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Profile of Antibacterial Resistance of the Enterobacteriaceae Family in Pediatric and Adult Patients

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Abstract

Background: Bacterial infections are the main cause of hospitalization, with those associated with health care caused by gram-negative bacteria the most frequent. Many of the most serious and difficult infections to treat occur in the Intensive and Intermediate Care Units, not only because it is where patients with serious infections are hospitalized but also because of the intensive use of antibiotics.

Objective: To describe the antibacterial resistance profile of *Enterobacteriaceae* in adults and pediatric patients at Central Hospital of Maputo.

Methods: This is a cross-sectional, epidemiological, quantitative approach, with a retrospective analysis of secondary data in the Bacteriology sector of the HCM Microbiology Laboratory of samples analyzed in 2017.

Results: In Pediatrics, *Enterobacteriaceae* accounted for 37.8% (48/127) of all infections, with *Klebsiella pneumoniae* (43%) being the most prevalent. In adults, *Enterobacteriaceae* accounted for 51.9% (27/52) of all infections, with Klebsiella spp (26%), *Escherichia coli* (22%) and *Klebsiella oxytoca* (19%) being the most prevalent. In pediatrics, *Enterobacter* cloacae (87%) and *Enterobacter agglomerans* (76.5%) and Klebsiela spp. (69.2%) had high resistance proportions. In the Adults the highest percentage of resistance was recorded in *Enterobacter* spp. (71.4%), *Klebsiella oxytoca* (60.5%) and *Escherichia coli* (56.4%). The mean resistance rate between the two sectors was 59.4%, 64% in Pediatrics and 52.4% in Adults, and this difference is significant.

Conclusion: Inadequate prescribing and impure treatment with cephalosporins may have been one of the factors that aided the emergence of third generation cephalosporin resistant *Enterobacteriaceae* isolates, as well as the high prescription of carbapenems could be related to the expressive number of imipenem resistant *Escherichia coli*. Patients infected with strains of *Enterobacter* species should receive a differentiated treatment for the remaining patients, as the high resistance rates recorded show the exhaustion of the therapeutic treatment in a wide range of antibacterial agents.

Keywords: ***Enterobacteriaceae*; Antibacterial Resistance; Mozambique**

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Introduction

Bacterial infections are the main cause of hospitalization, with those associated with health care caused by gram-negative bacteria the most frequent. Many of the most serious and difficult infections to treat occur in the Intensive and Intermediate Care Units, not only because it is where patients with serious infections are hospitalized but also because of the intensive use of antibiotics [1-4].

Among the most important pathogens frequently isolated are *Enterobacteriaceae* due to the production of Extended-Spectrum-Beta-Lactamase (ESBL), AmpC, and Carbapenemase, which may result in a greater possibility of inadequate antimicrobial therapy, reflecting higher rates of hospital mortality, longer time of permanence and high costs to hospitals [5].

Although increased antimicrobial resistance among *Enterobacteriaceae* is a concern in the hospital environment, epidemiological studies show that these rates are higher in severe patients [6].

Enterobacteriaceae are part of the resident microbiota of the intestinal tract of mammals, the main microorganisms isolated from this family being *Escherichia coli* responsible for the greatest urinary infections, *Klebsiella pneumoniae* and *Enterobacter* spp. frequently isolated in pneumonia infections and the others associated with infections of the bloodstream, soft tissue and intra-abdominal infections [7].

The emergence and spread of resistance in *Enterobacteriaceae* complicates the treatment of serious infections [8]. Approximately 20% of healthcare-associated infections by *Klebsiella pneumoniae* and 31% of infections by *Enterobacter* spp. involve strains not susceptible to third-generation cephalosporins [7]. Such resistance in *Klebsiella pneumoniae* to third generation cephalosporins is typically caused by the acquisition of plasmids containing genes encoding extended-spectrum beta-lactamases, and these plasmids often also carry other resistance genes [9].

ESBL-producing *Klebsiella pneumoniae* and *Escherichia coli* are currently common in hospital settings and are often resistant to multiple drugs, and ESBL-producing *Enterobacteriaceae* have emerged in the community [10].

Enterobacter spp. resistance to third generation cephalosporins is most typically caused by the overproduction of AmpC beta-lactamases and treatment with these antibiotics may select mutants of AmpC over production [11]. Some strains of *Enterobacter* cloacae are now producing ESBL and AmpC, conferring resistance to third and fourth generation cephalosporins [12]. The resistance of *Enterobacteriaceae* to quinolone is caused by chromosomal mutations leading to changes in target enzymes or drug accumulation [13]. Recently, plasmid-mediated quinolone resistance was found in *Klebsiella pneumoniae* and *Escherichia coli*, associated with the acquisition of the qnr gene [7,14].

Carbapenems are considered empirical treatment for serious infections caused by *Enterobacteriaceae*, including ESBL [10]. Resistance to carbapenems, though rare, appears to be increasing [15]. In Mozambique, the true weight of these diseases and their resistance rates remains largely unknown, but available evidence points to high rates of resistance to first-line treatments for all these diseases[16].

Knowledge of the antibiotic resistance pattern of bacteria isolated from the samples collected at the Intensive Care and Intermediate Care Units of the Central Hospital of Maputo will be essential for the reinforcement of policies for the rational use of antibiotics, and standardization of therapeutic protocols in all clinical departments and the need to introduce new medicines [17].

On the other hand, the knowledge of the etiological agents of infections associated with health care is fundamental to direct the specific therapy appropriate to the standards of resistance to antibiotics, preparation of treatment guides, as well as in the implementation of measures of surveillance and control of these infections [18].

Purpose of the study

To describe the antibacterial resistance profile of *Enterobacteriaceae* in adults and pediatric patients at Central Hospital of Maputo (HCM).

Material and Method

Study design

This is a cross-sectional, epidemiological, quantitative approach, with a retrospective analysis of secondary data in the Bacteriology sector of the HCM Microbiology Laboratory of samples analyzed in 2017.

Place and time of study

The study was carried out at the Pediatric Intensive Care Unit, Intermediate Care of Medicine and Surgery from January to December 2017. Subsequently the data were aggregated into Pediatric Patients (Pediatric Intensive Care Unit) and Adults (Intermediate Medical Care and Surgery). The study is focused on these services because it is where patients with lower immunity are hospitalized and infections occur more frequently.

Population and sample

The universe set considered for this research comprises information of all patients with criteria of bacteriological analysis admitted to the Pediatric Intensive Care Unit, Intermediate Care of Medicine and Surgery of HCM from January 1 to December 31, 2017, considered here finite.

Inclusion criteria

- Information on patients hospitalized in the Pediatric Intensive Care Unit, Intermediate Care of Medicine and Surgery with criteria of bacteriological analysis.
- All positive samples with antibiotic sensitivity test routinely used in the HCM Microbiology Laboratory, based on the standardization proposed by Clinical and Laboratory Standards Institute.

Procedure and tools for data collection

Data on the antibiotic resistance pattern were extracted from the HCM Microbiology Laboratory database. Samples were processed using standard microbiological methods used at the HCM Microbiology Laboratory (culture, identification and antibiotic susceptibility testing).

Identification of bacteria

The Gram-negative samples were identified as belonging to the family *Enterobacteriaceae* and the group of non-fermenting bacilli by Oxidation-Fermentation (OF) and oxidase tests. Identification at the gender and species level was performed by the following tests [19]:

- ***Enterobacteriaceae* family:** glucose and lactose fermentation, indole production, motility, citrate utilization, urea hydrolysis, sulfhydric gas production, phenylalanine deaminase, lysine and ornithine decarboxylase, methyl red reaction and Vogues-Proskauer reaction.
- **Non-fermenting Gram-negative *bacilli*:** nitrate reduction, gluconate use, citrate, pigment production, lysine decarboxylase activity, urease, indole production, hydrolysis of acetamide and esculin.

All isolated bacterial samples were stored in Brain Heart Infusion broth with 20% glycerol at -20°C.

Antimicrobial susceptibility testing

Kirby and Bauer technique was used for the testing. The samples were subcultured on trypticase soy agar at 35°C ± 2°C for 24 h, after which 2 to 3 colonies were diluted in saline solution to reach the standard concentration of 0.5 on the McFarland scale (2 × 108 CFU/mL), the samples were seeded on the surface of the Mueller-Hinton agar using a swab and stored at 35°C ± 2°C for 24 h. The susceptibility

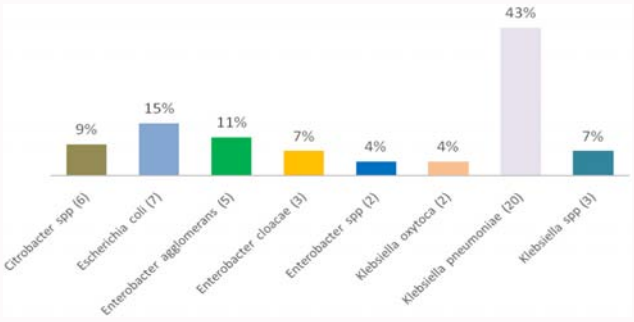

Figure 1: Frequency of *Enterobacteriaceae* associated with health care in Pediatrics.

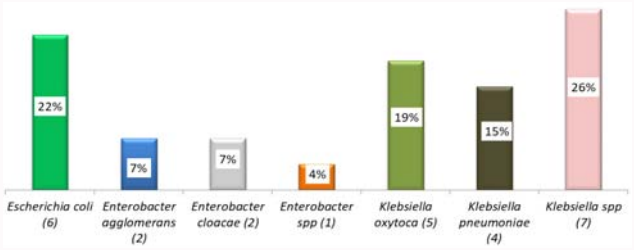

Figure 2: Frequency of *Enterobacteriaceae* associated with health care in Adults.

was determined by the diameter of the inhibition halo formed.

Data analysis

A descriptive statistical analysis was performed using graphs and frequency tables to understand the behavior of the variables under study. The chi-square test was used to analyze the relationship between the antibiotic resistance pattern of the bacteria isolated and provenance. For all tests, a significance level of 5% was used. Data analysis was done with the Statistical Package for Social Sciences (SPSS) version 20 and BioEst version 5.2.

Ethical

Potential risks and their minimization: The risks of the study were minimal except for some minimal possibility of identifying the patient through the use of the name in the HCM Laboratory database (for clinical reasons), and as a way to minimize it, the database manager passed the information to a coded guideline in order to guarantee the anonymity of the data at all times. Please note that this data is for academic purposes only.

Informed consent: As a retrospective study and without the possibility of contacting the patient from whom the sample comes and the results, before starting the data analysis, the request for authorization of the research was submitted to the Scientific and Pedagogical Department of HCM, and was granted the number 321/024/DCIEFHCM/18. After authorization of the research request, the project was submitted to the Institutional Health Bioethics Committee of ISCISA and approved under number TFCMCSFM05/18. The study complied with the Helsinki Declaration in its version of October 2013 on health research standards.

Limitations of the study: In the case of a retrospective study based on the electronic database and logbook, the sampling procedure, the preventive hygiene (asepsis) conditions, the technique and the place of collection, the time between collection and analysis, and the storage conditions of all samples are unknown.

Results

Pediatric patients

In Pediatrics, *Enterobacteriaceae* accounted for 37.8% (48/127) of all infections, with *Klebsiella pneumoniae* (43%) being the most prevalent (Figure 1). All strains of *Citrobacter* spp. were resistant to ampicillin, ceftriaxone, imipenem and gentamicin. This bacterium also presented high rates of resistance to cotrimoxazole (Table 1). *Escherichia coli* were 100% resistant to ampicillin, cefoxitin, amikacin and cotrimoxazole. Imipenem inhibited growth of all strains isolated from *Escherichia coli* (Table 1). The antibacterial ceftazidime, gentamicin, naldixic acid, cotrimoxazole, chloramphenicol and nintroforantoin did not inhibit growth of any single strain of *Enterobacter agglomeranses* (Table 1). *Enterobacter* cloacae showed 100% resistance to almost all antibiotics tested except for imipenem (66.7%), ciprofloxacin (66.7%) and chloramphenicol (50%) (Table 1).

The resistance rate of *Enterobacter* spp. was 100% to ceftazidime, ceftriaxone, imipenem, gentamicin and cotrimoxazole. Amikacin inhibited the growth of all strains of *Enterobacter* spp. (Table 1). The antibiotic resistance of *Klebsiella pneumoniae* ranged from 7.1% to 100%, with chloramphenicol (37.5%), cefoxitin (33.3%), amikacin (22.2%) and imipenem (7.1%) showing rates below 50% (Table 1). The antibiotics ceftazidime, imepenem, amikacin and chloramphenicol showed good antibiotic activity against strains of *Klebsiella oxytoca* (Table 1). All strains of *Klebsiella* spp. were resistant to cefoxitin, ceftriaxone, ciprofloxacin, chloramphenicol and nitroforantoin (Table 1).

Patients adults

In adults, *Enterobacteriaceae* accounted for 51.9% (27/52) of all infections, with *Klebsiella* spp. (26%), *Escherichia coli* (22%) and *Klebsiella oxytoca* (19%) being the most prevalent (Figure 2). *Escherichia coli* showed 100% resistance to ceftazidime, ceftriaxone, gentamicin, naldixic acid, ciprofloxacin and chloramphenicol (Table 2).

The antibiotics ceftazidime, ceftriaxone, imipenem, amikacin and ciprofloxacin inhibited the growth of all strains of *Enterobacter agglomerans* (Table 2). All strains of *Enterobacter* cloacae were resistant to cefoxitin, chloramphenicol, nitroforantoin and ampicillin (Table 2). The antibiotic sensitivity test of *Klebsiella pneumoniae* showed 100% resistance to ampicillin, ceftriaxone, naldixic acid, cotrimoxazole and nitroforantoin (Table 2). *Klebsiela oxytoca* showed high resistance rates to ampicillin, gentamicin and cotrimoxazole (Table 2). Amikacin (0.0%), imipenem (0.0%) and ceftazidime (20%) showed good activity against strains of Klebsiela spp (Table 2).

According to Table 3, *Enterobacter* cloacae (87%) and *Enterobacter agglomerans* (76.5%) and Klebsiela spp. (69.2%) had high resistance ratios in the Pediatrics. In adults, the highest percentage of resistance occurred in *Enterobacter* spp. (71.4%), *Klebsiella oxytoca* (60.5%) and *Escherichia coli* (56.4%). The mean resistance rate between the two sectors was 59.4%, being 64% in Pediatrics and 52.4% in Adults, and this difference is significant.

Discussion

In this study, the bacterium of the most isolated was *Klebsiella pneumoniae* in pediatric patients and *Klebsiella* spp. in adults. These data corroborate with the findings by Monteiro et al. [15] in which *Klebsiella* spp. was the most isolated *Enterobacteriaceae* from 2009-2010 in HCM. A study in South Africa identified *Klebsiella pneumoniae*

Table 1: Profile of antibacterial resistance of isolated samples of *Enterobacteriaceae* in pediatrics patients in 2017.

Antibacterials tested (CLSI)	*Enterobacteriaceaes*															
	Citr. spp		*E. coli*		*Enterobacter agglomerans*		*Enterobacter cloacae*		*Enterobacter spp*		*K.pneum*		*Klebsiella oxytoca*		*Kleb. spp*	
	N	n (%R)	N	n (%R)	N	n (%R)	N	n (%R)	N	n (%R)	N	n (%R)	N	n (%R)	N	n (%R)
Amoxicillin-clavulanic acid			1	0 (0.0)	3	3 (100.0)					6	5 (83.3)				
Ampicillin	3	3 (100.0)	4	4 (100.0)	4	3 (75.0)	3	3 (100.0)	1	0 (0.0)	13	11 (84.6)				
Cefoxitin	4	2 (50.0)	2	1 (50.0)	2	1 (50.0)	2	2 (100.0)			12	4 (33.3)			2	2 (100)
Ceftazidime			4	1 (25.0)	3	3 (100.0)	2	2 (100.0)	1	1 (100.0)	14	12 (85.7)	2	0 (0.0)	1	1 (50.0)
Ceftriaxone	4	4 (100.0)	5	5 (100.0)			2	2 (100.0)	2	2 (100.0)	8	7 (87.5)	1	1 (100)	2	2 (100)
Imipenem	4	4 (100.0)	4	0 (0.0)	5	0 (0.0)	3	2 (66.7)	2	2 (100.0)	14	1 (7.1)	1	0 (0.0)	2	0
Amikacin	4	2 (50.0)	2	2 (100.0)	1	0 (0.0)	2	2 (100.0)	2	0 (0.0)	9	2 (22.2)	2	0 (0.0)	2	0 (0.0)
Gentamicin	3	3 (100.0)	5	4 (80.0)	3	3 (100.0)	2	2 (100.0)	1	1 (100.0)	9	8 (88.9)	1	1 (100)		
Naldixic Acid	2	1 (50.0)	1	0 (0.0)	2	2 (100.0)	1	1 (100.0)			1	1 (100.0)				
Ciprofloxacin	4	1 (25.0)	6	5 (83.3)	4	4 (100.0)	3	2 (66.7)	2	1 (50.0)	14	8 (57.1)	2	1 (50.0)	2	2 (100)
Cotrimoxazole	5	4 (80.0)	3	3 (100.0)	4	4 (100.0)	1	1 (100.0)	1	1 (100.0)	9	8 (88.9)	1	1 (100)		
Chloramphenicol	5	1 (20.0)	5	1 (20.0)	2	2 (100.0)	2	1 (50.0)	2	1 (50.0)	8	3 (37.5)	1	0 (0.0)	1	1 (100)
Nitroforantoin	5	1 (20.0)	1	0 (0.0)	1	1 (100.0)									1	1 (100)
Total	**43**	**26 (60.5)**	**44**	**27 (61.4)**	**34**	**26 (76.5)**	**23**	**20 (87.0)**	**14**	**9 (64.3)**	**118**	**71 (60.2)**	**11**	**4 (36.4)**	**13**	**9 (69.2)**

N: Total strain tested; n: Total resistant strains; % R: Percentage of resistant strains

Table 2: Profile of antibacterial resistance of isolated samples of *Enterobacteriaceae* in adult patients in the year 2017.

Antibacterials tested (CLSI)	*Enterobacteriaceae*													
	E.coli		*Enterobacter agglomerans*		*Enterobacter cloacae*		*Enterobacter spp*		*K.pneum*		*Klebsiella oxytoca*		*Kleb. spp*	
	N	n (%R)	N	n (%R)	N	n (%R)	N	n (%R)	N	n (%R)	N	n (%R)	N	n (%R)
Amoxicillin-clavulanic acid									2	1 (50.0)				
Ampicillin	4	3 (75.0)	2	1 (50.0)	2	1 (50.0)	1	1 (100)	2	2 (100)	1	1 (100)	3	1 (100)
Cefoxitin	5	3 (60.0)	1	1 (100)	2	2 (100)	1	1 (100)	4	0 (0.0)	4	2 (50.0)	5	5 (100)
Ceftazidime	2	2 (100)	1	0 (0.0)	1	0 (0.0)	1	1 (100)	3	2 (66.7)	3	1 (33.3)	5	1 (20.0)
Ceftriaxone	4	4 (100)	1	0 (0.0)	1	0 (0.0)	1	1 (100)	3	3 (100)	3	0 (0.0)	4	3 (75.0)
Imipenem	5	1 (20.0)	2	0 (0.0)	2	0 (0.0)	1	0 (0.0)	5	0 (0.0)	2	0 (0.0)	6	0 (0.0)
Amikacin	6	0 (0.0)	1	0 (0.0)	2	0 (0.0)			3	1 (33.3)	4	1 (25.0)	2	0 (0.0)
Gentamicin	2	2 (100)	1	1 (100)					4	4 (0.0)	3	3 (100)		
Naldixic Acid	3	3 (100)			1	0 (0.0)			1	1 (100)				
Ciprofloxacin	2	2 (100)	1	0 (0.0)	1	0 (0.0)	1	0 (0.0)	4	3 (75.0)	4	2 (50.0)	3	3 (100)
Cotrimoxazole			1	1 (100)					3	3 (100)	2	2 (100)		
Chloramphenicol	2	2 (100)	1	1 (100)	1	1 (100)	1	1 (100)	3	2 (66.7)	3	1 (33.3)	2	2 (100)
Nitroforantoin	4	0 (0.0)			1	1 (100)			1	1 (100)			1	1 (100)
Total	**39**	**22 (56.4)**	**12**	**5 (41.7)**	**14**	**5 (35.7)**	**7**	**5 (71.4)**	**38**	**23 (60.5)**	**29**	**1 (44.8)**	**31**	**16 (51.6)**

N: Total strain tested; n: Total resistant strains; % R: Percentage of resistant strains

as the most frequent *Enterobacteriaceae* in clinical isolates [20]. A multicenter study in African countries identified *Citrobacter* spp. (36.8%), *Enterobacter* spp. (22.2%) and *Klebsiella pneumoniae* (20%) as the main pathogens of the family *Enterobacteriaceae* in the ICU [21].

Resistance to some antimicrobials, especially beta-lactams, is often found in hospitalized patients infected with *Enterobacteriaceae*. Isolated strains of pathogenic *Enterobacteriaceae*, such as *Klebsiella pneumoniae* and *Escherichia coli*, can produce ESBL, which hydrolyzes penicillins, cephalosporins and monobactans [5].

The results of this study reinforce the idea that penicillins are not suitable for the treatment of infections caused by *Enterobacteriaceae*. Data collected from 2013-2016 in African countries had an average resistance of 88.9% to amoxicillin, 96.7% to ampicillin [21]. These findings agree with the results of Monteiro et al. [15], in which the antimicrobial resistance of *Enterobacteriaceae* is higher in hospitalized patients, with an average of 88.8% of amoxicillin and 90.6% of ampicillin. Van der Meeren et al. [22] in urine specimens isolated from pediatric patients at the Beira Central Hospital (HCB) found resistance with 100% amoxicillin.

Beta-lactam antibiotics, especially cephalosporins of the 3rd generation and carbapenems, together with fluoroquinolones and aminoglycosides, are the main therapeutic choice for the treatment of infections caused by *Enterobateriaceae*. The resistance of

Table 3: Relationship between antibacterial resistance of *Enterobacteriaceae* and provenance.

Provenance							Chi-square	
Enterobacteriaceaes	Pediatrics		Adults		Total			
	N	%	n	%	n	%		P-val
Citrobacter spp	26	60.5			26	60.5		
Escherichia coli	27	61.4	22	56.4	47	59	0.9988	0.3176
Enterobacter agglomerans	26	76.5	5	41.7	31	70.5	4.4513	0.0349
Enterobacter cloacae	20	87	5	35.7	25	67.6	8.6161	0.0033
Enterobacter spp	9	64.3	5	71.4	14	66.7	0.0674	0.7952
Klebsiella oxytoca	71	60.2	23	60.5	94	60.3	0.0004	0.9848
Klebsiella pneumoniae	4	36.4	13	44.8	17	42.5	0.1962	0.6578
Klebsiella spp	9	69.2	16	51.6	25	56.8	1.0358	0.3088
Total	192	64	89	52.4	279	59.4	6.0791	0.0137

Enterobacteriaceae to beta-lactams is associated with the presence of ESBL, to fluoroquinolones by the mutations in the genes gyrA and parC, presence of the qnr gene, and to the aminoglycosides by the production of enzymes that modify these agents [5]. The resistance rates found in this study to cefolasporins differ significantly from those found by Monteiro et al. [15]. The results of this study are similar to those found by Van der Meeren et al. [22], where cephalosporins showed resistance of 76.3%. The WHO report on antibiotic resistance in Africa shows that resistance to cephalosporins of the 3rd generation ranges from 0% to 80% [23].

Carbapenems is a class of beta-lactams, of broad spectrum known to be the most effective against infections caused by Gram-negative bacteria. The resistance of *Enterobacteriaceae* to this class of antibiotics is due to the production of an enzyme called carbapenamases, which are of great clinical importance. In this study resistance to Carbapenems in pediatric patients was higher when compared to adults. In this study the imipenem presented lower resistance rates, corroborating with Monteiro et al. [15], Van der Meeren et al. [22] e Tedesse et al. [21].

Aminoglycosides are highly effective against Gram-negative bacilli and potentiate the effect of penicillins and cephalosporins in severe infections [24]. They are recommended for the treatment of multi-resistant bacterial infections that cause infections in a hospital environment. In this study amikacin was more effective against strains of *Enterobacteriaceae* when compared to gentamicin. Monteiro et al. [15] found very low resistance rates to amikacin (3.5%) when compared to gentamicin (52%). Van der Meeren et al. [22] Found a resistance of 0.0% to amikacin and 81.2% to gentamicin. These results show that amikacin is the main therapeutic antibiotic in the treatment of infection caused by *Enterobacteriaceae* resistant to cephalosporins and broad-spectrum penicillins and carbapenems.

Quinolones have been widely used, especially in the treatment of urinary tract infections and respiratory infections. Its indiscriminate use led to a significant increase in resistance [25,26]. Van der Meeren et al. [22] found a resistance of 54.8% naldixic acid and 39.2% resistance to ciprofloxacin, whereas Monteiro et al. [15] found a resistance of 31.7% nalixic acid and 16.5% to ciprofloxacin, a very low result when compared to the findings of the present study. Antibiotic resistance was significantly higher in pediatric patients compared to adult patients.

This is due to the slow maturation of the immune system, the development of which is less pronounced the lower the age, making the risk of acquiring communicable diseases higher.

Conclusion

Antibiotic resistance was significantly higher in Pediatric patients when compared to Adults patients. This is due to the slow maturation of the immune system, the development of which is less pronounced the lower the age, making the risk of acquiring communicable diseases higher. Inadequate prescribing and impure treatment with cephalosporins may have been one of the factors that aided the emergence of third generation cephalosporin resistant *Enterobacteriaceae* isolates, as well as the high prescription of carbapenems could be related to the expressive number of imipenem resistant *Escherichia coli*. Patients infected with strains of *Enterobacter* species should receive a differentiated treatment for the remaining patients, as the high resistance rates recorded show the exhaustion of the therapeutic treatment in a wide range of antibacterial agents.

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