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Epidemiology of Nosocomial Bacteremia Due to Bacteria from the "*Burkholderia cepacia* Complex" at Libreville University Hospital Center

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Abstract

Introduction: *Burkholderia cepacia* is a non-fermenting emergent bacterium common in nosocomial infections and can cause life-threatening infections whose multidrug resistance makes them a serious threat in hospitals. The aim of this study was to determine the prevalence of *B. cepacia* infections during nosocomial infections at Libreville University teaching hospital. **Methodology:** In this cross-sectional study, lasting 19 months, 412 blood cultures were analyzed. The BacT/ALERT 3D (Biomerieux, France) was used to detect the positivity of blood culture flasks and the Viteck 2 compact (Biomerieux, France) for the identification of germs and the study of their susceptibility to antibiotics. **Results:** Our study population consisted of 412 patients. The sex-ratio M/F was 1.06 in favor of the male gender (n = 201, 51%). The age of the patients varied between 0 and 82 years. The bacteremia of *B. cepacia* mainly affected children under 15 years of age with a prevalence of 7% (n = 28). The pediatric ward was more represented with a frequency of 36% (n = 10). The antibiotic sensitivity profile showed high resistance of 100% for aminoglycosides (amikacin, tobramycin, and gentamycin), tetracycline, beta-lactams (Amoxicillin, Imipenem, Ticarcillin, Cefoxitin and Cefotaxime), and ciprofloxacin. However, four molecules were active on *B. cepacia* (Levofloxacin 100%, Trimethoprim + sulfamethoxazole 92.3%, ceftazidime 80% and cefepime 35%). **Conclusion:** Ultimately, infection and multi-resistance due

to *Burkholderia cepacia* calls for a review of hospital hygiene in the pediatric ward and a review of antibiotic therapy in young children.

Keywords

Cross Infection, *Burkholderia cepacia*, Bacteremia, Blood Culture Test, Libreville University Hospital Center

1. Introduction

The problem of bacterial infections in hospital care is still topical and remains a major public health problem. The epidemiology of cross Infection according to the World Health Organization (WHO), 2009 showed that an average of 8.7% of hospitalized patients contracts a nosocomial infection. The report found that in the European and Western Pacific regions, the prevalence rate is 7.7% and 9.0%, respectively. This prevalence rate varies between 1.6% and 11% in Gabon [1]. The data suggest that nosocomial infections are widespread in sub-Saharan Africa, with ICU and surgical sites being the most represented. However, the etiologies of nosocomial infections and hospital unit sites are not well known in Gabon [1].

Burkholderia cepacia (*B. cepacia*) has become a major bacterium responsible for isolated nosocomial infections during bacteremia. This bacterium was formerly known as *Pseudomonas cepacia*, a Gram-negative, non-refermentable, multi-resistant aerobic bacillus.

Immunocompromised and hospitalized patients are particularly vulnerable to this bacterium with severe bacteremia leading to death [2]. *B. cepacia* is primarily involved in two groups of infections namely nosocomial infections (bacteremia, respiratory and urinary tract infections), most often occurring in patients subjected to invasive maneuvers (intravenous catheterization, urinary catheterization) and colonization as part of cystic fibrosis, the severity of which is very variable; Those from simple asymptomatic colonization to necrotizing pneumonia, with or without sepsis ("cepacia syndrome") are often fatal [2]. *B. cepacia* is a common bacterium of nosocomial infections that can cause life-threatening infections and that, due to its multidrug resistance, is a serious threat in a hospital setting [3].

Today, emergence of multi-resistance in Gram-negative pathogens (particularly *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, *Acinetobacter* spp. and the Enterobacteriaceae) is the main problem in medicine. In these organisms, three-component multidrug efflux systems play important roles in both intrinsic and acquired multi-resistance [4].

Moreover, in the last decade, along with the problem of nosocomial infections, multidrug-resistant bacteria in community and hospitals have soared. High frequencies of multidrug-resistant bacteria have been grouped under the acronym ESKAPE: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. [5].

The purpose of this cross-sectional study was to determine the prevalence of *B. cepacia* infection at the Libreville University Hospital Center (LUHC), to identify the clinical features associated with it and to present the level of resistance of molecules commonly used in therapy.

2. Methodology

A descriptive 19-month cross-sectional study was conducted from February 2017 to October 2018, based on laboratory surveillance of cases of invasive bacterial infections due to pathogens responsible for bacteremia in the hospitalization departments of the Libreville University Hospital Center.

The study was carried out within Libreville. Libreville is located on the Gabon, a country of Central Africa. Our study population consisted of patients of both sexes and of all ages hospitalized in the different hospital departments of the University Hospital of Libreville and other health facilities of Libreville. We included in this study patients of both sexes and of any age from blood culture vials of the BacT Alert type of Biomerieux referred to the microbiology unit for suspicion of bacteremia. Not included in this work were all outpatient patients and those whose blood culture collection was done in other types of culture media other than Bact Alert vials.

All patients with bacteremia due to *B. cepacia* were included in the study. Patients colonized with *B. cepacia* in sites other than blood were excluded from the study. Data were obtained from blood culture results. Monitoring for nosocomial infection was performed on the basis of patient laboratory records during the study period. The diagnosis of nosocomial infection was made according to WHO criteria. Patient data were collected and analyzed: age, sex, department, length of hospitalization, presence of previous antibiotic treatment, microbiological data and blood culture results. The bacteria were identified using the Vitek 2 Compack technique (Biomérieux).

The antimicrobial susceptibility study of *B. cepacia* clinical isolates was conducted using the Viteck method with a bacterial suspension equivalent to 0.5 McFarland.

The ethics committee's approval for the study was obtained. The analysis of the data was evaluated on the basis of a questionnaire developed. The data was captured and analyzed on Excel software and Epi Info 7 software version 7.1.3.0. The chi2 test was used for statistical analysis of variables. Continuous data were expressed as mean and standard deviation and categorical data were expressed as frequency and percentage.

3. Results

In this study, individual microorganisms were isolated from clinical samples of blood cultures test in 412 patients. The prevalence of *B. cepacia* as an etiological agent was 7% (n = 28) of nosocomial isolates. The data collected showed that 53% (n = 218) of blood cultures test were positive (bacteremia). Table 1 presents

Table 1. Distribution of nosocomial pathogens by departement.

Microorganismes	CARDIO	EXTERNE	GASTRO ENTERO	INFECTIO	MED	NEO NAT	NEURO	PED	REA	URG	Total
A. baumanii				2	3			5			10 (5%)
***Bacillus* spp.**				1	1			2			4 (2%)
***Bacteroides* spp.**								1			1 (0.5%)
B. cepacia					1	2		24		1	28 (13%)
C. freundii					1	1		3	1		6 (3%)
***Corynebacter* spp.**			1	1				1			3 (1%)
***Enterobacter* spp.**	*1*		1	2	1	4		1		1	11 (5%)
E. faecalis						1					1 (0.5%)
E. coli		*2*			8	2		2			14 (6%)
***K. pneumoniae* spp.**	*1*			4	6	9		1	4	2	27 (13%)
***Kocuria* spp.**				1							1 (0.5%)
***Micrococcus* spp.**				2	1	1		2			6 (3%)
***Pantoea* spp.**			1	1		2		15		1	20 (9%)
P. stuortie								1			1 (0.5%)
***Pseudomonas* spp.**					2					1	3 (1%)
Raoultella							1				1 (0.5%)
***Salmonella* spp.**								2			2 (1%)
S. odorifera				1	4	2		6			13 (6%)
***Staphylococcus* spp. (*SCN*)**	*1*		3		8	7		19	4	1	43 (20%)
S. aureus			1	1	6	1	1	6			16 (7%)
S. maltophilia					1	1	1	1			4 (2%)
S. porcinus					1						1 (0.5%)
Total	3 (1%)	2 (1%)	7 (3%)	16 (7%)	44 (20%)	33 (15%)	3 (1%)	92 (43%)	9 (4%)	7 (3%)	216 (100%)

*Departements: Cardiology (CARDIO); Pediatrics (PED); Resuscitation (REA); Gastroenterology (GASTRO-ENTERO); Medicine (MED); Infectious Disease (INFECTIO); Neurology (NEURO); Neonatology (NEO-NAT), Emergency (URG).

the profile of microorganisms that cause nosocomial bacteria. 28 strains of *B. cepacia* were isolated from blood cultures test of which 22 (79%) were male and 6 (21%) were female. The sex-ratio Male/Female was 3.66. The average age was 2.89 3.96 years. The average length of stay in hospital was 15.2 9.9 days (median 15 days). Previous antibiotic use was observed in 381 patients (38.5%).

The majority of *B. cepacia* infections were observed in pediatrics. The most exposed age group is children under one year of age with a frequency of 36% (n = 10). Figure 1 shows the age distribution of *B. cepacia* infection.

The demographic characteristics of patients with *B. cepacia* infection are presented in Table 2. Figure 2 summarizes the antimicrobial susceptibility of *B. cepacia* isolates. The most active antimicrobial agents were trimethoprim + sulfamethoxazole, levofloxacin, ceftazidime and cefidomide.

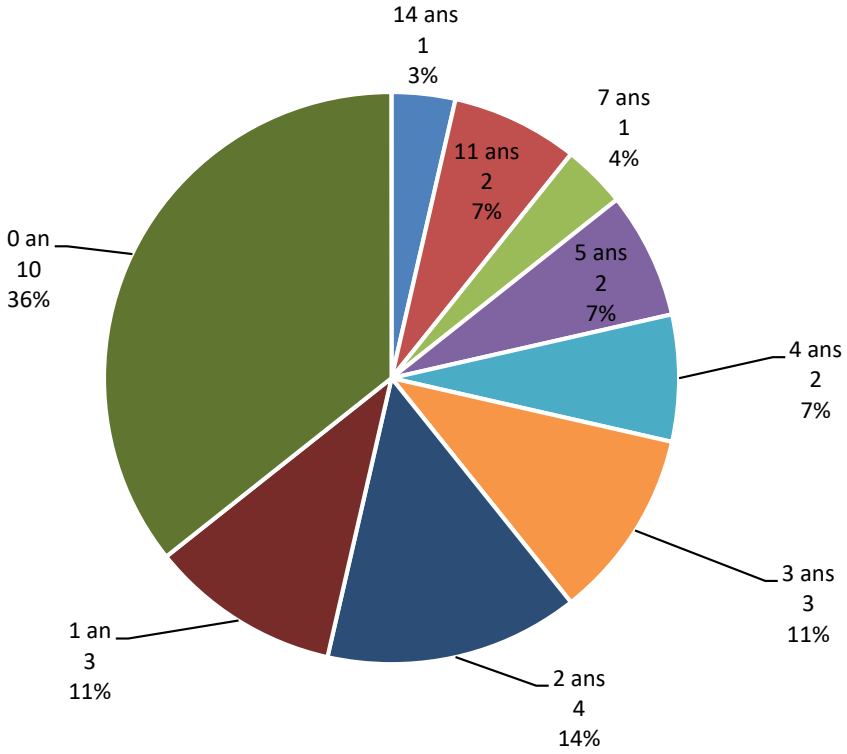

Figure 1. Distribution of *B. cepacia* infection by age group.

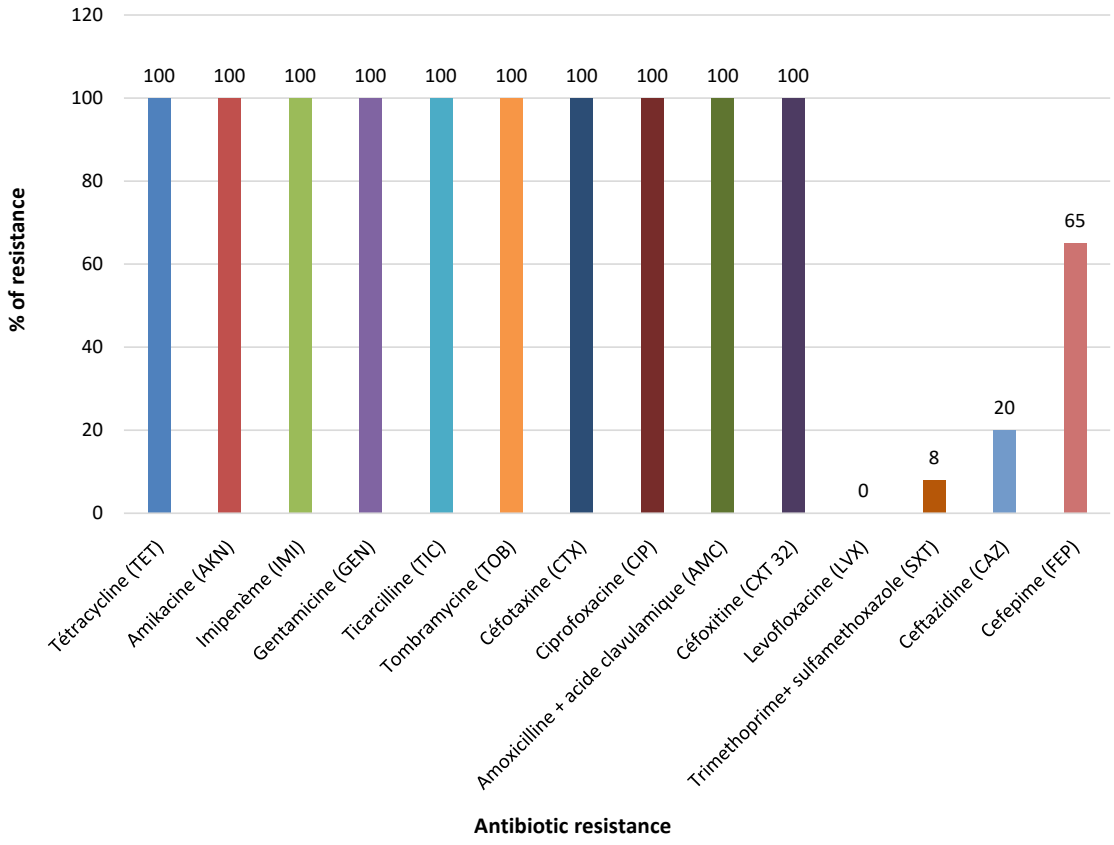

Figure 2. Antibiotic resistance profile (%) of *B. cepacia* isolates.

Table 2. Demographic characteristics of the population with *B. cepacia*.

	B. cepacia	Other bacteria	Sterile culture
Average age	2.89	20.89	23.89
Standard deviation	3.75	22.74	22.44
Minimum	0	0	0
Maximum	14	73	82
Frequence	28 (7%)	188 (46%)	196 (47%)
Sexe			
• **Féminin**	6 (3%)	95 (47%)	101 (50%)
• **Masculin**	22 (11%)	93 (44%)	95 (45%)

4. Discussion

The main findings of the study were indicated: *Burkholderia cepacia* is found mostly in children as adults and in the department with the most inadequate hygiene (paediatrics). *Burkholderia cepacia* is present in patients without cystic fibrosis and without immunosuppression. The antibiotic therapy for paediatric bacteremia treatments should be revised because of the recurrence of *Burkholderia cepacia* in paediatrics and its multi-resistance.

B. cepacia is now considered to be a nosocomial pathogen that causes serious problems in the clinical setting due to its high inter-patient transmissibility and multidrug resistance [6].

B. cepacia has also been recognized, although rarely, as a cause of fatal disease in healthy individuals. This microorganism is associated with a wide variety of infections including pneumonia, bacteremia, skin and soft tissue infections, infection of the genito-tracturinary tract secondary to urethral instrumentation or by exposure to contaminated solutions in hospitalized patients. It is the cause of increased mobility and mortality [7] [8].

The study population consisted of 412 patients of all genders. The average age was 21.09 - 22.39 years. The most affected age group was 0 - 15 years old from pediatrics with a frequency of 55% (N = 228), these children did not have cystic fibrosis. Bacteremia to *B. cepacia* mainly affects children with a frequency of 7% (n = 28) and an average age of 2.89 3.96 years. The risk factors for nosocomial bacteriomial predisposition in paediatrics are: age, length of hospitalization, invasive procedures, parenteral feeding and administration of broad-spectrum antibiotics.

Our hospital data showed that the male gender was more represented (79%, n = 22) than the female gender (21%, n = 6) with a sex-ratio of H/F = 3.66. This result is superimposed on the literature which reported in 46 cases that 30.4% (n = 14) were women and 69.6% (n = 32) were men [9] [10]. However, other studies have reported that there is no difference between the two sexes [2]. Generally speaking, during bacteremia regardless of the germ, sex-ratio is in favor of the male gender. In Rabat one study reported a sex-ratio of 1.25 [11]. Other au-

thors reported a sex-ratio of 1.28 [10]. These differences in humoral immunity exist from birth and are reinforced after puberty by estrogens [12]. The services that have the highest percentage of positive blood cultures at *B. cepacia* are: pediatrics (87%, n = 24), neonatal (10%, n = 3), and pediatric emergencies with 3% (n = 1).

This is not supported by Selçuk Nazik [9] who had the following results: Anesthesia Unit (19.6%, n = 9), Infectious Diseases Unit (17.3%, n = 8) and 13% (n = 6) for the Internal Medicine Intensive Care Unit and Urology Unit. On the other hand, Kyu Yeun Kim [2] found 14 paediatric cases and 35 adults. However, for Paramanantham [13], all subjects came from the neonatal department.

All these results are disparate from one study to another. These results can be explained by the difference in recruitment in the structures, the delays in the delivery of samples but also and especially by the misuse of antibiotics in self-medication [14]. In the study a total of 212 positive blood cultures (53%) were obtained. This is much higher than data from other studies such as the study conducted in Rabat by Benzriouil [9], which found a frequency of 21%, Michael Osthoff [15], in Switzerland found a frequency of 6% - 10% and Boukerouaz Amel [12] found a frequency of 31%. These variations may be related to the heterogeneity of the different hospital departments and the indications for blood cultures. This high bacteremia would certainly be due to blood culture contamination or improper sampling, hence the large number of negative coagulase staphylococcus isolated in our study.

The overall bacteriological profile was marked by a predominance of Gram-negative pathogens (33%, n = 134) compared to Gram-positive cocci 17% (n = 67). The prevalence of *B. cepacia* isolates (7%, n = 28) in our study corroborates with Keating and Schaffer in 2015 [10] where prevalence peaked at 7.6% in 2010 and then dropped to about 6%. However, some studies have reported much higher prevalence than ours. In Iran, strains of *B. cepacia* were isolated in respiratory samples with a frequency of 15.1% [16]. In Egypt, the percentage of isolates from the *B. cepacia* complex was 23% [17]. In the United States, the percentage isolates of *B. cepacia* was 18.9% in patients without cystic fibrosis [18]. In Spain, the prevalence rate of *B. cepacia* strains was 14.9% [19]. Other authors reported lower prevalences than ours. In Ireland the prevalence of *B. cepacia* complex was 2.75%. In China, one study found that *B. cepacia* accounts for about 3.81% of nosocomial infections [20].

These differences can be explained by factors such as inadequate hospital hygiene, sample type, study period, study population, hospital type and geographic location [21]. The majority of *B. cepacia* strains showed high resistance (100%) to many antibiotics of the beta-lactam, aminoglycoside, quinolone and cycline family, respectively. These antibiotics were: (Amoxicillin, Imipenem, Ticarcilline, Cefoxitin and Cefotaxime), (Gentamicin, Tobramycin and Amikacin), Ciprofloxacin and tetracycline. This result is well above the studies reported in other countries. *B. cepacia's* carbapenem (Imipenem) resistance isolated from nosocomial infections with cystic fibrosis was 48% - 89% [19] [22]. Di-Yong *et*

al. [23] found 41.1% resistance. These results do not corroborate with Selçuk Nazik [7] who reported 65.2%, and Murat Dizbay [24] reported 22.23% sensitivity to imipenem.

With regard to cephalosporin resistance cefotaxitin, and cefoxitin, the result was high according to studies reported in the literature [9] [24] which have resistance (65.5%, 46.1%) for cefotaxime. Beta-alactamine resistance observed in *B. cepacia* species is related to the expression of a chromosomal and inducible beta-lactamase called Penna, described in 1988 by Prince *et al.*, and Proenca *et al.*, in 1993, in a *B. cepacia* isolate in the United States. The resistance of *B. cepacia* to aminoglycosides in our study is inconsistent with the study by Hassen *et al.* [25] which found sensitivity rates of 20% and 15.3% for gentamycin and that of Abdel Fattah Ahmed *et al.* in 2013 [3] which reported sensitivity of 15.3% and 13.3% for gentamycin and amikacin respectively.

Resistance to aminosides is due to a lack of lipopolysaccharide binding sites with reduced permeability of the external membrane and flow pumps that leads to intrinsic resistance to cationic antimicrobials, polymyxins and aminoglycosides [26]. These high rates of resistance to aminosides justify that aminosides are no longer currently recommended for probabilistic treatment of *B. cepacia*. With regard to resistance to ciprofloxacin, the result is similar with several studies that reported very high levels of resistance to ciprofloxacin [17] [23] [24] [25]. For resistance to tetracycline, the result corroborates with Omar *et al.* [17] who reported a resistance of 84.2%. However, our results disagree with Alaa Fahim Abdas, [21] and Omar *et al.* [17] who reported sensitivities of 60% and 5.8% respectively.

The multi-resistance of this complex to antibiotics may be explained by the fact that the species of the *B. cepacia* complex have the capacity to induce the production of modifying enzymes or the production of enzymes that degrade antimicrobials, alteration of the target site and changes in cell permeability [27]. Levofloxacin showed good activity (100%) to *B. cepacia*. This finding is consistent with a study conducted in Taiwan that reported a sensitivity of (80%) levofloxacin [28], in Babylon Alaa Fahim Abdas [19] reported a sensitivity of 73.3% Trimethoprime + sulfamethoxazole had a sensitivity of 92.3% and 73.3%, this result is in line with the literature [21] [28].

Ceftazidime is 80% active on *B. cepacia* strains, this finding corroborates those of Alaa Fahim Abdas [21] who have a sensitivity of 66.7%, Tseng *et al.* [28] reported (65%) and Avgri *et al.* (2009) 73.7%. Another study showed that (73.7%) of patients who received ceftazidime were cured [29]. However, this result is not consistent with that of Murat Dizbay [24] which achieved a resistance of 61.5%, and Hassen *et al.* [25] which had an opposite result, a resistance of 80%. Cefpimus was active on 35% of *B. cepacia* strains; this result is below that of Murat Dizbay (56.4%) and Selçuk Nazik (65%) [9] [24].

5. Conclusion

This work revealed a widespread spread of strains of *B. cepacia* primarily in

children under one year of age in hospital and at the Libreville university hospital. *B. cepacia* is particularly found in newborns. The multiresistance of these bacteria to antibiotics commonly used for the treatment of paediatric infections calls on the need to adapt treatment regimens to local epidemiology and on a review of paediatric hospital hygiene. The problem of management of nosocomial infections due to bacteria *B. cepacia* lies in the difficulty of making the diagnosis given the low availability of laboratory equipment in the various health centers. Today *B. cepacia* should be considered as an emerging multidrug-resistant bacterium given its high frequency of isolation in care services and especially in pediatrics.

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Authors Contribution

Séverin Medzégué Nguéma conducted the study, developed the concept and study design and written the manuscript; **Priest Davin Nguema** conducted the study, collected and analyzed the samples; **Sophie Aboughe Angone** read and corrected the manuscript and interpreted data and drafted the manuscript; **Léonard Kouegnigan Rerambiah** supervised all the work and offered guidance. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

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

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