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ANTIMICROBIAL SUSCEPTIBILITY OFEXTENDED-SPECTRUM BETA-LACTAMASE PRODUCING *ENTEROBACTERIACEAE* CAUSING URINARYTRACT INFECTIONS IN OUAGADOUGOU, BURKINA FASO

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ABSTRACT
Objective: To determine the frequency of extended-spectrum beta lactamase producing *Enterobacteriaceae*(ESBL) and other antibioticsresistant bacteria in urinary tract isolates.
Study Design: prospective and experimental study.
Methodology: Place and duration of study :YalgadoOuedraogo University Hospital Center, Charles De Gaulle Pediatric Hospital Center, Saint Camille Hospital and National Public Health Laboratory, Ouagadougou, from November 2014 to October 2015.
All*Enterobacteriaceae*strains isolated from urinary samples of patients were identifiedusing API 20E chemical gallery (BioMerieux, France). All strains were subjected to an array of 14 antibiotics to study their drug susceptibility by using Kirby-Baeurdisk diffusion method. Detection of ESBL was carried out by double disk diffusion technique. Statistical analysis was performed by Microsoft Excel and Anova one-way GrapPad Prism version 5.01. Chi-square ($\chi 2$) test was used to determine significance. A $p < 0.05$was considered to be statistically significant.
Results: A total of 324 isolates of *Enterobacteriaceae* were identified during the study period, including211(65%) *E. coli*, 75 (23%)*Klebsiella* spp., 18 (6%) *Enterobacter* spp., 11 (3%)*Proteus* spp., 5 (2%) *Citrobacter* spp., *Serratia* spp. 3 (1%).All the clinical isolates were susceptible to imipenem. Resistance to amikacinwas 14% (45/324); gentamicin 54% (175/324); tobramycin 58% (187/324); nalidixic acid 72% (234/324),ciprofloxacin 63% (204/324) and to cotrimoxazole 83% (269/324).The overall rate of the EBSL producing strains was 35% (114/324). Their susceptibility to antibiotics was (imipenem,amikacin, cefoxitin and fosfomycin) 100% (114/114), 93% (106/114), 74% (84/114) and 84% (96/114) respectively. ESBL positivity within individual organism group was highest in*Escherichia coli* 64% (73/324) followed by*Klebsiella*spp. 28% (32/324), *Enterobacter*spp. 3% (4/324), *Proteus* spp. *and Citrobacter*spp. 2% (2/324).
Conclusion: The results showeda high frequency of ESBL producing *Enterobacteriaceae*, especially *Escherichia coli* and *Klebsiella*spp. The data points to theneed of routine detection and surveillance of ESBL producing bacteria in Burkina Faso.

Keywords: Antimicrobial susceptibility, *Enterobacteriaceae*, Urine, Burkina Faso

SENSIBILITE DES ENTEROBACTERIES PRODUCTRICES DE BETA-LACTAMASESA SPECTRE ELARGI ISOLEES DES INFECTIONS URINAIRES, OUAGADOUGOU, BURKINA FASO

Résumé

Objectif : Déterminer la fréquence des entérobactéries productrices de bêta-lactamases à spectre élargi(BLSE)et la résistance aux autresantibiotiques utilisésle traitement des infections urinaires.
Type de l'étude : Etude prospective et expérimentale
Méthodologie : Lieu et période : Centre Hospitalier Universitaire YalgadoOuedraogo, Centre Hospitalier UniversitairePédiatrique Charles De Gaulle, Hôpital Saint Camille et Laboratoire National de Santé Publique, Ouagadougou, de Novembre 2014 à Octobre 2015.
Toutes les entérobactéries isolées des urines de patients et identifiées sur galerie API 20^{E} (BioMerieux, France). Quatorze (14) antibiotiques ont été utilisés pour tester la sensibilité des souches cliniques par la méthode de diffusion des disques selon Kirby-Bauer. La détection des souches productrices de BLSE a été faite en utilisant la technique de test à double synergie. Le logiciel Excel et Anova one-wayGrapPadPrism version 5.01ont été utilisés pour l'analyse statistique et le test de $\chi 2$au seuil de $p < 0.05$ était considéré statistiquement significatif.
Résultats: Un total de 324 souches d'*Enterobacteriaceae* ont été collectées durant la période d'étude composées de 211 (65%) souches de *E. coli*, 75 (23%)*Klebsiella*spp. ,18 (6%) *Enterobacter*spp., 11 (3%) *Proteus*spp.,5 (2%)*Citrobacter*spp. , 3 (1%) *Serratia*spp.
Toutes les souches d'entérobactéries étaient sensibles àl'imipenème. La résistanceà l'amikacineétait de 14%(45/324); la gentamicine 54% (175/324); la tobramycine 58% (187/324); l'acidenalidixique 72% (234/324), la ciprofloxacine 63% (204/324) et le cotrimoxazole 83% (269/324). La fréquence des souches productrices de BLSE était 35% (114/324). Leurs taux de résistance aux antibiotiques étaient de 100% (114/114), 93% (106/114), 74% (84/114) et 84% (96/114) respectivement àl'imipeneme, à l'amikacine, à la cefoxitineetà la fosfomycine.Lafréquence des souches productrices de BLSE par espèceétaitélevée chez*Escherichia coli* 64% (73/324) suivie de*Klebsiella*spp. 28% (32/324), *Enterobacter*spp. 3% (4/324), *Proteus*spp.et*Citrobacter*spp. 2% (2/324).

Conclusion:35% des souches cliniques étaient productrices de BLSE. Une fréquenceélevée des entérobactéries productrices de BLSE aétéobservée chez l'espèce*E. coli* et *Klebsiella*spp parmi les souches cliniques testées. Les résultats montrent une nécessité de mettre en place un système de surveillance des souches productrices de BLSE au Burkina Faso.
Mots clés: Sensibilité aux antibiotiques, *Enterobacteriaceae*, Urine, Burkina Faso

INTRODUCTION

Urinary tract infections(UTI) is one of the most common infectious diseases ranking next to upper respiratory tract infection, it is an important cause of morbidity and mortality in human. Infected urine, renal calculi, obstructive uropathy, vesico ureteral reflux and avoiding disorders can lead to urinary stasis and may predispose to the development of UTIs and complications [1].It has been estimated that nearly 10% of the human population will experience an UTI during the life time [2, 3, 4]. Resistance to commonly-prescribed antibiotics is an expanding global problem and has been observed in both developed and developing countries[5, 6, 7, 8]. *Enterobacteriaceae* are the major causative organisms of UTIs and are responsible for more than 81% of UTIs cases. *Escherichia coli* is the most prevalent causative organisms of UTIsand is solely responsible for more than 69% of the infections [1,9,10].

Bacterial resistance to antibiotics has emerged even to newer, more-potent antibacterial agents [11]. A number of epidemics have recently occurred caused by multiple resistant organisms [12, 13].

In Burkina Faso, UTIs due to *Enterobactriaceae* are common and represent a frequent cause of morbidity in outpatients as well as a frequent cause of nosocomial infections in many hospitals. Most infections are treated on an empirical basis. Clinical experience has indicated the presence of numerous cases of infection resistant to conventional antibiotics therapy. Microbial resistance rates to commonly prescribed antibiotics have increased recently. Updated knowledge of urinary tract infections *Enterobacteriaceae*, the frequency of ESBL strains and the susceptibility patterns to other antibiotics is important for the proper selection and use of antibiotic and for the development of an appropriate prescribing policy. The aim of this study was to determine the frequency of ESBL strains and the susceptibility patterns of other antibioticresistant bacteria of clinical importance responsible for urinary tract infections in Ouagadougou, Burkina Faso.

Materiel and methods

Study population and settings

This study was an experimental study ofbeta-lactam and other antibiotics resistance expression of*Enterobacteriaceae*.The socio demographic data and*Enterobacteriaceae* strains were obtainedfrom patients who came for an etiological diagnosis for bacterial infectionfrom November 2014 to October 2015.

The *Enterobacteriaceae*strains were obtained from thefollowing 3 health centers in Ouagadougou: YalgadoOuedraogo University Hospital (CHU-YO), the largest public medical institution, Charles De Gaulle Pediatric University Hospital (CHUP-CDG), the referral public pediatric hospital with 120 bedsand

Saint Camille Hospital (HOSCO), the confessional hospital.

All *Enterobacteriaceae* strains collected at these 3 different sites were transported to the LNSP Bacteriology-Virology Laboratoryfor *Enterobacteriaceae* investigation. Strains identification was performed using API 20 E gallery (Biomérieux, Marcy- L'étoile, France) after 24 hours incubation at 37 ° C.

The isolated and identified strains were seeded on Mueller-Hinton (MH) agar for 18 to 24 hours in order to have young and pure colonies.All clinical isolates were stored at -30°C for future investigations at Institut Pasteur de Côte d'Ivoire (IPCI).

Antibiotic Susceptibility Testing

All isolates were tested for susceptibility to 14 different antimicrobial agents using the disk diffusion method on Mueller-Hinton agar (BioRad, France) following the European Committee on Antimicrobial Susceptibility Instructions (EUCAST) guidelines (CA-SFM/EUCAST, 2016). *E. coli* ATCC 25922 and ATCC 35218 were used as a control. The antimicrobial disks (Bio-Rad, France) used were:gentamicin (15 µg), amikacin (30 µg), tobramycin(15µg), Amoxicillin (25µg), amoxicillin + clavulanic acid (20µg), cefepim (30µg), cefotaxim (30µg), ceftriaxon (30µg), cefoxitin (30µg), imipenem (10µg), ciprofloxacin (5µg), cotrimoxazole (1.25 / 23.75µg), nalidixic acid (30ug) and fosfomycin (50µg).

ESBL strains screening

The double-disk synergy tests (DDST) to detect ESBL-producing isolates was performed on Mueller-Hinton agar, placingcefepim, cefotaxim, and ceftriaxone discs around the amoxicillin + clavulanic acid diskat a distance of 3cm from the center to center, according to theEuropean Committee on Antimicrobial Susceptibility Instructions (EUCAST) guidelines (CA-SFM/EUCAST, 2016) (14).

Determination of multiple antibiotic resistance index

Multiple antibiotic resistance index (MAR) was determined using the formula MAR=*x/y*, where *x* was the number of antibiotics to which test isolate displayed resistance and *y* is the total number of antibiotics to which the test organism has been evaluated[15].

Statistical analysis

Statistical analysis was performed with Excel and Anova one-way GrapPad Prism version 5.01. Chi-square ($\chi 2$) test was used to calculate probabilities and determine significance. A p-value of less than 0.05 was considered to be statistically significant ($p<0.05$).

RESULTS

Characteristic of the study population and distribution of strains

(162 men and 162 women) in 3 hospital centers in Ouagadougou, Burkina Faso.The mean age of these patients was 33.7 ± 2 years and the sex ratio 1.7.

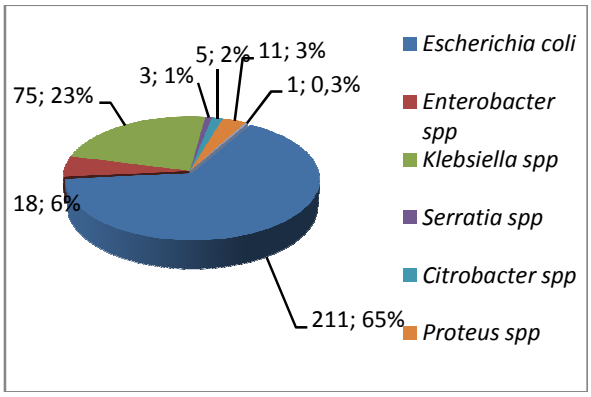


FIGURE 1: DISTRIBUTION OF DIFFERENT SPECIES BELONGING TO*ENTEROBACTERIACEAE* FAMILY ISOLATED DURING THE STUDY

This figure showed that urine samples are the samples which predominant 65% (211)

Out of 324 *Enterobacteriaceae* isolates, 211(65%)were *E. coli*, 75 (23%) *Klebsiella* spp., 18 (6%) *Enterobacter* spp., 11 (3%)*Proteus* spp., 5 (2%) *Citrobacter* spp., *Serratia* spp. 3 (1%)as shown inFigure 1.

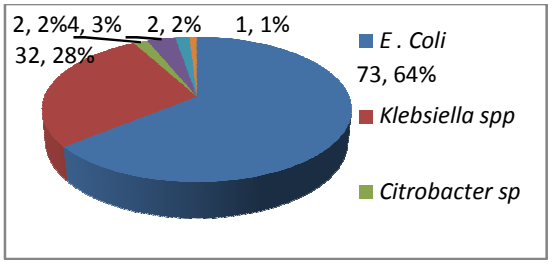


FIGURE 2: ESBL PRODUCING ISOLATES WITHIN INDIVIDUAL STRAINS DIVIDED BY TOTAL ISOLATES OF THAT ORGANISM REPRESENT PERCENT ESBL ISOLATES. ESBL PRODUCING *E. COLI* IS DOMINANT

The most frequent urinary *Enterobacteriaceae* isolated were *E. coli, Klebsiella species, and Enterobacter species.* Other urinary tract bacteria were isolated in relatively few number. These included *Citrobacter* spp., *Proteus* spp. *Serratia* spp. and *Providencia* spp.

A total of 324 clinical isolates belonging to *Enterobacteriaceae* family were obtainedfrom patients

TABLE 1:AGE WISE DISTRIBUTION OF ESBL-PRODUCING *ENTEROBACTERIACEAE* IN DIFFERENT AGE GROUPS

Age groups (years)	Total number of isolates (n=324)	ESBL positive (n=114)	Percent ESBL positive	P-value
< 15 years	67	28	42%	
15-45 years	135	44	33%	0.5321*
46-60 years	38	12	32%	
>60 years	84	30	36%	

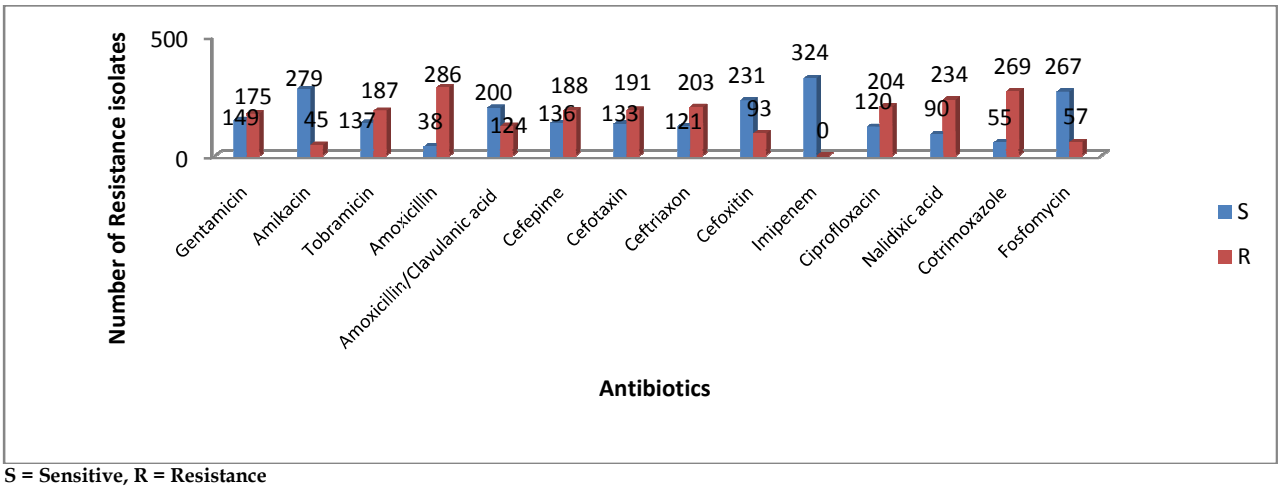
***p = 0.5321, no significant statistically**

TABLE 2:RESISTANCE RATE OF44 ESBL-PRODUCING *ENTEROBACTERIACEAE* TO ANTIBIOTICS IN OUAGADOUGOU, BURKINA FASO

Antibiotics	Resistance rate	
	I+R(%)	S(%)
Gentamicin	37(84)	7(16)
Amikacin	1(2)	43(98)
Tobramicin	36(82)	8(18)
Amoxicillin	44(100)	0
Amoxicillin/ clavulanicacid	9(20)	35(80)
Cefoxitin	8(18)	36(82)
Ceftriaxon	42(95)	2(5)
Cefotaxim	43(98)	1(2)
Cefepime	42(95)	2(5)
Imipenem	0	44(100)
Nalidixicacid	38(86)	6(14)
Ciprofloxacin	40(91)	4(9)
Cotrimoxazole	44(100)	0
Fosfomycin	12(27)	32(73)

Antibiotics susceptibility test

The antibiotic resistance profile of the urinary tract isolates is shown in figure 3. All the strains isolated showed high resistance to amoxicillin 88% (286/324), amoxicillin/clavulanicacid 38% (124/324), gentamicin 54% (175/324), tobramycin 58% (187/324), ciprofloxacin 63% (204/324), nalidixic acid 72% (234/324) and to cotrimoxazole 83% (269/324). However, there was low resistance toamikacin 14% (45/324)and fosfomycin 18% (57/324) (Figure 3). All strains were susceptible toimipenem. *Escherichia coli and Klebsiella pneumonia* showed high rate of resistance to gentamicin, tobramycin, amoxicillin and all the 3rd generation cephalosporins (Figure 3).



S = Sensitive, R = Resistance

FIGURE3: RESULTS OF OVERALL RESISTANCE AND SENSITIVITY OF ALL *ENTEROBACTERIACEAE*ISOLATES TO ANTIBIOTICS. AMIKACIN, IMIPENEM AND FOSFOMYCIN SHOWED THE BEST SUSCEPTIBILITY RATE.

Occurrence of ESBL-producing *Enterobacteriaceae*

The overall rate of ESBL-producing *Enterobacteriaceae* in UTIs in both male and female patients was found to be 35% (114/324). The frequency of ESBL strains within individual organism group was *E. coli* 64% (73/324),*Klebsiella*spp. 28% (32/324), E*nterobacter*spp. 3% (4/324), *Proteus* spp.and*Citrobacter* spp.2% (2/324)as shown in Figure 2.*E. coli* strains producingESBL were higher than those of the other species.

Considering the clinical isolates origin, ESBL strains rate was 24 % (78/324) at CHU-YO, 4% (13/324) at Saint Camille Hospital (HOSCO) and 7 % (23/324) at CHUP-CDG.The mean age of patients with ESBL producing organisms was 32.38 years compared to 27.66 years for patients with non-ESBL strains. ESBL production among various age groups ranged from 32% to 42%. However, there was no statistically significant difference between the age groups (Table 1) with respect to ESBL production (p = 5321).ESBL producing strains showed high susceptibility rateswith imipenem 100% (114/114), amikacin 93% (106/114), cefoxitin 74% (84/114) and fosfomycin 84% (96/114) (Table 2)

DISCUSSION

In this study, we investigated the frequency of ESBL production by *Enterobacteriaceae* isolates in three hospitals in Ouagadougou, Burkina Faso.

A total of 324 clinical isolates belonging to *Enterobacteriaceae* family were obtained from urine samples from these3 centers in Ouagadougou, Burkina Faso from November 2014 to October 2015. These bacteriawere isolated from 162 females and 162 males. The patients mean age was33.7 ± 2 years and the sex ratio 1.7.

UTIs are the most common nosocomial infections, comprising about 35% of such occurrences in both hospitals and nursing homes [16].

More than 95% of UTIs are caused by a single bacterial specie and *Escherichiacoli* is by far the most frequent infecting organism in acute infections[17]. The spectrum of strains isolated from urinary samples in this study is not different from those reported in literature.

In this study, all of the 324 *Enterobacteriaceae* strains, *Escherichia coli* predominated followed by *Klebsiella* spp. and *Enterobacter*spp.*Citrobacter*spp. and*Proteus* spp. were less significant.

In several others studies in Burkina Faso,Sudan, India,Pakistanand Ivory Coast[18,19,20,21,27]the authorsreported that *Escherichiacoli* was also the most common isolate followed by *Klebsiella*spp., *Enterobacter*spp. and *Proteus* spp.

E. coli remains an essential bacterium in urinary tract infections. Wilson and Gaido[28]also reported that *E. coli*is the major bacterial etiology of urinary tract infections. This corroborates the high frequency of *E. coli* isolates reported in our study.

The antibiotic susceptibility tests revealed in our study high levels of resistance to certain molecules used in common practice.Our study also revealed that 88% (286/324)of isolates were resistance to amoxicillin, which may be due to the frequent and possiblemisuse of this antibiotic. The resistance rate to amoxicillin + clavulanicacid was38% (124/324).In contrast with the report of Adonis-Koffi*etal.*[30] in Ivory Coast who obtained a resistance rate of 68% to amoxicillin + clavulanic acid.

The high levelresistance of the *Enterobacteriaceae*to 3rd and 4th generation cephalosporin antibiotics were also observed (cefepim showed 58%, cefotaxim 59% and ceftriaxon 63%).

The most active molecule among the aminoglycosideantibiotic family was amikacinand the resistance rate of strain was 14%;BonniCisse et *al.* [27] did observe the same trend in Ivory Coast. Other aminoglycoside antibiotics tested were gentamicin and tobramicinwith resistance rates of 54% and 58%respectively.Leski et *al.*[29]in Sierra Leone however reported ahigh percentage (73%) resistance to gentamicin.

Furthermore, the clinical strains showed very high resistance to ciprofloxacin and nalidixic acid and the

resistance rates were 63% (204/324) and 72% (234/324)respectively.Results of our study is similar to that of Guessennd et *al*. [25] conducted from 2005 to 2006 in which the resistancerateto quinolones was 71% to ciprofloxacin and 77% tonalidixic acid. Fosfomycin had the bestactivity among antibiotics used, where strains showed 82% susceptibility. We observed high resistance rate tocotrimoxazolewith 83% (269/324), this is in line with reports of BonniCisse *et al*.[27] and Guessennd *et al*. [25]in which they reported 76% and 91% resistance to cotrimoxazole respectively in Ivory Coast. These high rates could be attributed to the use of cotrimoxazole in chemoprophylaxis in the treatment of opportunistic infections in immunocomprimised patients.

The resistance to antibiotics and ESBL production spares no country in the world.The frequencies of ESBL producing strains vary from country to country and from species to species in the world [22, 23].

Studies carried out by Ouedraogo et *al*. [24]in Burkina Faso. Mohantyet *al*. [26]in India reported the overall prevalence of 58% and 69% ESBL producing bacteria respectively. Our study showed a prevalence of 35% ESBL producing strain which is relatively high and is almost similar to other data which showed high prevalence.

This resistance is often associated with antibiotics such as aminoglycosides and quinolones (Table 2). The emergence of these Bacteria Multi-Resistances (BMRs) in hospitals of Ouagadougou could lead to therapeutic failures despite the administration of aminoglycosidesand 3rd generation cephalosporins. While the issue of antibiotic resistance has long been considered a concern in hospitals for nosocomial infections, in recent years the problem has been extended to include community medicine [32]. One of the reasons is the high consumption of antibiotics in human medicine, the illicit sale of antibiotics on the streets, and the increased movement of colonized or infected patients between hospitals and community settings [32].

However, the good susceptibility of the ESBL-producing*Enterobacteriaceae* to imipenem100% (114/114) and also to amikacin93% (106/114), cefoxitin74% (84/114) and fosfomycin84% (96/114) makes them the molecules of choice in alone treatment or in combination of other antibiotics (Table 2).

These results should act as an impetus for the establishment of antibiotic control policies. Indeed, currently there is no restriction in the use of antibiotics in Burkina Faso.

Conclusion

UTIs antibiotics therapyshould be guided by antimicrobial susceptibility as increasing numbers of urinary isolates are developing resistance to commonly use antibiotics. Increasing antimicrobial resistance of *Enterobacteriaceae* has led to reconsideration of traditional treatment of recommendations in many areas. This experimental study should be followed by several studies on antimicrobial resistance among patients in Burkina Faso hospitals and other regions of West Africa as there is relatively few data concerning the antibiotic susceptibility spectrum of bacteria isolated from patients with UTIs.

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