RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Paper

Open Access

Delineation of infections in a university hospital by bacteria producers of metalobetalactamases: mapping the enemy!

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Submitted: 31-03-2023 Resubmitted: 23-06-2023 Accepted: 04-09-2023

Double blind peer review

Abstract

Objetive: to determine the prevalence of metallo-beta-lactamase (MBL) infections, as well as to outline the epidemiological, clinical, and microbiological profile of these infections and the therapeutic approaches used to combat them in a hospital in Ceará, Brazil, during the period of 2021 and 2022. **Methods:** A cross-sectional retrospective study was conducted. Systematic data collection was performed from medical records of hospitalized patients, which were subsequently stored in a database. All patients admitted to the ward or ICU who were diagnosed with MBL infection based on microbiological tests conducted after 48 hours of hospitalization were included in this study. According to these criteria, 79 patients were included in our study. The data were evaluated based on their absolute frequency (n), relative frequency (%), and measures of central tendency. **Results:** The prevalence of MBL infections among all resistant infections was 47,9%. The average age of the patients was 61.8 years, and the male gender was the most affected (65,8%). The medical clinic had the highest number of cases (20,3%). In 40,5% of the cases, patients were using mechanical ventilation. Blood culture was the most prevalent microbiological test (38%) for diagnosing the infections. Neoplasms were the main cause of patient admissions (34%). The most isolated bacterium was Klebsiella pneumoniae (65,8%), and the prevalent resistance gene was New Delhi Metallo-beta-lactamase (NDM), present in 77,2% of cases. The isolates showed resistance to almost all tested antimicrobials (AMs). The most effective AMs in vitro against these infections were colistin, gentamicin, and amikacin. Polymyxin B was the most commonly used AM, comprising either entirely or partially the treatment for 41,8% of patients. The mortality rate was 43%. Thus, we report for the first time the presence of MBL-producing bacteria in Ceará, with a high prevalence and mortality rate. **Conclusion:** These results indicate the depletion of therapeutic options against these pathogens and the urgent need to seek new treatments.

Key-words: drug resistance; multiple; bacterial; cross infection; beta-lactam resistance; bacterial infections.

Delineamento de infecções em um hospital universitário por bactérias produtoras de metalobetalactamases: mapeando o inimigo!

Resumo

Objetivo: determinar a prevalência e a mortalidade relacionada a infecções causadas por metalobetalactamases (MBL) e descrever o perfil epidemiológico, clínico e microbiológico dessas infecções e a terapêutica utilizada, em um hospital universitário do Ceará-BR, no período de 2021 e 2022. **Método**: foi realizado um estudo transversal, retrospectivo. Foi feita a coleta sistemática de dados de prontuários de pacientes internados no hospital, que foram, posteriormente, armazenados em um banco de dados. Foram incluídos todos os pacientes internados em leitos de enfermaria ou de UTI, que tiveram o diagnóstico de infecção com perfil de resistência ampliada, após 48 horas de internação. Os dados foram avaliados de acordo com sua frequência absoluta (n), frequência relativa (%) e medidas de tendência central. **Resultados:** A prevalência de infecções por MBL, entre todas com resistência ampliada, foi de 47,9%. A média de idade dos pacientes foi de 61,8 anos e o gênero masculino foi o mais acometido (65,8%). A área de internação com maior número de casos foi a Clínica Médica (20,3%). Em 40,5% dos casos, os pacientes estavam em uso de ventilação mecânica. A hemocultura foi o exame microbiológico mais prevalente (38%) no diagnóstico das infecções. As neoplasias foram a principal causa das internações dos pacientes (34%). A bactéria mais isolada foi a *Klebsiella pneumoniae* (65,8%) e o gene de resistência prevalente foi o *New Delhi* Metalobetalactamase (NDM), estando presente em 77,2% dos casos. Os isolados se mostraram resistentes a quase todos os antimicrobianos (ATMs) testados. Os ATMs mais capazes de combater essas infecções *in vitro* foram a colistina, a gentamicina e a amicacina. A polimixina B foi o ATM mais utilizado, compondo, total ou parcialmente, o tratamento de 41,8% dos pacientes. A taxa de mortalidade foi de 43%. Com isso, relatamos, de forma inédita, a presença de bactérias produtoras de MBL no Ceará, com elevada prevalência e mortalidade. **Conclusão:** Nossos resultados apontam para o esgotamento das opções terapêuticas contra esses patógenos e para a urgência de buscar novos tratamentos.

Palavras-chaves: farmacorresistência bacteriana múltipla; infecção hospitalar; resistência beta-lactâmica; infecções bacterianas.

Introduction

Metallo-Beta-Lactamases (MBLs) are enzymes that confer bacteria the ability to resist the action of practically all known antimicrobials (ATMs)[1]. As they are difficult to treat, infections caused by bacteria that produce MBLs increase hospitalization time and morbidity/mortality in hospitals[2] and increase the costs of health systems[3]. The World Health Organization (WHO) identifies antimicrobial resistance as one of the biggest threats to global Public Health. Therefore, there is an urgent need to fight against MBLs[4].

MBLs are enzymes capable of hydrolyzing all beta-lactams, with the exception of aztreonam[5]. As a result, there are few therapeutic options left to treat patients infected with MBL-producing bacteria[6,7]. In addition to being integrated into chromosomal DNA, the genes for these enzymes are present in mobile genetic structures, such as plasmids, which eases their dissemination[8,9]. Countless subclasses of clinically-important MBLs have been described in the medical literature, the most frequent being the following: New Delhi Metallo-Beta-Lactamase (NDM), Imipenemase (IMP), Verona Imipenemase (VIM), São Paulo Metallo-Beta-Lactamase (SPM), German Imipenemase (GIM) and Seoul Imipenemase (SIM)[10,11].

In general, MBLs can cause what is called infections with an expanded resistance profile. These infections were classified as follows by Pearson et al.: Multi-Drug-Resistant (MDR), which are resistant to at least three antimicrobial categories; Extensively-Drug-Resistant (XDR), which are sensitive to a maximum of two antimicrobial categories; and Pan-Drug-Resistant (PDR), which are resistant to all antimicrobial categories[12]. The main microbial genera and species that produce beta-lactamases in Brazilian hospitals and the respective percentages of strains resistant to beta-lactams are as follows: *Klebsiella pneumoniae* (~40%), *Pseudomonas aeruginosa* (~40%), *Escherichia coli* (~10%), *Acinetobacter spp.* (~85%) and *Enterobacter spp.* (~20%)[13].

Infections caused by MBL-producing bacteria are a major current concern for health agencies due to the global spread of these pathogens[14]. In a 2022 technical note, the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA), warned about the increase in this type of bacterial resistance and pointed out co-production of carbapenemases as an aggravating factor[15]. Current antibiotics have little effectiveness against these infections, confirming health professionals' concern about therapeutic exhaustion. In addition, the research studies carried out in recent years to find an effective and affordable treatment against these microorganisms have been quite limited. MBL inhibitors with registered patents do not have published data on *in vitro* and *in vivo* evaluations. There is no approved treatment in Brazil to treat these infections, which have a high mortality rate[7].

In Brazil, the first report of the in-hospital presence of MBL-producing bacteria dates back to 2013, in Rio Grande do Sul[16]. Since then, this resistance mechanism has been recorded in several other Brazilian states[15]. We did not find any reports in the scientific literature about the presence of MBL-producing bacteria in hospitals from Ceará, which shows the pioneering nature of this study in the state. Our objective was to determine the prevalence and mortality rate of infections caused by metallo-beta-lactamases and to outline the epidemiological, clinical and microbiological profile of these infections and the therapy used at a university hospital in Ceará-BR, during the 2021-2022 period.

Methods

A cross-sectional and retrospective study was carried out. The hospital complex where it was conducted is a tertiary-level institution integrated into the Unified Health System (*Sistema Único de Saúde*, SUS), where patients with various clinical and surgical pathologies, from different specialties, are referred. This hospital serves outpatients and inpatients and provides several high-complexity health services.

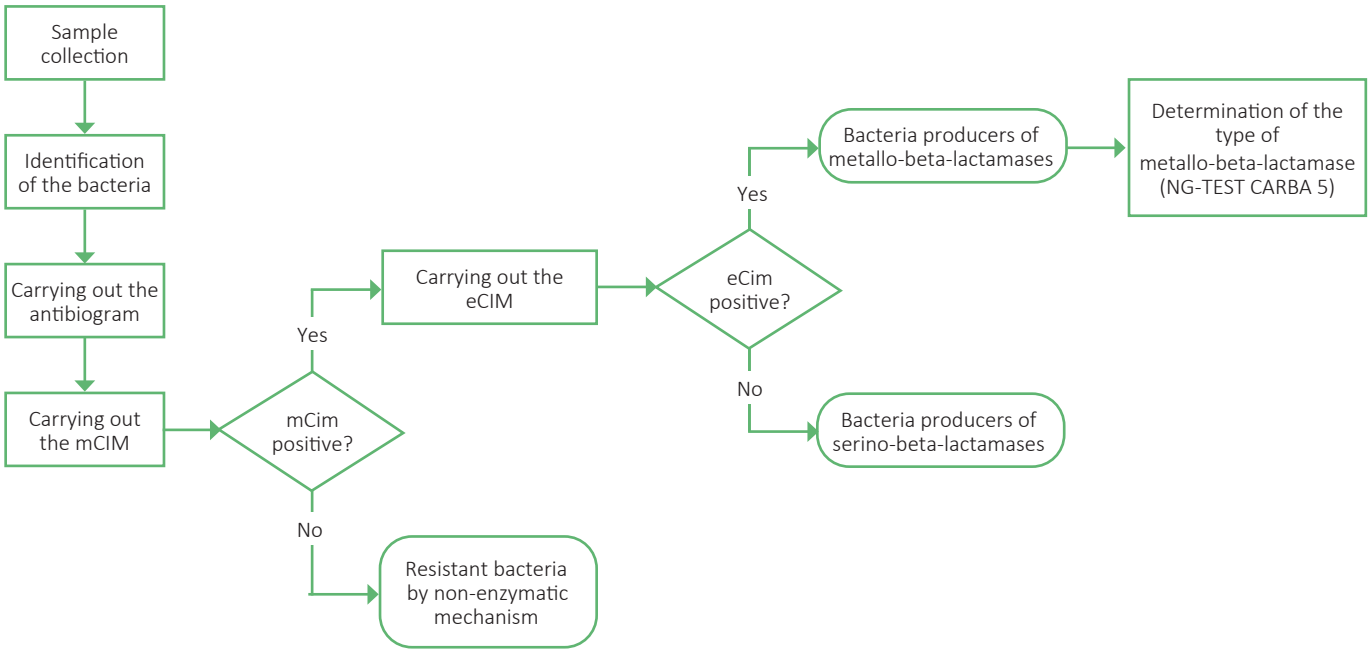
The data were systematically collected from medical records of patients hospitalized in ward or ICU beds during 2021 and 2022, diagnosed with infection by a pathogen with an expanded resistance profile, in microbiological tests carried out after at least 48 hospitalization hours. The microbiological data on the infections with an expanded resistance profile were provided by the hospital's Microbiology Laboratory. Infections with an expanded resistance profile were considered MDR, XDR and PDR, according to the definitions proposed by Pearson *et al.*[12] for these classes.

The data collected were stored in a database specifically built for this purpose. The following variables were included in the database: gender, age, reason for hospitalization, hospitalization sector, type of microbiological test, whether on invasive mechanical ventilation or not, bacteria isolated, resistance gene identified, sensitivity profile of the pathogen to ATMs, pharmacological treatment and clinical outcome. With this initial database, analyses of the prevalence of MBL infections were carried out among all those with an expanded resistance profile. Subsequently, only the infections caused by MBL-producing bacteria were filtered, for later analyses to be carried out. The data were evaluated according to absolute frequency (n), relative frequency (%) and central tendency measures using Microsoft Excel, version 2019. A correlation was made between the clinical outcome and the treatment used, using Fisher's exact test. For this purpose, the IBM SPSS Statistics version 24.0® program was used.

In the hospital's Microbiology Laboratory, identification of the bacteria and the ATM sensitivity test were carried out automatically, using VITEK2-COMPACT®. To interpret the ATM sensitivity test results, version 11.0 of the Brazilian Committee on Antimicrobial Susceptibility Testing (BrCAST) standardization was used. To identify the resistance profile of the bacteria isolated, the modified Carbapenem Inactivation Test (mCIM) for enterobacteria and pseudomonas and the modified Carbapenem Inactivation Test with EDTA (eCIM) for enterobacteria were performed, which made it possible to determine, respectively, the type of resistance mechanism (whether enzymatic or non-enzymatic) and, for pathogens with an enzymatic resistance mechanism, the beta-lactamase production phenotype (SBL or MBL). Finally, to determine the resistance gene, the NG-TEST CARBA 5® immunochromatographic test was performed (Figure 1).

The current study was approved by the Ethics Committee of the hospital where the patients included in this study were admitted, with opinion number 3,697,674.

Figure 1. Flowchart for determining the resistance phenotype of bacteria with expanded resistance



Results

A total of 165 cases of infections with an expanded resistance profile were identified. Of these, 79 produced MBLs. Therefore, the prevalence of MBL infections in the period was 47.9%. Between 2021 and 2022, a 39.4% increase in the number of MBL infections was observed.

The mean age of the patients infected with MBL-producing bacteria was 61.8 years old (54.5-73.5), of which 27 were female and 52 were male. The hospitalization area with the most affected patients was the Medical Clinic (n = 16), followed by Geriatrics (n = 11), Cardiology (n = 10) and Hematology (n = 10). Among the reasons for hospitalizations, the most prevalent were neoplasms (34%). In 40.5% of the cases, the patients were on invasive mechanical ventilation at the time of sample collection for the microbiological test. The most requested type of microbiological test was blood culture (n = 30), followed by tracheal aspirate culture (n = 22) and urine culture (n = 20). Table 1 presents information on the clinical-epidemiological profile of the patients included in this study.

Of the total, 83.5% of the MBL-producing microorganisms isolated were enterobacteria and all were Gram-negative bacilli. The most isolated MBL-producing bacteria was *K. pneumoniae* (65.8%), followed by *P. aeruginosa* (16.5%). The most identified MBL resistance gene was NDM (77.2%), followed by IMP (20.3%). Three cases of double expression of resistance genes were identified: two of NDM with *Klebsiella pneumoniae* carbapenemase (KPC) and one of IMP with KPC.

The isolates proved to be resistant to almost all available ATMs. In 15.2% of the cases (n = 12), the bacteria were resistant to all ATMs tested. The ATMs most capable of combating bacteria isolated *in vitro* were colistin (65.8% of the bacteria proved sensitive in the tests), gentamicin (45.8% of sensitive isolates) and amikacin (42.4% of sensitive isolates). Table 2 displays the microbiological characteristics and Table 3 presents the *in vitro* sensitivity data corresponding to the isolates.

Table 1. Clinical-epidemiological profile of infections caused by MBL-producing bacteria at a university hospital from Fortaleza-CE-Brazil. during 2021 and 2022.

Characteristic	Frequency n (%)
Age (years old)	61.8 (54.5-73.5)
Gender	
Male	52 (66%)
Female	27 (34%)
Hospitalization unit	
Medical Clinic ward	16 (20.2%)
Geriatrics	11 (13.9%)
Cardiology	10 (12.7%)
Hematology	10 (12.7%)
Others	32 (40.5%)
Reason for hospitalization	.
Neoplasm (Non-Hematological)	15 (19%)
Hematological Neoplasm	12 (15%)
COVID-19	10 (12.6%)
Others	42 (53.4%)
Use of mechanical ventilation	
Yes	32 (40.5%)
No	47 (59.5%)
Clinical outcome	
Discharge	45 (57%)
Death	34 (43%)
Microbiological test[1]	
Blood culture	30 (37.6%)
Tracheal aspirate	22 (23.1%)
Urine culture	20 (21.0%)
Others	23 (24.3%)

[1]More than one microbiological test was performed in some patients

Table 2. Species of isolated bacteria and resistance genes identified in infections with MBL-producing bacteria. at a university hospital from Fortaleza-CE-Brazil, during 2021 and 2022.

Microbiological Characteristic	Frequency (%)
Identified Bacteria	
Klebsiella pneumoniae	65.8
Pseudomonas aeruginosa	16.4
Providencia stuartii	5.1
Enterobacter cloacae	3.8
Klebsiella Oxytoca	3.8
Serratia marcescens	2.5
Morganella morganii	1.3
Proteus mirabilis	1.3
Resistance gene identified	
NDM	77.2
IMP	20.3
Not tested	2.5

Table 3. Sensitivity test of the infections caused by MBL-producing bacteria. at a university hospital from Fortaleza-CE-Brazil. during 2021 and 2022.

Antimicrobial	Susceptibility (%)	Resistance (%)
Ampicilin	0	100
Ampicilin/sulbactam	0	100
Piperacilin/tazobactam	0	100
Cefuroxime	0	100
Ceftazidime	0	100
Ceftriaxone	0	100
Cefepime	0	100
Imipenem	0	100
Meropenem	0	100
Amikacin	31.6	68.4
Gentamicin	34.2	65.8
Ciprofloxacin	0	100
Colistin	65.8	34.2

Polymyxin B was the most used ATM in the patients' treatments, comprising, wither totally or partially, the therapeutic strategy of 41.8% of the cases, mainly in association with amikacin (12.6%). The mortality rate among the patients with polymyxin B present in their treatments was 48.5%.

In total, 29 patients did not receive any specific treatment for infections with MBL-producing bacteria, with a death rate of 39.3% among them. In most of these cases (n = 18), the patients were clinically and laboratory stable at the time of receiving the microbiological tests, pointing to possible colonization. In the remaining cases (n = 11), the patients died early in time or the clinical condition led the medical team to opt for palliative care, without subjecting them to more aggressive pharmacological treatments.

During the entire study period, the mortality rate of the individuals identified with infection by MBL-producing bacteria was 43%. The treatments most used in the patients who evolved to death were the following combinations: polymyxin B with gentamicin (n = 7); polymyxin B with amikacin (n = 3); and polymyxin B monotherapy (n = 3). In all cases where the Ceftazidime/Avibactam-Aztreonam combination was performed (n = 4), the patients evolved to death, possibly due to the criticality of their clinical states.

The treatments most used in the individuals who were discharged (n = 45) were as follows: polymyxin B with amikacin (n = 7); polymyxin B with meropenem (n = 4); and polymyxin B monotherapy (n = 4). Table 4 shows the treatments used and the clinical outcomes of the patients included in this study.

Table 4. Antimicrobial regimes used to treat infections caused by MBL-producing bacteria, at a university hospital from Fortaleza-CE-Brazil, during 2021 and 2022.

Scheme used	Patients n (%)	Deaths n (%)
Polymyxin B + Amikacin	10 (12.6)	3 (30)
Polymyxin B + Gentamicin	7 (8.9)	7 (100)
Polymyxin B	7 (8.9)	3 (42.8)
Polymyxin B + Meropenem	7 (8.9)	2 (28.6)
Gentamicin	4 (5.1)	1 (25)
Meropenem	4 (5.1)	1 (25)
Ceftazidime/Avibactam + aztreonam	4 (5.1)	4 (100)
Amikacin	3 (3.8)	1 (33.3)
Others	4 (5.0)	3 (75)
No treatment due to clinical improvement	18 (22.7)	0 (0)
No treatment due to early death or palliative care	11 (13.9)	11 (100)

When applying Fisher's Exact test (p-value<0.001), we detected that the frequency distribution of the scheme used is different between the cases that evolved to death and those that did not.

Discussion

In the current study, the infections caused by MBL-producing bacteria presented almost 48% prevalence among the infections with increased resistance. In Brazil, the first reported case of this resistance mechanism dates back to 2013, in a hospital from Rio Grande do Sul[16]. In an unprecedented way, our results suggest that, 10 years later, these infections crossed the country and reached the state of Ceará. Therefore, when analyzed together with others in the specialized literature, this paper shows that these infections are spreading in Brazilian hospitals.

A prevalence result similar to that of this research was obtained in a multicenter study conducted in Cuba, where, from a total of 357 multi-resistant isolates, 42.5% of MBL-producing bacteria were isolated[17]. Ghasemian *et al.* concluded that approximately half of carbapenem-resistant *P. aeruginosa* isolates in Iranian hospitals were MBL producers[18]. Goel *et al.* also reached similar results when conducting a prospective study for 15 months at a tertiary-level hospital in India, with samples of endotracheal aspirates. They verified that 53.85% of *P. aeruginosa* isolates investigated and 48.72% of analyzed isolates from the *Acinetobacter* species were MBL producers[19]. These data generate considerable concern, as they indicate in-hospital dissemination of a mechanism that allows pathogens to resist practically all antibiotics available on the market.

In our study, the highest prevalence was in patients aged over 50 years old. In fact, older patients are more susceptible to in-hospital infections[20]. This is related to immunosenescence, which occurs with aging[21]. Furthermore, in our study, this can also be related to the patients' profile. The main reason for the patients' hospitalizations was neoplasms, which has higher incidence values among older people[22]. In a retrospective study carried out by Seo *et al.* between 2010 and 2019 in patients with MBL-producing enterobacteria isolates, all patients were over 50 years

old[23]. Therefore, with regard to age at onset, the epidemiological profile was similar to the patients in our study. This research was carried out in South Korea at a tertiary-level hospital, which is the same health care level as the hospital in this study.

In our research, two thirds of the affected patients were male, a prevalence twice as high as that of females. Similar results were achieved in several other studies. Garcia *et al.* outlined the epidemiological profile of hospital-acquired infections caused by highly resistant bacteria at a hospital from Minas Gerais. In it, greater predominance of infections was seen in males (57%)[24]. When analyzing 1,024 cases of hospital infections in Romania, Voidazan *et al.* indicated that 58.1% of these infections affected males[25]. In the study by Seo *et al.*, 66% of the patients affected by MBL-producing isolates were male[23]. Cohen *et al.* carried out a retrospective cohort study to investigate whether the risk of acquiring infections, either in the community or in a hospital, was influenced by the patients' gender. More than 200,000 patients of all ages and treated in hospitals from the United States were analyzed. The authors concluded that, across all age groups, the risk of acquiring bloodstream and post-surgical infections was significantly higher in men than in women. They pointed out some explanations for this, such as biological differences in the skin of men and women, greater bacterial colonization of the skin around catheters in men than in women and differences in hair morphology between the genders. Men's hair is rougher and thicker, which compromises adhesion of dressings and eases infection[26]. Therefore, it is also observed that male gender is a possible risk factor for the acquisition of in-hospital infections.

In addition to the age and gender profile, other factors may have predisposed the patients monitored in this study to greater risks of acquiring infections with increased resistance. One of them is the high prevalence of patients with neoplasms. Haukland *et al.* carried out a study in which, among other parameters, they compared the acquisition of in-hospital infections between a group of 812 patients with cancer and a group of 5,908 patients without cancer. They concluded that the acquisition of infections was significantly higher in the cancer patients[27]. Some explanations for this are the increased use of immunosuppressive medications such as chemotherapy drugs[28], the greater use of central venous access catheters and the greater use of tubes[29]. Another factor that increases the risk of acquiring infections is using invasive devices[30]. In 40.5% of the patients monitored in our study, invasive mechanical ventilation was used. The materials employed to artificially ventilate patients can be reservoirs of bacteria and, in general, using this type of device increases hospitalization time[31].

Enterobacteriaceae were, by and large, the most isolated pathogens in this study (83.5%). This is yet another indication of how this bacterial family causes resistant infections in hospitalized patients and how quickly they spread within the hospital environment. In Brazil, in an evaluation of national indicators of healthcare-associated infections and microbial resistance, it was found that 20% of all enterobacteria isolated in health services in the country were pathogens with increased resistance[13]. Among the microorganisms in this family, *K. pneumoniae* was the most isolated bacteria (65.8% of all MBL infections) in our study. Ehen conducting studies with patients infected by MBL-producing enterobacteria, Seo *et al.* also obtained a higher isolation rate for *K. pneumoniae*[23]. However, the rate they obtained (26%) was significantly lower than the one found in the current study. In Brazil, 40% of the *K. pneumoniae* strains have increased resistance[13]. Therefore, our results point to a significant predominance of *K. pneumoniae* in MBL-producing infections.

Another pathogen with significant presence in isolates from patients in this study was *P. aeruginosa*. This bacterium causes several infectious conditions in humans, such as pneumonia and gastrointestinal infections. In addition to that, these infections are difficult to treat, which causes high morbidity and mortality rates in the affected patients. A likely explanation for this difficulty in treatment is the global dissemination of MBL in strains of this bacterium[32]. Dawadi *et al.*, for example, observed that 14% of this bacterium isolates in hospitals from Nepal were MBL producers[33]. According to ANVISA, 40% of the *P. aeruginosa* strains in Brazil are resistant to beta-lactams[13]. In addition to that, this bacterium has other mechanisms, in addition to beta-lactamases, to resist the action of antibiotics. Therefore, presence of this pathogen in more than 16% of the infections analyzed in this study reinforces the alert to health agencies and the health care community about the urgency of seeking effective therapeutic solutions against these infections.

In this study, the MBL-producing isolates showed, *in vitro*, very high resistance rates to practically all the antibiotics tested. As can be seen in Table 3, all strains were resistant to most of the ATMs. This reinforces that the therapeutic options for treating these infections have been exhausted. Tan *et al*. reviewed the treatments used in patients infected by MBL-producing pathogens and the advances made in this therapy. According to the authors, the ATMs that are most historically used to treat these patients are polymyxins, aminoglycosides, tetracyclines and phosfomycin. However, according to the same review, there are no robust clinical studies in the literature supporting widespread use of these drugs for the treatment of patients affected by MBL-producing bacteria[34].

In the patients evaluated in our study, polymyxin B was the most used drug, either as monotherapy or in combination with other ATMs, mainly amikacin. One of the reasons for this is the observation made in the literature that polymyxins constitute the therapeutic resource with the most clinical findings that suggest good efficacy against MBL-producing pathogens. However, they should be used with caution, as this drug is nephrotoxic[35]. The possible efficiency of this drug against MBL-producing bacteria can be partially justified by its mechanism of action. Polymyxins act on lipopolysaccharides (LPS) present in the outer membrane of these pathogens. In turn, MBLs are located in the cell cytoplasm and, therefore, cannot, in theory, hydrolyze this antibiotic[36]. However, our study does not reinforce these findings, as patients treated with polymyxin B had a high mortality rate, with almost half of them evolving to death.

Regarding advances in the therapy against MBL-producing bacteria, Tan *et al.* observed that the combined use of ceftazidime-avibactam with aztreonam proved to be promising[34]. In our study, four patients were treated with this combination of drugs. However, all of them evolved to death Cefiderocol has also been presented as a very promising clinical treatment. However, this drug is not commercially available in Brazil[34].

This paper was conducted in a large tertiary-level health care center, which generally serves patients with complex diseases such as neoplasms. Many of these pathologies predispose patients to a greater risk of acquiring in-hospital infections. For this reason, in this hospital the number of patients suffering from infections of increased resistance may naturally be higher than in other institutions. In addition to that, the greater complexity of the underlying diseases also increases the mortality rate of the patients who acquire in-hospital resistant infections. In our paper

it was not possible to remove this variable from the mortality rate analyses. In subsequent studies, comparisons should be made between groups of patients infected with bacteria with an expanded resistance profile and groups of patients with clinical conditions similar to the first, but who were not affected by these infections.

Conclusion

In this study, we reported, in an unprecedented way, the presence of MBL-producing bacteria in a hospital from the state of Ceará-BR. With this, we draw the attention to the in-hospital dissemination of bacteria with expanded resistance mediated by MBLs in the country. The prevalence of these pathogens was extremely high, with a high mortality rate. When outlining the clinical-epidemiological profile of these infections, we point to advanced age, male gender, use of invasive mechanical ventilation and presence of neoplasms as possible risk factors. The microbiological profile herein outlined points to Enterobacteria as the widely prevalent bacterial family among MBL infections and to *K. pneumoniae* and *P. aeruginosa* as the species most likely to replicate this resistance mechanism. Our paper joins the major effort of the scientific community to draw the attention to the widespread resistance that MBLs have to ATMs. The isolates herein analyzed showed resistance to almost all ATMs tested and, in several cases, PAN-resistant bacteria were identified. No treatment used in the patients included in this study showed the ability to effectively combat these infections. Our results reinforce the need to seek new pharmacological treatments against these pathogens.

Funding sources

The study did not receive any funding for its conduction.

Collaborators

HPR, AGN, FLR and MLL: Data collection from patient records, construction of the database, data analysis and interpretation, bibliographic review, writing of the article; VNA: Data collection from patient records, construction of the database, data analysis and interpretation, writing of the article; ESG: Data analysis and interpretation, literature review, writing of the article; RMO and JLR: Data analysis and interpretation, writing of the article; GPA: Data collection from patient records, writing of the article.

Declaration of conflict of interests

The authors declare that there is no conflict of interest in relation to this article.

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