Pseudomonas aeruginosa: An Analysis of Carbapenem Resistance in Brazil

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Abstract. *Pseudomonas aeruginosa* is a ubiquitous Gram-negative bacterium and a common opportunistic pathogen that causes healthcare-associated infections (HAIs), particularly in immunocompromised patients and those in intensive care units (ICUs). In Brazil, the increase of carbapenem-resistant *P. aeruginosa* (CRPA) represents a significant public health concern given the high mortality rates and limited therapeutic options. This review aims to critically analyze current data on CRPA in Brazil, focusing on the mechanisms driving resistance and the resulting clinical implications. An exploratory, analytical-descriptive literature review was conducted, including original scientific articles published from 2010 to 2024 that discuss resistance mechanisms and clinical implications of CRPA infections in Brazilian hospitals and ICUs. Systematic searches were performed in SciELO and PubMed databases using the keywords "*Pseudomonas aeruginosa*", "carbapenem resistance", "antibiotic resistance mechanisms", and "Brazil". Eleven articles that comply with the inclusion criteria were analyzed. The incidence of CRPA in Brazilian hospitals is significantly influenced by intrinsic and acquired resistance mechanisms. Among them, is the production of metallo-β-lactamases (MBLs) and other mechanisms, such as efflux pump overexpression, mutations in the oprD gene, and AmpC overproduction. The coexistence of multiple resistance mechanisms within individual isolates further restricts therapeutic options. The spread of CRPA is linked to nosocomial factors like prolonged hospital stays, use of invasive devices, and inadequate infection control measures, as well as clonal dissemination within healthcare settings. Inappropriate empirical therapy has been associated with higher mortality rates, underscoring the need for rapid and accurate diagnostic methods. The escalating incidence of CRPA in Brazil, driven by diverse resistance mechanisms and nosocomial factors, poses a significant public health challenge. Thereby, there's a need for comprehensive measures, including enhanced surveillance, strict infection control practices, rapid diagnostic methods, reassessment of empirical treatment guidelines, and robust antimicrobial stewardship programs. Implementing these strategies is crucial for controlling the spread of CRPA and improving patient outcomes in Brazilian healthcare settings.

Keywords. Pseudomonas aeruginosa, carbapenem resistance, antibiotic resistance mechanisms, Brazil.

1. Introduction

Pseudomonas aeruginosa is a ubiquitous Gram-negative bacterium belonging to the family Pseudomonadaceae [1]. It is a common opportunistic pathogen that causes healthcare-associated infections (HAIs), particularly in immunocompromised patients or those admitted to intensive care units (ICUs) [2]. These infections are often difficult to treat due to the bacterium's intrinsic and acquired resistance mechanisms [3].

The genome of *P. aeruginosa* is relatively large compared to other sequenced bacteria, such as Escherichia coli and Mycobacterium tuberculosis, encoding a large proportion of regulatory enzymes crucial for its metabolism. This genetic complexity allows *P. aeruginosa* to have high metabolic versatility and adaptability to environmental changes. As a result, these bacteria show resistance to a wide range of antibiotics, including aminoglycosides, quinolones, and β-lactams [1].

Focusing on the β-lactams, their representative, carbapenems, are considered a vital agent in the treatment of *Pseudomonas aeruginosa* infections [3].

However, *P. aeruginosa* resistant to this class of antimicrobial agents has been increasingly isolated in ICUs in Brazil. Its most common form of resistance is through either lack of drug penetration (i.e., porin mutations and efflux pumps) and/or carbapenem-hydrolyzing β-lactamases, such as metallo-β-lactamases (MβL) [4]. In this context, the World Health Organization (WHO) has recently classified CRPA as one of three bacterial species for which there is an urgent need to develop new antibiotics [1].

In Brazil, the situation is particularly concerning, with CRPA increasingly reported in hospitals across the country, especially in ICUs where the pressure of antibiotic use is high [5]. The resistance of *P. aeruginosa* to carbapenems has been recorded at rates exceeding 60% in certain Brazilian hospitals, compared to approximately 50% in other developing countries, such as Iran [6]. The widespread presence of these resistant strains poses significant clinical challenges, contributing to increased morbidity and mortality among critically ill patients [4].

Thus, considering the increase in carbapenem-resistant *Pseudomonas aeruginosa* in Brazil, this review aims to critically analyze the current data on CRPA in Brazil, focusing on the mechanisms driving this resistance and its clinical implications.

2. Research Methods

The objective of this study is to conduct an exploratory, analytical-descriptive literature review focusing on carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) in Brazil. The review will include original scientific articles published in full from 2010 to 2024 that discuss resistance mechanisms and clinical implications associated with CRPA infections, in hospitals and ICUs in the country.

A systematic search for relevant articles was performed using databases including SciELO and PubMed. The search was restricted to articles published in English. Key search terms included "*Pseudomonas aeruginosa*," "carbapenem resistance," "antibiotic resistance mechanisms," and "Brazil."

Exclusion criteria involve duplicate articles across different databases; studies that do not specifically address nosocomial infections; and articles older than fifteen years.

The analysis will synthesize the findings from the selected articles and provide a comprehensive overview of CRPA in Brazil, emphasizing intrinsic and acquired resistance mechanisms, as well as the resulting clinical challenges.

3. Results

In this section, we present a summary of the key findings from the selected studies in Table 1, providing a comprehensive overview of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). The table includes information on the study context, country of research, and the key findings.

In accordance with the inclusion criteria, eleven articles related to CRPA were selected.

4. Discussion

The increasing prevalence of carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA) is a major concern for public health, particularly in Brazil. Our review reveals that CR-PA incidence in Brazilian hospitals is significantly influenced by both intrinsic and acquired resistance mechanisms. Among them, the production of metallo-β-lactamases (MBL), such as SPM-1, VIM, and IMP, has been highlighted as a predominant mechanism responsible for carbapenem resistance in Brazilian isolates [4]. Furthermore, studies have identified additional mechanisms, such as efflux pump overexpression, mutations in the oprD gene, and AmpC overproduction, which further complicate the treatment outlook for CR-PA [6].

One of the notable findings in Brazilian studies is the presence of multiple carbapenem resistance mechanisms within individual *P. aeruginosa* isolates, which significantly restricts therapeutic options [7]. This aligns with global observations where CR-PA has demonstrated high intrinsic resistance to antibiotics and an extraordinary ability to acquire new resistance determinants [5]. The persistence and spread of carbapenem-resistant strains within healthcare facilities in Brazil have been linked to nosocomial factors, such as prolonged hospital stays, use of invasive devices like catheters, and suboptimal infection control measures [8].

Moreover, the spread of CR-PA in healthcare settings is also strongly related to clonal dissemination, which has been reported in several Brazilian states, indicating that cross-transmission between patients remains an important mechanism for dissemination [2]. Notably, the epidemiological evidence points towards a predominant clone known as the Brazilian epidemic clone, highlighting the potential role of community or environmental dissemination in addition to nosocomial transmission [9].

It is essential to point out that inappropriate empirical therapy has been linked to higher mortality rates among patients infected with CR-PA [10]. This calls attention to the urgent need for improved diagnostic methods that can facilitate

rapid and accurate detection of resistant strains, thereby guiding effective antibiotic use. Studies have shown that incorporating enrichment broths and selective media can significantly enhance the detection of CR-PA, although this may increase the turnaround time for results [3].

Tab. 1 - Summary of Selected Studies on Carbapenem-Resistant *Pseudomonas aeruginosa*.

Author (Year)	Country	Background	Key Findings
Qin Xiang Ng et al. (2023)	Singapore	*Pseudomonas aeruginosa* is a common pathogen associated with healthcare-acquired infections, often antibiotic-resistant, causing significant morbidity and mortality in cases of bacteremia.	This systematic review examined the incidence rates of *P. aeruginosa* bacteremia during and before the COVID-19 pandemic. While prevalence was on the rise before the pandemic, a slight increase in rates during the pandemic was observed. The importance of good infection control practices and appropriate antibiotic administration was highlighted.
Andrea C. Büchler et al. (2023)	Netherlands and Indonesia	Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) is a serious cause of healthcare-associated infections. Outbreak investigations are necessary after identifying CRPA to prevent further transmission.	This systematic review summarized outbreak investigations conducted after the detection of CRPA in hospital settings. Only 19 out of 126 studies reported screening of contact patients, suggesting underreporting and possible under- or overscreening in practice. Environmental screening was identified as useful for understanding transmission modes.
Selvi N. Shahab et al. (2024)	Netherlands and Indonesia	Detecting carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA) in humans is crucial to prevent transmission, but the most effective culture method for detection is unknown.	The systematic review found that an enrichment broth increases the detection of CR-PA, although it extends the turnaround time. Most samples in outbreak surveillance studies were taken from perianal or stool sites. More research is needed to determine the most sensitive culture method and sampling site.
Felipe Lira de Sá Cavalcanti et al. (2024)	Brazil	An investigation was carried out into the genetic mechanisms responsible for multidrug resistance in carbapenem-resistant *Pseudomonas aeruginosa* isolates from different hospitals in Recife, Brazil.	The loss of OprD along with the overexpression of efflux pumps and β-lactamase production were found to be responsible for multidrug resistance in the analyzed isolates. Various β-lactamase genes were detected, and an association between the loss of OprD and the overexpression of MexAB-OprM was observed in most isolates.
Zheng Pang et al. (2019)	Canada	*Pseudomonas aeruginosa* is an opportunistic pathogen that significantly contributes to morbidity and mortality, particularly in cystic fibrosis patients and immunocompromised individuals. P. aeruginosa has become increasingly difficult to eradicate given its resistance to antibiotics.	This review highlights the mechanisms of antibiotic resistance in *P. aeruginosa*, including intrinsic and acquired resistance, biofilm-mediated resistance, and multidrug-tolerant persister cells. It discusses alternative therapeutic strategies, with several promising approaches in preclinical stages that show effectiveness against drug-resistant strains.
M C	Brazil	Carbapenem-resistant	Among the 29 CRPA isolates, a significant clonal

Scheffer et al. (2010)		*Pseudomonas aeruginosa* (CRPA) has been increasingly isolated in Brazilian hospitals, particularly in a teaching hospital in Florianópolis. The study aimed to investigate the minimal inhibitory concentration (MIC) and the presence of Metallo-β-lactamase (MβL).	relationship was observed, with 62% belonging to a clonal group. The study found that the high-level resistance clone suggested cross-transmission as a key dissemination mechanism, emphasizing the need for improved infection control strategies and ongoing surveillance in healthcare settings.
F C Tenover et al. (2022)	USA	Carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA) is a significant healthcare-associated pathogen, with a rising percentage of isolates resistant to carbapenems and the presence of carbapenemases complicating treatment options.	The article discusses the varying prevalence of carbapenemases in *P. aeruginosa*, emphasizing the importance of rapid detection methods for carbapenemase-producing strains. Effective treatment options depend on local profiling of resistance, which can be guided by molecular and phenotypic methods, although both have limitations.
Jie Qin et al. (2022)	China	The prevalence and clinical impact of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) infection on mortality in elderly patients are unclear. This study aimed to clarify the prevalence, manifestations, resistance profiles, and outcomes.	Among 600 elderly patients, the overall rates of CRPA and multidrug-resistant *Pseudomonas aeruginosa* (MDR PA) were found to be 25.8% and 22.3%, respectively. Risk factors for CRPA infection included cerebrovascular disease and previous antibiotic exposure. The mortality rate for CRPA was 16.8%, highlighting the need for antimicrobial stewardship and infection control.
J E Urzedo et al. (2020)	Brazil	Investigated high mortality rates due to nosocomial infections caused by carbapenem-resistant *Pseudomonas aeruginosa* in a Brazilian referral hospital over a ten-year period. Assessed 5-day and 30-day in-hospital mortality and evaluated correlations between the type III secretion system (TTSS) genotype and metallo-β-lactamase (MBL) production.	Found 30-day and 5-day mortality rates of 36.6% and 17.9% among 262 patients. ExoU-positive isolates were associated with lower 5-day survival rates (70.55%) compared to exo-negative isolates (86%). Use of urinary catheters, comorbidities, and secondary bacteremia were independently associated with increased mortality. ExoU genotype was more frequent among multidrug-resistant strains. MBL genes were not detected in 92% of isolates. Inappropriate therapy was a crucial factor in worse prognosis.
L C Cacci et al. (2016)	Brazil	This study investigated the mechanisms of carbapenem resistance in *Pseudomonas aeruginosa* isolates after the decline of an SPM-1 metallo-β-lactamase-producing strain in an ICU over eight years in a university hospital in Rio de Janeiro.	Among 472 clinical isolates, 10 (29%) were carbapenem-resistant. None produced carbapenemases, with resistance mechanisms including efflux and AmpC overexpression. The study revealed a polyclonal profile after the decline of the SPM-1 epidemic genotype.

E H Campana et al. (2016)	Brazil	The mechanisms behind an uncommon resistance phenotype in *Pseudomonas aeruginosa* isolates—carbapenem resistance coupled with susceptibility to broad-spectrum cephalosporins were investigated.	Decreased expression of the OprD porin, rather than carbapenemase production, was responsible for carbapenem resistance. Outer membrane protein analysis indicated alterations in the 46 kDa porin. Genetic profiling revealed 17 genotypes without a dominant pattern, emphasizing multiple chromosomal mechanisms in resistance.

The virulence of *P. aeruginosa* also plays a relevant role in the clinical outcomes of infected patients. The presence of type III secretion system (TTSS) genes, such as exoU and exoS, has been associated with worse clinical outcomes and increased mortality [9]. In Brazil, the coexistence of multidrug resistance (MDR) and these virulence factors results in a "perfect storm" that complicates the treatment and management of nosocomial infections [8].

Our findings strengthen the call for continued surveillance and improved infection control strategies in Brazilian hospitals. Such measures include strict adherence to hand hygiene, appropriate use of personal protective equipment (PPE), and enhanced environmental cleaning, all of which are critical in preventing the spread of CR-PA [1]. Additionally, strengthening antimicrobial stewardship programs to ensure the judicious use of carbapenems and other antibiotics is crucial in attenuating the spread of resistant strains [11].

The high prevalence of CR-PA in Brazilian healthcare settings and its significant clinical impact show that it is imperative to reassess empirical treatment guidelines to address the changing epidemiology of these resistant strains. Furthermore, future research should focus on identifying the most sensitive culture methods and optimal sampling sites for detecting CR-PA carriage, since this may be of critical relevance for controlling outbreaks and improving patient outcomes [3].

In conclusion, the rising incidence of CR-PA in Brazil, a result of multiple resistance mechanisms and nosocomial factors, represents a significant public health challenge. Comprehensive measures involving surveillance, infection control, rapid diagnostic methods, and antimicrobial stewardship are crucial for controlling the spread of these resistant pathogens and improving patient care outcomes.

5. Conclusion

The increasing incidence of carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA) in Brazil has become a significant public health challenge, driven by diverse resistance mechanisms, high mortality rates, and the prevalence of virulent clones. This complexity is complicated by nosocomial factors and the coexistence of several resistance determinants, narrowing therapeutic alternatives and pointing out the interest in better infection control measures. Addressing this challenge requires rapid diagnostics, reassessment of empirical treatment guidelines, strict adherence to infection control, and effective antimicrobial stewardship. The impact of CR-PA could be minimized by improved surveillance, prevention practices, and focused research for improved patient care outcomes in healthcare settings within Brazil.

6. References

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