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Phenotipic Prevalence of Antibiotic Resistance in Gabon

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Abstract

Background: The increasing phenomenon of bacterial resistance to antibiotics is a real public health problem. The main causes are poor management of hygiene and water quality, but also the use of antibiotics without precaution. The objective of this study was to isolate and determine the antibiotic resistance profile of the different bacteria found in the main hospitals and bacteriology laboratories in Gabon. **Methods:** 6034 samples were taken from hospitals in seven main cities of Gabon, and analyzed according to the usual techniques. The pathogenic strains were identified by Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry. Antimicrobial susceptibility testing was performed by the agar disc diffusion method, according to the Antibiogram Committee of the French Society for Microbiology guidelines. **Results:** 974 pathogenic bacterial strains were found, including 890/974 (91.4%) Gram-negative bacilli. The systematic antimicrobial susceptibility testings identified 160/974 (16.4%) multi-resistant strains. *Escherichia coli* was the most represented species. 12.5% - 25% of *Escherichia coli*, *Klebsiella pneu-*

moniae, *Enterobacter cloacae*, and *Citrobacter sedlakii* strains were resistant to amoxicillin + clavulanic acid, third and fourth generation cephalosporins. Aminoglycoside resistance rates of 8.5% - 19% were also noted. 4.5% to 25% of the bacteria found were resistant to quinolones and cotrimoxazole. Resistance rates to carbapenems ranged from 1% to 10.5%. 16% of *Staphylococcus aureus* were methicillin-resistant (MRSA). Rates of extended spectrum beta-lactamase-producing enterobacteriaceae (ESBL-PE) ranged from 2.5% to 25%. **Conclusion:** This study showed an increasing evolution of bacterial resistance to antibiotics that are spreading throughout Gabon. This constitutes a threat to the health of Gabonese population.

Keywords

Gabon, Antibiotic Resistance Profiles, Methicillin-Resistant *S. aureus* (MRSA), Extended Spectrum Beta-Lactamase-Producing Enterobacteriaceae (ESBL-PE), Carbapenems

1. Introduction

Antibiotics have significantly reduced mortality due to bacterial infectious diseases during the 20th century. However, the remarkable efficacy of these molecules has motivated their massive and repeated use in human and animal health. This created selection pressure on bacteria, resulting in the emergence of resistance [1].

Beta-lactams are the molecules of choice for the treatment of bacterial infections. But their systematic and abusive use has led to resistance to these antibiotics. More and more bacteria are becoming resistant to broad-spectrum beta-lactams, such as third and fourth generation cephalosporins (C3G and C4G) and carbapenems [2]. The inappropriate use of antibiotics for prophylaxis varies between 40% to 75%, depending on the various studies, and 30% to 75% of patients with pulmonary infiltrates receive antibiotics for a non-infectious cause [3] [4] [5]. The link between the use of antibiotics and the emergence of bacterial resistance is clear: the indiscriminate use of antibiotics promotes the emergence of bacterial resistance [1].

Hospital practitioners must increasingly face the problem of the treatment of infections with methicillin-resistant *Staphylococcus aureus* (MRSA) and of reduced sensitivity to glycopeptides (GISA), to glycopeptides-resistant enterococci (GRE), to multi-resistant Gram negative bacilli [6].

Some bacteria have become multi-resistant, highly resistant, even totally resistant to antibiotics [7]. This phenomenon, which is constantly increasing, often places physicians in a therapeutic impasse, having as consequences an increase in the duration of hospital stay and a higher cost of hospitalization. Antimicrobial resistance has become a public health problem worldwide.

Knowledge of the epidemiology of infection and antibiotic resistance patterns

is essential to guide optimal empirical treatment in critically ill patients. Antimicrobial susceptibility patterns and bacterial spectra vary geographically, highlighting the importance of local surveillance data [8]. In industrialized countries, these data are available at regional, national and international levels, as shown by the database of the European surveillance system for antimicrobial resistance [9]. In intermediate countries, such as Latin America [10] and Asia [11] [12], good quality data also exist. However, epidemiological data are scarce in Africa, particularly in Central Africa [13] [14].

In Gabon, there are poor data on the epidemiology of resistance at a national level, despite some studies on antimicrobial resistance [2] [8] [15] [16].

Based on these observations and background, we propose for the first time to conduct a prospective study in the main cities of Gabon, outlining a national map of the prevalence of bacterial resistance to antibiotics.

2. Materials and Methods

2.1. Settings

This is a multicenter prospective study carried out over a period of 27 months (from January 2016 to March 2018) in hospitals in seven main cities of Gabon. The samples were taken from:

- Libreville at the Hôpital d'Instruction des Armées Omar Bongo Ondimba (HIAOBO), the Hôpital d'Instruction des Armées d'Akanda (HIAA) and the Polyclinique El RAPHA (PER);
- Lambaréné at the Centre Hospitalier Régional Georges Rawiri (CHRGR);
- Mouila at the Centre Hospitalier Régional de Mouila (CHREM);
- Tchibanga at the Centre Hospitalier Régional Benjamin Ngoubou (CHRBN);
- Franceville at the medical analysis laboratory of the Centre Interdisciplinaire de Recherches Médicales de Franceville (CIRMF);
- Koulamoutou at the Centre Hospitalier Régional Paul Moukambi (CHRPM);
- Makokou at the Centre Hospitalier Régional Omar Bongo Ondimba (CHROBO) (**Figure 1**).

2.2. Inclusion and Exclusion Criteria

The aim of our study was to carry out analysis on all types of biological samples from patients of both sexes, hospitalized or ambulatory, and anal swabs from inpatients were intended for research of the carriage of multi-resistant bacteria (MRB). Samples for research of mycobacteria, chlamydia or mycoplasma were excluded from this study.

2.3. Samples

The samples were all types intended for bacteriological analysis, and meeting the inclusion criteria defined above. They were from inpatients or outpatients of all ages and both sexes. Only the urine samples were stored at 4˚C for possible deferred analysis if necessary. All other samples were analyzed upon receipt at the

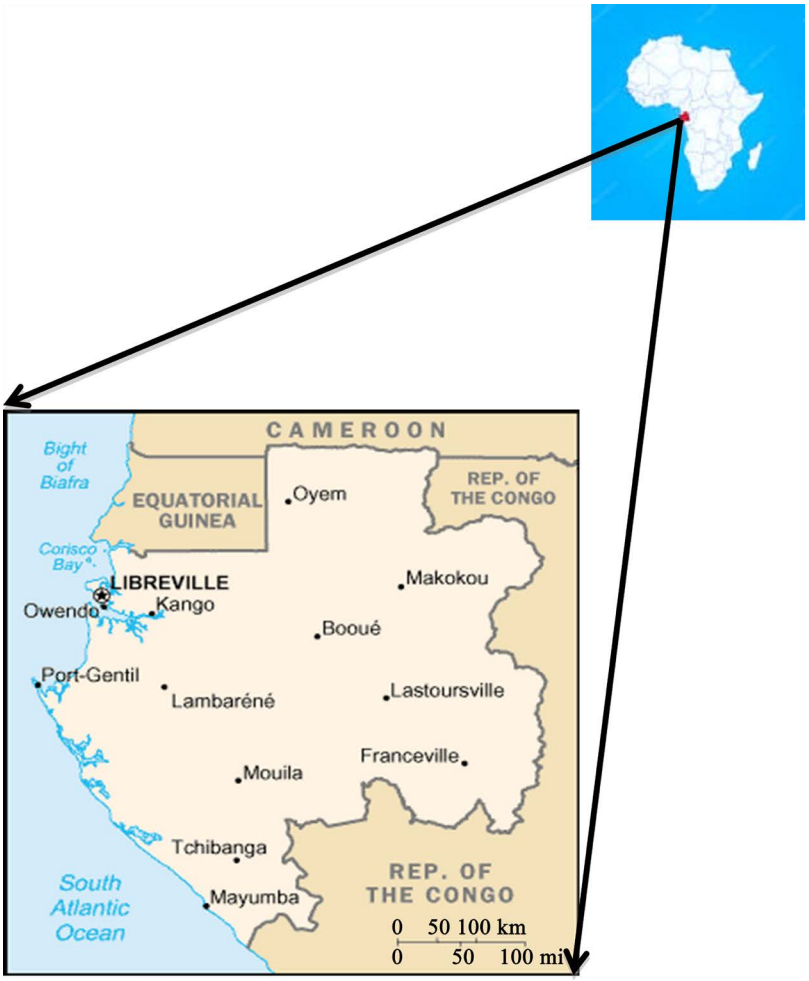


Figure 1. Location of main cities in Gabon [47].

laboratory. Samples were collected according to protocols commonly used, specific to each type distributed to all hospital departments. They were sent to the laboratory according to these protocols. During the same period, in order to research the carriage of multi-resistant bacteria, anal swabs were collected from hospitalized patients for more than 48 hours without digestive pathology.

2.4. Isolation of Bacterial Strains

The samples were seeded on specific solid culture media (chocolate + polyvitex agar, Columbia + sheep blood agar, BCP (Bromo-cresol-purple) agar, EMB (eosin methylene blue) agar, mac Conkey agar, blood + ANC (nalidixic acid-colistin) agar, SS (Salmonella-Shigella) agar, Hektoen agar according to the type of sample and/or the suspected species. The petri dishes were incubated 24 to 48 hours at 37˚C under an atmosphere of 10% CO_2 for the isolation of anaerobic species, and in aerobic conditions for the others.

The choice of culture media was made according to the type of sampling:

- Pus, puncture fluids: blood enriched media (fresh, chocolate), selective media (Chapman).

- Blood: liquid media (blood culture bottles), enriched media for a subculture (fresh blood agar, chocolate).
- Bronchial aspirations and Protected distal samples: blood enriched media (fresh, chocolate), selective media (Chapman; EMB, Mac Conkey).
- Urine: selective medium (EMB, Mac Conkey), multi-purpose medium for Gram positive and Gram negative bacteria (CLED, Uriline®).
- Faeces (coproculture): selective media (EMB and SS for enterobacteria such as Salmonella and Shigella), sometimes Chapman for staphylococci.
- Anal swabs: selective media (BLSE medium, chromID® CARBA SMART).

2.5. Identification and Antimicrobial Susceptibility Testing

The suspicious colonies were identified by the Api staph, Api 20E and Api 20NE systems and by the Vitek 2 compact automated system (BioMérieux, Marcy-l'Etoile, France).

The antimicrobial susceptibility testings were performed by the Vitek 2 compact.

The confirmation of identifications was carried out by Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) Mass Spectrometry (Bruker Daltonics, Bremen, Germany) at the bacteriology laboratory of Arnaud de Villeneuve hospital in Montpellier. All the antimicrobial susceptibility testings were confirmed by the Kirby-Bauer disc diffusion method, using Sirscan discs (i2a, Pérols cedex, France). Measurement of the inhibition zone diameters was performed on "Sirscan automatic" zone reader (i2a, Pérols cedex, France). The interpretation of the antibiogram results was performed according to the recommendations of the Antibiogram Committee of the French Society for Microbiology (CA-SFM) [17].

2.6. Search for Extended Spectrum Beta Lactamases (ESBL)

Research for ESBL was based on the highlighting of a synergy between a disc of C3G (cefotaxime, ceftazidime) and/or aztreonam, and a disc of amoxicillin (or ticarcillin) + clavulanic acid. The discs were arranged equidistant from 3 cm center to center.

The appearance of a characteristic image of synergy between the discs, also called "champagne cork", indicated the occurrence of an ESBL (double disc synergy method) [18].

Since the synergy can be masked in cephalosporinase hyper-producing isolates, its detection was facilitated by bringing together the cefepime and/or aztreonam discs with that containing clavulanic acid, or by performing the double-disk synergy test using cloxacillin-supplemented medium (250 mg/L).

2.7. Carbapenem Resistance Assessment

If the inhibition zone diameter was less than the susceptibility breakpoint around

an Imipenem disc (17 mm), Ertapenem disc (22 mm), Meropenem disc (16 mm) (CA-SFM 2019), the minimum inhibitory concentration (MIC) was performed using an E-test strip (Liofilchem Diagnostici, Roseto degli Abuzzi, Italy). Rapid Carba NP® test [19] was performed when MIC less than 0, 5; 4 and 8 respectively, for ertapenem, imipenem and meropenem (CA-SFM 2019), as confirmation of carbapenemase-producing strains [17].

2.8. Detection of Methicillin-Resistant Staphylococci

The research for methicillin resistance was performed by bringing a disc of cefoxitin (30 µg) into contact with a standard bacterial inoculum of 0.5 Mac-Farland. An inhibition zone diameter less than 22 mm (CA-SFM 2019) indicated oxacillin resistance's, and the strain was called methicillin-resistant *Staphylococcus aureus* (MRSA) [17].

2.9. Glycopeptide Resistance Assessment

The research for resistance to glycopeptides of *Staphylococcus aureus* strains was carried out exclusively by the Vitek 2 compact automated system on one hand.

On the other hand, the measurement and interpretation of the inhibition zone diameters made it possible to detect the presence or not of *Enterococcus* strains of the vanA phenotype (resistant to teicoplanin and vancomycin), and/or vanB phenotype (resistant to vancomycin).

2.10. Search for Associated Resistances

For all ESBL-producing Enterobacteriaceae (ESBL-PE), carbapenem-resistant bacterial strains IMP-R (imipenem-resistant) and ETP-R (ertapenem-resistant), and Methicillin-Resistant *Staphylococcus aureus* (MRSA), the resistance to other antibiotics such as quinolones, aminoglycosides and β-lactams have been sought by performing antimicrobial susceptibility testing such as defined above.

2.11. Statistics

Statistical analysis was performed using R software.

We compared different parameters using the Chi-square (χ^2) method.

Differences were considered statistically significant at 0.05 confidence level.

2.12. Ethics Approval

This study was approved by the hospital ethics committee for biomedical research and by the Gabonese Staff of military health service (No 00000228/MDN/DGSSM/DCP).

All methods were performed in accordance with the relevant guidelines and regulations.

Informed consent was waived by the hospital ethics committee for biomedical research and by the Gabonese Staff of military health service.

3. Results

3.1. Socio-Demographic

Table 1 showed the origin of the different samples. The results showed that urine: 3640/6034 (60.33%) was the most representative, followed by vaginal swabs 954/6034 (15.81%), blood, urinary catheters and stool respectively 5.55%, 5.17% and 3.80%. The other samples constitute 9.35%.

The average age of the patients was 39.70 years (the youngest was 5 days old and the oldest was 78 years old). These results also pointed out that the rate of male patients (45.94%) was lower than that of female patients (54.06%) ($p < 0.05$). While the rate of inpatients 4012/6034 (66.5%) was higher than that of outpatients 2022/6034 (33.5%) ($p < 0.05$).

3.2. Identification and Abundance

Table 2 and Table 3 showed that 974 pathogenic bacterial strains belonging to 19 different species were identified. Gram-negative bacilli (Enterobacteriaceae, Acinetobacter, Pseudomonas) were more representative 890/974 (91.38%) compared to Gram-positive cocci.

Among the 974 isolates, the following were distinguished:

- 896 clinical isolates (including 712 Enterobacteriaceae) were identified from pathogenic samples (infectious process).
- 78 enterobacteriaceae (non pathogenic) isolated from anal swabs coming from hospitalized patients (colonizing organism).

Table 1. Distribution of samples by sex and patient category.

Types of samples	Men n (%)	Women n (%)	p-value	Inpatients N (%)	Outpatients N (%)	p-value	TOTAL
Urine	1984 (32.88)	1656 (27.45)	<0.001	2720 (45.08)	920 (15.25)	<0.001	3640 (60.33)
Vaginal swabs	-	954 (15.81)		12 (0.20)	942 (15.61)	<0.001	954 (15.81)
Tools	100 (1.66)	129 (2.14)	<0.001	79 (1.31)	150 (2.48)	<0.001	229 (3.79)
Bronchial aspirations	20 (0.33)	35 (0.58)	0.059	55 (0.91)	-		55 (0.91)
Protected distal sample	40 (0.66)	50 (0.83)	0.345	90 (1.49)	-		90 (1.49)
Pus	30 (0.50)	32 (0.53)	0.8997	52 (0.87)	10 (0.16)	<0.001	62 (1.03)
Central venous catheter	23 (0.38)	18 (0.30)	0.53	41 (0.68)	-		41 (0.68)
Bedsore	20 (0.33)	40 (0.66)	0.014	60 (1.00)	-		60 (1.00)
Anal swabs	50 (0.83)	28 (0.46)	0.018	78 (1.29)	-		78 (1.29)
Blood	100 (1.66)	235 (3.89)	<0.001	335 (5.55)	-		335 (5.55)
Redon	65 (1.08)	-		65 (1.08)	-		65 (1.08)
Intubation catheter	80 (1.32)	33 (0.55)	<0.001	113 (1.87)	-		113 (1.87)
Urinary catheter	260 (4.31)	52 (0.86)	<0.001	312 (5.17)	-		312 (5.17)
TOTAL	2772 (45.94)	3262 (54.06)	<0.001	4012 (66.5)	2022 (33.5)	<0.001	6034 (100)

n = number.

Table 2. Antibiotic resistance rates (in percentage) of Gram-negative bacilli (Enterobacteriaceae, Pseudomonas, Acinetobacter).

Antibiotics	*Acinetobacter baumanii* (*n* = 68)	*Pseudomonas aeruginosa* (*n* = 32)	*Citrobacter freundii* (*n* = 18)	*Citrobacter Koseri* (*n* = 10)	*Citrobacter sedlakii* (*n* = 4)	*Enterobacter cloacae* (*n* = 106)	*Escherichia coli* (*n* = 308)	*Klebsiella aerogenes* (*n* = 26)	*Klebsiella pneumoniae* (*n* = 204)	*Leclercia adecarboxylata* (*n* = 3)	*Morganella morganii* (*n* = 45)	*Proteus mirabilis* (*n* = 65)	*Salmonella spp* (*n* = 1)
TEM	-	-	0	0	0	1	3.5	4	5.5	0	0	0	0
AMC	-	-	5.5	8	25	19	15.5	4	22	0	4.5	1.5	0
FOX	21	-	6	1	25	19	7.5	4	10	0	2.5	0	0
CTX	21	-	2	0	25	12.5	15.5	4	20	0	2.5	3	0
CAZ	6	4.5	0	0	25	13	15	4	20	0	0	3	0
FEP	10.5	9	0	2	25	10.5	14.5	0	18.5	0	2.5	3	0
ATM	-	5.5	1	0	25	10.5	13.5	4	18.5	0	0	3	0
TZP	16.5	0	0	0	25	7.5	11	4	15	0	0	0	0
ESBL	0	0	0	0	25	10.5	14	0	18.5	0	2.5	3	0
HCASE	5	0	0	0	0	3	2	0	5	0	0	0	0
IMP	10.5	0	0	0	0	1	1	0	1.5	0	0	0	0
ETP	-	-	0	0	0	2	1	0	4	0	0	0	0
MIC IMP > 2	9	0	0	0	0	1	1	0	1.5	0	0	0	0
MIC ETP > 0.5	-	-	0	0	0	1	1	0	4	0	0	0	0
GEN	19	8	0	2	25	10.5	8.5	0	16	0	4.5	4.5	0
TOB	16	6	0	2	25	10.5	12.5	0	16	0	4.5	3	0
NET	-	-	0	0	25	10.5	11.5	0	13	0	0	3	0
AK	7.5	4	6	0	0	1	4.5	0	1.5	0	0	3	0
NA	-	-	8	4	25	12.5	19	0	17	0	4.5	4.5	0
OFX	-	-	8	0	25	12.5	18.5	0	17	0	4.5	4.5	0
CIP	19	10	8	0	25	11.5	17.5	0	16	0	4.5	4.5	0
LEV	19	10	4	0	0	7.5	16	0	15	0	4.5	4.5	0
SXT	16	-	2	0	25	14	20	0	18	0	4.5	4.5	0

TEM: temocillin; AMC: amoxicillin + clavulanic acid; FOX: cefoxitin; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; ATM: aztreonam; TZP: piperacillin + tazobactam; ESBL: extended-spectrum beta lactamase; HCASE: hyperproduced cephalosporinase; IMP: imipenem; ETP: ertapenem; MIC: minimum inhibitory concentration; GEN: gentamicin; TOB: tobramycin; NET: netilmicin; AK: amikacin; NA: nalidixic acid; OFX: ofloxacin; CIP: ciprofloxacin; LEV: levofloxacin; SXT: trimethoprim+sulfamethoxazole. n = number.

Results of specific abundance showed that in Gram-negative bacilli, *Escherichia coli* (34.61%) was the most frequently isolated, followed by *Klebsiella pneumoniae* (22.92%). While the moderately isolated species were *Enterobacter Cloacae* (11.91%), *Acinetobacter baumanii* (7.64%), and *Proteus mirabilis* (7.30%).

Table 3. Antibiotic resistance rates (in percentage) of Gram-positive cocci (Staphylococcus, Streptococcus, Enterococcus).

Antibiotics	*Staphylococcus aureus* (*n* = 35)	*Staphylococcus haemolyticus* (*n* = 10)	*Staphylococcu sciuri* (*n* =9)	*Streptococcus agalactiae* (*n* =16)	*Enterococcus faecalis* (*n* =8)	*Enterococcus Faecium* (*n* = 6)
AM	-	-	-	0	33,5	33,5
P	100	-	-	-	-	-
PIP	100	30	11	0	33,5	33,5
FOX	16	30	11	-	-	-
AMC	16	30	11	-	-	-
CTX	16	30	11	0	-	-
IMP	16	30	11	0	0	33,5
GEN	18	30	0	15	-	-
KAN	-	-	-	15	-	-
TOB	15	30	0	15	-	-
AK	15	30	0	15	-	-
TE	33	30	2	25	-	-
ERY	13	20	0	50	100	0
LIN	13	20	0	50	100	-
OFX	10	30	4	-	-	-
NOR	-	-	-	10	12,5	17
LEV	-	-	-	10	0	0
SXT	6	30	11	5	-	-
RA	2	20	0	20	37,5	33,5
VA	0	0	0	0	0	0
TEC	0	0	0	0	0	0
FOS	0	0	0	0	0	0

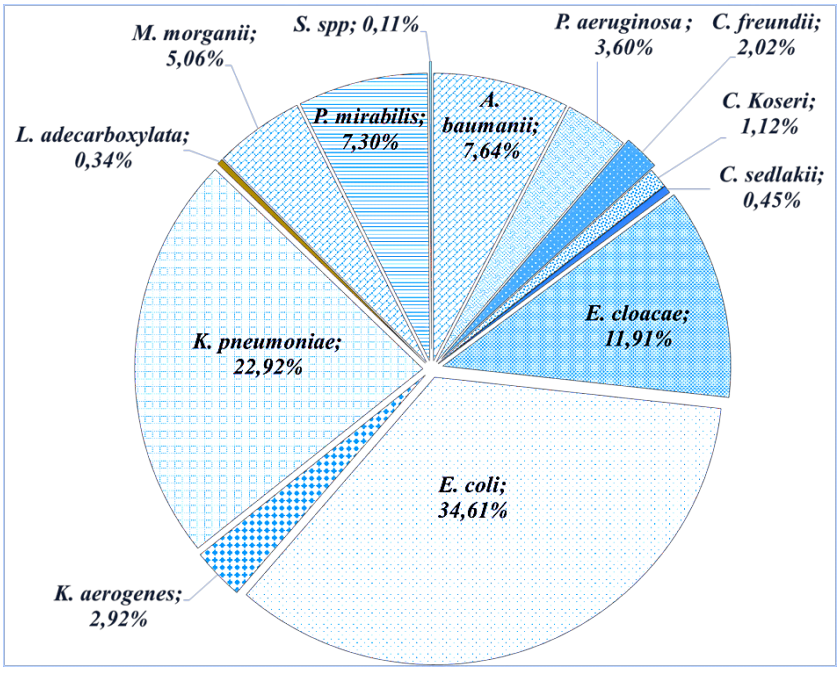
AM: Ampicillin; P: penicillin; PIP: piperacillin; FOX: cefoxitin; AMC: amoxicillin + clavulanic acid; CTX: cefotaxime; IMP: imipenem; GEN: gentamicin; KAN: Kanamycin; TOB: tobramycin; NET: netilmicin; AK: amikacin; TE: tetracycline; ERY: erythromycin; LIN: lincomycin; OFX: ofloxacin; NOR: norfloxacin; LEV: levofloxacin; SXT: trimthoprim + sulfamethoxazole; RA: rifampicin; VA: vancomycin; TEC: teicoplanin; FOS: fosfomycin. n = number.

Finally, the weakly found were *Morganella morganii* (5.06%), *Pseudomonas aeruginosa* (3.6%), *Klebsiella aerogenes* (2.92%), *Citrobacter freundii* (2.02%), *Citrobacter koseri* (1.12%), *Citrobacter sedlakii* (0.45%), *Leclercia adecarboxylata* (0.34%) and *Salmonella spp* (0.11%) (Figure 2(a)).

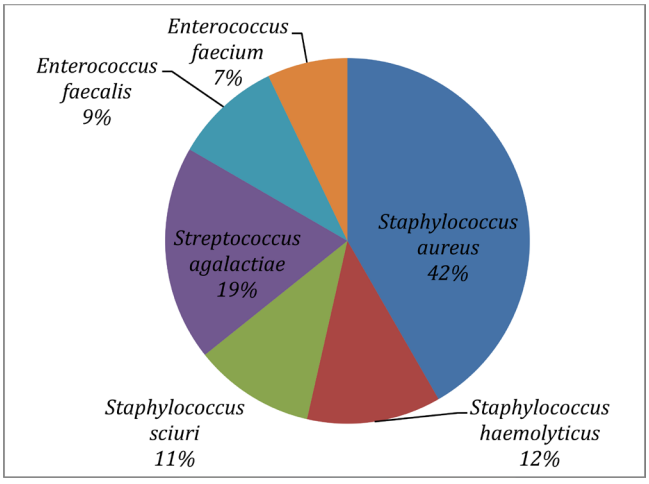
In Gram-positive cocci, *Staphylococcus aureus* (42%) was the most representative species, followed by *Streptococcus agalactiae* (19%), *Staphylococcus haemolyticus* (12%), *Staphylococcus sciuri* (11%), *Enterococcus faecalis* (9%), and *Enterococcus faecium* (7%) (Figure 2(b)).

3.3. Antibiotic Resistance Profile

The results in Table 2 revealed that *Acinectobacter baumanii* had a low resistance rate to ceftazidime (CAZ 6%), amikacin (AK 7.5%), cefepime (FEP 10.5%)



(a)



(b)

Figure 2. (a) Specific abundance of Gram-negative bacterial species; (b) specific abundance of Gram-positive bacterial species.

and imipenem (IMP 10.5%). However, they showed moderate resistance of 16% to tobramycin (TOB) and cotrimoxazole (SXT), 16.5% to piperacillin + tazobactam (TZP), 19% to gentamicin (GEN), ciprofloxacin (CIP) and levofloxacin (LEV), 21% to cefoxitin (FOX) and cefotaxime (CTX).

Pseudomonas aeruginosa had a low resistance rate to AK (4%), CAZ (4.5%), aztreonam (ATM 5.5%), TOB (6%), GEN (8%), and 10% for CIP and LEV.

Citrobacter freundii had a low resistance rate to ATM (1%), CTX (2%), SXT (2%), LEV (4%), AMC (5%), FOX (6%) and 8% respectively to nalidixic acid (NA), ofloxacin (OFX) and CIP. In addition, our study showed that the *Citrobacter sedlakii* had a mean resistance rate of 25% for each antibiotic tested. The

results also revealed that *Leclercia adecarboxylata* and *Salmonella spp* strains were all susceptible to all antibiotics tested in this study. The *Klebsiella* species exhibited different behaviors. Indeed, our study pointed out that *Klebsiella aerogenes* had low resistance to temocillin (TEM), AMC, FOX, CTX, CAZ, ATM, TZP, respectively 4%. While *Klebsiella pneumoniae (Kp)* had low resistance to IMP (1.5%), ETP (4%), TEM (5.5%), AMC (10%) and NET (13 %). On the other hand, they presented resistance rates of 15% to AK, LEV and TZP, 16% to CIP, GEN and TOB, 17% to NA and OFX, 18% to SXT, 18.5% to FEP and ATM, 20% to CTX and CAZ, and 22% to FOX. The behavior of *Escherichia coli* for antibiotics tested was also variable.

It had low resistance to IMP (1%), ETP (1%), TEM (3.5%), AK (4.2%), FOX (7.5 %), GEN (8.5%), NET (11.5%), TOB (12.5%) and ATM (13.5%), while it had mean resistance rates of 14.5% to FEP, 15% to CAZ, 15.5% to CTX and AMC, 16% to LEV, 17.5% to CIP, 18.5% to OFX, 19% to NA and 20% to SXT. Finally, low rates of antibiotic resistance were established for *Morganella morganii* and *Proteus mirabilis* (Table 2).

Also, these results showed that the rates of extended-spectrum beta-lactamases (ESBL) were 2.5%, 10.5%, 14%, 18.5% and 25%, respectively, for *Morganella morganii*, *Enterobacter cloacae*, *E. coli*, *Kp*, and *Citrobacter sedlakii*. They also suggested hyperproduction rates of cephalosporinases of 5%, 3%, and 2% respectively for *Acinetobacter baumanii* and *Kp*, *Enterobacter cloacae*, *E. coli.*

The resistance rates of Gram-positive cocci are shown in Table 3.

The analysis of these rates reveals variable behavior of Gram-positive cocci. In fact, *S. aureus* were completely resistant to penicillin (100%) and piperacillin (100%), but they exhibited mean resistance to lincomycin (LIN) and erythromycin (ERY) (13%), TOB and AK (15%), IMP, CTX, AMC and FOX (16%), GEN (18%) and tetracycline (33%). However, they had low resistance to SXT (6%), OFX (10%). In contrast, the *Staphylococcus haemolyticus* strains all had mean resistance rates of 20% to rifampicin (RA), LIN and ERY, 30% to PIP, FOX, AMC, CTX, IMP, TOB, AK, tetracycline (TE), OFX and SXT. *Staphylococcus sciuri* had low rates of resistance to TE (2%), OFX (4%), PIP, FOX, AMC, CTX, IMP and SXT (11 % each). *Streptococcus agalactiae* were highly resistant to ERY (50%), LIN (50%), moderately resistant to TE (25%), RA (20%), GEN, kanamycin (KAN), TOB and AK (15%), and weakly resistant to norfloxacin (NOR) and LEV (10%), and SXT (5%).

The study also revealed high resistance rates of *Enterococcus faecalis* to ERY (100%), LIN (100%). They were moderate for RA (37.5%), ampicillin (AM 33.5%), PIP (33.5%), and low for NOR (12.5%).

Finally, the *Enterococcus faecium* strains showed moderate resistance rates for AM (33.5%), PIP (33.5%), IMP (33.5%), RA (33.5%), and NOR (17%).

Table 4 showed the antimicrobial susceptibility rates (β-lactams, quinolones and aminoglycosides) of enterobacteriaceae of carriage (colonizing organisms) and clinical enterobacteriaceae (pathogens causing infections). Apart from im-

ipenem (p = 0.044), all other antibiotics showed no statistically significant difference in antimicrobial susceptibility (p > 0.05) between the two subgroups.

Table 5 showed different rates of resistance to aminoglycosides, quinolones and ß-lactam antibiotics of MRSA, ESBL-PE and carbapenem-resistant enterobacteria (IMP and ETP) (associated resistances).

Thus, 50% of MRSA were resistant to GEN, TOB, and AK, 66.7% to OFX.

75% of ESBL-PE were resistant to GEN and NET, 86.5% to TOB, 17.7% to AK, 91.7% to NA, 90.6% to OFX, 87.5% to CIP, and 79.2% to LEV.

21.4% of enterobacteriaceae resistant to carbapenems were also resistant to GEN, 28.6% to TOB and NET, 7.1% to AK, 42.9% to NA, OFX, CIP and TZP, 35.7% to LEV, FOX, CTX, and CAZ.

23.1% of enterobacteriaceae were resistant to GEN, 30.8% to TOB and NET, 7.7% to AK, 46.2% to NA, OFX, CIP and TZP, 38.5% to LEV, FOX, CTX, and CAZ.

4. Discussion

Our study revealed a high predominance of urine among all types of samples. This is in line with previous studies which established that urinary tract infections are among the most common bacterial infections contracted in the community and in

Table 4. Antibiotic resistance rates (in percentage) of clinical enteriobacteriaceae vs enterobacteriaceae of carriage.

	β-lactams													Quinolones			Aminoglycosides	
Antibiotics	**AM**	**TIC**	**PIP**	**AMC**	**TZP**	**CF**	**FOX**	**CAZ**	**FEP**	**ATM**	**CTX**	**IMP**	**ERT**	**NA**	**OFX**	**LVX**	**GEN**	**TOB**
Enterobacteriaceae of carriage (n = 78)	24.36	24.36	24.36	24.36	18	24.36	14.1	21.8	20.5	18	24.36	3.8	6.4	24.36	24.36	20.5	21.8	23.1
Clinical Enterobacteriaceae (n = 712)	18.7	18.4	17.7	18.5	14.3	16	12.9	16.7	14.9	13.3	16.7	8.1	13.5	17.1	18.5	14.3	17.3	17.4
p-value	0.41	0.37	0.31	0.39	0.57	0.17	0.93	0.44	0.34	0.42	0.21	0.044	0.15	0.25	0.39	0.28	0.51	0.39

n = number. AM: ampicillin; TIC: ticarcillin; PIP: piperacillin; AMC: amoxicillin + clavulanic acid; TZP: piperacillin + tazobactam; CF: cefalotin; FOX: cefoxitin; CAZ: ceftazidime; FEP: cefepime; ATM: aztreonam; CTX: cefotaxime; IMP: imipenem; ERT: ertapenem; NA: nalidixic acid; OFX: ofloxacin; LVX: levofloxacin; GEN: gentamicin; TOB: tobramycin.

Table 5. Associated resistances rates.

Antibiotics	**Aminoglycosides**				**Quinolones**				***β*-lactams**			
	GEN n (%)	**TOB n (%)**	**NET n (%)**	**AK n (%)**	**NA n (%)**	**OFX n (%)**	**CIP n (%)**	**LEV n (%)**	**FOX n (%)**	**CTX n (%)**	**CAZ n (%)**	**TZP n (%)**
ESBL-PE (n = 96)	72 (75)	83 (86.5)	72 (75)	17 (17.7)	88 (91.7)	87 (90.6)	84 (87.5)	76 (79.2)	-	-	-	-
IMP-R (n = 14)	3 (21.4)	4 (28.6)	4 (28.6)	1 (7.1)	6 (42.9)	6 (42.9)	6 (42.9)	5 (35.7)	5 (35.7)	5 (35.7)	5 (35.7)	6 (42.9)
ETP-R (n = 13)	3 (23.1)	4 (30.8)	4 (30.8)	1 (7.7)	6 (46.2)	6 (46.2)	6 (46.2)	5 (38.5)	5 (38.5)	5 (38.5)	5 (38.5)	6 (46.2)
MRSA (n = 6)	3 (50)	3 (50)	-	3 (50)	-	4 (66.7)	-	-	-	-	-	-

GEN: gentamicin; TOB: tobramycin; NET: netilmicin; AK: amikacin; NA: nalidixic acid; OFX: ofloxacin; CIP: ciprofloxacin; LEV: levofloxacin; FOX: cefoxitin; CTX: cefotaxime; CAZ: ceftazidime; TZP: piperacillin + tazobactam; IMP-R: imipene-resistant; ETP-R: ertapenem-resistant; ESBL-PE: extended-spectrum beta-lactamase producing enterobacteriaceae; MRSA: methicillin resistant *Staphylococcus aureus.* n = number.

hospitals [20] [21] [22].

In regard to specific abundance, *E. coli* (34.67%) for Gram-negative bacilli, and *S. aureus* (42%) for Gram-positive cocci, were the most representative species.

These proportions corroborate those of Rerambya *et al.* at the Libreville national public health laboratory [23]. Indeed, the endogenous origin (that is to say coming from the patient himself) of most of the bacteria responsible for the urinary tract infections, places these two species, frequently encountered in the digestive tract, as the most potentially uro-pathogenic [24]. In addition, a study carried out by Guibert *et al.* established that *E. coli* is responsible for 80% to 85% of cystitis [25].

According to the EARS-Net (European Antimicrobial Resistance Surveillance Network) data for 2019, our study revealed variations in the occurrence of antimicrobial resistance across the country depending on the bacterial species and antimicrobial group.

Beta-lactam antibiotics are the treatment of choice for infections caused by Gram-negative bacilli. However, we can increasingly note high resistance rates of these bacteria to beta-lactam antibiotics such as third and fourth generation cephalosporins (C3G and C4G) and carbapenems.

In this study, the resistance rate of *E. coli* to CAZ (C3G) was higher than that observed by K. Rerambiah *et al.* at the Libreville national laboratory [23].

In the same line with our results, a study carried out in Senegal on infections caused by enterobacteriaceae also showed that the main ESBL-producing enterobacteriaceae (ESBL-PE) were *Enterobacter cloacae*, *E. coli*, *Kp* [26].

The ESBL rates revealed by our study (2.5% to 25%) were in the same proportions as those observed by A. S. Alabi *et al.* who established an ESBL production of 13.2% to 18.9% at the Albert Schweitzer hospital in Lambaréné (Gabon) between 2009 and 2012 [8].

Yala *et al.* also revealed, using the combined disc method, an ESBL rate of 18% at the Hôpital d'Instruction des Armées Omar BONGO ONDIMBA of Libreville [2]. With respectively 44% and 22.4%, the ESBL-producing *Kp* rates observed in Latin America and in Pacific Asia were higher than those of our study, which are themselves higher than in Europe (13.3%) and North America (7.5%) [27] [28].

The cephalosporinase hyperproduction rates that we established remained low (2% to 5%). These rates were similar to those observed by De Mouy *et al.* in a multicenter study in France [29].

The high-level cephalosporinase resistance phenotype results in resistance to all beta-lactams, except carbapenems. There may remain an activity of broad spectrum cephalosporins (cefepime, cefpirome). This is a phenotype found mainly in bacteria naturally having an ampC cephalosporinase which can be overexpressed (*Enterobacter cloacae*, *Citrobacter freundii*, *Escherichia coli*, *Morganella morganii,* other enterobacteriaceae in the same group) [30].

Resistance to carbapenems suggested the emergence of a production of car-

bapenemases by germs, although additional phenotypic and molecular tests remained to be confirmed. This resistance leads to therapeutic impasses in patients, since carbapenems remain the last indication in the event of ESBL [31].

In Gabon, apart from a study by Moussounda *et al.* who observed the fecal carriage of carbapenemases in a patient hospitalized at HIAOBO [15], very little data exist on this problem. However, Mahamat *et al.* observed in three main hospitals in N'djamena (Chad), respective prevalence rates of 2.5% and 6.5% in carbapenemase-producing clinical strains and carbapenemase-producing faecal carriage strains [32].

Regarding to the prevalence of MRSA, similar results to those of our study (16%) were observed in Tunisia by Mastouri *et al.* (15.5% of MRSA at Monastir University Hospital), with the same resistance rate to gentamicin (18%) [33]. However, our study revealed a higher prevalence of MRSA than that observed by Alabi *et al.* (5.8%) in a retrospective analysis of antimicrobial resistance at the Albert Schweitzer hospital in Lambaréné (Gabon) [8].

Resistance to glycopeptides does not yet seem to be a real concern in hospitals in Gabon, since our results confirmed a global trend, even if studies had reported the existence of MRSA with reduced susceptibility to glycopeptides (GISA) [34] [35].

The analysis of their resistance to antibiotics in this study confirmed the multi-resistant nature of MRSA, usually known for their ability to resist several antibiotics [36].

Unlike K. Rerambiah *et al.* [23], *Streptococcus agalactiae* were all susceptible to beta-lactam antibiotics. This should support physicians in the option of penicillins, or even first-generation cephalosporins, as first choice in antibiotic therapy for streptococci infections. Caution should however be exercised in the choice of macrolides and lincosamides for the treatment of streptococcal infections, given the high rate (50%) of resistance to these antibiotics that we observed.

Compared to streptococci, enterococci were less sensitive to penicillins (33.5% of the resistance rate).

Enterococcus faecalis is naturally resistant to lincosamides. So, the high resistance rate to lincomycin (100%) seemed rather to be a good orientation for identification.

The complete absence of glycopeptide-resistant enterococci (GRE) in our study was a piece of good news because, as with MRSA, glycopeptides are the best therapeutic option for infections caused by beta-lactam-resistant enterococci [37]. While, in Europe, as revealed by the annual (2019) epidemiological report on antimicrobial resistance in the European Union (EU) or Economic European Area (EEA), the percentage of vancomycin-resistant isolates of *Enterococcus faecium* increased from 10.5% in 2015 to 18.3% in 2019.

The first case of vancomycin-resistant *Enterococcus faecium* was described in Europe in 1986 [38] [39] [40]. In 2007 and 2008, three cases of GRE were observed in Algeria [41] [42].

Our study showed no significant difference between the antimicrobial resis-

tance rates of enterobacteriaceae of carriage and clinical enterobacteriaceae ($p > 0.05$). However, it has been shown that colonization is essential to the spread of antimicrobial resistance in the population [43]. A link can therefore be established between the patient's colonization by resistant bacteria and the existence of these resistances among bacteria causing infections.

In addition to being resistant to β-lactam antibiotics, MRSA in this study also was resistant to aminoglycosides and quinolones.

In our study, some ESBL-PE were also resistant to aminoglycosides and fluoroquinolones.

Some carbapenem-resistant Enterobacteriaceae, in addition to being resistant to third-generation cephalosporins, were also resistant to aminoglycosides and fluoroquinolones.

All this points to the multi-resistant nature of MRSA, ESBL-PE and carbapenem-resistant enterobacteria, as demonstrated in previous studies [44] [45] [46]. This multi-resistance often leads to therapeutic impasse, especially for carbapenemase-producing bacteria.

5. Conclusion and Perspectives

This study showed the existing variations, in time and space, on antimicrobial resistance. It has allowed us to confirm the continuous increase of antimicrobial resistance, which implies, by prospective studies, updated knowledge of the prevalence of these resistances. Finally, our study would benefit from being supplemented by molecular analysis of resistant strains, in order to identify and determine a national epidemiology mapping of the various resistance genes in Gabon. So much information is essential for physicians to choose an appropriate antibiotic treatment.

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Authors' Contributions

Conceptualization, R.O., A.C.D. and S.G.; Methodology, A.C.D., L.G.M., B.A.I., and F.K.K. Software, E.M.K.; Formal Analysis, R.O., E.B.N., B.B.M. and A.C.D.; Investigation, A.C.D.; Resources, R.O, S.G and E.M.K.; Writing—Original Draft Preparation, A.C.D.; Writing—Review & Editing, R.O., J.F.Y., SG, E.B.N.; Visualization, R.O. and P.P.M.N.; Supervision, A.C.D. and R.O.; Project Administration, R.O.; Funding Acquisition, R.O., S.G. and A.C.D.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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