

## ORIGINAL ARTICLE

**Inappropriate empirical antimicrobial treatment in bloodstream infections patients in the era of multidrug resistance***Tratamiento antimicrobiano empírico inadecuado en pacientes con infecciones del torrente sanguíneo**Terapia Empírica Inapropriada no Tratamento de Infecções de Corrente Sanguínea na Era da Multirresistência Antimicrobiana*Jane Eire Urzedo<sup>1</sup> ORCID 0000-0002-3254-9765Ralciane de Paula Menezes<sup>1</sup> ORCID 0000-0001-8499-9090Melina Lorraine Ferreira<sup>1</sup> ORCID 0000-0002-7038-085XCristiane Silveira de Brito<sup>1</sup> ORCID 0000-0002-3462-2639Raquel Cristina Cavalcanti Dantas<sup>1</sup> ORCID 0000-0003-1559-5775Paulo P. Gontijo-Filho<sup>1</sup> ORCID 0000-0002-4192-1100Rosineide Marques Ribas<sup>1</sup> ORCID 0000-0001-9295-6832<sup>1</sup>Universidade Federal de Uberlândia, Uberlândia, Minas Gerais, Brasil.

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**ABSTRACT**

**Background and objectives:** Bloodstream infection (BSI) by multidrug-resistant *Pseudomonas aeruginosa* is a severe infection. This study aimed to evaluate and identify the predictors of mortality in patients who had bloodstream infection by carbapenem-resistant *P. aeruginosa*. **Methods:** This is a retrospective cohort study, approved by Committee of Ethics in Research with Human Participants, which included 87 consecutive patients hospitalized in a referral hospital in Brazil. Clinical and demographic information about each patient were obtained from hospital records. The Student's T-test was used to compare continuous variables and  $\chi^2$  or Fisher's exact tests to compare categorical variables. To determine independent risk factors for 30-day mortality, a multiple logistic regression model was used. A survival curve was constructed using the Kaplan–Meier method. **Results:** Among the patients, 87.3% use antibiotics previously, 60.9% received inadequate empirical treatment, and the 30-day

mortality rate was 57.5%. Inappropriate antibiotic empirical therapy was independently associated with a 30-days death and mortality rate. **Conclusion:** These findings can show some insights about the relationship between higher mortality and inappropriate empirical therapy for patients with BSI by *P. aeruginosa*. There is a need for better diagnostic tests and infection control programs should focus on de-escalation the antibiotic inappropriate therapy, mainly in BSI caused by carbapenem-resistant *P. aeruginosa*.

**Keywords:** *Pseudomonas aeruginosa*, Carbapenem, bloodstream infection, mortality.

## RESUMEN

**Justificación y objetivos:** La infección del torrente sanguíneo por *Pseudomonas aeruginosa* multirresistente es grave. Este estudio tuvo como objetivo evaluar e identificar predictores de mortalidad en pacientes ingresados en una Unidad de Cuidados Intensivos que presentaban infección del torrente sanguíneo por *P. aeruginosa* resistente a carbapenémicos. **Métodos:** Se trata de un estudio de cohorte retrospectivo, aprobado por el Comité de Ética en Investigación con Participantes Humanos, que incluyó 87 pacientes consecutivos ingresados en un hospital de referencia en Brasil. La información clínica y demográfica de cada paciente se obtuvo mediante el análisis de las historias clínicas de los pacientes. Se utilizó la prueba t de Student para comparar variables continuas y  $\chi^2$  o prueba exacta de Fisher para comparar variables categóricas. Para determinar los factores de riesgo independientes para la mortalidad a los 30 días, se utilizó un modelo de regresión logística múltiple. Se construyó una curva de supervivencia utilizando el método de Kaplan-Meier. **Resultados:** Del total de pacientes, el 87,3% utilizaba antibióticos previamente, el 60,9% recibió tratamiento empírico inadecuado y la tasa de mortalidad a los 30 días fue del 57,5%. La terapia empírica inadecuada fue un factor de riesgo independiente de mortalidad. **Conclusión:** Estos hallazgos revelan algunos conocimientos sobre la relación entre el aumento de la mortalidad y la terapia empírica inadecuada para los pacientes con infección del torrente sanguíneo por *P. aeruginosa*. Además, destacan la necesidad de mejores pruebas de diagnóstico y los programas de control de infecciones deben centrarse en reducir la terapia con antibióticos inapropiados, particularmente en infección del torrente sanguíneo causados por *P. aeruginosa* resistente a carbapenémicos.

**Palabras clave:** *Pseudomonas aeruginosa*, carbapenémicos, infección del torrente sanguíneo, mortalidad.

## RESUMO

**Justificativa e objetivos:** Infecção da corrente sanguínea (ICS) por *Pseudomonas aeruginosa* multirresistente é grave. Este estudo teve como objetivo avaliar e identificar os preditores de mortalidade em pacientes admitidos em uma Unidade de Terapia Intensiva que apresentaram infecção da corrente sanguínea por *P. aeruginosa* resistente aos carbapenêmicos. **Métodos:** Trata-se de um estudo de coorte retrospectivo, aprovado pelo Comitê de Ética em Pesquisa com Seres Humanos, que incluiu 87 pacientes consecutivos internados em um hospital de referência no Brasil. As informações clínicas e demográficas de cada paciente foram obtidas através de análise dos prontuários dos pacientes. O teste T de Student foi usado para comparar variáveis contínuas e o teste  $\chi^2$  ou exato de Fisher para comparar variáveis categóricas. Para determinar fatores de risco independentes para mortalidade em 30 dias, foi utilizado um modelo de regressão logística múltipla. Uma curva de sobrevida foi construída pelo método de Kaplan-Meier. **Resultados:** Do total de pacientes, 87,3% faziam uso prévio de antibióticos, 60,9% receberam tratamento empírico inadequado e a mortalidade em 30 dias foi de 57,5%. A terapia empírica inadequada foi fator de risco independente para mortalidade. **Conclusão:** Esses achados revelam alguns *insights* sobre a relação entre maior mortalidade e terapia empírica inadequada para pacientes com ICS por *P. aeruginosa*. Além disso, destacam a necessidade de melhores testes diagnósticos e os programas de controle de infecção devem se concentrar na

redução da terapia inadequada com antibióticos, principalmente na ICS causada por *P. aeruginosa* resistente a carbapenêmicos.

**Palavras-chave:** *Pseudomonas aeruginosa*. Carbapenêmicos. Infecção da corrente sanguínea. Mortalidade.

## INTRODUCTION

*Pseudomonas aeruginosa* is a ubiquitous opportunistic Gram-negative bacillus and is one of the main pathogens responsible for the occurrence of infections related to health care, contributing to the increase in morbidity and mortality rates, hospitalization time and patient costs.<sup>1,2</sup>

It mainly affects individuals with comorbidities, such as diabetes, cystic fibrosis and neoplasms; hospitalized and in prolonged use of invasive devices and antimicrobial therapy.<sup>3,4</sup> Among the most common infections are ventilator-associated pneumonia and bloodstream infection (BSI).<sup>3,5,6</sup>

Severe infections due to *P. aeruginosa*, such as BSI, results in higher morbidity and mortality, longer hospitalization, and high costs, especially among hospitalized patients in less developed countries, like Brazil. The problem is greater in large hospitals with many beds complex care levels.<sup>5,6</sup>

BSI in the resource-limited countries is largely caused by Gram-negative bacilli multidrug-resistant (MDR) strains that have been increasing in the last few decades<sup>3,5,6,7</sup> and, for this reason, empirical antibiotic treatment of patients with this infection has become a major challenge for physicians, considering that inappropriate empirical antibiotic treatment might be more frequent than desirable.<sup>3,6,7,8,9</sup>

Treatment of BSI in countries like Brazil is largely empirical and a challenge for patients with infections for multidrug-resistant (MDR) *P. aeruginosa*.<sup>3</sup> These patients had limited treatment options and are highly vulnerable to receiving inappropriate empiric therapy, which contributes to increased length of hospitalization and worst clinical outcomes.<sup>5,6,8</sup>

In the current study, we aimed to describe the rates of inappropriate antimicrobial therapy in a cohort of patients with bloodstream infection by carbapenem-resistant *P. aeruginosa* in the era of widespread antimicrobial resistance. Second, this study explored characteristics associated with the clinical outcomes of these patients in a large Brazilian tertiary-care hospital.

## METHODS

### **Study design, Patients, and setting**

A cohort study was employed to identify the predictors of mortality in the last ten years, and the impact of inappropriate therapy on the outcomes of patients with BSI by carbapenem-resistant *P. aeruginosa*. Clinical and demographic information about each patient was obtained from hospital records, such as age, gender, days in the hospital, admission to the Intensive Care Unit (ICU), surgery, invasive procedures, such as mechanical ventilation, central venous line, urinary catheter, tracheostomy, hemodialysis, catheter enteral or gastric nutrition, and use of surgical drain, underlying conditions such as diabetes mellitus, chronic renal failure, heart failure, and cancer.

Furthermore, the previous use of one or more of the following antibiotics was verified: piperacillin/tazobactam, gentamicin, amikacin, cefepime, ciprofloxacin, colistin, and carbapenems. These antibiotics exhibit antipseudomonal activity and are part of the local antibiotic policy.

This study was carried out at the Clinical Hospital of the Federal University of Uberlândia, Brazil, a tertiary-care hospital. The clinical microbiology laboratory database was reviewed, and 87 patients who had BSI by carbapenem-resistant *P. aeruginosa* were selected for the study. Only the first episode of infection was analyzed. Microbial identification and antimicrobial susceptibility test were performed on a Vitek 2 system (bioMérieux Vitek Systems, Hazelwood, MO, USA) for the following antimicrobials: piperacillin/tazobactam, gentamicin, amikacin, cefepime, ciprofloxacin, colistin, imipenem, and meropenem.

Antimicrobial therapy was considered inappropriate when the patient received antimicrobials that did not present "in vitro" activity and/or when treatment was started over 48 hours after the infection diagnosis.<sup>10</sup> Multidrug resistance (MDR) was defined as acquired non-susceptibility to at least one agent belonging to three or more antimicrobial categories.<sup>11</sup>

### **Statistical analysis**

The Student's T-test was used to compare continuous variables and  $\chi^2$  or Fisher's exact tests to compare categorical variables. To determine independent risk factors for 30-day mortality, a multiple logistic regression model was used to control the effects of confounding variables. A survival curve was constructed using the Kaplan–Meier method. *P* values of  $\leq 0.05$  were considered statistically significant.

### **Ethical approval**

The research was approved by the Federal University of Uberlandia Committee of Ethics in Research with Human Participants (Approval No. 2.527.621, CAAE: 77541517.9.0000.5152).

## RESULTS

Among patients with BSI by carbapenem-resistant *P. aeruginosa* was observed a high ICU admission rate (63.2%). The previous use of antibiotics and central venous catheter use was common, with 87.3% and 88.5%, respectively. Of 87 eligible patients, 53 (61%) received inappropriate empirical antibiotic therapy of BSI onset, and 67.9% of these patients the infection was caused by *P. aeruginosa* MDR. The 30-day mortality rate was 57.5% for all patients. However, the 30-day mortality rates were 55% in patients with BSI by *P. aeruginosa* MDR (33/60). Table 1 summarizes the multivariate analysis of predictors for mortality in BSI by carbapenem-resistant *P. aeruginosa*.

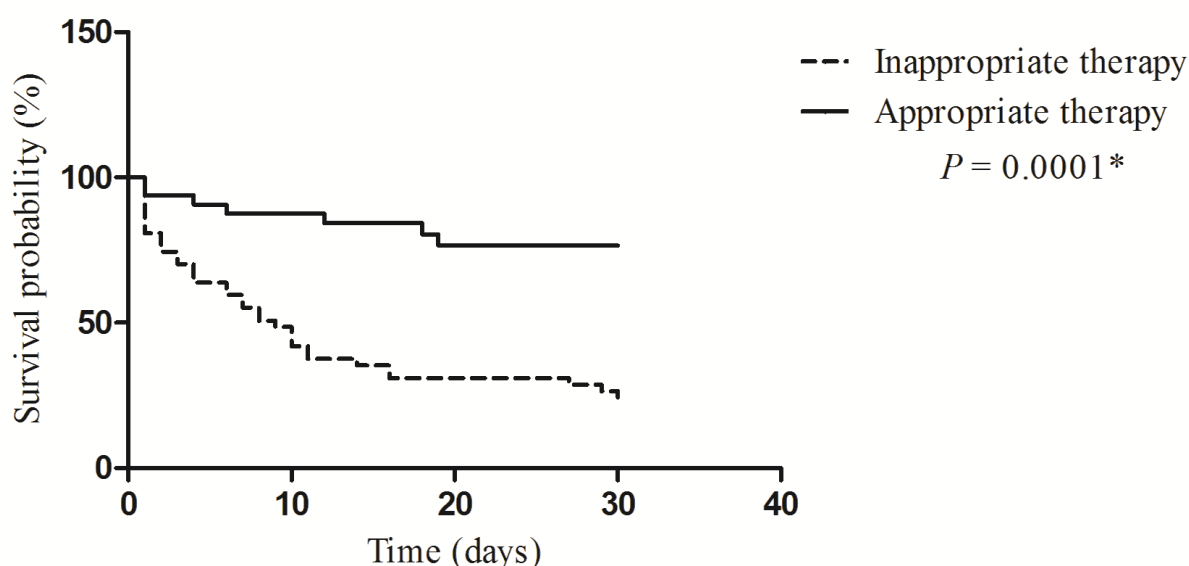
**Table 1.** Univariate and multivariate analysis of factors associated with the mortality of 87 patients with bloodstream infection caused by Carbapenem Resistant *P. aeruginosa*

Characteristics	Total N=87(%)	Outcome		Statistical analysis			
		Death 30days N=50(%)	Discharge N=37(%)	Univariate OR <sup>1</sup> (IC <sup>2</sup> 95%)	P <sup>3</sup>	Multivariate OR <sup>1</sup> (IC <sup>2</sup> 95%)	P <sup>3</sup>
Mean age in years (DS)	57.12±20.5	60.2± 20.7	52.9±19.6		0.0295*		--
Male Sex	58 (66.7)	32 (64)	26 (70.3)		0.5396		--
Length of hospital stay-mean (days)	63.6±57.6	41.6±31.1	87±68.1		0.0007*		--
Intensive Care Unit	55 (63.2)	35 (70)	20 (54)		0.1273		--
Length of ICU stay-mean (days)	18.66±23.63	23.1±17.9	40.8±28.5		0.9158		--
Days at risk (time from admission to BSI)	38.71±37.36	34.4±28.9	44.7±46		0.5278		--
Hospitalization during summer months	37 (42.5)	17 (34)	20 (54)		0.0614		--
Comorbidity/ Underlying disease	52 (59.8)	38 (76)	14 (37.8)		0.0030*		0.3117
Heart Failure	21 (24.1)	15 (30)	6 (16.2)		0.1374		--
Cancer	14 (16.1)	13 (26)	1 (2.7)		0.0031*		0.7225
Diabetes Mellitus	13 (15)	10 (20)	3 (8.1)		0.1428		--
Chronic Renal Failure	20 (23)	14 (28)	6 (16.2)		0.1965		--
Lung disease	5 (5.7)	3 (6)	2 (5.4)		1.000		--
Invasive devices							
Central venous catheter	77 (88.5)	46 (92)	31 (83.8)		0.3128		--
Vesical cateter	63 (72.4)	39 (78)	24 (64.9)		0.1754		--
Mechanical ventilation	64 (73.6)	38 (76)	26 (70.3)		0.5491		--
Probes enteral or gastric nutrition	69 (79.3)	44 (88)	25 (67.6)		0.0200*		0.1819
Traqueostomy	49 (56.3)	26 (52)	23 (62.2)		0.3448		--
Hemodialysis	31 (35.6)	22 (44)	9 (24.3)		0.0582		--
Surgery	47 (54)	25 (50)	22 (59.4)		0.3814		--
Prior use of antibiotic	76 (87.3)	46 (92)	30 (81.1)		0.1923		--
Inappropriate antibiotic empirical therapy	53 (61)	42 (84)	11 (29.7)		0.001*		0.0001*
Primary bacteremia	57 (65.5)	31 (62)	26 (70.3)		0.4223		--
Secondary bacteremia	30 (34.5)	19 (37)	11 (29.7)		0.4223		--
MDR <sup>4</sup>	60 (69)	33 (66)	27 (73)		0.6450		--
Polymicrobial bloodstream infection	11 (12.6)	6(12)	5(13.5)		1.000		--

**Note:** <sup>1</sup>Odds ratio; <sup>2</sup>Confidence interval; <sup>3</sup>P value; <sup>4</sup>Multidrug Resistance; \*P statistically significant ( $\leq 0,05$ ).

The mean age among patients who died was 60.2 years (range 9 months to 89 years) and the majority of these patients had more comorbidities than the patients who survived (76% versus 37.8%). Also, a major frequency of invasive devices used was observed among patients with death outcomes within 30 days: CVC (92%), vesical catheter (78%), and mechanical ventilation (76%). The major of patients who died used previous antibiotic therapy (92%) and were submitted to inappropriate empirical antibiotic therapy (84%). Furthermore, inappropriate antibiotic empirical therapy was independently associated with death ( $P=0.0001$ ).

The mean length of hospitalization was 87 days for survivors and 41.6 days for non-survivors. The Kaplan–Meier cumulative survival estimates (Figure 1) for patients with inappropriate versus appropriate therapy showed that the first group had a lower probability of survival ( $P=0.0001$ ). The 30-day mortality rate of the first group was 79.2%, while the second group was 23.5%.



**Figure 1.** Survival curve (30 days) using the Kaplan–Meier method for patients who received antimicrobial appropriate therapy compared with those who received inappropriate therapy

## DISCUSSION

The rapid emergence and spread of carbapenem-resistant *P. aeruginosa* are a worldwide public health problem, especially in less developed countries like Brazil, where there is a lack of efficient prevention and control actions.<sup>5,12</sup>

In Brazil, the mortality rate associated with infection by multidrug-resistant *P. aeruginosa* is close to 50%, with most patients evolving to death within 30 days after infection.<sup>13</sup> In countries of the world In the Middle East, mortality reaches 60%,<sup>14</sup> while in Asia this rate is 20%.<sup>15</sup>

The development of BSI contributes to the severity of the clinical condition during the hospitalization of the patients who have surgery, are immunocompromised, and use invasive devices. Currently, infection by carbapenem-resistant *P. aeruginosa* increases the risk of inappropriate empirical antibiotic therapy, frequent in hospitals worldwide, but more frequent in lower and middle-income countries.<sup>5,6,16</sup>

This study indicates that older patients, who remained hospitalized for a long period, with some comorbidity and that were in use of inappropriate empirical antibiotic therapy, were associated with worse outcomes. Moreover, our study confirms that a high number of patients with BSI by MDR *P. aeruginosa* receive inappropriate empirical treatment. According to the literature, the rates of escalation of antibiotic resistance and inadequate therapy considerably increase morbidity and mortality, days of hospitalization, and costs related to the treatment of the infection.<sup>3,7,17</sup>

We also identify some factors related to mortality (mean age in years, mean days of hospitalization, cancer, and use of probes for enteral or gastric nutrition) by univariate analysis that concurs with previous research conducted mainly in patients with IRAS and BSI by *P. aeruginosa*.<sup>16,17</sup> Also, we identify that inadequate empirical therapy was associated with a 14-fold increase in mortality. This factor is important because it can be modified.<sup>18</sup>

According to the literature, BSI by resistant *P. aeruginosa* is complex and the impact of inappropriate empirical antibiotic therapy in the mortality of these patients has been a matter of great discussion by researchers and health professionals.<sup>7,16,17</sup> That's why protocols must be developed for each hospital, based on data from active epidemiological surveillance, which allows knowing the predominant species in each hospital unit, as well as the most frequently observed resistance mechanisms.

This study observed that *P. aeruginosa* causing BSI in this hospital were highly resistant to most antibiotics commonly used in our setting. This trend of resistance could be accounted for by the increasingly empirical, indiscriminate, and intense use of antibiotics. Countless papers showed empiric treatments often fail and increase mortality in these patients.<sup>17,18</sup>

In our study, a remarkable number of patients with BSI by carbapenem-resistance *P. aeruginosa* received inappropriate antibiotic therapy, and this percentage increased when considering MDR *P. aeruginosa* strains. In light of these results, novel ways of identifying patients with a high risk of MDR *P. aeruginosa* isolation is mandatory, as well as microbiological diagnosis might help to diminish inappropriate empirical antimicrobial therapy.



Our study had limitations. It was a single-centered, retrospective with small sample size. However, this study generated valuable data regarding infection control aspects, and how it impacts the outcomes of hospitalized patients who had BSI by carbapenem-resistant *P. aeruginosa* and were treated with inappropriate antibiotic therapy. Results should be validated in other centers and on larger populations.

This study concludes that the rate of inappropriate therapy among ICU patients who developed *P. aeruginosa* infection was high (61%), being higher among those who died (84%). In addition, the independent risk factors for 30-day mortality were: inappropriate antimicrobial therapy, use of gastric tube and presence of comorbidities, especially cancer.

Ultimately, these findings add some insights about the relationship between higher mortality and inappropriate empirical therapy for patients with BSI by *P. aeruginosa*. There is a need for better diagnostic tests and infection control programs should focus on de-escalation the antibiotic inappropriate therapy, mainly in BSI caused by carbapenem-resistant *P. aeruginosa*.

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## **CONFLICT OF INTEREST**

None.

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#### Authors' contributions:

**Jane Eire Urzedo\***, **Paulo P. Gontijo** and **Rosineide Marques Ribas** contributed to the conception, design of the article, analysis and writing of the article;

**Ralciane de Paula Menezes\*** contributed to the analysis, writing, review and final approval of the article;

**Melina Lorraine Ferreira** contributed to the analysis, review and final approval of the article;

**Cristiane Silveira de Brito** and **Raquel Cristina Cavalcanti Dantas** contributed to the review and final approval of the article.

All authors have approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

\* These authors contributed equally to the writing of this work.

Layout Version