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Risk Factors of Bacterial Resistance to Antibiotics in Internal Medicine and Hemodialysis Nephrology Services at the Edith Lucie Bongo Ondimba General Hospital

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Abstract

Introduction: Antibiotic resistance is a public health problem. It is due to multi-resistant bacteria (MRB). The objective of this study was to determine bacterial resistance to antibiotics in chronic renal failure at the Edith Lucie BONGO ONDIMBA general hospital (HGELBO). Patients, material and method: This was an analytical cross-sectional study conducted from January 1 to August 31, 2019 at the HGELBO. It concerned all patients admitted to the HGELBO with positive bacteriological samples. After a study of the sensitivity to isolated species, the patients were divided into two (02) groups: those MRB positive (+) and not MRB or negative (−). Epi Info software version 3.5.1 was used for the calculation of the rates and the comparison of the variables. The adjusted odds ratio (ORa) with a 95% confidence interval was used to measure the specific effect of each risk factor such as chronic kidney disease and diabetes, in order to rule out confounding factors. Multivariate analysis by binomial logistic regression was used. Results: There were 375 bacteriological samples from 258 patients, among them 247 patients with 235 positive samples or 63%. The eleven (11) are healthy patients. The median age was 33 with extremes ranging from 16 to 90. The female sex was predominant with a sex ratio of 0.6. The majority of MRB+ cases were found in internal medicine and nephrology with 12 cases (38.7%) and hemodialysis with 4 cases (12.9%). Urinary samples were in the majority with 74.5%. *Escherichia coli* was predominant in 30.3%. After studying the sensitivity to antibiotics of the 247 species included, 113 were MRB+ and 134 BMR− *i.e.* a frequency of

45.7%. Methicilin-resistant *Staphylococcus aureus* (MRSA) was predominant (51.3%). Multivariate logistic regression analysis showed that the main risk factor was antibiotic use (0Ra: 3.2 [1.9 - 5.4]; p-value < 0.01). Chronic renal failure and diabetes were not risk factors for carriage. The other risk factors identified were: hospitalization of more than 7 days (prolonged), *S. aureus* infection and male sex. Conclusion: Probabilistic antibiotic therapy leads to the selection of BMRs. Long hospital stays, male sex, and MRSA are risk factors or determinants of antibiotic resistance, but not chronic kidney disease.

Keywords

Risk Factors, Bacterial Resistance, Antibiotics, Chronic Renal Failure, General Hospital Edith Lucie BONGO ONDIMBA

1. Introduction

Bacterial resistance to antibiotics is the ability of certain bacteria to withstand a higher concentration of antibiotics than can be achieved *in vivo* during medical treatment [1]. Bacteria are said to be multi-resistant (MRB) when they accumulate acquired resistance to more than three families of antibiotics [2]. Antibiotic resistance is a public health problem. Bacterial resistance to antibiotics has increased alarmingly in recent years as newer antibiotics are less and less marketed [3] [4] [5] [6]. It is due to multi-resistant bacteria (MRB). Globally, resistance to C3Gs for *Escherichia coli* was 10.2% in France; 15.6% in Portugal; 16.6% in Croatia and 29.5% in Italy [7] [8]. Resistance to ceftazidime for *P. aeruginosa* was 12.2% in France; 18.6% in Portugal; 19.5% in Croatia and 20.0% in Italy. The frequency of MRSA was 12.9% in France; 15.2% in Portugal; 28.5% in Croatia and 33.9% in Italy.

In Africa Mboyo, F.C. in 2016 in Morocco, reported 15% resistance to *E. coli*; 5.6% for *P. aeruginosa* and 1.3% for *S. aureus* [9]; Deguenovo *et al.* in 2016 in Senegal reported a frequency of 62% for EBLSE and 13% for *P. aeruginosa* [10].

In Congo, Moyen R. *et al.* in 2014 showed that beta-lactam resistance was 77.9% for *S. aureus*; 44.4% for *P. aeruginosa*; and it ranged from 56.3 to 83.3 for Enterobacteriaceae [11]. However, the determinants of this resistance are not known in our region. The objective of this study was; in general to analyze the determinants of bacterial resistance to antibiotics at the Edith Lucie BONGO ONDIMBA general hospital (HGELBO), and specifically of: 1) Determine the frequency of multiresistant bacteria to HGELBO; 2) Describe in a comparative manner the socio-demographic and clinical characteristics of patients carrying multi-resistant bacteria (MRB+) and those carrying non-multi-resistant bacteria (MRB−) to HGELBO; 3) Determine bacterial resistance to antibiotics in chronic renal failure to HGELBO. 4) Identify the bacteria determining multidrug resistance to HGELBO antibiotics.

2. Patients, Material and Method

This was an analytical cross-sectional study carried out from January 1 to August 31, 2019 at the HGELBO. Our study took place at the Edith Lucie BONGO ONDIMBA General Hospital (HGELBO) which is located in the Cuvette department and more precisely in the Oyo district. It is a public establishment that was put into service on March 10, 2017. It has 200 beds of which 148 are active with a monthly attendance of 255 patients. Our study was performed in the biomedical analysis laboratory. Patient recruitment was done on an outpatient basis, in inpatient departments or directly in the biomedical analysis laboratory. The target population consisted of any patient admitted to the HGELBO regardless of age, sex, origin, existence or not of an infectious pathology and in whom a bacteriological examination of the samples showed a positive culture for one of the following germs: *Staphylococcus aureus*, Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*. We included patients with:

- gave their informed consent to the study.
- is the subject of the following samples: urine, vaginal secretions, put, puncture of joint fluid, hemodialysis catheter tip, probe tip.
- a positive culture.

Contaminations and epidemiological duplicates were excluded from our study.

The sampling was carried out from a simple random selection.

The sample size was calculated from Schlesselman's formula to ensure its representativeness. N: sample size; r: MRB+/MRB− ratio that we have arbitrarily chosen 1 MRB+ for 3 MRB− *i.e.* r = 1/3; P = (P0 + P1)/2 = the average of the proportions; P0 - P1: the difference between the proportions. P0 = Proportion of affected in the subject group (MRB+) and P1 = Proportion of affected in the control group (MRB−). For a = 0.05; Za = 1.65; a being the type error I = Probability of wrongly saying that there is a difference in the two groups, therefore wrongly rejecting the null hypothesis. For b = 0.1; Zb = 1.28; b being the type II error = Probability of wrongly saying that there is no difference in the two groups, therefore false admission of the null hypothesis. Numerical application: Given the fact that no study was available in Congo to use the variables, we used data from the case-control study carried out in Morocco in 2014 on the risk factors for infections with multidrug-resistant bacteria. At the level of the intensive care units, CHU Ibn Rochd, Casablanca [12] see **Table 1**. The parameter we considered was the antecedent of diabetes, *i.e.* 65% of patients presented an infection with ESBL+ *E. coli* (P0) and 12% had ESBL− (P1) *E. coli* infection. We have P1 = 0.12; P0 = 0.65; r = 1/3; Z a = 1.65; Z b = 1.28. The calculation gives N = 29; hence we have a minimum size of 29 BMR+ and 87 MRB−. It concerned all patients admitted to the HGELBO with positive bacteriological samples. After a study of the sensitivity to the isolated species, the patients were divided into two (02) groups: those MRB positive (+) and not MRB or negative (−). Data collection was centered on a threefold survey: epidemiological, clinical and bacteriological

Table 1. Comparison of our results zith those reported in 2014 in Morocco [12].

	Majida H' serie	**Our serie**
	ORb [95%]	ORb
Sex	1.58 [0.5 - 4.6]	2.01 [1.20 - 3.37]
Age	3.19 [0.83 - 12.2]	3.55 [2.09 - 6.04]
Diabetis	3.8 [1.12 - 14.6]	2.10 [1.22 - 3.62]
Old re hospitalisation	8.5 [1.1 - 69.54]	2.48 [1.47 - 4.18]
Time of hospitalisation	10.2 [3.36 - 30.6]	15 [1.65 - 136.20]
Vein catheter	2.08 [0.39 - 11.2]	3.95 [1.39 - 11.24]
New surgery	3.98 [1.4 - 11.25]	2.23 [1.24 - 4.03]
Antibiotic		4.08 [2.32 - 7.18]
Imipeneme	17.5 [2.2 - 139.4]	
Fluoroquinolones	6 [1.26 - 28.4]	
G3C	13 [4.23 - 43.9]	
	MRB(Kp-BLSE)	**MRB+**

G3C: Third generation fluoroquinolones.

surveys. Epidemiological and clinical investigations: Before carrying out the investigations, the patients were informed about the study (theme, framework, advantages and objectives), the conditions of the examination and the sampling from an information sheet in order to obtain their informed consent. After obtaining their written and signed informed consent, patients were subjected to a standardized questionnaire to collect socio-demographic and clinical data. We conducted interviews in French (official language), Lingala (national language) according to the patient's preference. A code and an identification number were assigned to each patient in order to guarantee data confidentiality and anonymity. Bacteriological investigation: The bacteriological investigation was carried out respecting the three phases of the biological examination: the pre-analytical, analytical and post-analytical phases. The pre-analytical phase, after having collected the clinical information of the patients, the bacteriological samples were taken according to the recommendations in force [7] [8] [9]. The analytical phase of the samples was carried out respecting the following steps: macroscopic examination, cytological examination, bacteriological examination, cultivation, identification of the species and carrying out antibiograms. During the statistical analysis, Excel version 2016 software was used for the compilation of the database, the construction of tables and graphs. And Epi Info software version 3.5.1 was used for the calculation of the rates and the comparison of the variables. For the qualitative variables we used frequencies; for the quantitative variables we used the mean and standard deviation or the median and quartiles when the standard deviation was greater than one tenth of the whole part of the mean. The extreme values were specified. Pearson's chi-square test was used for the comparison of qualitative variables, when the conditions for its application were

not met the exact Fischer test was used. The t-Student test was used for comparison of means. Mann Whitney test was used for comparison of medians. The test was considered statistically significant if the p-value was less than 0.05. The raw odds ratio (ORb) with a 95% confidence interval was used to measure the association between carry at MRB and the explanatory variables. To do this, we performed a bivariate analysis between the dependent variable (sensitivity) with two modalities (MRB+ and MRB−) and the explanatory variables (independent variables or exposure variables) coded in binary mode. The adjusted odds ratio (ORa) with a 95% confidence interval was used to measure the specific effect of each risk factor in order to rule out confounding factors (confusions that exist between BMR infection and certain independent variables). Multivariate analysis by binomial logistic regression was used. For each given variable, when the odds ratio was greater than 1, then it multiplied the risk for a patient to be a carrier of BMR provided that his confidence interval does not contain the value 1 and that the p-value is lower to 0.05.

3. Results

There were 375 bacteriological samples from 258 patients. Among them 247 patients with 235 positive samples or 63%. The eleven (11) healthy patients. The median age was 33 with extremes ranging from 16 to 90. The female sex was predominant with a sex ratio of 0.6. The internal medicine, nephrology and hemodialysis departments had more patients in hospital, 16 out of 31, or 51.6%. The majority of MRB+ cases were found in internal medicine and nephrology with 12 cases (38.7%) and hemodialysis with 4 cases (12.9%) see Table 2. Urinary samples were in the majority with 74.5%. The germ *Escherichia coli* predominated in 30.3%. See Table 3. After the study of antibiotic susceptibility of species included 247, 113 and 134 were BMR+ a frequency of 45.7%. Methicilin-resistant *Staphylococcus aureus* (MRSA) was predominant (51.3%). Multivariate logistic regression analysis showed that the main risk factor was antibiotic use (0Ra: 3.2 [1.9 - 5.4]; p-value < 0.01). Chronic renal failure and diabetes were not risk factors for carriage. The other risk factors identified were: hospitalization of more than 7 days (prolonged), *Sthaphylococcus aureus* infection and male sex. See Tables 4-7.

Table 2. Patients with a positive culture according to inpatient services.

Impatients services	POSITIVE CULTURE	
	n	%
Gynaecology obstetric	5	16.1
Pediatric	2	6.5
Reanimation	8	25.8
Internal medecine	12	38.7
Hemodialysis	4	12.9
All	31	100

Table 3. Species isolated according to the type of sample.

Type of sample species isolated	Urine n (%)	Vaginal secretion n (%)	Put n (%)	joint fluid n (%)	Hemodialysis catheter tip n (%)	Urinary catheter tip n (%)	Total n (%)
Escherichia coli	71 (79.8)	14 (15.7)	2 (2.2)	0 (0)	0 (0)	2 (2.3)	89 (100)
Klebsiella pneumoniae	21 (65.6)	6 (18.8)	5 (15.6)	0 (0)	0 (0)	0 (0)	32 (100)
Enterobacter cloacae	11 (91.7)	0 (0)	1 (8.3)	0 (0)	0 (0)	0 (0)	12 (100)
Citrobacter freundii	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)
Proteus mirabilis	6 (75)	0 (0)	2 (25)	0 (0)	0 (0)	0 (0)	8 (100)
Pseudomonas aeruginosa	16 (69.6)	5 (21.7)	2 (8.7)	0 (0)	0 (0)	0 (0)	23 (100)
Aeromonas hydrophila	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	0 (0)	5 (100)
Staphylococcus aureus	66 (82.5)	4 (5)	4 (5)	2 (2.5)	4 (5)	0 (0)	80 (100)
Staphylococcus saprophiticus	30 (71.4)	12 (28.6)	0 (0)	0 (0)	0 (0)	0 (0)	12 (100)
Total	224 (76.2)	41 (13.9)	21 (7.1)	2 (0.7)	4 (1.4)	2 (0.7)	294 (100)

Table 4. Bivariate analysis of risk factors for MRB carriage.

	Total N = 247	**Sensibility MRB+ n = 113**	**Sensibility MRB− n = 134**	**rOR (CI 95%)**	**p-value**
	n (%)	**n (%)**	**n (%)**		
Age in years				3.8 (2.2 - 6.7)	<0.0001˚
≥40	80 (32.4)	54 (47.8)	26 (19.4)		
≤40	167 (67.6)	59 (52.2)	108 (80.6)		
Sex				2 (1.2 - 3.4)	0.0094˚
Male	102 (41.3)	57 (50.4)	45 (33.6)		
Feminine	145 (58.7)	56 (49.6)	89 (66.4)		
Professional activity				3.1 (1.7 - 5.8)	0.0002˚
No renumerating	179 (72.5)	95 (84.1)	84 (62.7)		
Renumerating activity	68 (27.5)	18 (15.9)	50 (37.3)		
Educational level				2.4 (1.4 - 4.2)	0.02˚
Schooled	72 (29.1)	44 (28.9)	28 (20.9)		
No schooled	175 (70.9)	69 (61.1)	106 (79.1)		
Origin				3.2 (1.5 - 6.8)	0.003˚
Inpatient	36 (14.6)	25 (22.1)	11 (8.2)		
Outpatient	211 (85.4)	88 (77.9)	123 (91.8)		
Hospital stay				15 (1.7 - 136.2)	0.009˚
≥7	20 (55.6)	15 (60.0)	1 (9.1)		
≤7	16 (44.4)	10 (40.0)	10 (90.9)		
Hospitalization during the year				2.5 (1.5 - 4.2)	0.0007˚
Yes	98 (39.7)	58 (51.3)	40 (29.9)		
No	149 (60.3)	55 (48.7)	94 (70.1)		

˚significative p-value; rOR raw odds ratio; CI confidence interval.

Table 5. Bivariate analysis of risk factors for MRB carriage.

	Total	MRB+	MRB−	rOR (CI 95%)	p-value
	n (%)	n (%)	n (%)		
Surgery in 30 days				2.2 (1.2 - 4)	0.008˚
Yes	61 (24.7)	37 (32.7)	24 (17.9)		
No	186 (75.3)	76 (67.3)	110 (82.1)		
Diabetis				2.1 (1.2 - 3.6)	0.009˚
Yes	79 (32.0)	46 (40.7)	33 (24.6)		
No	168 (68.0)	67 (59.29)	101 (75.4)		
Antibiotic in 30 days				4.1 (2.3 - 7.2)	<0.0001˚
Yes	82 (33.2)	56 (49.6)	26 (19.4)		
No	165 (66.8)	57 (50.4)	108 (80.6)		
Injectable treatment				3.95 (1.4 - 11.2)	0.009˚
Yes	20 (8.1)	14 (12.4)	5 (3.7)		
No	227 (91.9)	99 (87.6)	129 (96.3)		
Indwelling surgery				3.0 (1.1 - 8.1)	0.03˚
Yes	20 (8.1)	14 (12.4)	6 (4.5)		
No	227 (91.9)	99 (87.6)	128 (95.5)		
Spacies (*pseudomonas aeroginosa*)				1.1 (0.5 - 2.6)	0.83
Yes	23 (9.3)	11 (9.7)	12 (9.0)		
No	224 (90.9)	102 (90.3)	122 (91.0)		
Spacies (*staphylococcus aureus*)				5.4 (3.0 - 9.7)	0.0001˚
Yes	80 (32.4)	58 (51.3)	22 (16.4)		
No	167 (67.6)	55 (48.7)	112 (83.6)		

˚significative p-value; rOR raw odds ratio; CI confidence interval.

Table 6. Logistic regression of MRB risk factors.

	Total	MRB+	MRB−	aOR (CI 95%)	p-value
	n (%)	n (%)	n (%)		
Age in years					0.25
≥40	80 (32.4)	54 (47.8)	26 (19.4)	1^	
≤40	167 (67.6)	59 (52.2)	108 (80.6)	1.8 (0.6 - 5.9)	
Sex					0.001˚
Male	102 (41.3)	57 (50.4)	45 (33.6)	1^	
Feminine	145 (58.7)	56 (49.6)	89 (66.4)	2.8 (1.5 - 5.1)	
Professional activity					0.26
No renumerating	179 (72.5)	95 (84.1)	84 (62.7)	1^	

Continued

Renumerating activity	68 (27.5)	18 (15.9)	50 (37.3)	0.3 (0.05 - 2.22)	
Educational level					0.60
Schooled	72 (29.1)	44 (28.9)	28 (20.9)	1^	
No schooled	175 (70.9)	69 (61.1)	106 (79.1)	1.3 (0.6 - 2.5)	
Origin					0.0004˚
Inpatient	36 (14.6)	25 (22.1)	11 (8.2)	1^	
Outpatient	211 (85.4)	88 (77.9)	123 (91.8)	5.71 (2.2 - 15.1)	
Hospital stay					<0.0001˚
≥7	20 (55.6)	15 (60.0)	1 (9.1)	1^	
≤7	16 (44.4)	10 (40.0)	10 (90.9)	18.1 (9.6 - 31.1)	
Hospitalization during the year					0.07
Yes	98 (39.7)	58 (51.3)	40 (29.9)	1^	
No	149 (60.3)	55 (48.7)	94 (70.1)	2.2 (0.9 - 4.1)	

˚significative p-value; ^aOR ajusted odds ratio; CI confidence interval.

Table 7. Logistic regression of MRB risk factors.

	Total	MRB+	MRB−	aOR (CI 95%)	p-value
	n (%)	n (%)	n (%)		
Surgery in 30 days					0.75
yes	61 (24.7)	37 (32.7)	24 (17.9)	1^	
No	186 (75.3)	76 (67.3)	110 (82.1)	1.4 (0.2 - 11.3)	
Diabetis					0.06
yes	79 (32.0)	46 (40.7)	33 (24.6)	1^	
No	168 (68.0)	67 (59.29)	101 (75.4)	1.7 (0.9 - 2.9)	
Antibiotic in 30 days					<0.001˚
yes	82 (33.2)	56 (49.6)	26 (19.4)	1^	
No	165 (66.8)	57 (50.4)	108 (80.6)	3.2 (1.9 - 5.4)	
Injectable treatment					0.50
yes	20 (8.1)	14 (12.4)	5 (3.7)	1^	
No	227 (91.9)	99 (87.6)	129 (96.3)	1.3 (0.7 - 2.5)	
Indwelling surgery					0.62
yes	20 (8.1)	14 (12.4)	6 (4.5)	1^	
No	227 (91.9)	99 (87.6)	128 (95.5)	1.3 (0.6 - 2.5)	
Spacies (*staphylococcus aureus*)					0.02˚
Yes	80 (32.4)	58 (51.3)	22 (16.4)	1^	
No	167 (67.6)	55 (48.7)	112 (83.6)	5.9 (1.3 - 26.3)	

˚significative p-value; ^aOR ajusted odds ratio; CI confidence interval.

4. Discussion

The different stages from the sampling to the post analytical were respected according to the standards and recommendations in force [12]-[17].

In this study, the frequency of multidrug resistance bacteria (MRB) was 45.7%. In the majority of cases these were MRSA (51.3%), EBRC3G (38.9%) and PAMR (9.7%). We have not isolated strains of *Acinetobacter baumannii*. In France, Pierrot S had returned 28.5% in 2015 [18] while in Morocco, Azmoun S had brought back 25.5% to the CHU of MARRAKECH in 2016 [17] and Saadaoui M in 2008 had found 19% to the Hassan II hospital in Settet [14]. Several reasons can explain these results.

Male sex was statistically associated with antibiotic resistance as reported by Pierrot S, in 2015 in France [18], Birgand G and al in 2013 in France [19], MBOYO F and al in 2016 in Morocco [9], then Koujane L in 2011 in Morocco [16]. The involvement of the male sex in the occurrence of BMR is not clearly established despite the unanimity of several authors [10] [15] [18] [20]. In the present study, a statistically significant association was found between hospitalization and BMR carriage. These results were also reported by MBOYO F. *et al.* 2016 in Morocco [9] and Deguenevo L *et al.* in Senegal [10]. Normal (sensitive) flora can be replaced by resistant flora (hospital strains) during hospitalization. Invasive manipulations increase the risk of developing MRB [18] [19]. It is thus that in this series patients were treated by injection and had an indwelling catheter.

The impact of the consumption of antibiotics on the occurrence of resistance has been documented [21] [22] [23]. Antibiotics do not induce resistance in themselves, but they lead to the selection of resistant mutants by reducing or even destroying the patient's sensitive normal flora, thus allowing resistant bacteria to proliferate [23]. These MRBs acquired during hospitalization can persist for several months or even years [24]-[31]. This explains the predominance of MRB in our series in patients with a history of hospitalization within the year, surgery within 30 days and antibiotics taken within 30 days. The existence of an underlying pathology such as chronic renal failure, diabetes mellitus; recurrent urinary tract infections and HIV infection in the acquisition of BMRs had been reported by several authors [32] [33] [34]. In our series, diabetes mellitus was statistically associated with a risk of MRB as in the work of Majida H and al in 2014 [12]. Recurrent urinary tract infections, chronic renal failure and HIV have not been statistically associated with risk factors for the occurrence of resistance to MRB as has been proven in other studies [12] [35] [36]. This can be explained by the small size of our sample.

5. Conclusion

Probabilistic antibiotic therapy leads to the selection of MRBs. Visits to hospital patients by community populations lead to the dissemination of these MRBs, first of all SARMs, to the community. Kidney failure is not a risk factor for bac-

terial resistance. Short hospitalizations and the rational use of antibiotics are effective means of combating this phenomenon.

Confidentiality and anonymity

The study was carried out with respect for patient anonymity and the confidentiality of information.

Conflicts of Interest

The authors or anyone who participated in this study declare no conflict of interest.

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