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Major Article

Incidence of infections caused by carbapenem-resistant *Acinetobacter baumannii*

Iara Rossi MSc [a,*], Sabrina Royer PhD [a], Melina Lorraine Ferreira PhD [a], Paola Amaral Campos PhD [a], Bruna Fuga PhD [a], Gabriel Nogueira Melo PhD [a], Luiz Gustavo Machado PhD [a], Daiane Silva Resende PhD [a], Deivid Batistão PhD [a,b], Jane Eire Urzedo MSc [c], Paulo P. Gontijo-Filho PhD [a], Rosineide Marques Ribas PhD [a,c]

[a] *Laboratory of Molecular Microbiology, Biomedical Science Institute, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil*
[b] *School of Medicine, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil*
[c] *Hospital Infection Control Committee, Hospital das Clínicas, Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil*

Key Words:
Carbapenem-resistance
Outbreak

Background: Carbapenem-resistant *Acinetobacter baumannii* (CR-Ab) has become a worrying health care problem, mainly in developing countries, such as Brazil. The objective was to investigate the prevalence and prognostic factors for CR-Ab infections at a Brazilian university hospital and examine the impact of inappropriate antimicrobial therapy on patient outcome.
Methods: A retrospective study on hospitalized patients with CR-Ab infections was carried out from January 2013 to December 2017. An epidemiologic analysis was carried out to determine the frequency of infections, the epidemiologic indicators by year, the risk factors for 30-day mortality, and the impact of inappropriate therapy.
Results: A total of 489 patients were included in the study. A rate of 0.7 per 1,000 patient-day CR-Ab infections was observed, mostly in the lungs (54.7%), and predominantly in the adult intensive care unit. The occurrence of infections by CR-Ab per 1,000 patient-days in November 2014 exceeded the established control limit, confirming an outbreak.
Conclusions: The prevalence of CR-Ab increased in the investigated hospital, passing to an endemic pathogen with a direct impact on mortality and the control of these strains.

Nosocomial infections associated to the carbapenem-resistant *Acinetobacter baumannii* (CR-Ab) have become an important health care concern, mainly in low- and middle-income countries.[1-3] CR-Ab has increased worldwide, and its presence in critical care units has become significantly more difficult to treat and is increasingly associated to higher morbidity, mortality, and hospital costs.[4]

Based on epidemiologic studies, incidence rates due to CR-Ab infections are approximately 2- to 5-fold higher in intensive care units (ICUs) compared with other wards.[5,6] Additionally, antimicrobial resistance in these microorganisms usually leads to a high rate of treatment failure.[6] Although resistance is a strong marker associated to mortality, a high number of other risk factors also contribute to increasing the difficulties regarding the choice of antimicrobials used in the treatment of severe infections caused by this microorganism, resulting in a worse prognosis.[7]

In this study, the frequency and risk factors of patients presenting with CR-Ab infections in an ICU and the impact of inappropriate antimicrobial therapy on clinical outcomes were investigated and analyzed.

METHODS

Patients and setting

This study was conducted using the database of Uberlandia University Hospital, a 530-bed teaching medical center located in Uberlandia, Minas Gerais, Brazil. The records were reviewed to identify patients with CR-Ab infections from 2013 through 2017. The medical data and outcome were obtained retrospectively. Microbial identification and antimicrobial susceptibility testing were performed on the Vitek-2 system (bioMérieux, Marcy l'Etoile, France) in the hospital. Antibiotics tested included aminoglycosides (gentamicin,

* Address correspondence to Iara Rossi Goncalves, Laboratory of Molecular Microbiology, Biomedical Science Institute, Federal University of Uberlândia, 1720 Pará Avenue, 38400000 Uberlândia, Minas Gerais, Brazil.
E-mail address: iararossi@ufu.br (I. Rossi).
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amikacin), carbapenems (imipenem, meropenem), cephalosporins (cefepime), fluoroquinolones (ciprofloxacin), β-lactam-lactamase inhibitors (piperacillin-tazobactam), and polymyxins (colistin). Surveillance cultures are tested only to carbapenems. An endemic level of infection by CR-Ab per 1,000 patient-days was calculated as described previously.[8] For the analysis of mortality and prognosis factors only the first episode of infection was evaluated.

Ethical approval

The study was performed in accordance with the ethical protocol (protocol number 0119/11).

Study design

A retrospective cohort study was employed to identify the risk factors of CR-Ab infection, the predictors of mortality, and to evaluate the impact of inappropriate therapy in the outcome of patients. For each patient, the following characteristics were recovered: age, sex, the length of total hospital stay, admission to ICU, surgery, underlying conditions, and invasive procedures during the current hospitalization. Data from patients who died were compared with those from patients who survived to determine factors associated with 30-day mortality.

Definitions

Health care–associated infections are defined as any infection acquired after a patient's admission to the hospital. Health care–associated infections may manifest during hospitalization or after discharge because they are related to hospitalization or procedures performed during the hospitalization.[9] Antimicrobial treatment with agents that had no in vitro activity and or treatment for <48 hours was considered inadequate.[10] Hospital mortality was evaluated at 30 days after the onset of CR-Ab infections. Multidrug-resistant bacteria was defined as nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories; extensively drug-resistant was defined as nonsusceptibility to at least 1 agent in all, but 2 or fewer antimicrobial categories; and pandrug-resistant was defined as nonsusceptibility to all agents in all antimicrobial categories.[11] Prior antibiotic therapy was defined as the use of an antimicrobial agent for at least 2 days within 30 days of the current hospitalization.

Statistical analysis

The Student t test was used to compare continuous variables, and the χ^2 or the Fisher exact test was used to compare categorical variables. To determine independent risk factors for 30-day mortality, a multiple logistic regression model was used to control for the effects of confounding variables. Variables with $P \leq .05$ in the univariate analysis were candidates for multivariate analysis. All P values were 2-tailed, and $P \leq .05$ was statistically significant.

RESULTS

Incidence rates

A total of 489 nonrepetitive patients presenting with CR-Ab infections were included in this study, over a 5-year study period,

Table 1
Episodes of multidrug-resistant *Acinetobacter baumannii* infections between 2013 and 2017

	Period (year)					
	2013	2014	2015	2016	2017	Total
Total of episodes of infection	15	187	150	156	134	644
Number of patients included	9	131	117	123	109	489
Wards						
Adult ICU	12 (80.0)	118 (63.1)	94 (62.7)	80 (51.3)	84 (62.7)	388 (60.2)
Emergency room	0	17 (9.1)	16 (10.7)	22 (14.1)	9 (6.7)	64 (9.9)
Surgery	2 (13.3)	37 (9.1)	20 (13.3)	30 (19.2)	25 (18.7)	114 (17.7)
Medical clinic	1 (6.7)	9 (4.8)	4 (2.7)	13 (8.3)	10 (7.5)	37 (5.7)
Others*	0	6 (3.2)	16 (10.7)	11 (7.0)	6 (4.5)	39 (6.1)
Sites						
Blood	3 (20.0)	27 (14.4)	35 (23.3)	14 (9.0)	9 (6.7)	88 (13.7)
Respiratory tract	8 (53.3)	103 (55.1)	74 (49.3)	94 (60.3)	73 (54.5)	352 (54.7)
Urine	1 (6.7)	19 (10.2)	16 (10.7)	21 (13.5)	20 (14.9)	77 (11.9)
Surgical site/wound	3 (20.0)	37 (19.8)	25 (16.7)	27 (17.3)	26 (19.4)	118 (18.3)

ICU, intensive care unit.
*Infectious diseases, oncology, transplant, pediatrics, neonatal or pediatric ICU.

Table 2
Epidemiologic indicators of multidrug-resistant *Acinetobacter baumannii* health care–associated infections at the intensive care unit of Uberlandia University Hospital

	Indicators (year)					
Variables	2013	2014	2015	2016	2017	General indicators
Acinetobacter baumannii per 1,000 patient-days	0.1	1.0	0.8	0.8	0.7	0.7
Average of hospital length (days)	91	64	50	59	56	64
Average age	58	55	54	58	59	57
Infection in ICU per 1,000 patient-days	0.06	0.61	0.49	0.41	0.43	0.40
Pneumonia in ICU per 1,000 patient-days	0.04	0.5	0.4	0.5	0.4	0.36
Bacteremia in ICU per 1,000 patient-days	0.02	0.14	0.18	0.07	0.05	0.09
Urinary infection in ICU per 1,000 patient-days	0.01	0.10	0.08	0.11	0.10	0.08
Surgical site or wound infection in ICU per 1,000 patient-days	0.02	0.19	0.13	0.14	0.13	0.12
30-day mortality in ICU (%)	2	28	26	23	31	22
Total 30-day mortality (%)	2	46	46	50	47	38

ICU, intensive care unit.

Table 3
Demographic and clinical characteristics of patients included in multidrug-resistant *Acinetobacter baumannii* outbreak in November 2014

Patient	Age (years)	Diagnostic(s)	Date of infection	Site	Ward	Days of hospitalization	Prior antibiotic therapy	Treatment	Appropriate definitive therapy	Outcome
A	44	Head trauma	11/01/2014	Respiratory tract	ER	38	MEM, VAN, PTZ, ERT, TEC, TIG	PB+TIG+AMS	Yes	Death
B	44	Pneumonia	11/03/2014	Respiratory tract	ER	25	CLI, CPM, PTZ, TEC, IPM, VAN	None	No	Death
C	41	Esophagus cancer	11/03/2014	Respiratory tract	SUR	52		PB	Yes	Death
D	45	Pleural effusion	11/03/2014 11/13/2014	Respiratory tract Urine	ER ICU	43	TIG, IPM, PB, TEC, MEM, PTZ	PB+TIG	Yes	Death
E	37	Gun injury	11/03/2014	Respiratory tract	ICU	30	CPM, TEC, OXA	None	No	Survival
F	25	Lupus	11/03/2014 11/06/2014	Blood Respiratory tract	ICU	99	CPM, TEC, VAN, IPM, MEM, PB, TIG	PB+TIG	Yes	Survival
G	69	Chronic renal insufficiency	11/04/2014	Wound secretion	TRA	36	CFZ, ERT, TEC	TIG	Yes	Death
H	56	Brain cancer	11/04/2014	Respiratory tract	ICU	84	CPM, CFZ, PTZ, PB, ERT, MEM, TEC	PB+TEC	Yes	Death
I	74	Urinary insufficiency	11/04/2014	Respiratory tract	ICU	102	TEC, MEM, TIG, CIP, PB, VAN, IPM	None	No	Death
J	71	Acute abdomen	11/05/2014	Ascitic liquid	SUR	64	CRO, MET, CIP, PTZ	None	No	Survival
K	77	Femur fracture	11/07/2014 11/07/2014	Respiratory tract Bone fragment	SUR	30	CFZ, ERT, VAN	PB+TIG	Yes	Death
L	79	Pulmonary edema	11/09/2014 11/10/2014	Urine Respiratory tract	ICU ER	108	CPM, PTZ, TEC	AMK	Yes	Survival
M	25	Head trauma	11/11/2014 11/11/2014	Respiratory tract Blood	ICU	58	CFZ, CRO, CLI	PB+TIG	Yes	Survival
N	14	Cerebral palsy	11/12/2014	Respiratory tract	MC	6	CLI, CPM	None	No	Survival
O	21	Gun injury	11/12/2014	Wound secretion	SUR	52	CFZ, CLI, CIP	TIG		Survival
P	19	Head trauma	11/14/2014 11/24/2014	Respiratory tract Blood	ICU ER	37	CFZ, CPM, VAN, OXA, MEM, TIG, PB	PB+TIG	Yes	Survival
Q	17	Head trauma	11/17/2014	Respiratory tract	ICU	7	CRO, CLI	None	No	Death
R	75	Stroke	11/25/2014	Wound secretion	ICU	96	PTZ, TEC, MEM	None	No	Survival
S	62	Hypertension	11/22/2014	Respiratory tract	MC	75	TEC, PTZ, CLI, CRO	AMS	No	Death
T	89	Stroke	11/23/2014	Respiratory tract	ER	43	VAN, CPM, TEC, OXA	PB+TIG	Yes	Death
U	42	Hydrocephalus	11/24/2014 11/25/2014	Urine Respiratory tract	ICU	40	CFZ, OXA, MEM, VAN, AMK	PB	Yes	Death
V	51	Head trauma	11/25/2014	Wound secretion	ICU	33	CPM, TEC, OXA, CRO, PTZ, MEM	PB+TEC	Yes	Death
W	74	Chronic renal insufficiency	11/25/2014	Urine	SUR	52	ERT, CPM, CIP	None	No	Death
X	52	Head trauma	11/28/2014	Respiratory tract	ICU	20	CFZ, CRO	TIG	Yes	Death
Y	77	Pneumonia	11/30/2014	Respiratory tract	SUR	22	CRO, PTZ	PB	Yes	Death

AMK, amikacin; *AMS*, ampicillin-sulbactam; *CFZ*, cefazolin; *CIP*, ciprofloxacin; *CLI*, clindamycin; *CPM*, cefepime; *CRO*, ceftriaxone; *ER*, emergency room; *ERT*, ertapenem; *ICU*, intensive care unit; *IPM*, imipenem; *MC*, medical clinic; *MEM*, meropenem; *MET*, XXXX; *OXA*, oxacillin; *PB*, polymyxin B; *PTZ*, piperacillin-tazobactam; *SUR*, surgery; *TEC*, teicoplanin; *TIG*, tigecycline; *TRA*, transplant; *VAN*, vancomycin.

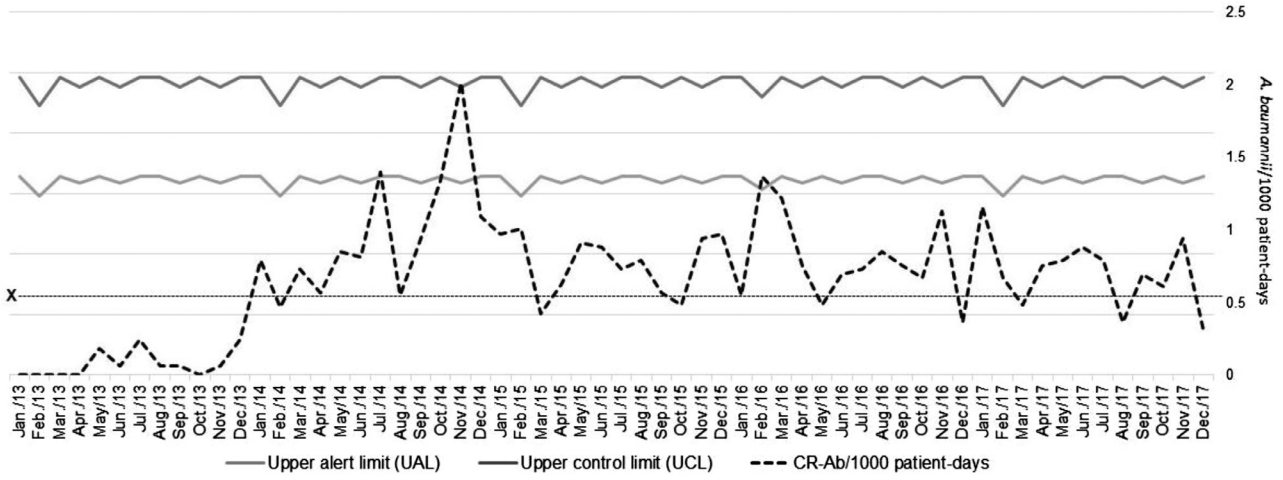

Fig 1. Endemic level of carbapenem-resistant *Acinetobacter baumannii* per 1,000 patient-days from January 2013 to December 2017. Upper control limit ($3\sigma + X$); upper alert limit ($2\sigma + X$); X: center line (average rate of *Acinetobacter baumannii* per 1,000 patient-days = 0.66). *CR-Ab*, carbapenem-resistant *Acinetobacter baumannii*.

totaling 644 episodes. Most infections (60.2%) were identified in patients cared for in the adult ICU, with an incidence density of 0.4 per 1,000 patient-days. A predominance of lung infections (54.7%) was observed. Extremely prolonged hospital lengths (approximately 58 days) were also verified, and high total mortality rates (39.0%, 191 of 489 patients). Most of the evaluated patients (60.8%) received inappropriate empirical therapy. CR-Ab episodes and the epidemiologic characteristics of the infected patients are displayed in Table 1 and Table 2, respectively.

Concerning the endemic background, almost a 6-fold increase occurred in the incidence of CR-Ab infections from 2013 to 2014 (0.1 per 1,000 patient-days to 1.0 per 1,000 patient-days). Moreover, CR-Ab infection rates per 1,000 patient-days had a progressive increase from December 2013 to November 2014, when they exceeded the control limit established at 3σ above the average incidence of infection, confirming a CR-Ab outbreak (Table 3). The infection acquisition rates were 2.01 per 1,000 patient-days in early November 2014, decreasing to 1.09 per 1,000 patient-days by the end of the month (Fig 1).

Mortality predictors and risk factors associated with antibiotic resistance and treatment outcome

Patient demographic and clinical characteristics are displayed in Table 4. A total of 340 (69.5%) patients were men, with median age of 57 ± 21 (range, 0-97) years. Factors associated to hospital mortality included long hospital stay, invasive procedures such as mechanical ventilation, central venous catheter, nasogastric probes, bladder catheter and hemodialysis, comorbidities such as heart failure and chronic renal failure, and previous use of carbapenems and polymyxins.

Table 4
Clinical and demographic characteristics and risk factors associated with 30-day mortality in patients with carbapenem-resistant *Acinetobacter baumannii* infections

	Total	Death	Survival	Univariate		Multivariate	
Risk factors	N = 489 (%)	N = 191 (39.0)	N = 298 (61.0)	OR (CI 95%)	*P*†	OR (CI 95%)	*P*
Age mean, ± SD	57 ± 21	64 ± 19	52 ± 20	–	<.0001*	–	–
Sex							
Male	340 (69.5)	66 (34.5)	215 (72.1)	–	–	–	–
Female	149 (30.5)	125 (65.4)	83 (27.8)	–	–	–	–
Hospital length of stay, mean ± SD	58 ± 61	39 ± 35	71 ± 71	–	<.0001*	–	–
More than 30 days	343 (70.1)	100 (52.3)	243 (81.5)	0.2 (0.2-0.4)	<.0001*	1.3 (0.85-2.02)	.2
Intensive care unit	320 (65.4)	129 (67.5)	191 (64.1)	1 (0.8-2)	.4344	–	–
Surgery	324 (66.2)	120 (62.8)	204 (68.4)	0.8 (0.5-1)	.199	–	–
Invasive procedures	472 (96.5)	188 (98.4)	284 (95.3)	3 (0.9-11)	.0782	–	–
Mechanical ventilation	350 (71.6)	154 (80.6)	196 (65.7)	2 (1-3)	.0004*	1.2 (0.73-1.98)	.4
Tracheostomy	354 (72.4)	143 (74.9)	211 (70.8)	1 (0.8-2)	.3267	–	–
Central venous catheter	438 (89.6)	180 (94.2)	258 (86.5)	3 (1-5)	.0068*	1 (0.47-2.03)	.9
Surgical drain	115 (23.5)	41 (21.5)	74 (24.8)	0.8 (0.5-1)	.3918	–	–
Nasogastric probes	415 (84.9)	179 (93.7)	236 (79.2)	4 (2-7)	<.0001*	0.7 (0.35-1.3)	.2
Bladder catheter	386 (78.9)	161 (84.3)	225 (75.5)	2 (1-3)	.02*	0.8 (0.85-2.25)	.1
Hemodialysis	205 (41.9)	111 (58.1)	94 (31.5)	3 (2-4)	<.0001*	1.3 (0.89-2.07)	.1
Parenteral nutrition	55 (11.2)	26 (13.6)	29 (9.7)	1 (0.8-3)	.1851	–	–
Comorbidity conditions	271 (55.4)	133 (69.6)	138 (46.3)	3 (2-4)	<.0001*	1.4 (0.9-2.15)	.1
Heart failure	55 (11.2)	33 (17.3)	22 (7.4)	3 (1-5)	.0007*	1 (0.56-1.9)	.9
Cancer	58 (11.9)	29 (15.2)	29 (9.7)	2 (1-3)	.0689	–	–
Diabetes mellitus	94 (19.2)	43 (22.5)	51 (17.1)	1 (0.9-2)	.1394	–	–
Chronic renal failure	91 (18.6)	49 (25.6)	42 (14.1)	2 (1-3)	.0014*	0.6 (0.37-1.1)	.1
Lungs diseases	63 (12.9)	28 (14.7)	35 (11.7)	1 (0.8-2)	.3479	–	–
HIV	7 (1.4)	3 (1.6)	4 (1.3)	1 (0.3-5)	1	–	–
Previous use of antibiotics	444 (90.8)	176 (92.1)	268 (89.9)	1 (0.7-3)	.4087	–	–
Carbapenems	241 (49.3)	111 (58.1)	130 (43.6)	2 (1-3)	.0018*	1.02 (0.81-1.79)	.300
Cephalosporins	280 (57.3)	101 (52.9)	179 (60.1)	0.7 (0.5-1)	.117	–	–
Glycopeptides	286 (58.5)	119 (62.3)	167 (56.0)	1 (0.9-2)	.1703	–	–
Fluoroquinolones	92 (18.8)	32 (16.7)	60 (20.1)	0.8 (0.5-1)	.3507	–	–
Polymyxins	34 (6.9)	19 (9.9)	15 (5.0)	2 (1-4)	.0371*	0.8 (0.4-1.77)	.6
Tigecycline	33 (6.7)	11 (5.8)	22 (7.4)	0.8 (0.4-2)	.4851	–	–
Inappropriate empirical therapy	317 (64.8)	116 (60.7)	201 (67.4)	0.8 (0.7-1)	.1291	–	–
Inappropriate definitive therapy	184 (37.6)	55 (28.8)	129 (43.2)	0.5 (0.4-0.8)	.0012*	0.9 (0.62-1.39)	.7
Monotherapy	221 (45.2)	76 (39.8)	145 (48.7)	0.7 (0.5-1)	.0546	–	–
Tigecycline	72 (14.7)	17 (8.9)	55 (18.4)	0.4 (0.2-0.8)	.0036*	0.6 (0.33-1.02)	.05*
Polymyxins	114 (23.3)	50 (26.2)	64 (21.5)	1 (0.8-2)	.2303	–	–
Aminoglycosides	22 (4.5)	8 (4.2)	14 (4.7)	0.9 (0.4-2)	.7909	–	–
Carbapenems	7 (1.4)	1 (0.5)	6 (2.0)	0.3 (0.03-0.2)	.176	–	–
Combined therapy	121 (24.7)	45 (23.6)	76 (25.5)	0.9 (0.6-1)	.6271	–	–
With carbapenems	49 (10.0)	20 (10.5)	29 (9.7)	1 (0.6-2)	.7904	–	–
Without carbapenems	74 (15.1)	26 (13.6)	48 (16.1)	0.8 (0.5-1)	.4526	–	–
With polymyxins	108 (22.1)	43 (22.5)	65 (21.8)	1 (0.7-2)	.8553	–	–
Origin of infection							
Blood	60 (12.3)	34 (17.8)	26 (8.7)	2 (1-4)	.0028*	0.5 (0.27-0.99)	.04*
Lungs	286 (58.5)	111 (58.1)	175 (58.7)	1 (0.7-1)	.8938	–	–
Urine	56 (11.4)	18 (9.4)	38 (12.7)	0.7 (0.4-1)	.2596	–	–
Surgical site or wound	87 (17.8)	28 (14.7)	59 (19.8)	0.7 (0.4-1)	.1471	–	–
Antimicrobial resistance							
MDR	459 (93.9)	178 (93.2)	281 (94.3)	0.8 (0.4-2)	.6	–	–
XDR	203 (41.5)	71 (37.2)	132 (44.3)	0.7 (0.5-1)	.1	–	–

CI, confidence interval; *HIV*, human immunodeficiency virus; *MDR*, multidrug-resistant; *OR*, odds ratio; *SD*, standard deviation; *XDR*, extensively drug-resistant.
†**P* statistically significant (≤ .05).

Inappropriate definitive therapy with tigecycline and bloodstream infections were found as independent risk factors.

DISCUSSION

This large analysis indicates that infections rates by CR-Ab quickly become endemic after it is introduced into the hospital. These infections are an increasing problem worldwide as they are difficult to treat considering the limited treatment options.[12] Currently, CR-Ab infections are highly prevalent in Brazil, as evidenced in the Rossi et al[13] study, who indicated a 30%-70% increase in CR-Ab infections between 2010 to 2014. CR-Ab incidence can vary according to hospital characteristics, geographic area, type of ward, and anatomic sites from which culture specimens were obtained, and is of major concern in hospitals in countries with limited resources.[14,15]

The data evidenced herein indicate that the rates of infections caused by CR-Ab increased approximately 4-fold from 2013 to 2017, especially in ICU patients, and was especially remarkable in 2014. Thus this study evidenced an endemic situation concerning CR-Ab in the evaluated institution, probably influenced by several factors such as heavy workload, low compliance with hand hygiene, and other infection and control-based measures, resulting in patient-to-patient cross-infection.

The analysis of the hospital database indicated a multidrug-resistant *A baumannii* outbreak detected in November 2014. As in other reports, this outbreak was related to prolonged hospital stays, with most patients cared for in the adult ICU.[16-18] Because this was a retrospective study, no control and intervention measures could be developed. Nevertheless, further outbreaks caused by other microorganisms were reported, and 1 required closing the unit.[17,19,20] Although the reported outbreak was not detected in 2014, an infection control service in the hospital is used to avoid or contain the dissemination of resistant strains, and to indicate the rational use of antibiotics. Thus the need for rationally strong surveillance and infection control practices is highlighted, in addition to functional microbiology labs, strong stewardship antibiotic programs, and political commitment to facilitate the early detection and implementation of effective infection control measures, preventing or containing future outbreaks owing to this microorganism.[15]

It is known that early proper antibiotic treatment is very important in ICUs.[21] Many studies carried out in the last decade have highlighted the strong relationship between the choice of empirical antimicrobial treatment and the risk of death in patients hospitalized with serious infections.[22-26] In the present study, most of the evaluated patients received inappropriate empirical therapy. In this sense, the higher probability of inappropriate empirical antibiotic therapy and resistance phenotype of the microorganism seems to result in worse prognoses for patients with CR-Ab infections.

CONCLUSIONS

This 5-year study demonstrates that the prevalence of CR-Ab increased in the investigated hospital, passing to an endemic pathogen with a possible impact on mortality and the epidemiologic dissemination control of these strains. These results, alongside the detection of an outbreak by this organism, suggest that early infection detection, in addition to surveillance and strong stewardship antibiotic programs, will aid in preventing infections and increase quality of care in the investigated hospital.

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