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Short Communication

Genetic, antimicrobial resistance profile and mortality rates of *Acinetobacter baumannii* infection in Brazil: A systematic review

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Abstract

The increase of multidrug-resistant bacteria - including *Acinetobacter baumannii* (*A. baumannii*) - has been reported globally. The aim of this systematic review was to determine the risk factors of *A. baumannii* infection, its resistance profile, reservoirs and mortality rates in Brazil. Data from over 3,000 patients were included. Results suggested that *A. baumannii* is widely transmitted in Brazil and the endemic clones ST1, ST15, ST 25, ST79, ST162 and ST730 were the most reported; also, bla_{OXA23}, bla_{OXA51} and bla_{OXA143} were common resistant genes. The risk factors for *A. baumannii* infection included the procedure of using invasive devices, previous antibiotic therapy, hemodialysis, comorbidities and higher scores on the Sequential Organ Failure Assessment (SOFA). Two out of five studies identified multidrug resistant *A. baumannii* to polymyxin. Mortality rates varied between 43.7% to 81%, except for the ST25 strain in which there was a 100% mortality rate. Mortality was associated with sepsis, respiratory infection, septic shock, old age (>60 years) and administration of norepinephrine. Nonetheless, this review highlights the need for more data on *A. baumannii* infection across Brazil to support public policies aiming to control and prevent the dissemination of this bacteria.

Keywords: *A. baumannii*, multidrug-resistant, resistant profile, antibiotic resistant, Brazil

Introduction

Reports of increasing outbreaks of multidrug-resistant microorganisms have been growing significantly around the world. The resistance of microorganisms stems from mutations, transposable genetic materials (plasmid, transposon, and integron), and inadequate use of antimicrobials in humans, animals, and environments, thus representing a global threat that requires effective interventions [1]. In 2008, Rice grouped six emerging bacteria capable of rapidly developing antimicrobial resistance mechanisms ("ESKAPE bugs"), including *Acinetobacter baumannii (A. baumannii)* [2]. Of the 31 species of the genus *Acinetobacter*, the one that stands out for its opportunism, and which causes numerous global outbreaks, is *A. baumannii*. Outbreaks associated with *A. baumannii* have been described in hospitals globally [3] *A. baumannii* causes severe infections in hospitalized and critically ill patients, mostly in those with severe underlying diseases and undergoing invasive procedures [4].

A. Baumannii acquired resistance phenotypes to multiple drugs [5]. Carbapenem is considered effective against *A. baumannii* infection, although resistance to this antibiotic is

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increasing because *A. baumannii* produces a variety of β-lactamase enzymes, such as carbapenemases and oxacillinase (OXA).

The Centers for Disease Control and Prevention (CDC) reported 8,500 cases of *A. baumannii* infection in 2017 and 700 deaths in the United States [6]. In Brazil, data about transmission, incidence, and the resistant profile of *A. baumannii* infection are scarce; such information might better assist in the decision-making involving clinical interventions and could likewise provide a precise understanding of the burden in the country. Indeed, to the best of our knowledge, there are no systematic reviews on the prevalence of *A. baumannii* and its resistance profile in the country.

Therefore, the aim of this systematic review was to determine the risk factors of *A. baumannii* infection, its resistance profile and mortality rates in Brazil. Beyond its immediate application for Brazilian health institutions, the study might aid in the management of *A. baumannii* infection in other regions, particularly in developing countries.

Methods

Study setting

A systematic review of the literature was performed covering Brazilian national and international databases. The focus of this systematic review was on studies conducted in Brazil that reported on incidence, resistance profiles, mortality and risk factors associated with *A. baumannii* infection. The investigation had been registered at the International Prospective Register of Systematic Reviews (PROSPERO; record: CRD42021249563) and was conducted following the PRISMA guidelines [6-9].

Search strategy

A search for previous systematic review was carried out in the Cochrane Library using "Acinetobacter", "Brasil" and "Brazil" as descriptors and records were identified. Subsequently, the following string was used to locate potential studies: "*Acinetobacter baumannii*" OR ""*A. baumannii*" AND "intensive care" OR "critical care" AND "resistant" AND "Brasil" OR "Brazil". Searches were conducted between April and May 2021 in two databases: PubMed and the Virtual Health Library (*Biblioteca Virtual em Saúde* - BVS). BVS covers the most relevant literature on health sciences in Brazil.

Inclusion and exclusion criteria

Studies that provided data on the incidence of *Baumannii* infection in Brazil (analytical, prospective, retrospective, experimental, randomized trials, cohort and case-control) were considered eligible. Moreover, studies were included when information on resistance profile was available. Only reports written in Portuguese, Spanish and English from the last five years were included. As such, research published more than five years ago, conducted in other countries, literature reviews, editorials, letters, comments, conference abstracts, and case reports were excluded. Studies without a clear focus on *A. baumannii*, unpublished, or published in the gray literature were excluded.

Data extraction and risk of bias assessment

Data were collected by two investigators (MCBS and HMBW), blindly and independently. Researchers used a standardized sheet form designed according to the inclusion and exclusion criteria. The evaluation was carried out in two stages. Firstly, titles and abstracts were evaluated. Secondly, full texts were read and evaluated. After these selection stages, manual searches were conducted in the articles' references. Any disagreements between the two investigators while selecting the eligible studies were solved consulting a third investigator (DV). The results obtained were then summarized in a table containing the following characteristics: study name, region of the study, database and journal name, study design and participants, methods, objectives, results, and conclusions.

The assessment of the risk of bias was performed using the New Castle Ottawa Scale. Specific questionnaires according to different study types were used [8-10].

Results

Characteristics of the studies

The identification phase returned 19 and 15 results from PubMed and BVS, respectively (**Figure 1**). From these, 19 studies were removed (13 due to duplication; 6 for other reasons). In addition, 10 other studies were excluded, mainly because of inappropriate study type (n=5), descriptive studies (n=4) or for not having identified *A. baumannii* (n=1). Finally, 5 articles [11-15] were included in the final review: four from PubMed [12-15] and one from BVS [11]. A manual search was performed in the references of the included articles and resulted in no further studies to be included.

The characteristics of the studies are summarized in **Table 1** and the results of the risk of bias assessment are reported in **Table 2**. Overall, there was both good quality and low risk of bias in the reports reviewed (**Table 2**). From these, four were carried out in central Brazil (Goiás (n=1), Minas Gerais (n=1), Mato Grosso (n=1), and Southern Mato Grosso (n=1)) and one was conducted in the South of the country (Paraná; n=1). Four studies were conducted in ICUs [12-15] and one reported data at a hospital level [11].

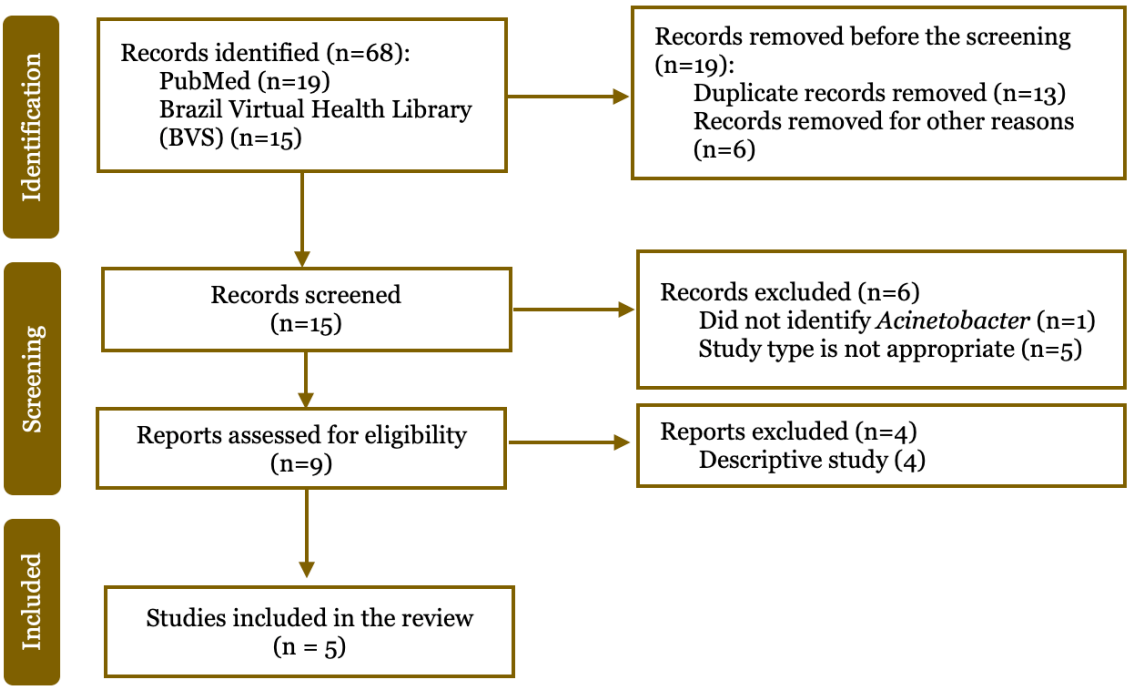

Figure 1. Flowchart of literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Genetic and antimicrobial resistance profile of *A. baumannii* in Brazil

Four studies identified carbapenemase-producing *A. baumannii* and the $bla_{\text{OXA-23}}$ gene was identified in all samples [11-14]. Two studies identified $bla_{\text{OXA-143}}$ while the $bla_{\text{OXA-24}}$ was the most prevalent resistant gene [11, 14] A positive association was identified between the presence of $bla_{\text{OXA-51}}$ and $bla_{\text{OXA-23}}$ in all strains [13]. Resistance to polymyxin and tigecycline was also reported [11, 14].

In 2 studies, predominant genotypes of *A. baumannii* were ST1, ST15, ST25, ST79 [13], ST162, and ST730 [11]. One investigation reported the ST79 as the most widespread genotype [13]. ST30 was associated with higher mortality rate while ST162 appeared to be linked to higher survival rates [14]. Also, 2 studies found endemic features for the ST1 genotype [11,13].

Table 1. Characteristics of the studies and the main findings

Reference	Study location	Study design	Setting and study time	Results
Neves *et al.* (2016) [11]	Minas Gerais	Cohort study	In 500-bed tertiary teaching hospital Prospective data collection of patients over 18 years old colonized with carbapenem-resistant *Acinetobacter baumannii* (CRAB). 12 months (December 2009 to December 2010)	• The study included 56 individuals, and the risk factors for CRAB were: use of invasive devices (83%) and antibiotic therapy in the past (77%). • The mortality rate was 59%. • Carbapenem resistance was associated with a high prevalence of *bla*$_{OXA-23}$ (51%) and/or *bla*-$_{OXA-143}$ genes (28%). • Three strains exhibited resistance to polymyxin and 10 strains to tigecycline. • Infection was associated with poor outcomes.
Castilho *et al.* (2017) [12]	Goiás	Cohort study	In five ICUs with 10 beds Healthcare-associated infections of *A. baumannii*. Those infected less than 48 hours of admission was excluded. 6 months (June to December 2010)	• Out of 82 patients (41 cases, 41 controls). 1333 patients included, 64 had with *A. baumannii* infection in 84 isolates, with a frequency of 4.8%. Of the 64, 56 were infected (87.5%) and 6 (9.4%) were colonized. • Most isolates were resistant to beta-lactams and 91.1% were multi-resistant (MDR). The most frequent gene was *bla*$_{OXA-23}$ (55.1%) and often associated with MDR strains. • There were 76.8% of the isolates were able to form biofilm. The classes of effective antimicrobials were polymyxins and tigecycline.
da Silva *et al.* (2018) [13]	Mato Grosso do Sul	Case-control	Two adult ICUs. Case: patients with confirmed OXA-23 enzyme-producing *A. baumannii*. Control: patients with negative isolates for *A. baumannii* in the first 48 hours after admission. 19 months (September 2013 to April 2015)	• Of the 275 infections/colonization caused by *A. baumannii*, 41 strains were OXA-23 producers. • The predominant genotypes were ST1, ST15, ST25 and ST79 in which ST79 was the most widespread clone. • All patients infected with the strain ST25 producing OXA-23 died. • Associations between the presence of *ISAba1* with OXA-51, as well as the presence of *ISAba1* with OXA-23 were found in all strains. • Risk factors infection: nasogastric tube, hemodialysis, and use of cephalosporin. • 82.9% of patients had previous exposure to carbapenems and the use of cephalosporins resulted in six times greater risk of acquiring A. *baumannii* producer OXA-23 enzyme.
Azevedo *et al.* (2019) [14]	Mato Grosso	Cohort study	Clinical data were obtained from the patients' records. 43 months (June and December 2010)	• 87 patients with *A. baumannii* isolates: 61 (70.2%) with healthcare-associated infections, and 26 (29.8%) colonization. 74 isolates (73.5%) were from patients in ICU. • The mortality rate was 43.7%. • 80 (91.9%) isolates showed resistance to imipenem. Both *bla*$_{OXA-23}$ gene (78.2%) and *ISAba1* (55.2%) were prevalent. Moreover, the study also reported on the *bla*$_{OXA-24}$ (55.2%) and on the *bla*$_{OXA-143}$ (28.7%). The *bla*$_{OXA-23}$ *ISAba1* gene was independently linked with imipenem resistance. • Respiratory infection, elderly and use of norepinephrine were factors associated with lethality. • ST730 (was associated with higher mortality and ST162 was associated with a higher probability of survival.
Talizin *et al.* (2020) [15]	Paraná	Cohort study	A historical cohort of patients who received polymyxin in the treatment of ventilator-associated pneumonia in the ICUs 12 months (January 2017 to January 2018)	• 179 cases of ventilator-associated pneumonia treated with polymyxin were identified. 158 (88.3%) had chronic diseases. • A. *baumannii* was the etiologic agent in 67.6% cases of ventilator-associated pneumonia

Reference	Study location	Study design	Setting and study time	Results
				• The mortality rate was 81%. • Comorbidities and scores of the Sequential Organ Failure Assessment (SOFA) at the moment of polymyxin prescription were risk factors for patient mortality. • A two-weeks survival probability analysis indicated that higher mortality was linked with sepsis and septic shock.

CRAB: carbapenem-resistant *Acinetobacter baumannii*; *ISA*: insertion sequence Acinetobacter; MDR: multi-resistant; SOFA: sequential organ failure assessment

Table 2: Risk of bias assessment results

Case-control study	Adequate case definition	Representation	Selection of controls	Definition of controls	Control for important factor or additional factor	Verification of exposure	Same method for cases and controls	Non-response rate	Total (0-9)
Da Silva *et al.* (2018) [13]	*	*	*	*	**	*	*	*	9
Cohort study	Adequate representation of the exposed cohort	Selection of the non-exposed cohort	Confidence in measuring the exposure	The outcome of interest is not present at baseline	Control for an important or additional factor	Adequate outcome measurement	Long follow-up Enough for event development	Adequate cohort follow-up	Total (0-9)
Castilho *et al.* (2017) [12]	*	*	*	*	*	*	*	*	8
Azevedo *et al.* (2019) [14]	*	*	*	*	**	*	*	*	9
Talizin *et al.* (2020) [15]	*	*	*	*	**	*	*	*	9
Neves *et al.* (2016) [11]	*	*	*	*	*	*	*	*	8

Risk factors and mortality rates of *A. baumannii* infection in Brazil

Risk factors of *A. baumannii* infection were assessed in 3 studies [12,14,15]. Moreover, the use of invasive devices, previous antibiotic therapy, use of nasogastric tube, and hemodialysis increased the risks of infection [15]. Biofilm formation was described in 1 study, in which most isolates (76.8%) presented with this feature [12]

A. baumannii-associated mortality rates were reported in 3 studies, ranging from 43.7%to 81% [11,14,15]. One study identified an association of *A. baumannii* infection with poor prognosis [11] and another study indicated higher mortality of patients with *A. baumannii*-associated sepsis and septic shock that received polymyxin [15]. Respiratory infection, age (>60 years), and noradrenaline administration constituted the main risk factors for mortality in those with *A. baumannii* infection [11]. Notably, patients infected or colonized by the ST25 strain that harbored $bla_{\text{OXA-23}}$ had a 100% mortality rate [13]. Previous use of cephalosporins and carbapenems associated with a six-fold increase in the risk of carbapenem-resistant *A. baumannii* infection; comorbidities and higher scores on the Sequential Organ Failure Assessment (SOFA) significantly predicted patients mortality [15].

Discussion

Based on the review of studies published between 2016 and 2020, nosocomial infections caused by *A. baumannii* seem to represent a significant risk to the health of hospitalized patients, particularly in the ICU and, indisputably, when resistance to carbapenems occurs. This risk is explained by the patients' vulnerability, particularly those with severe comorbidities and receiving invasive procedures. Therefore, ICUs seem to be a main source of acquired infections of *A. baumannii* [3].

In Brazil, there is the evidence that *A. baumannii* produced carbapenemases, in particular OXA. The most responsible phenotypes associated with nosocomial outbreaks were *A. baumannii* producing OXA-23-, OXA-40/24, and OXA-58-like enzymes; among carbapenem-resistant *A. baumannii*, the most detected was $bla_{\text{OXA-23}}$ [12]. The first outbreak of $bla_{\text{OXA-23}}$-producing *A. baumannii* was described in 1999 in the city of Curitiba, State of Paraná, Brazil, 14 years after the first identification of the enzyme in Scotland. Since then, several studies have identified this pathogen with a similar resistance profile in several Brazilian states [16]. Results from these investigations revealed that *A. baumannii* harbored a high prevalence of $bla_{\text{OXA-23}}$, followed by $bla_{\text{OXA-51}}$; $bla_{\text{OXA-143}}$ was found in *A. baumannii* isolates in Brazil and other Latin American countries [12, 15, 17, 18].

Biofilms are communities of bacteria organized within an envelope of substances. They are produced by the bacteria and protect chemical agents and antibiotics used to fight infections. Wet surfaces are more prone to biofilm formation; moreover, the greater the degree of adhesion, the harder it is to remove biofilms. The penetration of antimicrobials and the selective pressure exerted by them contribute in developing resistance mechanisms by bacteria [19,20].

Our study suggests that the risk factors associated with *A. baumannii* infection that may influence both the rates of resistance and spread in the ICU includes: having comorbidities, undergoing invasive procedures, prolonged hospitalization, previous exposure to many classes of antimicrobials and old age [12, 21]. A study carried out in several countries also linked these risk factors to a higher prevalence of infections and colonization of *A. baumannii* in the ICUs; moreover, seasonality was cited as a considerable risk factor in warmer seasons [22].

There is a consensus that colonized or infected patients represent reservoirs for horizontal transmission and dissemination of multidrug resistance bacteria, especially in ICUs. Transfers of patients between units and health teams working in different institutions within the same city are facilitators for the occurrence of this transmission in Brazil [12].

The most frequent clonal variants in Brazil were ST15, ST79, and ST51 and these are also the most frequent ones found in South America. Therefore, these endemic variants represent major risks in ICUs. Importantly, sequencing of strains across regions are needed to better understand the trajectories of these clones [23].

Overall, there was a low risk of bias in the studies reviewed here. This is partially explained by the strict inclusion and exclusion criteria of our protocol. All reports employed the National

Health Surveillance Agency criteria to define hospital-acquired infections. However, the lack of experiments and the poor national representation might encourage and support future investigations.

In summary, this systematic review included recent data from more than 3,000 hospitalized patients and reviewed the resistance profile of *A. baumannii*, the potential reservoirs, risk factors associated with the infection and mortality rates in Brazil. However, the external validity of the results might be limited due to the non-uniform distribution of the studied regions since 80% of data came from central regions.

Conclusion

This systematic review demonstrates the relevance of hospital-acquired infections caused by multidrug-resistant *A. baumannii*, especially strains resistant to carbapenems and polymyxin. It characterized *A. baumannii* as both a threat and a challenge to patients' health and safety in Brazil due limited treatment options, coupled with the occurrence of biofilm formation. Information provided in this review points to a need for robust studies while highlighting the need for data from different regions of the country to determine genetic variety and resistance factors for *A. baumannii* infection. Such data might guide protocols to control transmission and could optimize national public policies for detecting and controlling *A. baumannii*.

Ethics approval

Not required.

Acknowledgments

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Conflict of interest

The authors declare that they have no competing interests.

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Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

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