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Original article

Prevalence and antimicrobial susceptibility of faecal carriage of Extended-Spectrum β-lactamase (ESBL) producing *Escherichia coli* at the "Hôpital de la Mère et de l'Enfant" in N'Djamena, Chad

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ABSTRACT

In recent times, some strains of *Escherichia coli* have become a serious public health problem, due to their increasing ability to resist to usual antibiotics and their potential dissemination rates. The present study aimed to determine the prevalence of faecal carriage of ESBL-producing *E. coli* and their susceptibility to antimicrobial agents. Clinical isolates of *E. coli* were isolated onto MacConkey agar plates supplemented with cefotaxim (CTX, 2µg/mL) and tested for ESBL production by using the Double disk synergy test (DDST). Susceptibility to antibiotics was tested according to the guidelines of Clinical and Laboratory Standards Institute. Out of the 219 stool samples investigated, 56 (25.57%) contained *E. coli* resistant to cefotaxim. Among these strains, 20.09% was detected to be *E. coli* producers ESBL and 5.47% tested non-producers ESBL. Multidrug-resistance to antibioctics was significantly associated with ESBL production ($p < 0.05$). This study shows a significant rate of ESBL producing strains among the *E. coli* isolated from patients at the "Hôpital de la Mere et de l'Enfant" in Chad and indicates the need to

rationalize the use of antibiotics and perform initiatives to control their dissemination.

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1. Introduction

ESBL-producing bacteria have since been reported worldwide (Bradford, 2001). In recent years, ESBL-producing *E. coli* strains are the most implicated bacteria in urinary and digestive infections (Hsueh et *al*., 2011; Andriatahina et *al*., 2010). The production of these enzymes confers to this bacterium the resistance to all β-lactams except cephamycins and carbapenems which are a group of β-lactam antimicrobial agents with an exceptional broad spectrum of activity (Uzunovic-Kamberovic et *al*., 2006). ESBL are encoded by transferable plasmids, which often confer resistance to other classes of antimicrobial agents and are also responsible for the dissemination of resistance to other Gram-negative bacteria in the community and in hospitals (De Champs et *al*., 1989). Many studies have been performed in the world with the aim to know the prevalence of ESBL producing bacteria. These studies should help to institute correctly, targeted treatment and to reduce the escalation of resistance to antibiotics (Datta et *al.*, 2012). Recent studies in Africa showed high prevalence of ESBL producing *E. coli* in Madagascar, Tunisia, Sudan and Niger (Andriatahina et *al*., 2010; Sallem et *al*., 2012; Mutasim et *al*., 2013; Woerther et *al*., 2014). Since resistance can differ according to geographic location, continuous monitoring of resistance patterns is necessary in each country for adequately select an empirical antimicrobial therapy. The main objective of this study was to evaluate the prevalence and the antimicrobial sensitivity of ESBL producing *E. coli* isolated from hospitalized and ambulatory patients in Chad. The results of this kind study are very important because prevalence of multidrug-resistant organisms should be taken into account when choosing therapeutic agents for patients.

2. Materials and methods

This prospective study was carried out from the 1st November 2012 to the 30th June 2013 at the "Hôpital de la Mere et de l'Enfant" of N'Djamena in Chad. It is a Hospital of reference for the treatment of the children from 0 - 14 years and the women. This hospital has a capacity of 295 beds and 598 employees. In this study the demographic variables noted were the age of patients and their provenance (inpatient or outpatient).

2.1. Specimen collection and isolation of *E. coli*

A total of 219 stool samples from 92 inpatients and 127 outpatients were collected in sterile disposable bottles and appropriately labelled. The specimens were transported immediately to the microbiology laboratory for bacteriological analysis. The samples were seeded onto MacConkey agar plates supplemented with cefotaxim (CTX, 2µg/mL) and incubated at 35 - 37 °C for 18 - 24 hours. The colonies which grew on the MacConkey agar were suspected to be Gram-negative bacilli and were sub-cultured on Mueller Hinton agar for the purification. Isolates were identified by, Gram strains, indole production, Methyl Red, Voges Proskauer and Citrate tests, and then confirmed by API 20E identification system (bioMerieux).

2.2. Antimicrobial susceptibility testing

Sensitivity of isolates *E. coli* trains to antibiotics were determined by agar diffusion method according Kirby–Bauer method as recommended by the Clinical and Laboratory Standards Institute (CLSI) (CLSI, 2011). The following antimicrobial agents were tested, amoxicillin/clavulanic acid (20/10 µg), cefoxitin (30 µg), cefotaxim (30 µg), ceftazidim (30 µg), imipenem (10 µg), aztreonam (30 µg), gentamicin (10 µg), amikacin (30 µg), ciprofloxacin (5 µg), ofloxacin (5 µg) and trimethoprim-sulfamethoxazole (1.25/23.75 µg). Quality control was conducted using the reference strain *E. coli* ATCC 25922.

2.3. Detection of ESBL production

Detection of ESBL production was screened on Muller-Hinton agar using a double-disc synergy test (DDST) according to the procedure of Jarlier et *al*. (1988). The plates were inoculated with *E. coli* strains as for standard

disk diffusion test. Antibiotic disks containing aztreonam and expanded-spectrum cephalosporins were then placed 30 mm (center to center) from an amoxicillin/clavulanic acid disk prior to incubation. After overnight incubation at 35 - 37 °C, the production of ESBL by the tested organism was detected by the presence of characteristic distortions of the inhibition zones, indicative of clavulanate potentiation of the activity of the test drug. Negative double-disk tests were repeated with a disk spacing of 20 mm (center to center).

2.4. Statistical analysis

All outcome data were analyzed using Statistical Package for Social Sciences (SPSS) Version19.0. The differences between resistance patterns of *E. coli* strains were determined using Chi-square test of Pearson. All differences in which the probability of the null hypothesis was $p < 0.05$ were considered significant.

2.5. Ethical consideration

This study was authorized by the authorities of the "Hospital de la Mere et de l'Enfant" of N'Djamena. Research was carried out on the samples received from the laboratory for the clinical diagnoses. The results were given back to the doctors for the patient's treatment.

3. Results

3.1. Prevalence of ESBL-producing *Escherichia coli*

Figure 1 shows characteristic distortion of the inhibition zones of cefotaxin and amoxicillin/clavulanic acid distant to 30 mm. Out of 219 cultures made, 56 (25.57%) were *E. coli* strains resistant to the third-generation cephalosporin. Among which, 20.09% were identified as ESBL producing *E. coli* and 5.47% were non-ESBL producing *E. coli*. The rates of ESBL-producing strains were higher among inpatients (22.82%) than the outpatients (18.11%), but this difference was not statically significant (Table1). Among the patients studied, children from 0 - 4 years were the most infected than others age groups (table 2). These data show a high prevalence of faecal carriage of ESBL-producing *E. coli* in children of 0 - 4 years particularly.

3.2. Antimicrobial susceptibility

The antimicrobial resistance pattern tested for ESBL-non-producers and ESBL-producers *E. coli* is presented on Table 3. Globally, the rates of antimicrobial resistances of ESBL-non-producers were lower than those obtained with ESBL producers. Among ESBL-producers, 40.90% were resistant to amoxicillin/clavulanic acid, 22.72% to cefoxitin. However all ESBL-producers were resistant to third-generation cephalosporins (CRO, CTX) (100 %), but none of ESBL-producers was resistance to imipenem. As far as other antimicrobial families are concerned, the resistance to gentamicin, amikacin, ciprofloxacin, ofloxacin and trimethoprim-sulfamethoxazole were 65.90%, 38.63%, 72.72%, 50.09% and 100%, respectively. The antimicrobial susceptibility from ESBL-producing strains in this study showed that cefoxitin and imipenem were the most efficient tested antibiotics. The least efficient were amoxicillin/clavulanic acid, gentamicin, and ciprofloxacin. Trimethoprim-sulfamethoxazole was ineffective (Table 3).

Table 1
Prevalence of ESBL-producing *E. coli* from inpatients and outpatients.

	sample	***E. coli***	**ESBL+**	**ESBL -**
Inpatients	92	30 (32.60%)	21 (22.82%)	9 (9.78%)
Outpatients	127	26 (20.47%)	23 (18.11 %)	3 (2.36%)
Total	219	56 (25.57%)	44 (20.09%)	12 (5.47%)

ESBL +: positive DDST; **ESBL - :** negative DDST

4. Discussion

The work reported here set out to evaluate the prevalence and antimicrobial susceptibility of faecal carriage of ESBL-producing *E. coli* from patients at the "Hôpital de la Mère et de l'Enfant" of N'Djamena in Chad. The prevalence was found to be 20.09% which is low compared to the study carried out in Sudan by Ibrahim et *al*.

(2013) who recorded ESBL producing *E. coli* as 32.2%. Similar studies carried out in others countries reported, 31% in Niger (Woerther et *al*., 2014), 32.2% in Madagascar (Andriatahina et *al*., 2010). Lower rates were reported such as, 7.3% in Tunisia (Sallem et *al*., 2012), 1.5% in Brazil (Minarini et *al*., 2007), 2.4% in Lebanon (Moubareck et *al*., 2005) and 3.7% in Spain (Valverde et *al*., 2004). In China, 7% of carriage rate observed among elderly (Tian et *al*., 2008) and 8% of carriage rate on admission to hospital in Israel (Friedmann et *al*., 2009).

These results from outpatients and hospitalized in Chad raise the question of asymptomatic carriage of ESBL in the community which contributes to the spread of resistance genes by human-to-human transmission or to the contamination of the environment or foods (Levin, 2001; Canton et *al*., 2003; Kagambega et *al*., 2013).

Table 2

Distribution of ESBL-producing *E. coli* according different age group.

Age (in years)	Number of isolates	Frequency of ESBL+ (%)	Frequency of ESBL - (%)
[0-4]	27	20 (37.71%)	7 (12.5%)
[5-9]	12	10 (17.85%)	2 (3.57%)
[10-14]	8	5 (8.92%)	3 (5.35%)
[15 and+ [	9	9 (16.07%)	0 (0%)
Total	56	44 (78.57%)	12 (21.42%)

Fig. 1. Strains of *Escherichia coli* showing positive DDST when swabbed on Mueller Hinton Agar and incubated with cefotaxim (CTX) applied to 30 mm of amoxicillin/clavulanic acid (AMC).

Table 3

Resistance to antimicrobial of ESBL producing *E. coli* and non-producer ESBL.

Antimicrobial tested	ESBL + (n = 44) Resistance (%)	ESBL - (n = 12) Resistance (%)	P-value[a]
Amoxicillin/ clavulanic acid	18 (40.90)	2 (16.66)	0.120
Cefoxitin	10 (22.72)	3 (25.00)	0.869
Ceftriaxon/Cefotaxim	44 (100)	12 (100)	NS [b]
Ceftazidim	43 (97.72)	12 (100)	0.598
Aztreonam	44 (100)	10 (83.33)	0.006
Imipenem	0 (0%)	0 (0%)	NS [b]
Gentamicin	29 (65.90)	4 (33.33)	0.042
Amikacin	17 (38.63)	1 (8.33)	0.046
Ciprofloxacin	32 (72.72)	4 (33.33)	0.012
Ofloxacin	26 (50.09)	2 (16.66)	0.009
Trimethoprim-sulfamethoxazol	44 (100)	12 (100)	NS [b]

a Exact P-values were determined by the X^2 test. P-value < 0.05 was considered statistically significant,
NS [b] : Non significant :

In our study, the prevalence was higher in the group of children between 0 - 4 years (37.71 %) than others group of children (5 - 9 years, 10 - 14 years). This rate was high than reported by Andriatahina et *al*. (2010) in Madagascar (12.3%) from children (< 5 years). The reasons of the exposure of these age groups could be due to their immunological status. At these ages people are more vulnerable and get easily infected. In the other hand, this could be also linked to the empirical use of antimicrobial compound in the hospitals and or at home. The susceptibility of the antimicrobial compounds the most used in the treatment of bacterial infections had showed the level of resistance of 40.90% to amoxicillin/clavulanic acid (augmentin). However, resistance to cefoxitin by ESBL-producing bacteria could be due to an alteration in the cell permeability to cefoxitin, which is associated with a low expression of a 36 kDa outer membrane protein (Gazouli et *al*., 1998). As far as the Carbapenem is concerned, all strains were sensitive to imipenem. Similar results were reported also in Algiers (Messai et *al*., 2006) and at Madrid (Tamoyo et *al*., 2007).

In the present study, ESBL-producing isolates showed high resistance rates for gentamicin (65.90%) and amikacin (38.46%). Highest level of resistance to gentamicin were reported in Nigeria (80 - 87%) (Iroha et *al*., 2009) and in Madagascar, it varies from 73.3% to 94.7% (Andriatahina et *al*., 2010). However, for amikacin the low resistance rate were reported in Sudan (4.3%) (Ibrahim et *al*., 2013) compared to our data and that obtained from Israel (25%) (Bishara et *al*., 2005). The mechanism of resistance to Aminoside is not yet elucidated. Others authors report that similar resistance could be related to the 6 ' acétyl-transféase amino [aac (6 ')] often noted with the ESBL-producing *Enterobacteriaceae* (CA-SFM, 2008).

Concerning the Fluoroquinolons, high resistances were observed with ciprofloxacin (72.72%) and to ofloxacin (50.09%). we note a higher level of resistance to ciprofloxacin compared to ofloxacin. This difference is due most likely to the difference of mechanism of resistance which may vary from one Fluoroquinolon to another (Jacoby, 2005). These could affect genes such as Aac(6')-Ib-cr (genes) (Robicsek et *al*., 2006) and QepA (efflux pumps) (Perichon et *al*., 2007), that decrease susceptibility only to ciprofloxacin and norfloxacin. In Sudan, the resistance rates were even higher, 81.4% to ciprofloxacin and 80% to ofloxacin (Ibrahim et *al*., 2012). Such level of resistance could be due to abusive prescription of antibiotics by professionals of health care without prior laboratory investigations or parallel care at home, self-medication and also the use of street drugs which is very spread in Africa. Other works indicated the high rates of resistance to ciprofloxacin over than 72 % in Israel, Spain, London and Nigeria (Aruna et *al*., 2012; Iroha et *al*., 2009; Melzer et *al*., 2007, Tamayo *al*., 2007). In Chad, the increase of resistance in *E. coli* to ciprofloxacin can be explained by two reasons. The first reason is lack of laboratories for microbiological analysis before prescriptions. Antibiotics are prescribed in the majority of case on the empirical basis. The second reason is the large use of street antibiotics due to the poverty and the level of the education of the population. In this country, antibiotics and over drugs are sometimes sold by the unqualified people, exposing the community to consumption of uncontrolled antibiotics.

The resistance to triméthoprim-sulfamethoxazole was 100%. This loss of sensitivity was reported by several studies. The rate was 91% in Nigeria (Iroha et *al*., 2009), 98.6% in Soudan (Ibrahim et *al*., 2012). In France, the resistance of *E. coli* to the triméthoprim-sulfamethoxazole varies from 50 to 80% (Goldstein et *al*., 2006). The results obtained in different countries were practically similar and should indicate that the prescription of this antibiotic must be directed.

5. Conclusions

This study revealed high prevalence of the strains of *E. coli* with higher level of resistance to antibiotics which colonizes the human digestive tract. All age groups are concerned by high resistances of the ESBL-producing trains to antibiotics families. Such result indicates the urgent need to rationalize the use of antibiotics and perform initiatives to control the dissemination of these multi drugs resistant bacteria. Further studies on the large scale on various clinical samples could help to learn more about the antibacterial drug resistance. At the molecular level, it is evident that much remains to be learnt about the control of expression of drug resistance genes.

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