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CLINICAL MICROBIOLOGY - RESEARCH PAPER

Oral doxycycline to carbapenem-resistant *Acinetobacter baumannii* infection as a polymyxin-sparing strategy: results from a retrospective cohort

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Abstract

Acinetobacter baumannii infection presents a high mortality rate and few therapeutic options. This study aimed to evaluate clinical-microbiological characteristics and prognosis factors of patients diagnosed with *A. baumanni*. infections treated with oral doxycycline. A retrospective cohort of hospitalized patients with confirmed *Acinetobacter* spp. infection between 2018 and 2020 receives at least 3 days of oral doxycycline. Clinical and microbiological data were evaluated, including the outcome and molecular characterization of *A. baumannii*. Doxycycline minimal inhibitory concentrations were evaluated by the broth dilution method. One hundred patients were included with a median age of 51 years. The leading site of infection was pulmonary ($n=62$), followed by the soft tissues and skin ($n=28$). *A. baumannii* resistant to carbapenem was found on 94%. The gene *bla*OXA-23 and *bla*OXA-51 were amplified in all recovered isolates of *A. baumannii* ($n=44$). Doxycycline MIC50 and MIC90 were 1 µg/mL and 2 µg/mL, respectively. Death rate at 14 days and 28 days of follow-up was 9% and 14%, respectively. The prognostic factors related to death at end of follow-up were age > 49 years [85.7% *vs.* 46%, CI 95% 6.9 (1.4–32.6), $P=0.015$] and hemodialysis [28.6% *vs.* 7%, CI 95% 5.33 (1.2–22.1), $P=0.021$]. Patients treated with doxycycline to *A. baumannii* presented a relatively low death rate, and risk factors related to death were age and hemodialysis. Further and larger studies should compare polymyxin to doxycycline to better understand the differences between these therapeutic options.

Keywords Acinetobacter · OXA-23 · Doxycycline · Tetracycline · Tigecycline

Introduction

Acinetobacter spp. are ubiquitous non-fermenting gram-negative bacilli. It was first described as *Mima* spp. during the early twentieth century [1]. The genus *Acinetobacter* was proposed during the 1960s, but it has been reported as an important human pathogen since the 1940s [2, 3]. *Acinetobacter baumannii* emerged as a pathogen related to health-associated infections (HAIs) [4–6]. Multidrug resistance of this pathogen has been demonstrated around the world, increasing the failure of treatment and mortality, mainly the resistance to carbapenem (carbapenem-resistant *Acinetobacter baumannii*—CRAB) [7, 8].

The treatment of CRAB is based on a few options, including polymyxin and tigecycline [9, 10]. According to the SENTRY surveillance program, polymyxin and minocycline are the most active therapeutic options [7]. Among tetracyclines, minocycline or doxycycline-based therapy presents a clinical success rate of 76% [11]. However, these options usually are used as adjunctive therapies once few data of monotherapy are available on literature [11]. The large volume of distribution (Vd) of tetracyclines may be an attractive pharmacokinetic property if used to non-severe infections.

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However, its use in critically-ill patients and/or blood stream infections is questionable.

Even before COVID-19, there were global efforts to decrease the antimicrobial resistance through antimicrobial stewardship programs which are based in sparing carbapenem, polymyxin, and tigecycline, considering the last therapeutic sources for the treatment of multidrug-resistant bacteria, including CRAB. After COVID-19 pandemic, antimicrobial resistance increased significantly due to the indiscriminate use of carbapenems and/or polymyxins to *Acinetobacter* spp. infections and further restricts therapeutic options. The use of tetracycline for *A. baumannii* can be an alternative to cephalosporins, carbapenems, and fluoroquinolones. This study aimed to evaluate clinical-microbiological characteristics and prognosis factors of patients diagnosed with *Acinetobacter baumannii* infections treated with oral doxycycline.

Methods

Settings

This was a retrospective cohort study of patients diagnosed with *Acinetobacter baumannii* infections treated with oral doxycycline. Data collection included 2 years (November 2017 to December 2020) from a University Hospital in the South of Brazil. Follow-up occurred until discharge or death. This study was approved by the Ethical committee from PUCPR (22,320,619.6.0000.0020).

Participants

Inclusion criteria for patients were as follows: (i) ≥ 18 years, (ii) admitted to hospital wards or ICU, (iii) confirmed infection due to doxycycline susceptible *A. baumannii*, and (iv) medical prescription of oral doxycycline for *A. baumannii* infection. Patients with a lack of clinical and microbiological information were excluded.

Antimicrobial stewardship program and microbiological tests

Since 2017, the antimicrobial stewardship program of the hospital included active surveillance of patients using intravenous antibiotics to evaluate the possibility of change to oral therapy (see details of the protocol for the oral switch in supplemental material – S1). Beyond the intravenous to oral switch approach, the carbapenem and polymyxin sparing approach were started, and alternative therapies were introduced. Considering the susceptible profile of *A. baumanni* in the institution published previously [12, 13], doxycycline was included in the routine susceptibility tests by disk diffusion [14]. All isolates were identified using MALDI-TOF Vitek® MS (BioMérièux, Marcy-l'Etoile, France) and susceptibility profile for other than doxycycline antibiotics by automated system MicroScan WalkAway (Beckman Coulter, Brea, CA).

Molecular analysis

In order to evaluate similarities between environmental and clinical isolates, consecutive CRAB isolates were stored – 80 °C to further molecular analysis for *the bla*OXA-23 gene and *bla*OXA51. Briefly, to determine oxacillinase-encoding genes, polymerase chain reaction (PCR) was performed for all isolates by using the following primers: *bla*OXA-23 (F-5′ GACACTAGGAGAAGCCATGAAG 3′; R-5′ CAGCATTACCGAAACCAATACG 3′; 6-FAM-CCAGTCTATCAGGAACTTGCGCGA-BHQ_1) and *bla*OXA-51 (F-5′ TGTCTAAGGAAGTGAAGCGTG 3′; R-5′ TGGATTGCACTTCATCTTGG 3′; CY5-XN-ACTTGGGTACCGATATCTGCATTGCC-BHQ-2) [15, 16].

Genetic similarity

Fifty isolates were inoculated in 300 µL of ultrapure water and 900 µL of 99% absolute alcohol followed by vortexing for 5 min and centrifugation at 17,005 g for 1 min. The size sample includes all isolates available and viable to test. The supernatant was discarded, and the mixture was vortexed for 5 min after the addition of 50 µL of 70% formic acid. Acetonitrile (50 µL) was added followed by vortexing for 5 min and centrifugation at 17,005 g for 1 min. Direct detection of the microorganism was performed using MALDI-TOF. Quality control of the readings was performed using the reference strain of *E. coli* ATCC® 8739. The detected pattern was analyzed for similarity using the taxonomy tool in the Saramis software (bioMérièux, Marcy-l'Étoile, France). Clones were considered those with > 75% similarities [17].

Variables and definitions

Confirmed infection due to *A. baumannii* was defined as fever ≥ 38 °C, leukocytosis ≥ 10.000 cells/mm [3], clinical symptoms on each site of infection, and positive culture from the suspected site of infection according to Infectious Disease Society of America recommended cut-offs values [18].

Patients were evaluated on end-of-therapy and end-of-hospitalization. Demographic and clinical characteristics, comorbidities, intensive care unit (ICU) support, and clinical and microbiological outcomes were evaluated. Additionally, acute physiology and chronic health evaluation II (APACHE II) was assessed on day of suspected infection.

Clinical cure was defined as an absence of fever, improvement in clinical symptoms and laboratory exams, and absence of need for antimicrobial therapy according to the medical decision. Clinical failure was defined as death or changing on antimicrobial therapy choice due to clinical worsening. The microbiological cure was defined as a negative culture from the site of infection after antimicrobial therapy. Microbiological failure was defined as persistent positive cultures after antimicrobial therapy.

Statistical analysis

Continuous variables were expressed as median values and interquartile range (IQR) and analyzed by Student *t*-test or Mann Whitney *U* test. Categorical variables were expressed as absolute frequencies and proportions and analyzed by Chi-square or Fisher test. Variables with $P < 0.2$ were selected to binary logistic regression. SPSS (IBM, Chicago, IL, USA) was used for statistical analysis. Statistically significant values were considered if $P < 0.05$.

Results

Sample size

A hundred and sixteen patients with *Acinetobacter* spp. infections were found between November 2017 and December 2020. From these, six were non-*A. baumannii* and ten were excluded due to lack of sufficient clinical information for analysis.

Clinical characteristics

One hundred patients were included, 81 (81%) were male, and median age was 51 years [33–62]. Site of infection were pulmonary ($n = 62$), soft tissues and skin (SST) ($n = 28$), osteomyelitis ($n = 6$), urinary tract infection ($n = 2$), and intra-abdominal ($n = 2$). Twenty-three patients (23%) were admitted to ICU (APACHE = 14 [10–23]), and six patients (6%) with vasoactive drugs prescription. The duration of hospitalization was 49 days [31–87], while the length of stay before and after culture were 21 days [11–32] and 23 days [11–46]. Median doxycycline time of treatment was eight days [6–12]. Clinical-microbiological characteristics are on Table 1.

Microbiologic characteristics

Carbapenem-resistant *A. baumannii* was found on 94 (94%) using an automated antimicrobial susceptibility test. Resistance to amikacin, cefepime, and quinolones was found in 91%, 96%, and 97%, respectively. All *A. baumannii* isolated were susceptible to doxycycline using disk diffusion method. Fourteen clinical isolates were recovered to evaluate (i) doxycycline MIC by broth dilution and (ii) molecular analysis. Doxycycline minimal inhibitory concentration varied from 0.25 to 2 µg/mL (MIC50 = 1 µg/mL and MIC90 = 2 µg/mL). The gene *bla*OXA-23 and *bla*OXA-51 were amplified in all isolates of carbapenem-resistant *Acinetobacter baumannii.*

From the general microbiological isolates (environmental and clinical), results were the same that from the fourteen clinical isolates (MIC50-90 1–2 mg/L and gene *bla*OXA-23/*bla*OXA-51 amplified in all strains) (Supplementary Material – Table 1). The hierarchical clustering of the MALDI-TOF peak profiles identified three different *A. baumannii* clusters, with an average genomic similarity rate of 75%. Cluster I had a cluster of 47 isolates, cluster II comprised 2 isolates, and cluster III had only one bacterial isolate (Supplementary Material – Fig. 1).

Concomitant pathogens

In 31 patients, *A. baumanni* was identified together with other pathogens. Gram-negative bacilli and gram-positive cocci concomitants with *Acinetobacter* spp. infection account for 20 (60.6%) and 13 (39.3%) isolates, respectively (Table 2). Thirty-eight (38%) patients received other antibiotic therapy with a gram-negative bacilli spectrum along with doxycycline. Considering the susceptibility pattern, three patients (3%) received double antibiotic coverage to *Acinetobacter* spp. along with doxycycline*:* cefepime ($n = 1$), amikacin ($n = 1$), and polymyxin ($n = 1$).

Outcomes and prognosis factor

Death at 14 days of follow-up occurred in 9 patients (9%). In univariate analysis, death was related to age [63 years (50–74) *vs.*49 years (32–61), $P = 0.029$], vasoactive drug (22.2% *vs.* 4.4%, $P = 0.03$), and doxycycline days of treatment [5 days (3–7.5) *vs.* 8 days (6–13), $P = 0.001$) (Table 3). In binary logistic regression, death at 14 days of follow-up was associated with age > 49 years [89% *vs.* 51%, CI 95% 8.5 (1.02–71.13), $P = 0.047$] (Table 3). Combination therapy was not associated with better outcomes.

Death at 28 days of follow-up occurred in 14 patients (14%). In univariate analysis, death was related to age [63.5 years (50–70) *vs.*47.5 years (32–60), $P = 0.002$], hemodialysis (28.6% *vs* 7%, $P = 0.013$), and doxycycline days of treatment [6 days (3–8) *vs.* 8 (5–13), $P = 0.014$] (Table 4). In binary logistic regression age > 49 years [85.7% *vs.* 46%, CI 95% 6.9 (1.4–32.6), $P = 0.015$] and hemodialysis [28.6% *vs.* 7%, CI 95% 5.33 (1.2–22.1), $P = 0.021$] (Table 4). Combination therapy was not associated with better outcomes.

Table 1 Clinical-microbiological characteristics of patients with *Acinetobacter baumannii* infections treated with doxycycline

Clinical-microbiological characteristics	*N* = 100
Age, median [IQR]	51 [33–62]
Male, *n* (%)	81 (81)
Comorbidities	
HIV, *n* (%)	2 (2)
Diabetes mellitus, *n* (%)	14 (14)
Dialysis, *n* (%)	10 (10)
COPD, *n* (%)	4 (4)
Hypertension, *n* (%)	35 (35)
Neoplasm, *n* (%)	4 (4)
Site of infection	
Pulmonary, n (%)	62 (62)
Skin and soft tissue, n (%)	28 (28)
Bone, n (%)	6 (6)
Urinary, n (%)	2 (2)
Abdominal infection, n (%)	2 (2)
ICU admission, *n* (%)	23 (23)
Vasoactive drug, *n* (%)	6 (6)
More than one pathogen with Acinetobacter. spp. *n* (%)	31 (31)
Concomitant antibiotic with gram-negative bacilli spectrum, *n* (%)	38 (38)
A. baumannii monotherapy*	100 (100)
Meropenem resistance, *n* (%)	94 (94)
Ampicillin-sulbactam resistance, *n* (%)	96 (96)
Amikacin resistance, *n* (%)	95 (5)
Doxycycline MIC50 (mg/L)	1
Doxycycline MIC90 (mg/L)	2
Days of hospitalization before *A. baumannii* culture, median [IQR]	21 [11-32]
Length of stay after infection, median [IQR]	23 [11–46]
Doxycycline time of treatment, median [IQR]	8 [6-13]
Death at day 14, *n* (%)	9 (9)
Death at day 28, *n* (%)	14 (14)

*Considering *Acinetobacter* spp. susceptibility patterns

Table 2 Concomitant isolated bacteria with *Acinetobacter baumannii* in clinical samples (*N* = 33)

Concomitant isolated bacterial	*N* = 33
Staphylococcus aureus	8
Escherichia coli	5
Pseudomonas aeruginosa	5
Stenotrophomonas maltophilia	3
Enterococcus faecalis	3
Proteus mirabilis	2
Klebsiella pneumoniae	2
Enterobacter cloacae	2
Citrobacter koseri	1
Streptococcus. pneumoniae	1
Staphylococcus epidermidis	1

Discussion

In this retrospective cohort, patients with *A. baumannii* infections were treated with oral doxycycline (*n* = 100); the therapy was employed in different scenarios, including mild to moderate infections. Twenty-three patients (23%) were in ICU when *A. baumannii* infection occurred, six of them were in weaning order of vasoactive drugs. Thirty-eight patients (38%) received double antimicrobial therapy with GNB spectrum. However, neither ICU was related to worse prognosis nor combination therapy was related to better outcomes. Factors associated with death at 28 days of follow-up were age > 49 years and hemodialysis.

The last data regarding *A. baumannii* susceptibility based on the SENTRY surveillance program demonstrates polymyxin and tetracyclines as the most effective antimicrobial options [7]. However, the variability between world regions is also demonstrated. In Latin America, 90% of *A.*

Table 3 Prognosis factors related to death due to *Acinetobacter baumannii* infection at 14 days of follow-up

Variables	Death ($n=9$)	Survival ($n=91$)	P	
Male, *n* (%)	8 (89)	73 (80)	0.527	
Age, median [IQR]	63 [50–74]	49 [32–61]	0.029	
Comorbidities				
HIV, *n* (%)	0	2 (2.2)	0.653	
Diabetes Mellitus, *n* (%)	2 (22.2)	11 (12.1)	0.388	
Dialysis, *n* (%)	2 (22.2)	8 (8.8)	0.2	
COPD, *n* (%)	0	4 (4.4)	0.521	
Hypertension, *n* (%)	5 (55.6)	30 (33)	0.175	
Neoplasm, *n* (%)	0	4 (4.4)	0.521	
ICU admission, *n* (%)	4 (44.4)	19 (20.9)	0.109	
Vasoactive drug, *n* (%)	2 (22.2)	4 (4.4)	0.03	
More than one pathogen with Acinetobacter. spp. *n* (%)	2 (22.2)	29 (31.9)	0.551	
Concomitant antibiotic with gram-negative bacilli spectrum, *n* (%)	3 (33.3)	35 (38.5)	0.762	
Days of hospitalization before Acinetobacter baumannii culture, median [IQR]	15 [10–45]	22 [11-32]	0.918	
Doxycycline time of treatment, median [IQR]	5 [3–7.5]	8 [6-13]	0.011	
Binary logistic regression	Death ($n=9$)	Survival ($n=91$)	P	CI 95%
Age > 49 years, *n* (%)	8 (89)	47 (51)	0.047	8.5 (1.02–71.13)
Dialysis, *n* (%)	2 (22.2)	8 (8.8)	0.2	-
Hypertension, *n* (%)	5 (55.6)	30 (33)	0.18	-
ICU admission, *n* (%)	4 (44.4)	19 (20.9)	0.109	-
Vasoactive drug, *n* (%)	2 (22.2)	4 (4.4)	0.055	-
Doxycycline time of treatment < 8 days, *n* (%)	8 (89)	51 (57)	0.098	

Table 4 Prognosis factors related to death due to *Acinetobacter baumannii* infection at 28 days of follow-up

Variables	Death ($N=14$)	Survival ($N=86$)		P
Male, *n* (%)	13 (93)	68 (79)	0.223	
Age, median [IQR]	63.5 [50.7–70.5]	47.5 [32–60]	0.002	
Comorbidities				
HIV, *n* (%)	0	2 (2.3)	0.564	
Diabetes mellitus, *n* (%)	4 (28.6)	9 (10.5)	0.062	
Dialysis, *n* (%)	4 (28.6)	6 (7)	0.013	
COPD, *n* (%)	0	4 (4.7)	0.41	
Hypertension, *n* (%)	7 (50)	28 (32.6)	0.204	
Neoplasm, *n* (%)	1 (7.1)	3 (3.5)	0.518	
ICU admission, *n* (%)	5 (35.7)	18 (20.9)	0.223	
Vasoactive drug, *n* (%)	2 (14.3)	4 (4.7)	0.159	
More than one pathogen with Acinetobacter. spp. *n* (%)	4 (28.6)	27 (31.4)	0.832	
Concomitant antibiotic with gram-negative bacilli spectrum, *n* (%)	4 (28.6)	34 (39.5)	0.433	
Days of hospitalization before Acinetobacter baumannii culture, median [IQR]	20.5 [11.2–31.2]	21 [10.7–35]	0.964	
Doxycycline time of treatment, median [IQR]	6 [3-8]	8 [5-13]	0.014	
Binary logistic regression	Death ($N=14$)	Survival ($N=86$)	P	CI 95%
Age > 49 years, *n* (%)	12 (85.7)	40 (46)	*0.015*	6.9 (1.4–32.6)
Diabetes mellitus, *n* (%)	4 (28.6)	9 (10.5)	0.074	-
Dialysis, *n* (%)	4 (28.6)	6 (7)	0.021	5.3 (1.2–22.1)
Vasoactive drug, *n* (%)	2 (14.3)	4 (4.7)	0.18	-
Doxycycline time of treatment < 8 days, *n* (%)	11 (78.9)	49 (57)	0.13	-

baumannii strains were susceptible to tetracyclines, while in Europe, rates dropped to 70%. Additionally, rates lower than 30% were also reported in Asia [19]. Therefore, doxycycline as an empirical treatment to *A. baumannii* must be based on careful susceptibility profile analysis. Considering it, we have previously described the doxycycline susceptibility profile of CRAB in our hospital of 80% in patients with healthcare-associated bacteremia and meningitis [13].

The pharmacokinetics of doxycycline confers interesting properties for the treatment of mild-to-moderate infections in the lungs, skin and soft tissues, bone, and central nervous system. Doxycycline may be prescribed as 100 mg PO q12h or 200 mg q24h. Once the volume of distribution is 0.7L/kg, and half-life varies between 18 and 24, 200 mg q24h or even q12h regimens may benefit severe patients due to earlier steady-state achievement [20]. Doxycycline peak serum concentrations vary according to the dose regimen. Single 100 mg PO may achieve 1.7–2 mg/L while 200 mg PO reaches 5–6 mg/L [21]. Bactericidal pharmacodynamic target is demonstrated to be 8–16 times the minimal inhibitory concentration (MIC), although 2–4 times the MIC may present a bacteriostatic effect [22].

Doxycycline MIC ranged from 0.25 to 2 mg/L with a MIC50 and MIC90 of 1 and 2 mg/L, respectively. This susceptibility profile is very different from other studies with CRAB from different regions of the world. Several studies with CRAB present higher resistance, including MIC50/90 of 32/64 mg/L in Iran and in a multicentric study in Europe [23, 24]. Doxycycline pharmacokinetic parameters, patient clinical presentation, and pathogen MIC must be analyzed to avoid potential therapy failure due to insufficient tissue levels. Doxycycline MIC50 was 1 µg/mL, suggesting that doxycycline has bacteriostatic activity in patients with *Acinetobacter baumannii*. This hypothesis could be confirmed by in vitro tests (time kill-curve). Twelve isolates presented MIC lower than 1 mg/L, a good susceptibility profile for possible bactericidal activity of doxycycline.

Our molecular findings are in accordance with previous studies demonstrating that carbapenem resistance in *A. baumannii* is strongly associated with the *bla*OXA-23 gene [25]. Carbapenems MICs are also demonstrated to be higher when *bla*OXA-23 or *bla*OXA-51 genes are associated with insertion sequences such as IS*Aba1*. Once *bla*OXA-23 is also associated with *A. baumannii* hospital outbreaks due to widespread capacity, infectious disease specialists could see tetracyclines as an option to spare polymyxin or tigecycline overuse during outbreaks also. The clonality analysis showed that the largest proportion of *A. baumannii* belongs to cluster I, and only 3 isolates from different clusters. Other species of *Acinetobacter* spp. were not included in this analysis. The genetic similarity was evaluated using MALDI-TOF as tool for investigation of *A. baumannii* outbreaks [26]. The advantage of MALDI-TOF is the low cost and speed.

Differently from extensively drug-resistant *Enterobacteriaceae*, combined therapy to CRAB did not demonstrate better survival rates [28]. In our study, from 100 patients, 38 received another antibiotic. However, considering the *A. baumannii* susceptibility profile, all of them received only doxycycline as active drug. Additional combinations described in our study were used with the intention to expand the antimicrobial spectrum, once 31 (31%) patients with *A. baumannii* infection presented another pathogen isolated from the same site. Traditional therapeutic options to CRAB treatment, such as tetracyclines, polymyxin, and tigecycline, were evaluated in previous studies with full results variability. A common conclusion of a meta-analysis is that combined therapy to non-fermenting GNB infections is not superior to monotherapy [29, 30]; nevertheless, divergences among therapeutic options are reported.

Oral therapy in severe patients is a questionable approach. A recent study with critically-ill patients demonstrated that oral switch could be safe in patients with adequate enteral feeding after improving the initial signs of sepsis [31]. The authors included doxycycline in the intravenous-to-oral antibiotic switch therapy. However, the number of patients and their outcome was not detailed. In our study, polymyxins and tigecycline would be alternatives to doxycycline; however, these drugs should be considered last treatment resources if we evaluate toxicities, environmental selective pressure, and costs. Doxycycline is a less expensive option and as safe as classical ones available. Death rate at 14 and 28 days of follow-up were 9% and 14%, respectively. This finding may support the safety of doxycycline in the treatment of *A. baumannii*. Similar to our results, tetracycline-based therapy presented a clinical failure of 23% [11]. In this cohort, the factors associated with death at end of follow-up were age and hemodialysis. Considering that doxycycline is not cleared by dialysis filters nor urine output, and that age is commonly demonstrated as a risk factor to death in patients with hospital acquired infections, our related findings might not be attributed to the oral doxycycline therapy, but a common risk factor to death in stable patients diagnosed with *A. baumannii* infection.

This is a retrospective cohort and may present bias considering the analysis of the authors' point of view. A control group with other therapy, as polymyxin, could be included as a comparator; however, another bias would be implied, different severity between doxycycline and polymyxin group. These drugs present different pharmacokinetics, route of administration, and the stewardship program of the institution claim to avoid the use of polymyxin due to the risk of polymyxin-resistance [32], costs [33], and high nephrotoxicity [34]. The combined therapy in some patients could be a risk of misinterpretation of the outcome due to synergic, additive, or antagonistic effects.

Conclusion

Patients treated with doxycycline to *A. baumannii* presented a relatively low death rate, and risk factors related to death were age and hemodialysis. Further and larger studies should compare polymyxin to doxycycline to better understand the differences between these therapeutic options. From this retrospective observational study, doxycycline appears to be a possible option to CRAB infections.

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Author contribution Felipe Francisco Tuon was responsible for the organization and coordination of the study and responsible for the data analysis.
Carolina Hikari Yamada was the chief investigator and wrote the draft of this manuscript.
Ana Paula de Andrade performed microbiological analysis.
Lavinia Nery Villa Stangler Arend performed microbiological analysis.
Dayana dos Santos Oliveira performed data analysis.
João Paulo Telles wrote the draft of this manuscript and performed statistical analysis.
All authors contributed to the writing of the final manuscript.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval This study was approved by the Ethical committee from PUCPR (22320619.6.0000.0020).

Competing interests The authors declare no competing interests.

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