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Prevalence of *Escherichia coli* Producing Extended Spectrum Beta-Lactamase (ESBL) Driven Septicaemia in Children Aged 0–2 Years in Two Districts Hospitals in Yaounde, Cameroon

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Abstract: Septicaemia is public health problem worldwide with a high rate of mortality among children. Epidemiological data on this phenomenon in Cameroon are still scarce. This study aimed to determine the prevalence and associated factors to septicaemia due to *E. coli* strains producing extended spectrum beta-lactamase (ESBL) in two hospitals in Yaoundé, Cameroon. A prospective, cross-sectional study was conducted on infants aged 0 to 2 years old at the consultation and neonatology care unit of two district hospitals of Yaoundé (UTHY and YGOPH) during a period of seven months (from August 2019 to March 2020). Each blood sample collected per infant was cultured in hemoline performance vials, and bacterial strains were identified using the Api-20 E system. In addition, an antibiotic resistant profile of isolates as well as the ESBL production were performed in accordance with the recommendations of the Antibiogram committee of the French Society of Microbiology 2019. Data were analysed in Epi-Info7.0 and for p less than 0.05, the difference was statistically significant. Of the 300 children enrolled, 130 (43.33%) were blood culture positive, and *E. coli*. was the most prevalent (69.23% (90/130)). Then antibiotic susceptibility test revealed that 77 over 90 *E. coli* strains were resistant to penicillin (with 85.55% to amoxicillin), and 34.44% were producing ESBL. Factors such as immunodeficiency, being on antibiotics, and particularly taking β-lactam were significantly associated with *E. coli* ESBL production ([aOR = 19.93; p = 0.0001], [aOR = 1.97; p = 0.04], and [aOR = 3.54; p = 0.01], respectively). Moreover, co-resistance to aminoglycosides, quinolones, fluoroquinolones, and cotrimoxazole were also found. This study highlighted a high prevalence of *E. coli* ESBL in blood samples of children aged 0–2 years in Yaoundé and prompts the development of more efficient strategies against *E. coli* ESBL associated mortality in infants in Cameroon.

Keywords: sepsis; *Escherichia coli*; ESBL; antibiotics; neonates and infants; associated factors; Cameroon

1. Introduction

Septicaemia is a generalised infection due to repeated discharge of pathogenic bacteria into the blood stream and is responsible for in- and outpatients hospital admission [1]. Clinical manifestations documented include hyperthermia, hypothermia, rise in respiratory frequency, tachycardia, hyperleukocytosis, and leukopenia [2]. Septicaemia is frequent in newborns and children due to their immature immune system [3] and includes mostly

bacteria such as *Escherichia coli*, group B *Streptococcus* and *Klebsiella* [3]. According to the WHO, 49 million cases of sepsis and 11 million sepsis-related deaths occurred worldwide in 2017, accounting for approximately 20% of all-cause deaths, and 41% (20 million) of all global sepsis cases in 2017 were amongst children under five years of age [4]. In emerging countries of sub-Saharan Africa, neonatal septicaemia is responsible for about 6 million deaths annually [3]. In Cameroon, previous studies reported in 2016 an incidence of 20.34% and 2.8% of neonatal infections due to septicaemia in Yaoundé [5] and Douala, respectively [6]. Other research works showed an incidence of 26% in University Teaching Hospital Center in Yaoundé in 2000 [7] and 48.2% at the Yaoundé Gynae-Obstetric and Pediatrics hospital in 2006 [8]. Treatment options are chosen on the basis of the severity of clinical signs, suspected pathogen, bactericidal antibiotic diffusion, and immune status [9]. In the presence of symptoms, a probabilistic treatment using broad spectrum antibiotics are generally initiated 4–8 h prior to antibiogram results [9]. Compared to monotherapy, cefoxitin (C3G) combined with aminoglycosides (gentamycin) has been shown to be more efficient in immuno-deficient children [3,10].

Previous studies in bloodstream infections have reported an increased incidence and antimicrobial resistance (AMR) in *Escherichia coli*, one of the most frequent pathogens causing bacteremia [11–13]. An antimicrobial resistant organism may be acquired by emergence of resistance in endogenous flora or by acquisition from other patients and the environment [14]. The most problematic mechanisms in *E. coli* correspond to the acquisition of genes coding for carbapenemases (conferring resistance to carbapenems), 16S rRNA methylases (conferring pan-resistance to aminoglycosides), plasmid-mediated quinolone resistance (PMQR) genes (conferring resistance to (fluoro)quinolones), mcr genes (conferring resistance to polymyxins), and extended-spectrum β-lactamases (conferring resistance to broad-spectrum cephalosporins) [15]

In vitro, carbapenems (ertapenem, imipenem) have been demonstrated to have better efficacy on *Escherichia coli* producing broad spectrum β-lactamases (ESBL), with an inhibition of about 98% of strains [16]. However, modern medicine has only driven further evolution of antimicrobial resistance by misuse, overuse, and abuse of antibiotics [17]. This can shortly lead to therapeutic crisis. One leading factor of antimicrobial resistance (AMR) in developed countries is the over-prescription by physicians of antimicrobials, particularly antibiotics, even in the absence of appropriate indications [14]; in low- and middle-income countries, on the contrary, it is self-medication due to poverty and poor education [18].

This study aimed to determine the prevalence and associated factors to septicaemia due to *E. coli* strains producing extended spectrum beta-lactamase (ESBL) in two hospitals in Yaoundé, Cameroon.

2. Results

Out of 300 neonates enrolled in this study, a female predominance with 55% (165/300) was observed. Equally, 77.66% (233/300) were immunocompromised, and 10.66% (32/300) have been admitted in the hospital for 3 months and above.

2.1. E. coli Isolation from Blood Culture and ESBL Production

Blood culture positivity accounted for 43.33% (130/300), with *Escherichia coli* being the predominant microorganism with 69.23% (90/130). About 34.44% (31/90) of the isolated *E. coli* strains produced ESBL (Figure 1).

2.2. Resistance Profile of E. coli Strains to β-Lactams

Antibiotic susceptibility testing of *E. coli* strains showed varying resistance levels to the antibiotics of the beta-lactams family. The greatest being amoxicillin with 85.55%, followed by cefoxitin with 62.5% and cefotaxim with 60.3% (Figure 2).

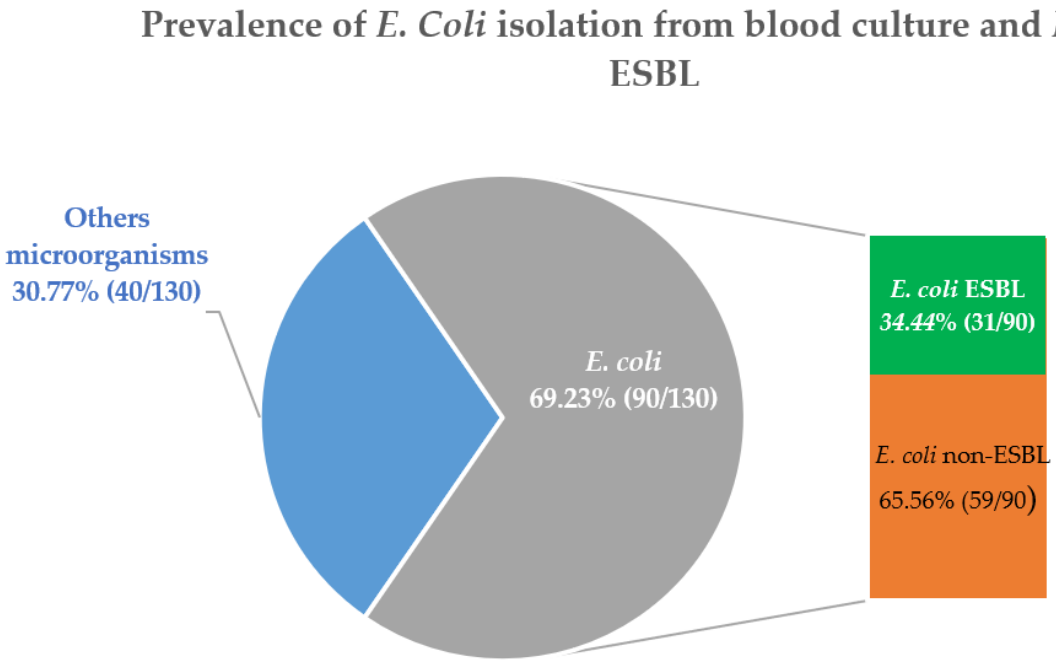

Figure 1. Prevalence of *E. coli* isolated from blood culture and ESBL producing *E. coli*.

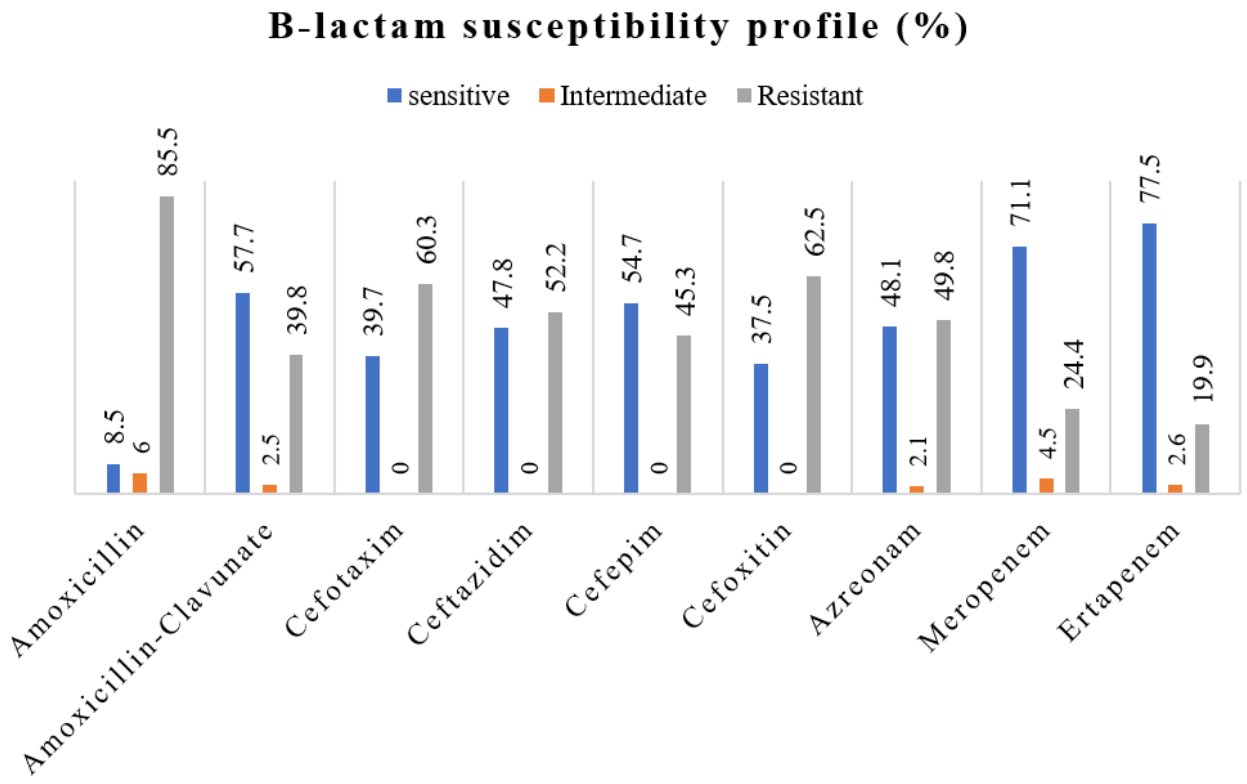

Figure 2. β-lactam susceptibility profile.

2.3. E. coli Antibiotic Susceptibility Testing to Other Antibiotic Families

The *E. coli* strains exhibited different levels of resistance to aminosides (54.6% to Amikacin, 57.8% to gentamicin, 27.3%), to quinolones (27.3% to ofloxacin and 34.5% to nalidixic acid), and to cotrimoxazole (92.2%) (Figure 3).

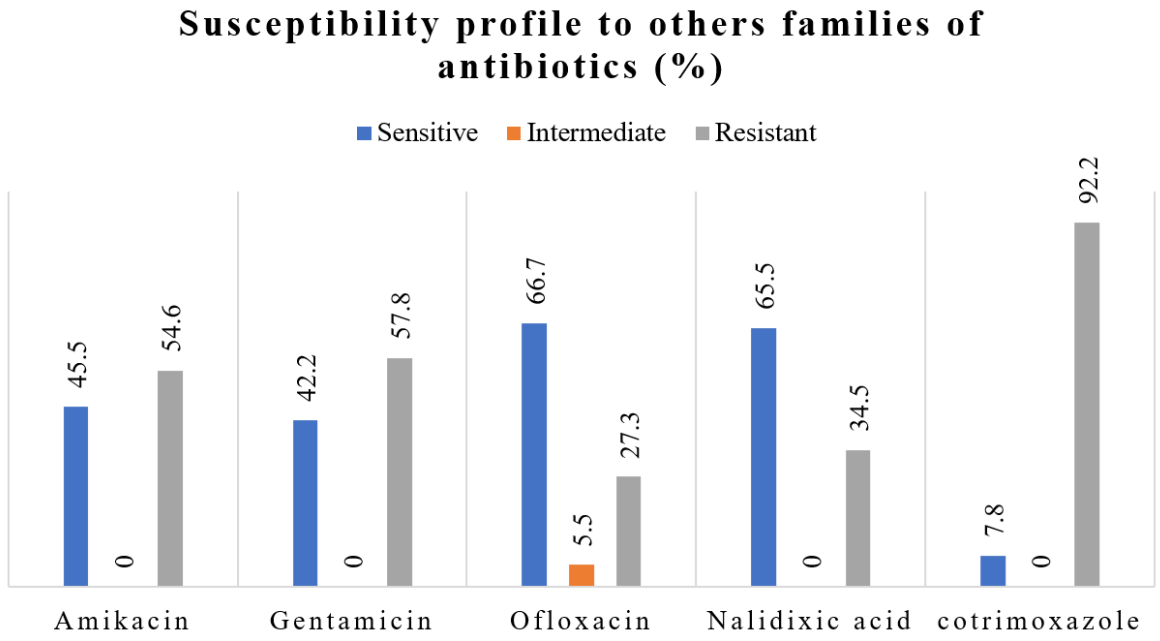

Figure 3. Susceptibility profile to other families of antibiotics.

2.4. Univariate and Multivariate Analyses of Factors Associated with E. coli Producing ESBL

The univariate analysis of factors associated with *E. coli* producing ESBL revealed a significant association with admission to hospital for at least 3 months ($p = 0.03$), antibiotherapy ($p = 0.02$), B-lactams resistance ($p = 0.003$), and immunodeficiency ($p = 0.0001$) (Table 1).

Table 1. Factors associated with *E. coli* producing ESBL.

Factors	Total (*N*)	*E. coli* ESBL *n* (%)	*E. coli* Non-ESBL *n* (%)	*p*-Value
Admission (≥3 months)				
No	268	22 (8.21%)	246 (91.79%)	
Yes	32	09 (28.13%)	23 (71.88%)	0.03
Use of Antibiotic				
No	230	17 (7.39%)	213 (92.61%)	
Yes	70	14 (20%)	56 (80%)	0.02
B-lactams (N = 70)				
No	04	1 (25%)	3 (75%)	
Yes	66	12 (18.19%)	48 (72.72%)	0.003
Quinolone (N = 70)				
No	37	13 (35.14%)	24 (64.87%)	
Yes	33	5 (15.15%)	28 (84.85%)	0.45
Aminosides (N = 70)				
No	10	2 (20%)	8 (80%)	
Yes	60	12 (20%)	48 (80%)	0.24
Others				
Bacterial infection	1	0 (0.0%)	1 (100%)	0.99
Immunodeficiency	233	14 (6.10%)	219 (94%)	0.0001
Blood Transfusion	20	0 (0.0%)	20 (100%)	0.06

Concerning multivariate analysis, no significant association was found between admission into hospital for at least 3 months and the presence of *E. coli* producing ESBL among children aged 0–2 years (aOR = 2.94; 95% CI = 0.97; 8.91; $p = 0.06$). However, immunodeficiency and antibiotics such as β-lactams were significantly linked to the presence of *E. coli* producing ESBL (aOR = 1.97; 95%CI = 8.82; 45.32; $p = 0.0001$; and aOR = 3.54; 95% CI = 1.28; 9.80; $p = 0.014$), respectively (Table 2).

Table 2. Multivariate analysis of factors associated with *E. coli* producing ESBL.

Factors	aOR	95% CI	*p*-Value
Admission (≥3 months)			
No	1		
Yes	2.94	[0.97–8.91]	0.06
On Antibiotic			
No	1		
Yes	1.97	[1.02–3.83]	0.04
B-lactams			
No	1		
Yes	3.54	[1.28–9.80]	0.01
Aminosides			
No	1		
Yes	1	[1–1.33]	0.41
Associated factors			
Immunodeficiency	19.93	[8.82–45.32]	0.0001
Blood transfusion	2.48	[0.95–6.45]	0.06
Bacterial infection	3.45	[1.19–2.95]	0.99

aOR = Adjusted OR; 95%CI = 95% Confidence interval.

3. Discussion

In total, 300 blood samples were cultured from symptomatic neonates; 43.33% had a positive blood culture of which 69% were *E. coli.* A recent study in Niger and Nigeria found similar high prevalence of septicaemia among neonates (55.1% and 42%, respectively), and the same study equally reported septicaemia as the main cause of morbidity and mortality among neonates [19,20]. Moreover, the high rate of *E. coli* in this study is quite similar to other studies in Abidjan [21] and England [22] with 68% and 36.4%, respectively. This can be explained by the fact that *E. coli* is present in the genital tract of about 13% of women at the time of delivery [23]. In addition, newborns have been shown to be highly colonized with *E. coli* at birth [24]. This clearly shows that hygienic measures among pregnant women are not always observed.

Drug susceptibility showed a synergic effect between clavulanic acid and third-generation cephalosporin on *E. coli* strains in 34.44% cases. A similar study in England found a slightly higher result in 2015 (43%) [22]. This difference could be related to the method used for strain identification. In their study, the diagnostic tool includes the molecular technique which is a much more specific than the Mueller–Hinton agar double synergy test used in ours [25].

Higher levels of co-resistances to aminoglycosides, quinolones, fluoroquinolones and cotrimoxazole were observed in this study. These results are similar to those reported in 2016 in Mali [26]. Indeed, most ESBL-producing strains are not only resistant to the majority of β-lactam antibiotics but also to many antibiotics of other families such as fluoroquinolones, aminosides, co-trimoxazole, and quinolones [27]. Moreover, immunodeficiency and antibiotics such as β-lactams were significantly linked to the presence of *E. coli* producing ESBL. It has been shown that newborns with immature immune systems promote the development of *E. coli* ESBL related septicaemia [28]. A significant association between antibiotics and ESBL production has also been reported [29,30]. These findings strongly suggests that the overuse of broad-spectrum antibiotics may lead to the development of resistance mechanisms such as the production of ESBLs by such species [31].

4. Materials and Methods

4.1. Study Type and Location

A cross-sectional, descriptive study was conducted to determine the prevalence of (ESBL) linked to septicaemia in children aged 0–2 years old admitted at the neonatal unit of the University Teaching Hospital, Yaoundé (UTCH) and the Yaoundé Gynaeco-Obstetrics and Pediatrics Hospital (YGOPH).

4.2. Study Duration

Samples were collected and analysed over a seven-month period from 17 August 2019 to 17 March 2020. A written informed consent of the parents or guardian of children and infants included in the study was obtained.

4.3. Sample Collection

Venous blood (1–3 mL) was collected per patient into cryovial tube following strict aseptic measures, and all samples were processed in the bacteriology laboratories of the UTCH and YGOPH. All infants living with HIV, those with recurrent infections, and admitted infants undergoing blood transfusion were considered as immunocompromised.

4.4. Bacteria Culture and Identification

The selective Medium Eosine Methylene Blue was used for *Enterobacteriae* culture, growth, and selection. Strain identification of the isolates was performed using Api 20E system. Each mini-gallery API 20E was inoculated with a bacteria suspension prepared with an opacity of 0.5 on the McFarland scale.

4.5. Antibiotic Susceptibility Testing for ESBL Phenotype

Antibiotic susceptibility test was performed using the Kirby–Bauer disk diffusion method on Mueller–Hinton agar as recommended by the (AC-FSM) 2017. The following antibiotics were tested: amoxicillin (30 µg); amoxicillin + Clavulanic acid (30 µg); cefotaxime (5 µg); ceftazidime (10 µg); cefepime (30 µg); cefoxitin (30 µg); amikacin (10 µg); Nalidixic acid (10 µg); ertapenem (10 µg); ciprofloxacin (10 µg); ofloxacin (5 µg); Fosfomycin (200 µg); Amikacin (10 µg); cotrimoxazole (25 µg); gentamycin (10 µg); and ticarcillin (75 µg). Inhibition zone diameters were indicative of sensitivity or resistance to each antibiotic. The production of broad-spectrum beta-lactamase (ESBL) by *E. coli* was indicated by the presence of a characteristic champagne cork obtained from the synergy between a third-generation cephalosporin (C3G) and beta-lactamases inhibitor (Augmentin disk).

4.6. Data Analysis and Interpretation

The different variables and results obtained after verification of their conformity were recorded in Excel 2010 software then analysed with the statistical software Statview 5.0 (SAS Institute Inc, Cary, NC, USA). The analyses included the calculation of the frequency (for qualitative variables) and mean or median (for quantitative variables).

4.7. Ethical Considerations

Prior to the study, authorisations from the head of each health facility involved as well as institutional ethical clearance was obtained from the institutional ethic committee of Université des Montagnes (N°2020/205/UdM/PR/CM, 3 June 2020).

5. Conclusions

In this study, a high prevalence and resistance rate to antibiotics of *Escherichia coli* ESBL in the blood of children aged 0–2 years in Yaoundé were highlighted. The significant associated factors to *E. coli* ESBL production were: admission to hospital for at least 3 months; antibiotherapy; resistance to B-lactams; and immunodeficiency. This study prompts the development of more efficient strategies against *E. coli* ESBL associated mortality in infants in Cameroon.

Author Contributions: C.I.D. conceived the project and designed the study. C.I.D. and P.D.D.D. searched relevant literature, scrutinized all relevant information, and drafted the manuscript. C.I.D. and B.D.T.P. conducted and coordinated the field study. S.T.L. and A.D. collected and processed the samples and data. P.D.D.D., R.K.W., H.G.K. and C.I.D. analysed the data and wrote the article. C.I.D., B.D.T.P. and T.A. revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethic committee of Université des Montagnes (N°2020/205/UdM/PR/CM, 3 June 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All data generated or analysed in the course of this study are included in this manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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