureus	R	S	R	R	N/A	R	R	S	S	N/A	N/A	N/A
C. albicans	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	R	S	S
P. aeruginosa	R	S	R	R	R	R	S	N/A	R	N/A	N/A	N/A
E. coli	R	S	R	R	S	R	R	N/A	R	N/A	N/A	N/A

R: Resistant, S: Sensitive, N/A: Not applicable, BL: Beta-lactams, CP: Carbapenems, AG: Aminoglycosides, QN: Quinolones, PM: Polymyxins, T: Tetracyclines, S: Sulfonamides, GP: Glycopeptides, M: Macrolides, A: Azoles, EC: Echinocandins, PE: Polyenes.

Table 4. Binary logistic regression model

	Bivariate			Multivariate		
	Crude OR	95%CI	p	Adjusted OR	95%CI	p
Age	-	-	-	-	-	-
< 1 year	1.28	0.62-2.64	0.50	-	-	-
Weight	-	-	-	-	-	-
Oncological cause	2.24	0.91-5.51	0.07	-	-	-
Days in ICU	-	-	-	-	-	-
HAIs	1.19	0.49-2.90	0.009	-	-	-
VAP	2.64	1.06-6.60	0.03	-	-	-
MDR	7.36	3.01-17.99	< 0.001	7.36	3.01-17.99	< 0.001
CVAI	1.96	0.705.49	0.20	-	-	-
CAUTI	1.16	0.25-5.31	0.85	-	-	-
ISQ	1.65	0.35-7.80	0.53	-	-	-

HAIs: healthcare-associated infections, VAP: ventilator-associated pneumonia, MDR: multidrug resistance, CVAI: central venous catheter-associated infection, CAUTI: catheter-associated urinary tract infection, SSI: surgical site infection, OR: odds ratio, CI: confidence interval. *Only the final step of the backward stepwise elimination using likelihood ratio is presented.

ratios. After 11 elimination steps, the model retained only the presence of MDR bacteria as the sole variable associated with mortality ($p < 0.001$) with an OR of 7.36 (95% CI: 3.01-17.99).

Nagelkerke R-squared indicated that the independent variables explained the mortality outcome by 9%, although the Hosmer-Lemeshow test showed that the model fit adequately (p: 0.69) (table 4). When comparing the presence or absence of MDR germs, the median length of stay in the PICU was 18 days vs. 6 days (IQR 14.5-34 vs 4-10, respectively) ($p = < 0.001$).

Discussion

This study analyzed the association between HAIs and mortality in pediatric patients admitted to the PICU of the *Hospital Baca Ortiz* in 2022. Similar to other research, such as that of Cambridge University Hospitals, the demographic profile showed a predominance of male sex and a median age of 3 years[10], a situation that could be highly variable depending on the type of intensive care unit investigated.

HAIs occurred in 23.4% of the study population, showing notably higher rates than in developed countries. Data from the United States and Canada indicate a prevalence of 2 to 9%[7,19,20]. European studies report a prevalence of 15.5%[4], with higher rates in Asian countries, reaching 25%[5]. In Africa, the figures are even higher, reaching 45%[6,7].

In middle-income countries in Latin America, where physical space is limited, staffing is insufficient, and specialty centers are scarse[21], mortality rates are close to 20%[22,23]. In this sense, we consider that the level of economic and social development could substantially influence the results.

In our series, VAP was the most prevalent (35.3%), similar to reports in India (30%) but much higher than in Europe and North America where this infection occurs between 10 to 20%[1]. It has been described that the presence of VAP is a marker of mortality[24], a situation consistent with our research, which indicates a 2.64-fold increase in the probability of death. The distribution of the other types of HAIs in relation to mortality did not show differences in frequency of presentation. This behavior is similar to the data reported in the 2016 Spanish series[25] and the 2017 European report[26].

Based on our data, it is known that those patients with HAIs had longer hospital stays, which was statistically significant in the bivariate analysis. Studies in Europe and Asia have also reported this finding[26,27]. Although there are vulnerable groups where HAIs can worsen prognosis, our research did not find an increase in mortality in oncology, transplant, or chronic kidney disease patients.

Our study showed a mortality of 10.7% (39 patients) comparable to other Latin American countries[21]. It should be noted that there is a wide variability of information regarding the death rates. Central American and Caribbean countries have the highest death rates with approximately 25%[21]while the United States reported 2.39%[28]. Although there are multiple risk factors to explain mortality in the PICU, this

research has focused on the presence of HAIs. In the bivariate analysis, three variables were found to be associated with mortality: presence of HAI, VAP, and MDR microorganisms.

Regarding the microbiological profile, *S. aureus* (25%) was the most frequent bacterium reported in cultures, followed by *P. aeruginosa*, and *C. albicans*. This profile is similar to other studies[26,27] (Aktar et al., 2016b; Zingg et al., 2017). The total percentage of microorganisms reported as MDR was 6.6%, and was the main variable associated with mortality. The length of stay in the PICU was significantly higher than the MDR group with 18 days vs. 6 days (IQR 14.5-34 vs. 4-10) ($p = <0.001$).

A review of the literature found that the percentage of MDR in the PICU exceeds 40% and is unfavorably associated with mortality[29].

Similar reports have been made in Egypt with a prevalence of 9.2%, highlighting an increase in the length of stay and days on mechanical ventilation[30]. An epidemiological study in Spain indicated a mortality of 16.3% with no statistical differences[31]. In Malaysia, the prevalence of MDR was 42.5% with a mortality of 37.3%, similar to Saudi Arabia, where the prevalence was 52% and 17% of mortality with no statistical difference with non-MDR[32].

Among the limitations of the research, we highlight a very low casuistry in certain causal agents probably associated with the short evaluation period, which does not allow us to generate categorical conclusions on mortality markers. The relevance of this study was centered on the possibility of establishing intervention strategies to strengthen the control of HAIs and thus reach standards similar to those of developed countries. The regression model using the available variables did not achieve an optimal predictive capacity, so it would be necessary to rethink the elements of analysis.

Conclusion

HAIs are highly relevant events in intensive care units due to their association with unfavorable outcomes. At the *Hospital Baca Ortiz* in Quito, the presence of HAIs was not associated by itself with mortality; however, those patients with MDR profiles presented high mortality rates and prolonged PICU stays.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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