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Antibacterial Resistance Pattern of Gram-Positive Bacteria Isolated in the ICU from A Reference Hospital in Southern Mozambique

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Abstract

Objective: To describe the resistance pattern of Gram-positive bacteria isolated from patients admitted to ICUs at Maputo Central Hospital (HCM) in 2017.

Methods: This was a cross-sectional, epidemiological, quantitative approach, with a retrospective analysis of secondary data, performed at the ICUs in Maputo Central Hospital.

Results: During the study, 179 cultures were found to be positive for bacteriological tests (127 Pediatrics ICU and 52 Adults ICU), of which 55 (30.7%) were Gram-positive bacteria. Antibiotic resistance was highest in isolates of *Staphylococcus* Spp. (89.5%), *Enterococcus* Spp. (63.1%), *Staphylococcus aureus* (46.4%), *Streptococcus* Spp. (38.9%). MRSA was prevalent in 21.2% (7/33), with 85.7% the Pediatrics ICU and 14.3% in the Adults ICU, which is very significant in a hospital environment. Beta-lactams presented high resistance indices to all Gram-positive *cocci*, with a higher prevalence of *Staphylococcus* Spp. and *Enterococcus* Spp. Glycoptides had an average resistance of 50%, with Vancomycin inhibiting the growth of all strains of *Staphylococcus aureus* and *Enterococcus* Spp.

Conclusion: Resistance to antibiotics in Gram-positive cocci is a persistent problem, with infection control, selective antibiotic pressure and continuous resistance monitoring being the important factors in its spread.

Keywords Gram-Positive bacteria; Antibacterial resistance; Intensive care; Mozambique

Introduction

Intensive Care Units (ICUs) have shown high rates of hospital infections, including the occurrence of multi-resistant microorganisms. Some factors that influence antibacterial resistance are the patient's immune system, the number of bacteria at the site of infection, the mechanism of action of the antibiotic, and the level of antibacterial that reach the bacterial population [1]. Resistance to antibiotics has become a major problem in the treatment of Gram-positive bacterial infections, it is extremely important, on both the inside and outside of the hospital environment [2].

Among Gram-positive bacteria, methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococcus (VRE), Vancomycin-resistant Staphylococcus aureus (VRSA), Coagulase-negative Staphylococcus and Penicillin resistant Streptococcus pneumoniae have become a problem in the environment due to high morbidity, mortality, and limited treatment options [3]. These bacteria are listed on WHO's priority pathogens for research and development of new antibiotics.

In contrast to Gram-negative bacterial infections, the prevalence and resistance pattern of Gram-positive pathogens have not been widely studied and has been largely neglected in Mozambique. Thus, this study was carried out with the aim of describing the resistance pattern of Gram-positive bacteria isolated from patients admitted to the ICUs in Maputo Central Hospital (HCM) in 2017.

Material and Methods

This is a descriptive cross-sectional, epidemiological, quantitative approach, with a retrospective analysis of secondary data in the HCM Microbiology Laboratory. The study was carried out in the Pediatrics ICU, Medicine ICU and Surgery ICU at HCM from January to December 2017. Subsequently the data were grouped in the Pediatrics ICU and Medicine and Surgery Adult ICU. HCM is a quaternary public and teaching hospital with about 1463 beds, provide 4 Intensive Care Services: the Emergency ICU with 16 beds, the Medicine ICU with 6 beds, and the Pediatrics ICU with 16 beds and the Surgery ICU with 12 beds. During the study period, 1913 patients of all ages and both sexes were admitted to HCM, including 1129 in the Pediatrics ICU, 355 in the Medicine ICU and 429 in the Surgery ICU.

Data on the profile of etiological agents was extracted from the WHONET electronic database of the HCM Microbiology Laboratory. WHONET database was set up at the end of October 2009 in order to monitor antimicrobial resistance in bacteria isolated from routine clinical samples. The database contains information on the cultures made, identification of the patient, growth or non-growth of infectious

agents, isolated bacteria, resistance and antibiotic sensitivity, as well as data from the patient justifying examination [4].

A descriptive statistical analysis was performed using graphs and frequency tables to understand the behavior of the variables under study. Data analysis was done with the Statistical Package for Social Sciences (SPSS) version 20 and BioEst version 5.2.

Before conducting data analysis, a request for authorization of the research was submitted to the HCM Scientific and Pedagogical Department under reference number 321/024/DCIEFHCM/18. After authorization of the research request, the project was submitted to the ISCISA Institutional Health Bioethics Committee and approved under reference number TFCMCSFM05/18.The study complied with the 2013 Helsinki Declaration on health research standards.

For the antibiotic resistance standards of the isolated etiological agents, the categories of sensitive (S), Intermediate (I) and Resistant (R) were considered by obeying the inhibition halo diameters based on the standardization proposed by the Clinical and Laboratory Standards Institute [5].

Results

During the study period, 179 cultures were positive for bacteriological exams, 127 in the Pediatrics ICU and 52 in the Adults ICU, of which 55 (30.7%) were Gram-positive bacteria.

In the Pediatrics ICU, Gram-positive bacteria accounted for 29.9% (38/127) of all infections, affecting 50% of the female patients. In this sector most samples were isolated from blood and urine with a percentage of 42.1% and 23.7% respectively. Staphylococcus aureus was more prevalent with 63.2%, followed by Enterococcus Spp (18.4%), Staphylococcus Spp (10.5%) and Streptococcus Spp (7.9%) from the 38 Gram-positive bacteria strains isolated in the Pediatrics ICU. There was no relation between the Gram-positive bacteria isolated with the site of infection (=0.130) and gender of patients (=0.555).

In adults, Gram-positive bacteria accounted for 32.7% (17/52) of the total infections, affecting 76.5% of the male patients. In this sector most samples were isolated from blood and urine with a percentage of 58.8% and 35.3%. In the Adults ICU, samples of *Staphylococcus aureus* (35.3%) and *Enterococcus* Spp (64.3%) were isolated. There is a relationship between the Gram-positive bacteria isolated with the infection site (= 0.039) as shown in Table 1.

Characteristics	Main etiological agents											
	S .aureus		*Staphylococcus Spp*		*Enterococcus Spp*		*Streptococcus Spp*		Sum			
	n	%	n	%	n	%	n	%	n	%	χ2	p-val
Pediatrics ICU	24	63.2	4	10.5	7	18.4	3	7.9	38	69.1		
Gender												
Feminine	9	37.5	3	75	4	57.1	3	100	19	50	5.643	0.13
Masculine	15	62.5	1	25	3	42.9			19	50		
Infection site												
Blood	11	45.8	1	25	3	42.9	1	33.3	16	42.1	0.555	10.692
Urine	3	12.5	2	50	4	57.1			9	23.7		
Pus	6	25	1	25					7	18.4		
Catheter tip	3	12.5							3	7.9		
CSF	1	4.2					2	66.7	3	7.9		
Adults ICU	6	35.3			11	64.7			17	30.9		
Gender												
Feminine	1	16.7			3	27.3			4	23.5	0.243	0.622
Masculine	5	83.3			8	72.7			13	76.5		
Infection site												
Blood	6	100			4	36.4			10	58.8	6.491	0.039
Urine					6	54.5			6	35.3		
Pus					1	9.1			1	5.9		

Sum	30	54.5	4	7.3	18	32.7	3	5.5	55	100		

Table 1: Relationship between the proportions of Gram-positive bacteria, infection site and the sex of pediatric and adult patients hospitalized in the HCM ICUs in the year 2017

According to the data in Table 2, beta-lactams presented high resistance indices to all Gram-positive cocci isolated from pediatric patients, with a higher prevalence of *Staphylococcus* Spp. (87.5%) and *Enterococcus* Spp. (86.7%). Penicillin resistance ranged from 66.7% to 100%, with amoxicillin (100%), oxacillin (88.9%) and ampicillin (80.0%) showing high proportions. The results also showed resistance of *Staphylococcus aureus* to oxacillin by 75%.

Cephalosporins had an average resistance of 55.9%, inhibiting the growth of all strains of *Streptococcus* spp. *Staphylococcus* spp. showed a higher percentage of resistance in 85.7%.

Carbapenems did not inhibit growth of any *Enterococcus* spp. strain. All strains of *Staphylococcus aureus* were sensitive to imipenem.

The aminoglycosides had a resistance of 51.7%. Amikacin did not inhibit growth of any strain of *Staphylococcus* spp. Gentamicin was 100% resistant to *Staphylococcus* spp. and *Enterococcus* spp.

Gram-positive bacteria isolated in the Pediatrics ICU showed an average resistance of 53.8% to quinolones. In this class of antibiotics, naldixic acid did not inhibit growth of any strain of Gram-positive bacteria.

Glycoptides had an average resistance of 50%. Vancomycin inhibited growth of all strains of *Staphylococcus aureus* and *Enterococcus* spp. This drug had a 100% resistance to *Staphylococcus* spp.

The proportion of resistance to macrolides against Gram-positive cocci strains was 60.7%. Erythromycin did not inhibit growth of any strain of *Staphylococcus* spp. and *Streptococcus* spp.

All strains isolated from genus species of *Staphylococcus* showed resistance to colistin.

Gram-positive isolated cocci strains had a resistance of 73.3% to co-trimoxazole, 57.9% to tetracycline, 50% to nitroforantoin, 34.5% to clindamycin and 26.3% to chloramphenicol.

Antibacterials tested	**Main etiological agents**							
	S.aureus		*Staphylococcus* spp.		*Enterococcus* spp.		*Streptococcus* spp.	
	N	n (%Res)	N	n (%Res)	N	n (%Res)	N	n (%Res)
Betalactam	53	32 (60.4)	16	14 (87.5)	15	13 (86.7)	7	4 (57.1)
Penicillins	27	21 (77.7)	6	6 (100.0)	11	10 (90.9)	6	4 (66.7)
Amoxiline	1	1 (100.0)	1	1 (100.0)				
Ampicillin	3	2 (66.7)	1	1 (100.0)	6	5 (83.3)		
Oxacillin	4	3 (75.0)	2	2 (100.0)			3	3 (100.0)
Penicillin G	19	15 (78.9)	2	2 (100.0)	5	5 (100.0)	3	1 (33.3)
Cefalosporinas	23	11 (47.8)	7	6 (85.7)	3	2 (66.7)	1	0 (0.0)
Cefazolin			1	1 (100.0)				
Cefoxitin	17	7 (41.2)	2	1 (50.0.0)				
Cefotaxime	3	2 (66.7)	1	1 (100.0)				
Ceftazidime	2	2 (100.0)	1	1 (100.0)				
Ceftriaxone	1	0 (0.0)	1	1 (100.0)	3	2 (66.7)	1	0 (0.0)
Cefepime			1	1 (100.0)				
Carbapenem	3	0 (0.0)	3	2 (66.7)	1	1 (100.0)		
Imipenem	3	0 (0.0)	1	1 (100.0)	1	1 (100.0)		
Meropenem			2	1 (50.0)				
Aminoglycosides	21	7 (33.3)	7	7 (100.0)	1	1 (100.0)		
Amikacin	5	0 (0)	5	5 (100.0)				

Gentamicin	16	7 (43.8)	2	2 (100)	1	1 (100.0)		
Quinolones	19	7 (36.8)	4	4 (100.0)	3	3 (100.0)		
Naldixic Acid	1	1 (100.0)	2	2 (100.0)				
Ciprofloxacin	18	6 (33.3)	2	2 (100.0)	3	3 (100.0)		
Glycoptides	2	1 (50.0)	3	3 (100.0)	3	0 (0.0)		
Teicoplamina	1	1 (100.0)	1	1 (100.0)				
Vancomycin	1	0 (0.00)	2	2 (100.0)	3	0 (0.0)		
Macrolides	21	11 (52.4)	4	4 (100.0)	2	1 (50.0)	1	1 (100.0)
Azithromycin			1	1 (100.0)				
Erythromycin	21	11 (52.4)	3	3 (100.0)	2	1 (50.0)	1	1 (100.0)
Colistina	1	1 (100)	1	1 (100)				
Clindamycin	21	7 (33.3)	3	2 (66.7)	2	1 (50.0)	3	0 (0.0)
Co-trimoxazole	10	7 (70.0)	4	4 (100.0)			1	0 (0.0)
Tetracycline	10	5 (50.0)	3	2 (66.7)	3	2 (66.7)	3	2 (66.7)
Others	15	5 (33.3)	4	4 (66.7)	4	1 (25.0)	3	0 (0.0)
Chlorphenicol	14	4 (28.6)	2	1 (50.0)			3	0 (0.0)
Nitroforantoin	1	1 (100.0)	1	1 (100.0)	4	1 (25.0)		
Total	174	83 (63.4)	49	44 (89.5)	33	23 (69.7)	18	7 (38.9)
N= Total strains tested; n= Total resistant strains; %Res= Percentage of resistant strains								

Table 2: Profile of antibacterial resistance of samples isolated from Gram-positive bacteria in Pediatrics ICU patients in 2017

In the Adults ICU, beta-lactams had a resistance of 72.7% to *Staphylococcus aureus* and 58.8% to *Enterococcus* spp. Ampicillin did not inhibit growth of any strain of *Staphylococcus aureus*. Cephalosporin resistance was higher against *Enterococcus* spp. strains with 80%, with cefotaxime and ceftazidime being 100% percent.

The quinolones and macrolides showed higher resistance against *Enterococcus* spp. strains with percentages of 100% and 87.5%.

Co-trimoxazole did not inhibit growth of any strain of Gram-positive cocci isolated from Adults ICU as shown in Table 3.

Antibacterials tested	**Main etiological agents**			
	S.aureus		*Enterococcus* spp	
	N	n (Res%)	N	n (Res%)
Betalactam	11	8 (72.7)	17	10 (58.8)
Penicillins	7	6 (85.7)	4	1 (25.0)
Ampicillin	1	1 (100.0)	2	0 (0.0)
Cloxacillin	1	1 (100.0)		
Penicillin G	5	4 (80.0)	2	1 (50.0)
Cefalosporinas	4	2 (50.0)	10	8 (80.0)
Cefoxitin	4	2 (50.0)		
Cefuroxime			3	2 (66.7)
Cefotaxime			1	1 (100.0)

Ceftazidime	1	0 (0.0)	3	3 (100.0)
Ceftriaxone	1	0 (0.0)	3	2 (66.7)
Carbapenem			3	1 (33.3)
Imipenem			2	1 (50.00)
Ertapenem			1	0 (0.0)
Aminoglycosides	5	1 (20.0)	7	3 (42.9)
Amikacin	4	0 (0.0)	1	1 (100.0)
Gentamicin	1	1 (100.0)	6	2 (33.3)
Quinolones	4	2 (50.0)	1	1 (100.0)
Ciprofloxacin	4	2 (50.0)	1	1 (100.0)
Glycoptides			4	0 (0.0)
Vancomycin			4	0 (0.0)
Macrolides	4	1 (25.0)	8	7 (87.5)
Erythromycin	4	1 (25.0)	8	7 (87.5)
Colistin			4	1 (25.0)
Clindamycin	5	1 (20.0)	2	2 (100.0)
Co-trimoxazole	1	1 (100.0)	1	1 (100.0)
Tetracycline	1	1 (100.0)	1	0 (0.0)
Others	4	0 (0.0)	6	4 (66.7)
Chloramphenicol	4	0 (0.0)	5	4 (80.0)
Nitroforantoin			1	0 (0.0)
Total	37	15 (40.5)	51	30 (58.8)
N=Total de estirpes testadas; n=Total de estirpes resistentes; %Res=Percentage de estirpes resistentes				

Table 3: Profile of antibacterial resistance of isolated samples of Gram-positive cocci in patients from Adults ICU in the year 2017

As shown in Table 4, the antibiotic resistance of Gram-positive *cocci* was 55.8%, being higher in pediatric patients with 57.3% compared to 51.1% of adults.

The bacteria with the highest resistance ratio were *Staphylococcus* spp. and *Enterococcus* spp. These results show that there is no relationship between the resistance of Gram-positive cocci and the type of ICU.

Bacteria	ICU Type				Sum		Statistical tests			
	Pediatric		Adults		Chi-square		Z Test			
	n	%	n	%	N	%	χ2	p-val	Z	p-val
S. aureus	83	47.7	15	40.5	98	46.4	0.5996	0.4387	0.7931	0.4277
Staphylococcus Spp	44	89.5	-	-	44	89.5	-	-	-	-
Enterococcus Spp	23	69.7	30	58.8	53	63.1	1.5695	0.2103	1.0086	0.3132
Streptococcus Spp	7	38.9	-	-	7	38.9				

Total	157	57.3	45	51.1	202	55.8	1.0283	0.3105	1.0128	0.3112
n= Total resistant strains; %Res= Percentage of resistant strains										

Table 4: Relationship between antibacterial resistance of Gram-positive cocci and ICU type

Discussion

In the present study, the most isolated Gram-positive bacterium was *Staphylococcus aureus* in 54.5% of the cases. About one-third of the population has *Staphylococcus aureus* as part of the transient flora of the skin constituting an important source of infection for the individual or for other people and is considered the main etiological agent of nosocomial and community infections [6].

According to Tavares [7], *Staphylococcus* has been shown to be resistant to penicillin G, ampicillin and amoxicillin in more than 70% of strains isolated, either in the hospital or in the community, and the use of these antimicrobials is no longer indicated for the treatment of *staphylococcal* infections. In the present study the resistance of *Staphylococcus* to amoxilin was 100%, 87.5% to penicillin G and 80% to ampicillin.

Oxacillin was introduced as the antibiotic of choice for the replacement of penicillin in the treatment of penicillin-resistant *Staphylococcus* infections, but results show that resistance to this drug has been increasing significantly in the hospital setting [8]. In this study the resistance of this drug against the strains of the genus *Staphylococcus* was 83.3% in the Pediatrics ICU and 100% in the Adults ICU.

MRSA was prevalent in 21.2% (7/33), with 85.7% the Pediatrics ICU and 14.3% in the Adults ICU, which is very significant in a hospital environment. Few studies in sub-Saharan Africa have described prevalence of MRSA and, although it has spread in Mozambique, its prevalence remains unknown. A study of the prevalence of MRSA in São Tomé and Príncipe, Angola and Cape Verde identified an average prevalence of 6.6%, highest in Angola (13.8%), Sao Tome and Principe (4.2%) and Cape Verde (1.3%). The same study reveals that the Pediatric and ICU Services were those where the percentages were high with an average of 18.5%, corroborating with the findings of the present study [9]. The presence of MRSA restricts the prophylaxis with the use of cephalosporins due to the intrinsic resistance by betalactamases, conditions that contribute to the increase of morbidity [10].

According to Luna [11], Vancomycin is used as a last resort antibiotic in the treatment of MRSA infections. Although frequent use has resulted in the overall emergence of MRSA strains with reduced sensitivity to this antibiotic, vancomycin is still considered effective against MRSA. In this study the resistance of the strains of species of genus *Staphylococcus* to vancomycin was 66.7% in agreement with the findings by Deyno at al. [12] which obtained 74.2% in a similar study. Teicoplanin is used as an alternative for the treatment of Gram-positive cocci infections, including MRSA, and is even more advantageous for vancomycin due to longer serum half-life allowing administration in a single daily dose, lower nephrotoxicity and lower need to monitor their serum levels [13]. The resistance to teicoplamine was 100%, and it was tested in isolates of pediatric patients.

Clindamycin exhibits good antibiotic activity against Gram-positive bacteria, and is active against infections caused by *Staphylococcus*. In this study the resistance of species of the genus *Staphylococcus* to clindamycin was 34.5%, a slightly higher result when compared to Parlak et al. [8] which obtained a resistance of 11.1%.

Enterococcus spp. has been of increasing importance in the etiology of hospital infections because it is considered to be a microorganism intrinsically resistant to antibiotics essentially used, such as ampicillin, aminoglycosides and glycopeptides, and is frequently associated with infections of the urinary tract [14]. In the present study, most strains of *Enterococcus* spp. were isolated in urine samples, presenting a mean resistance of 62.5% to ampicillin, 100% to amikacin, 50% to gentamicin and 0.0% to vancomycin. Mulla et al. [14] found similar results, with ampicillin having a resistance of 40%, 53% gentamicin and 8% vancomycin.

All species of the genus *Streptococcus* were identified in female patients from the Pediatrics ICU, with a higher prevalence in cerebrospinal fluid samples. This microorganism is more frequent in pediatrics and is the main etiological agent of bacterial meningitis in children and is frequently isolated in samples of cerebrospinal fluid [15]. In the last decades, with the appearance of penicillin resistant *Streptococcus pneumoniae*, and after the other antibiotics, there was an increase in its importance, being considered a public health problem and, increasingly, generating several studies. A study conducted in Mozambique on the prevalence of pediatric bacterial meningitis in Central Hospitals in Maputo, Beira and Nampula by Nhantumbo [16] found a resistance of 88.2% to penicillin G, a very high value when compared to the 33.3% of this study. The same study showed a resistance with a percentage of 23.5% erythromycin, 64.7% to tetracycline and 100% to co-trimoxazole. In the present study resistance to erythromycin was 100%, tetracycline (66.7%) and cotrimoxazole (0.0%). The difference in the results of these two studies is due to the difference in the characteristics of the two populations. These results show that the resistance indices of strains isolated from *Streptococcus* the class of penicillin tend to increase.

Conclusions

Resistance to antibiotics in Gram-positive *cocci* is a persistent problem. Infection control, selective antibiotic pressure and continuous resistance monitoring are the important factors regulating spread of Antibiotic Resistance. The development of novel effective antibacterial agents in the treatment of severe Gram-positive infections would also be welcomed.

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