


Risk Factors Associated with *Acinetobacter baumannii* Infections in Patients in an Intensive Care Unit of a Public Hospital in Paraná

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Abstract

To identify risk factors for *A. baumannii* infection in patients hospitalized in an Intensive Care Unit (ICU) of a tertiary public hospital in Paraná, Brazil, a retrospective paired case-control study (ratio 1:2) was conducted from January 2018 to December 2020. Patients in the case group were hospitalized in the ICU with *A. baumannii* (n = 68 cases) and were compared with patients in the control group, without infection by *A. baumannii* (n = 136). Both were matched by age (± 10 years), sex, and ICU stay (± 5 days). Conditional multiple logistic regression was used to determine statistically significant risk factors based on the results of bivariate analyses. Mortality was higher in infected (cases) than in non-infected patients (51.5% vs. 39.7%). The incidence and bacterial resistance increased annually. At bivariate analysis, cases had longer hospital stays (median 35 vs. 22 days, $p < 0.001$) and remained longer in the ICU (median 23 vs. 16 days, $p < 0.001$). Longer use of a central venous catheter (median 25 vs. 18 days, $p < 0.001$), the vesical catheter (median 29 vs. 20 days, $p < 0.001$), and mechanical ventilation (median 17 vs. 12 days, $p < 0.001$) were found among cases. Cases also presented a higher frequency of admission by transfer from another unit ($p < 0.001$), previous hospitalization ($p = 0.011$), colonization ($p < 0.001$), surgical procedure ($p = 0.013$), and use of an enteral tube ($p = 0.011$) than controls. The multivariate analysis showed that hospitalization time (OR = 1.06; CI_{95%}: 1.03 - 1.08), transfer from another unit (OR = 5.03; CI_{95%}: 2.30 - 10.98) and colonization (OR = 9.32; CI_{95%}: 3.52 - 24.72) were independently associated with infection. The study revealed an

increase in infections by *A. baumannii* and antimicrobial resistance. There is need for surveillance, and constant evaluation of control actions. Risk factors were colonization, previous hospitalization, and hospitalization time. This is essential for the decision-making of professionals and optimization of prevention, control, and therapeutic management actions.

Keywords

Acinetobacter baumannii, Risk-Factors, Infection, Intensive Care

1. Introduction

Care-related infections have been reported exponentially worldwide, mainly *A. baumannii* is an emerging nosocomial pathogen that causes severe infections in hospitalized patients [1]. It was defined as a critical priority by the World Health Organization (WHO), for its ability to rapidly develop antimicrobial resistance mechanisms [2] [3]. The mechanisms responsible for development and transference are the occurrence of mutation and the presence of transferable genetic material (plasmid, transposons, and integrons), inadequate and indiscriminate use of antimicrobials in human and animal health, which might result in resistant strains that require effective interventions to minimize associated problems [4].

Data from 2017 from the Centers for Disease Control and Prevention (CDC) indicate that in the United States in 2017, there were 8500 cases of *A. baumannii* infections with 700 deaths [5]. In Brazil, studies have shown that *A. baumannii* is widely disseminated and with high resistance to imipenem ranging from 81% to 91.9% and colistin sensitivity of 98.8%. Mortality rates ranged from 43.7% to 81% in those infected with *A. baumannii* [6] [7] [8]. In Paraná, data from 2018 and 2019 Online Hospital Infection Notification System (SONIH), showed that the *Acinetobacter baumannii* Complex ranked fifth position among reported microorganisms, moving upwards to the second position in 2020. During the first quarter of 2021, in the presence of the COVID-19 pandemic, there was a 90% increase in the shipment of resistant clinical isolates when compared to 2019 and 99% were resistant to carbapenems. Resistance to polymyxin reached 20% of the isolates in the period [9] [10] [11].

In a previous study conducted at the same institution, it was found that *A. baumannii* is endemic in the health service, reinforcing the findings of the literature that the longer hospitalizations, the transfer of other hospital services, and pneumonia associated with mechanical ventilation were considered significant risk factors for the presence of multidrug-resistant *A. baumannii*. It was found that 72.4% of the cases of *A. baumannii* were detected in the ICU, reinforcing the importance of a study directed to this hospitalization ward, since it aggregates all factors considered relevant to the presence of the bacterium and the

worst outcome to the patient [12]. Thus, the study was intended to identify the risk factors for infection by *A. baumannii* in patients in an Intensive Care Unit of a Public Hospital of Paraná.

2. Materials and Methods

2.1. Research Design

A paired case-control study with retrospective inclusion of cases and simultaneous selection of controls (1:2 ratio) was adopted.

2.2. Participants and Procedures for Data Collection

A case was defined as a patient that was hospitalized in an intensive care unit (ICU) and had positive for *A. baumannii* resistant to more than three classes of antimicrobials. Two controls were individually matched for each case by age (± 10 years), gender and ICU stay (± 5 days). The controls were selected among patients with negative for *A. baumannii* (Figure 1).

Data collection occurred from January 2018 to December 2020, at the Walter Alberto Pecóits Regional Hospital, which has 130 beds, exclusively accredited by the Unified Health System (SUS), of which 20 pertains to the ICU.

Data were collected from secondary sources, electronic medical records, intensive care unit records, and hospital infection control centers of patients treated by the study service, which were grouped into: demographic and hospitalization data, age, gender, year, ICU stay, the form of admission (referred from another hospital or direct from the community), diagnosis of hospitalization (morbidity) and the number of comorbidities. Prognostic index, Estimated

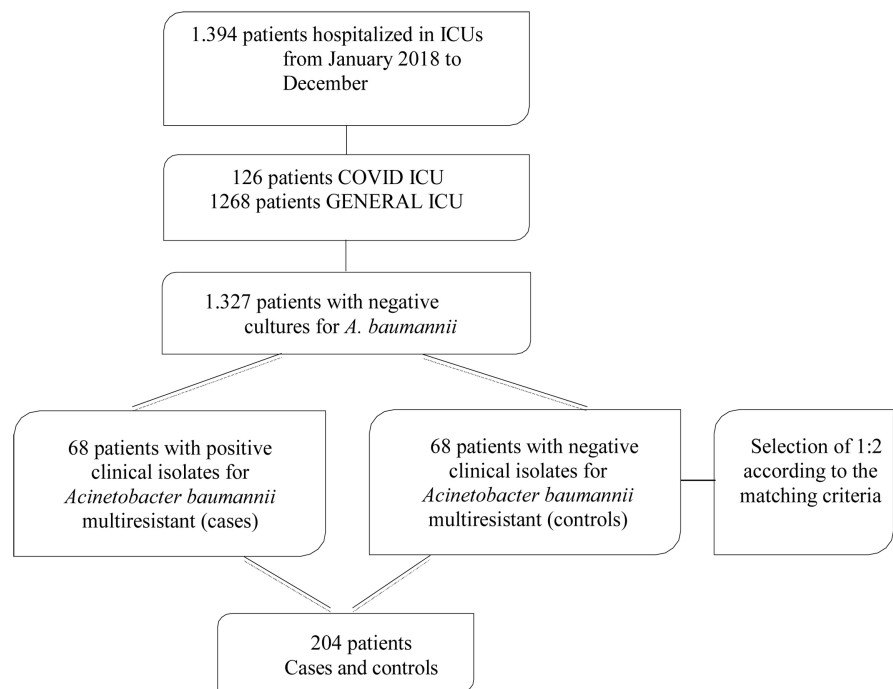


Figure 1. Study recruitment flowchart and case and control screening process.

percentage of death predicted by APACHE II at admission considering the clinical picture. Risk factors, recent previous hospitalization, use of invasive devices (catheter venous central, catheter vesical, and intubation), time of use of each device: days of use of the central venous catheter (CVC), of the vesical catheter (SVD), of the mechanical ventilation (VM) and use of an enteral tube. Hemodialysis procedure, previous antimicrobial use, and surgical procedure. Microbiological data, colonization, infection, isolated microorganism, antimicrobial resistance profile, site of infection (tracheal aspirate, nasal and rectal *swab*, blood culture, catheter tip, urine, wound, scar, pleural fluid), internment time until colonization and patient outcome (hospital discharge/death). The clinical isolates were obtained from the identification of signs and symptoms of suspected sepsis in patients hospitalized in the general ICUs and COVID ICU in the period. Surveillance cultures were performed at the time of admission and later every week in those with previous negative results.

Microbiological information was obtained from the laboratory reports of the school laboratory UNISEP (2018) and Biolabor (2019-2020) and epidemiological surveillance records of the Hospital Infection Control Commission (CCIH). Microbiological analyses were performed by manual disc-diffusion tests and microdilution polymyxin testing by the UNISEP Laboratory in 2018, following the criteria of the sensitivity protocol of the Clinical Laboratory *Standards Institute (CLSI)* [13]. From 2019, semi-automated analysis began with Micro Scan 4, microdilution polymyxin test, and PCR (polymerase chain reaction) is performed using the protocol of The European Committee on *Antimicrobial Susceptibility Testing* (EUCAST) [14]. According to SESA Resolution No. 0674/2010 and SESA Resolution No. 096/2018, the positive samples were sent to the Central Laboratory of Paraná (LACEN-PR), for genetic research, performed automated proves with *Vitek 2 and PCR for research of the bla_OXA-23 [15] [16].

2.3. Data Analyses and Ethical Aspects

Descriptive analyses were performed, using absolute (n) and relative (%) frequencies for categorical variables and measures of central tendency (mean and median) and dispersion (standard pattern and interquartile interval) for quantitative variables. The Kolmogorov-Smirnov test was used to test the distribution of the data. Since the assumption of normal distribution was not met for most variables, the Mann-Whitney test was used to compare quantitative variables between cases and controls. The chi-square test with Yates's continuity correction was used to verify the association between the categorized risk factors (independent variables) and infection by *A. baumannii* (case/control). After the crude analyses, binary logistic regression models were constructed to identify the main factors associated with *A. baumannii* infection. Initially, the variables with $p < 0.20$ in the crude analyses were tested individually in the models. Next, the final model (multivariate) was constructed with the manual input of the variables from the highest to the lowest odds ratio. Only the variables remained in

the adjusted model, which remained significant ($p < 0.05$). Thus, the results of the adjusted odds ratio and 95% confidence interval (logistic regression indicators) are presented only for the variables that comprised the final model. All analyses were performed in the SPSS 25.0 program.

The project was submitted for approval to the Ethics and Research Committee of the State University of Western Paraná (UNIOESTE), Opinion No. 4.681.274, and the Ethics and Research Committee of the coparticipant institution, Opinion No. 4.709.284.

3. Results

During the study period, a total of 1,394 patients were hospitalized in the General ICUs and COVID. 67 cases and 134 controls were included (**Table 1**). In the case group, all isolates were resistant to carbapenems, and none were resistant to polymyxin. The aminoglycosides had an annual increase in resistance between 2018 ($n = 1$), 2019 ($n = 7$), and 2020 ($n = 13$). Colonization occurred in 25 patients, of these 60% ($n = 15$), had a diagnosis of infection by *A. baumannii*. On the nasal swab and rectal swab collection for surveillance at ICU admission, 26.7% ($n = 4$) presented intestinal colonization.

Table 1 shows the main characteristics of cases and controls, unspecified trauma was the most common cause of hospitalization, while respiratory disorders were the second leading cause among cases and septicemia was among controls. Regarding the site of infection, almost 70% of the positive isolates for *A. baumannii* were aspirated tracheal, while a percentage of 10.3% of the controls had an infection. Finally, we observed a slightly longer time from hospitalization to colonization and a higher proportion of deaths among cases.

The cases presented longer hospitalization time, longer ICU time, in addition to a greater number of days using the central venous catheter, the urinary catheter, and mechanical ventilation when compared to controls. In addition, the cases presented a higher frequency of admission by transfer from another health unit, previous hospitalization, colonization, surgical procedure, and use of enteral catheter than controls (**Table 2**).

After the crude analyses, **Table 3** shows the logistic regression models with the main factors associated with Infection by *A. baumannii* in an adjusted manner. Considering the final model, the time of hospitalization, the form of hospital admission, and colonization were independently associated with the outcome. The main predictor was colonization, with an odds ratio almost 10 times higher in cases than in controls. In addition, we observed that each day of hospitalization increases by 6% the chance of infection by *A. baumannii* and that admission by transfer from another health unit increased 5 times the chances of infection.

4. Discussion

A. baumannii is an etiological agent defined as of critical interest in ICUs by the WHO, due to its ability to develop rapid resistance to multiple antimicrobials

Table 1. General characteristics of cases (n = 68) and controls (n = 136) hospitalized in an ICU in a Public Hospital in Paraná, Brazil from January 2018 to December 2020.

Variable	Case (n = 68)		Control (n = 136)	
	n	%	n	%
Sex				
Male	46	67.6	92	67.6
Female	22	32.4	44	32.4
Age				
Up to 60 years	28	41.2	50	36.8
More than 60 years	40	58.8	86	63.2
Year				
2018	13	19.1	26	19.1
2019	18	26.5	36	26.5
2020	37	54.4	74	54.4
Diagnosis of hospitalization				
Digestive tract disease	8	11.8	10	7.4
Unspecified trauma	19	27.9	33	24.3
Cardiovascular disease	4	5.9	19	14.0
Septicemia	8	11.8	25	18.4
Respiratory disorder	16	23.5	13	9.6
Genitourinary system disease	5	7.4	13	9.6
High-risk pregnancy woman	1	1.5	0	0.0
Neurological disorder	2	2.9	13	9.6
Covid-19	5	7.4	10	7.4
Site of infection				
None	11	16.2	104	76.5
Tracheal aspiration	46	67.6	14	10.3
Blood cultures	1	1.5	7	5.1
Urine	8	11.8	11	8.1
Wound	2	2.9	0	0.0
Internment time until colonization				
Up to 10 days	10	40.0	5	62.5
More than 10 days	15	60.0	3	37.5
Outcome				
Death	35	51.5	54	39.7
Discharge	33	48.5	82	60.3

Table 2. Bivariate analyses of factors associated with *A. baumannii* infection in ICU patients in a Public Hospital in Paraná, Brazil, from January 2018 to December 2020.

Continuous variables	Case (n = 68)		Control (n = 136)		p
	Mean/Median	DP/IQ	Mean/Median	DP/IQ	
Hospital stays (days)	34.8/35	17.2/22	23.8/22	11.5/14	<0.001
ICU stays (days)	25.4/23	15.5/19	16.8/16	6.8/10	<0.001
Estimated mortality percentage-APACHE-II	45.3/47	21.3/27	41.9/40	21.7/31	0.200
Number of morbidities	1.4/1	1.3/2	1.3/1	1.3/2	0.570
CVC Days	28.7/25	15.2/20	18.8/18	9.5/12	<0.001
SVD Days	30.9/29	16.1/21	21.1/20	10.2/13	<0.001
VM Days	21.4/17	15.6/17	11.9/12	8.6/13	<0.001
Categorical variables	n	%	n	%	p
Form of hospital admission					<0.001
Community	36	52.9	115	84.6	
Transfer of another health unit	32	47.1	21	15.4	
Recent prior hospitalization					0.011
No	33	48.5	91	66.9	
Yes	35	51.5	45	33.1	
Colonization					<0.001
No	43	63.2	128	94.1	
Yes	25	36.8	8	5.9	
Surgical procedure					0.013
No	32	47.1	90	66.2	
Yes	36	52.9	46	33.8	
Hemodialysis					0.468
No	47	69.1	102	75.0	
Yes	21	30.9	34	25.0	
Enteral tube					0.011
No	2	2.9	22	16.2	
Yes	66	97.1	114	83.8	
Use of previous antimicrobial					0.265
No	2	2.9	11	8.1	
Yes	66	97.1	125	91.9	

Note. DP, standard deviation; IQ, interquartile range; CVC, central venous catheter; SVD, vesical catheter; VM, mechanical ventilation.

Table 3. Crude and adjusted models of factors associated with *A. baumannii* infection in patients hospitalized in an ICU in a Public Hospital of Paraná, Brazil, from January 2018 to December 2020.

Risk factors	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
Hospital stays (days)	1.06 (1.03 - 1.08)	<0.001	1.06 (1.03 - 1.08)	<0.001
ICU stay (days)	1.08 (1.04 - 1.12)	<0.001	-	-
CVC Days	1.07 (1.04 - 1.10)	<0.001	-	-
SVD Days	1.06 (1.03 - 1.09)	<0.001	-	-
VM Days	1.08 (1.04 - 1.11)	<0.001	-	-
Form of hospital admission				
Community	1		1	
Transfer of another health unit	5.05 (2.59 - 9.85)	<0.001	5.03 (2.30 - 10.98)	<0.001
Recent prior hospitalization				
No	1			
Yes	2.24 (1.23 - 4.06)	0.008	-	-
Colonization				
No	1		1	
Yes	9.60 (4.03 - 22.89)	<0.001	9.32 (3.52 - 24.72)	<0.001
Surgical procedure				
No	1			
Yes	2.09 (1.15 - 3.78)	0.015	-	-
Enteral catheter				
No	1			
Yes	6.22 (1.42 - 27.29)	0.015	-	-

Note. Crude OR, the odds ratio of bivariate analyses; Adjusted OR, the odds ratio of the multivariate analysis; CI, confidence interval; CVC, central venous catheter; SVD, vesical catheter; VM, mechanical ventilation.

and unfavorable clinical outcomes. Economic burdens and physical, functional, and psychological consequences are also substantial [2] [17].

Our study is in agreement with epidemiological data of other studies that indicate that *A. baumannii* is responsible for 54% of ICU infections and 5% in internal wards [5]. A systematic review with a meta-analysis conducted in African, Eastern Mediterranean, and European regions demonstrated that infections by *A. baumannii* in the ICU corresponded to 15.3% (95% CI 11.7% - 19.7%) of all infections, being 20.9% (95% CI 16.5% - 26.2%) in ICUs and 16.3% in clinical wards (95% CI 8.0% - 30.5%) [18]. Furthermore, the incidence and prevalence of *A. baumannii* infections are 10 - 50 times lower in studies covering the entire

hospital than in those based only on the ICU [18]. In Brazil, most of the studies surveyed were developed in ICUs [6] [7] [8] [19] [20].

All clinical isolates in our study were resistant to carbapenems and demonstrated an increase in resistance to aminoglycosides and penicillin with beta-lactams over the years. None showed resistance to polymyxin. Two hundred and eleven (211) laboratories in 20 European countries recorded rates of more than 50% of clinical isolates with carbapenem-resistant *A. baumannii* between 2015 and 2017. Most laboratories were in Greece (n = 12), Turkey (n = 11), Italy (n = 9) and Romania (n = 7) [21]. A multicenter study in Serbia showed that 280 out of the 2.401 clinical samples studied had the presence of *A. baumannii*. Two hundred and twenty-seven (227) of the isolates were sensitive to colistin (95.7%), 178 to tigecycline (75.1%), and 10 were classified as drug multiresistant [5]. In Latin America, the carbapenem resistance rate was 90% for *A. baumannii* in different countries between 2002 and 2013 [22]. Data from the Central Laboratory of the State of Paraná highlighted *A. baumannii* as the fifth most frequent infectious agent in 2019, and the second in 2020, with high rates of resistance to carbapenems and with increasing resistance to polymyxin [10] [11].

Records from the SENTRY Antimicrobial Surveillance Program (2016 to 2019) showed increased meropenem susceptibility between 2016 (34.7%) and 2019 (71.0%) in Western Europe and from 54.6% to 70.4% during the same period in the United States [23]. Colistin and tobramycin were active in more than 50% of the isolates [23]. Other studies conducted in Germany and Lebanon have demonstrated, however, reduced resistance over the years added to continuous efforts in antimicrobial and infection control and prevention measures [24] [25]. Studies suggest that treatment with varied antimicrobials and extensive use of carbapenems, piperacillin/tazobactam, and vancomycin increased the resistance profile of strains year by year [26] [27]. However, there is insufficient data to define a combination of antibiotics for treatment for that microorganism. The recommendation in the literature is to combine antibiotics to obtain synergism of antibacterial activity, thus amplifying their efficacy [28] [29].

The risk factors for *A. baumannii* in the ICU were colonization, transfer of another unit, and the time of hospitalization. The colonization was the greatest factor, being in cases 10 times greater than in controls. Colonized or infected patients represent reservoirs for horizontal transmission and dissemination of multi-resistant mainly in ICUs [8] [30] [31] [32]. A high rate of colonization during ICU stay is associated with transmission among patients through the health team, objects and environmental surfaces, medical devices, and ineffective infection control measures [32]. Health teams working in different institutions within the same city can be facilitators for the occurrence of this transmission [8].

The transfer of another health unit increased 5 times the chances of infection. Indeed, a 10-year longitudinal study in Central Europe identified that, out of a total of 76 patients colonized at admission (56% by *A. baumannii*), 24% (n = 16) came from countries outside the European Union [33].

We identified that each day of hospitalization increased by 6% the chances of acquiring the infection by *A. baumannii*. Longer hospital stay has been associated with high mortality rates in the ICU [12] [34] [35] [36]. Colonization and infection by carbapenem-resistant enterobacteria also prolong the time of hospitalization and are associated with higher mortality rates between 25% and 70% [34] [35] [37] [38].

Importantly, the estimate of mortality calculated by APACHE II at admission had a negligible difference between cases and controls (mean/median 45.3/47 vs. 41.9/40). Nonetheless, we found that the mortality in cases was 51.5% (35/68) compared to 39.7% (54/136) in controls. This is nearly 12% higher among cases, and the infection is suspected to be a contributing factor to death. In this sense, the EPIC II study (2007), including 1.265 ICU patients from 75 countries reported an ICU mortality rate in infected patients twice as high when compared to uninfected patients (25% [1688/6659] vs. 11% [682/6352], respectively; $p < 0.001$), as well as the hospital mortality rate (33% [2201/6659] vs. 15% [942/6352]; $p < 0.001$), respectively [35]. Another international study in 2017 conducted in 1.150 centers from 88 countries demonstrated that carbapenem-resistant *Acinetobacter* infections (OR = 1.40 [95% CI, 1.08 - 1.81]; $p = 0.01$) were independently associated with a high risk of death when compared to infection by another microorganism [39]. High mortality rates are identified in other countries as well, ranging from 74.1% in Morocco and between 43.7% to 81% in Brazil [7] [19] [40].

In the bivariate analysis, the factors associated with *A. baumannii* infection were the time of hospitalization, longer ICU time, longer number of days using invasive devices (CVC, SVD, and VM), admission by transfer from another health unit, previous hospitalization, colonization, surgical procedure, and use of the enteral tube. National and international studies corroborate the factors associated with *A. baumannii* infection found in this study, the most frequently reported being: length of stay in the ICU [33] [35]-[40], central venous catheterization [38] [40] [41] [42], mechanical ventilation [37] [38] [40] [42], urinary device [38] [40] [41] [42], use of the enteral tube [25] [32] [37] [41] [43] and previous use of antimicrobials [6] [20] [25] [35]-[41] [43]. Those with lower frequency were invasive procedure [40], previous colonization [38], comorbidities [19] [38] [39], APACHE-II scores [39] [41] [43], hemodialysis [25] [38] [39], and SOFA score [19].

The use of invasive devices for a long time has been associated with the extraordinary ability to form biofilm and with the survival of *A. baumannii* on abiotic surfaces of medical and non-medical objects, in dry or humid environments [5] [44] [45]. One of the important virulence factors of *A. baumannii*, fibronectin-binding proteins (FPBs), is the main responsible for the pathogen's adhering to implantable materials [46]. While the formation of type I pili (CSU pili) is essential in the formation of biofilms and their maintenance on abiotic surfaces such as polystyrene [47]. Indeed, prolonged contact of biofilm with the host has been reported as the cause of outbreaks of medical device-related infec-

tions and ventilatory-associated pneumonia [48].

Use of mechanical ventilation was significantly higher in cases than in controls (mean/median 21.4/17 vs. 11.9/12) as well as respiratory tract infections (46/69, 67.11%). A previous study in the same institution also showed a higher prevalence of pneumonia associated with mechanical ventilation (OR = 4.48; IC 95%: 1.55 - 13.00; p = 006) [12]. In other countries, the incidence density of ventilator-associated pneumonia (VAP/1000 patient-days) ranged from 8.9 to 39.6 in Saudi Arabia, 11.8 in India, 14.7 in Southeast Asia, 15.2 in Poland, 21.40 in Nepal, and 36.3 in Brazil [19] [36] [41] [49] [50] [51]. These studies confirm the association of longer use of invasive devices, especially time on mechanical ventilation, as an important risk factor for ventilator-associated pneumonia caused by *A. baumannii*.

Few studies have verified the use of an enteral tube as an invasive device that can contribute significantly to the colonization of the gastrointestinal tract by eliminating the gastric barrier. The use of an enteral tube was independently associated with *A. baumannii* infection in this study. We were able to find some studies that also corroborate this finding [20] [32]. An in vitro study showed that the PH of hydrochloric acid (<4%) was able to eliminate 99.9% of enterobacteria in 30 minutes and constitutes one of the barriers to the progression of these bacteria to the intestinal tract [52]. Other studies also point to gastric acid suppression as a risk factor for colonization of the gastrointestinal tract by multidrug-resistant enterobacteria, especially in the use of proton pump inhibitors [53] [54] [55]. In this context, the enteral tube circumvents and buffers the natural barrier imposed by gastric acid and may contribute to intestinal colonization of *A. baumannii* [55].

5. Conclusion

The study showed an increase in the incidence of infection accompanied by increased antimicrobial resistance year by year in the study period. The risk factors associated with infection were colonization, transfer from another health unit, and hospitalization time. As therapeutic options have become limited due to increasing reports of infection by multidrug-resistant *A. baumannii*, there are challenges for planning prevention actions focused on institutional reality. Therefore, the knowledge of risk factors for infection in health institutions is essential to implement measures aiming to prevent the chain of transmission of infections by *A. baumannii*.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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