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Clinical, microbiological and pharmacoepidemiological identification of enterobacteria with increased resistance in a public hospital in Ceará

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Abstract

Objectives: to identify the clinical, microbiological and pharmacoepidemiological profile of patients with enterobacteria with increased resistance in a public teaching hospital in Ceará. **Methods:** Observational and retrospective study, carried out between January 2020 and December 2021. The microbiological and demographic profile was obtained through microbiology laboratory reports and information obtained from medical records. Variable frequencies were compared using the Chi-square test, considering $p < 0.05$. Study approved with opinion of the ethics committee nº 3.697.674. **Results:** A total of 164 patients had positive culture results (n=248) for enterobacteria with an enhanced resistance profile. The highest proportion was male (60.98%, n=100, with a mean age of 58.9 years and mean hospitalization time was 51.3 days. *Klebsiella pneumoniae* was the most isolated bacteria (88.31%, n=218), with tracheal aspirate (39.11%, n=97) being the most prevalent type of culture, followed by blood culture (27.42%, n=68) and urine culture (16.94%, n=42). The blaKPC gene was the most prevalent, being identified in 49.19% (n=122) of the isolates, followed by blaNDM with 11.29% (n=28). When checking the sensitivity profile, it is noted that 68.55% of the isolates are sensitive to colistin and only about 30% to aminoglycosides. In 18.57% they already showed resistance to ceftazidime-avibactam. As for the clinical outcome, 57.32% (n=94) of the patients died. Previous use of antimicrobials (p=0.024), surgical procedure (p=0.049), admission to an intensive care unit (p<0.001), presence of neutropenia (p=0.005) and use of invasive devices (p<0.001) were statistically significant. **Conclusion:** These findings show the importance of knowing the clinical profile of patients infected with enterobacteria with increased resistance, since targeted strategies should be designed in favor of better management of antimicrobials against microorganisms such as *K. pneumoniae*, a strong candidate for the production of carbapenemase, an important cause of bacteremia and which can sometimes be resistant to last-choice antimicrobials, facts associated with high mortality.

Keywords: drug resistance; enterobacteriaceae; antimicrobial stewardship

Identificação clínica, microbiológica e farmacoepidemiológica de enterobactérias com resistência ampliada em hospital público no Ceará

Resumo

Objetivos: identificar o perfil clínico, microbiológico e farmacoepidemiológico de pacientes com enterobactérias com resistência ampliada em hospital público de ensino no Ceará. **Métodos:** Estudo observacional e retrospectivo, realizado entre janeiro de 2020 a dezembro de 2021. O perfil microbiológico e demográfico foi obtido por meio dos laudos do laboratório de microbiologia e informações obtidas em prontuário. As frequências das variáveis foram comparadas usando o teste Qui-quadrado, considerando $p < 0,05$. Estudo aprovado com parecer do comitê de ética de nº 3.697.674. **Resultados:** Um total de 164 pacientes obteve resultado de cultura positiva (n=248) para enterobactéria com perfil de resistência ampliada. A maior proporção era de pessoas do sexo masculino (60,98%, n=100), com idade média de 58,9 anos e o tempo médio hospitalização foi de 51,3 dias. *Klebsiella pneumoniae* foi a bactéria mais isolada (88,31%, n=218), sendo aspirado traqueal (39,11%, n=97) o tipo de cultura mais prevalente, seguido de hemocultura (27,42%, n=68) e de urocultura (16,94%, n=42). O gene blaKPC foi o mais prevalente, sendo identificado em 49,19% (n=122) dos isolados, seguido de blaNDM com 11,29% (n=28). Ao verificar o perfil de sensibilidade, nota-se que 68,55% dos isolados apresentam sensibilidade à colistina e apenas cerca de 30% aos aminoglicosídeos. Em 18,57% já apresentavam resistência ao ceftazidima-avibactam. Quanto ao desfecho clínico, 57,32% (n=94) dos pacientes evoluíram a óbito. O uso prévio de antimicrobianos (p=0,024), a realização de procedimento cirúrgico (p=0,049), a internação em unidade de terapia intensiva (p<0,001), a presença de neutropenia (p=0,005) e utilização de dispositivos invasivos (p<0,001) mostraram-se estatisticamente significativos. **Conclusão:** Estes achados mostram a importância de conhecer o perfil clínico de pacientes infectados por enterobactérias com resistência ampliada, uma vez que devem ser traçadas estratégias direcionadas em prol do melhor gerenciamento de antimicrobianos contra microrganismos como a *K. pneumoniae*, forte candidata à produção de carbapenemase, importante causadora de bacteremia e que, por vezes, pode ser resistente aos antimicrobianos de última escolha, fatos estes associados a uma alta mortalidade.

Palavras-chave: resistência bacteriana a antibióticos; enterobactérias; gestão de antimicrobianos

Introduction

The discovery and development of antimicrobials (ATMs) was a major milestone in more effective treatments of infections that previously progressed rapidly to death[1-2]. However, irrational ATM use has contributed to bacteria developing several resistance mechanisms, such as the expression of enzymes that degrade or inactivate the antibiotic[3-4].

In this context, enterobacteria with an increased resistance profile have caused significant concern to health care systems worldwide due to their high pathogenicity, rapid spread and limited therapeutic options; in particular, enterobacteria producing carbapenemases of the *Klebsiella pneumoniae* carbapenemase (KPC) and metallobetalactamases (MBL) types, including *New Delhi* metallobetalactamases (NDM)[5-6].

Thus, due to the unexpected growth of strains with double expression of resistance genes, including the feared metallobetalactamases along with KPC, which may have been a reflection of overwhelming ATM use, allied to the already known fragile safety profile of many of these drugs and the increasing costs with this strategic class of medications, it becomes even more urgent to implement tools such as an Antimicrobial Stewardship Program (ASP) that can optimize use of antimicrobials, especially in hospitals, which concentrate the highest proportion of resistant strains[7-8].

As a mechanism for monitoring these patients we have the "bundle" of actions from the AMP/Stewardship. This clinical management program encompasses different strategies and interventions aimed at optimizing ATM use, such as: prospective audit with suggestions and feedback, treatment time management, de-escalation, escalation, switch therapy (oral sequential therapy) and permanent education, among others[9].

In addition, some risk factors can lead to the emergence of multidrug-resistant microorganism infections, for example, the use of invasive devices such as mechanical ventilation (MV), indwelling urinary catheters (IUCs) and central venous catheters (CVCs). In addition to that, there are factors related to the patients themselves, such as age group, gender and neutropenia; as well as others such as previous ATM use in the last 30 days, performing a surgical procedure and hospitalization time[10-11].

In this context, the objective of this paper is to identify the clinical, microbiological and pharmacoepidemiological profile of patients with increased-resistance enterobacteria in a public teaching hospital from Ceará.

Methods

This is an observational and retrospective study conducted between January 2020 and December 2021. The study population consisted of adult patients (over 18 years old) admitted to a university hospital in Fortaleza-CE, with positive cultures except swab for Enterobacteria with an increased resistance profile.

The data were collected according to the following sequence:

- 1st- The clinical pharmacist/pharmacy students perform a daily active search for reserve antimicrobial prescriptions (Liposomal Amphotericin B, Anidulafungin, Daptomycin, Ertapenem, Imipenem + Cilastatin, Linezolid, Meropenem, Polymyxin B, Tigecycline, Voriconazole, Micafungin, Vancomycin and Teicoplanin).
- 2nd- When identifying the prescription of a patient using a reserve ATM, the corresponding clinical-laboratory monitoring is initiated.
- 3rd- When a culture is identified with a specimen from the *Enterobacteriaceae* family with an increased resistance profile, all the information is added to the database.
- 4th- Subsequently, the data obtained are tabulated and the statistical analysis is performed.

The microbiological and demographic profile was obtained from the Microbiology laboratory reports and from diverse information obtained in medical records. In the positive cultures for Carbapenem-resistant enterobacteria, following cutoff points defined by BrCast, the following phenotypic tests were performed: modified Carbapenem Inactivation Method (mCIM) and modified Carbapenem Inactivation Method with ethylenediaminetetraacetic acid (eCIM). The first one detects presence or absence of the betalactamase enzyme and, if this test is positive, eCIM is performed, which differentiates serinobetalactamase from metallobetalactamase.

Infection was considered when there was any positive culture associated with suggestive clinical-infectious signs, with antimicrobial treatment initiation or change. For patients with positive blood cultures, the same microorganism was isolated in at least two samples taken from different accesses.

The variables analyzed were the following: demographic and microbiological profile, risk factors and clinical-infectious profile. The data obtained were represented in terms of absolute and relative (percentage) frequencies. The frequencies of the variables were compared with the Chi-square test, considering $p<0.05$.

The study was approved by the Research Ethics Committee of the Federal University of Ceará (*Universidade Federal do Ceará*, UFC), under approval opinion number 3,697,674. All the research stages were developed in full compliance with the requirements set forth in Resolution No. 466/12 of the National Health Council, dated December 12th, 2012.

Results

During the study period, 248 enterobacteria with expanded resistance profile were isolated in 164 patients. In relation to the patients' gender, there was higher prevalence of males (60.98%). The mean age of the patients was 58.9 years old, with the age group of over 60 years old as the predominant one (50.61%). The mean hospitalization time was 51.3 days. In relation to the clinical outcome, most of the patients evolved to death (57.32%). Table 1 described the characteristics of patients with infections by enterobacteria with expanded resistance profiles.

There was higher prevalence of patients admitted due to clinical (79.27%) than to surgical (20.73%) conditions, as well as a higher mortality rate in clinical patients (p=0.049), with a risk of death 2.1 times higher than in surgical patients.

Regarding previous exposure to antimicrobials, it is noted that 60.46% of the patients who used ATMs in the last 30 days before the infection evolved to death (p=0.024). In turn, specific exposure to the pharmacological class of quinolones did not result in a relevant value from the statistical point of view (p=0.078).

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Table 1. Frequency, percentage and relative risk of death among the patients with infections by expanded-resistance enterobacteria, according to sociodemographic and clinical variables (Ceará, Brazil).

		Total	Death		p value	RR	IC 95%	
			n	%				
Gender	Male	100	58	58.00	0.629	1.218	0.648	2.291
	Female	64	34	53.13				
Age group	18-40 years old	24	12	50.00	0.125			
	41-60 years old	57	27	47.37				
	60+ years old	83	53	63.85				
Mean age	58.9 years old							
Hospitalization time	Up to 15 days	17	10	58.82	0.127			
	16-30 days	37	26	70.27				
	31-45 days	39	24	61.53				
	46-60 days	25	12	48.00				
	>60 days old	46	20	43.47				
Mean hospitalization time	51.3 days							
Previous surgery	Yes	44	14	31.81	0.049	2.143	0.994	4.618
	No	120	78	65.00				
Previous ATM use	Yes	129	78	60.46	0.024	2.294	1.070	4.919
	No	35	14	40.00				
Previous quinolone use	Yes	31	21	67.74	0.078	1.834	0.802	4.191
	No	133	71	53.38				
Neutropenia	Yes	10	08	80.00	0.050	3.397	0.934	12.534
	No	154	84	54.54				
ICU admission	Yes	74	60	81.08	<0.001	7.768	3.765	16.028
	No	90	32	35.55				
Invasive devices	CVC	123	85	69.11	<0.001	10.865	4.422	26.694
	MV	93	70	75.26	<0.001	6.779	3.403	13.503
	IUC	79	53	67.09	<0.001	2.404	1.275	4.534

Key: RR=Relative Risk; CI= Confidence Interval; CVC=Central Venous Catheter; MV=Mechanical Ventilation; IUC=Indwelling Urinary Catheter; ATM=Antimicrobial; ICU=Intensive Care Unit. Source: Prepared by the authors.

Regarding neutropenia, 80% of the neutropenic patients evolved to death (p=0.050). In turn, regarding those admitted to the ICU mortality was 81.08% (p<0.001), with a 7.7 times higher risk of death in relation to those who were not in the Intensive Care Unit.

The presence of the CVC, MV and IUC invasive devices (p<0.005) proved to be an important risk factor associated with mortality in patients with multidrug-resistant enterobacteria.

On the other hand, in relation to the microbiological data, *Klebsiella pneumoniae* emerged as the most prevalent enterobacteria (88.31%), as represented in Table 2.

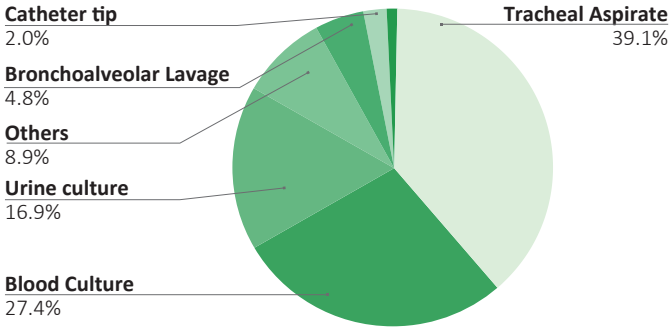
Table 2. Prevalence of the expanded-resistance enterobacteria in microbiological cultures (Ceará, Brazil).

Microorganism isolated	N (%)
Klebsiella pneumoniae	219 (88.31)
Klebsiella oxytoca	09 (3.64)
Serratia marcescens	07 (2.82)
Enterobacter cloacae	05 (2.02)
Providencia stuartii	04 (1.61)
Escherichia coli	02 (0.80)
Proteus mirabilis	01(0.40)
Klebsiella aerogenes	01 (0.40)
Total	**248 (100.00)**

Source: Prepared by the authors.

The most prevalent type of culture during the period analyzed was tracheal aspirate (39.11%), followed by blood culture (27.42%) and by urine culture (16.94%), as can be seen in Figure 1.

Figure 1. Distribution of the types of cultures with expanded-resistance enterobacteria isolates (Ceará, Brazil).



Source: Prepared by the authors.

In relation to the resistance genes, KPC was the most prevalent, identified in 49.19% of the 248 bacteria isolated. The NDM gene is second with 11.29%. It is noted that four bacteria expressing both the KPC and NDM genes were isolated, as described in Table 3.

Table 3. Distribution of the resistance genes in enterobacteria isolates (Ceará, Brazil).

Resistance gene	N (%)
Not tested	90 (36.30)
KPC	122 (49.19)
NDM	28 (11.29)
KPC + NDM	04 (1.60)
IMP	03 (1.22)
ESBL	01 (0.40)
Total	**248 (100.00)**

Key: ESBL=Extended Spectrum Beta-Lactamase; KPC=*Klebsiella pneumonie carbapenemase;* IMP=Imipenemase; NDM= New Delhi metallobetalactamase. Source: Prepared by the authors.

When verifying the sensitivity profile, it was noticed that 68.55% of the isolated microorganisms were sensitive to colistin, 29.03% to amikacin and 27.42% to gentamicin, as shown in Table 4.

In relation to the new antibiotics, most of the strains (81.43%) presented sensitivity to ceftazidime-avibactam, whereas 18.57% proved to be resistant.

Table 4. Sensitivity Frequency among the carbapenemase-producing enterobacteria in microbiological isolates (Ceará, Brazil).

Antimicrobials	Sensitive		Resistant		Total tested
	N	%	N	%	
Amikacin	72	29,03	176	70,97	248
Gentamicin	68	27,42	180	72,58	248
Colistin	170	68,55	78	31,45	248
Ceftazidime/Avibactam	193	81,43	44	18,57	237

Source: Prepared by the authors.

Discussion

In the current study, the profile of the patients showed predominance of males (60.98%); however, gender did not prove to be a risk factor for mortality (p=0.629). Another paper that also evaluated in-hospital infections by enterobacteria had 66% of its population comprised by men[12]. In addition, the study conducted by Souza (2015) at a university hospital showed that gender would also not be a risk factor for the death outcome.

The mean age of the population included in this study (58.9 years old) is also in line with the data found in the literature. According to Alves and Behar (2013), the age group from 51 to 71 years old was the most affected (50% of the population) by carbapenem-resistant enterobacteria (CRE) causing healthcare-associated infections (HAIs) in a tertiary-level care hospital from southern Brazil[14]. Although in this study increased age was not a significant risk factor (p=0.125) for higher mortality rates, several articles show that there is higher frequency of deaths as age advances[13].

In relation to the analysis of the clinical outcomes, 56.09% mortality was observed. A similar result was also found in a study by Borges *et al.* (2015), in which mortality was 56% among patients colonized by enterobacteria that produce the KPC enzyme[15]. Thus, the importance of developing actions to address this severe problem is highlighted, as 50% of the CRE infections are associated with high mortality rates in the hospital environment[16].

The mean hospitalization time of the patients included in this study was 51.3 days. Findings in the literature show different mean hospitalization times ranging from 35 to 77 days[13,17]. Such variations can be explained by factors intrinsic to the patients, for example, their age and underlying diseases. In addition to that, something quite reiterated in several studies is that infection by multidrug-resistant enterobacteria may contribute as a determinant factor for longer hospitalization times[18]. However, when making a direct association between hospitalization time and increased mortality, it was not possible to validate this relationship (p=0.127). In the study by Souza *et al.* (2015), the value for this relationship was also not statistically significant[13].

Regarding the invasive devices, it was observed that 81.11% of the patients had at least one, with CVCs as the most prevalent (75.00%). The extensive performance of invasive procedures in the hospital environment substantially increases the risk of developing HAIs. According to a study by Alencar et al. (2020), invasive procedures were performed in more than 84% of the patients with infections[19]. In addition to that, there is a relationship between using CVC, IUC and MV devices and increased risk of death (p<0.001).

In relation to whether the patients had undergone any surgery prior to isolation of the microorganisms, it is noted that 26.83% of the patients had done so. According to the literature, increased-resistance microorganisms can spread during a surgical procedure due to the use of invasive devices in surgery. Thus, it is necessary to use aseptic techniques, as well as rational use of antibiotic prophylaxis in the preoperative period[20]. In the current study, the mortality risk was higher in the patients who had undergone a surgical procedure when compared to those who had not (p=0.049).

Neutropenia (neutrophils <500 mm³) was only found in 6.10% of the patients. The vast majority (80%) evolved to death. In this context, neutropenia emerged as a risk factor for mortality (p=0.005). According to the literature, patients with hematologic neoplasms and undergoing hematopoietic stem cell transplantation are at a high risk of severe bacterial infection due to neutropenia[21].

Higher prevalence of the *Klebsiella pneumiae* species was observed, representing 88.30% of all the enterobacteria that were isolated. This bacterium is an important human pathogen that has been involved in infections in health environments during the last decades. Antimicrobial treatment to combat it has become increasingly difficult as a consequence of the emergence and spread of multi-antimicrobial resistant strains[22].

As for resistance genes, KPC was the most common, identified in 49.19% of the bacteria isolated. Pinto et al. (2015) found that 48% of the microorganisms expressed this resistance gene[23]. Another important finding was the concomitant expression of the KPC and NDM genes in 04 *Klebsiella pneumoniae* cultures in 2021. This unusual combination of resistance genes was observed in 10 patients in Turkey, warning about the importance of continuous monitoring to prevent the spread of these powerful isolates[24]. In 2022, ANVISA issued a technical note emphasizing the need to intensify laboratory and epidemiological surveillance aimed at early detection of these strains, so as to enable measures to prevent and control spread of these microorganisms.

Regarding the antimicrobial sensitivity profile, 29.14% of the enterobacteria were sensitive to amikacin and 68.82% to colistin (polymyxin). In a recent study by Mesquita *et al.* (2022), where the sensitivity profile of bacteria was evaluated over a time series

in a private hospital from Ceará, sensitivity to colistin was 76.20% in the *Klebsiella pneumoniae* species and 81.50% for amikacin[25], The results from hospitals in southern Brazil only showed 30.40% sensitivity to amikacin in *Klebsiella pneumoniae* samples in blood cultures[26]. Thus, rational antimicrobial use is an essential measure to control the progressive increase in antibiotic resistance, and management should be continuous due to the possibility of lack of pharmacotherapeutic options in the increasingly near future[27].

In relation to the new antibiotics, most of the strains (77.82%) presented sensitivity to ceftazidime-avibactam, whereas 17.74% proved to be resistant. In the results found by Mesquita et al. (2022), sensitivity to this ATM in the first year of analysis was 78.60%, with an increase in resistance over the years[25]. Thus, it is worth noting the pharmaceutical industries' lack of interest in developing new antibiotics due to the rapid emergence of resistance to them. According to data from the U.S. Food and Drug Administration (FDA), approval of new ATMs has been reduced by more than 50% over the past two decades; therefore, it is important to manage antimicrobial therapy to avoid irrational use and reduce the emergence of resistance to these newer drugs[28].

A study limitation was the fact that it was not possible to conduct a Control Group and randomization study; in other words, when analyzing the risk factors, it is not possible to assert that these factors alone are decisive for mortality or whether severity of the patients' clinical conditions influenced the outcomes observed. In this context, it becomes necessary to encourage randomized studies on the topic, and the results of this study are a way to instigate further related studies.

Therefore, studies such as this one are important in identifying the prevalence of increased-resistance enterobacteria, their sensitivity profile and resistance genes, as well as risk factors for mortality; so that efficient measures can be adopted to control infections and to manage antimicrobials properly, in view of the severe public health problem caused by the spread of microorganisms with increased resistance.

Conclusion

Hospital-acquired infections caused by multidrug-resistant enterobacteria are a major public health problem, as they are associated with high mortality rates in a scenario marked by therapeutic exhaustion.

Male patients aged over 60 years old were the most affected by increased-resistance enterobacteria infections, with *Klebsiella pneumoniae* as the most prevalent one. This microorganism has several resistance mechanisms, the most common being enzymatic expression of the KPC and NDM genes, causing decreased sensitivity even to the most modern antimicrobials, such as ceftazidime-avibactam.

In addition to the epidemiological data, it was possible to evaluate which risk factors are related to increased mortality in patients with enterobacterial infections, for example: prior antimicrobial use, prior surgical procedures, ICU admission, neutropenia and use of invasive devices such as CVC, IUC and MV.

In this context, these findings show the importance of knowing the clinical profile of patients infected with increased-resistance enterobacteria, as strategies should be devised towards the best management of antimicrobials against microorganisms such as *K. pneumoniae*, a strong candidate for the production of carbapenemase, an important cause of bacteremia and which can sometimes be resistant to last-choice antimicrobials, facts that are associated with high mortality rates.

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Collaborators

JCS, HPR, ESG, ROA and JLN participated in project design. JCS and TLS were in charge of data collection and interpretation. JCS, HPR and TLS wrote the article. HPR, ROA, GPA, TLS and JMAN critically reviewed the article. All the authors approved the final version to be published, are responsible for all information contained in the article, and guarantee accuracy and integrity of any of its parts.

Declaration of conflicts of interest

The authors declare that there are no conflicts of interests in relation to this article.

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