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Point-surveillance of antibiotic resistance in *Enterobacteriaceae* isolates from patients in a Lagos Teaching Hospital, Nigeria☆

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Summary
Objectives: This study was carried out to determine a point prevalence of drug resistance and extended-spectrum β-lactamase (ESBL) among members of the family *Enterobacteriaceae*.
Methods: Consecutive clinically significant non-repetitive isolates obtained from both hospitalized patients and outpatients' samples were studied. The isolates were identified using VITEK 2 while susceptibility testing was performed against 16 antibiotics using the *E*-test strips. Phenotypic production of ESBL was detected by *E*-test ESBL method. Positive isolates were confirmed by PCR.
Results: Of a total of 102 isolates studied, 43 (42.2%) were *Escherichia coli* and 32 (31.4%) *Klebsiella pneumoniae*. These isolates demonstrated remarkable high rates of resistance to the β-lactam antibiotics, except the carbapenems and piperacillin—tazobactam. Fifty-two (51%) were resistant to ≥3 classes of drugs and 29 (28.4%) to ≥5 drugs. Thirty-eight (37.3%) were ESBL producers. Of these, 21 (55.3%) were *E. coli* and 12 (31.6%) *K. pneumoniae*. Thus, the overall prevalence of ESBL-producing *E. coli* was 20.6% and *K. pneumoniae* 11.8%.
Conclusions: This study showed an alarmingly high prevalence of antibiotic resistance in invasive *Enterobacteriaceae* isolates and a high prevalence of ESBL producers in the study center. Antibiotic stewardship and other preventive strategies are recommended to reduce the high rate of resistant bacteria in this hospital.

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Introduction

Antibiotic resistance in clinical bacterial isolates is a major problem in health care settings and of grave public health concern worldwide [1—3]. There are several reasons for the emergence of antibiotic resistant microorganisms in the clinical setting. Empirical use of antibiotics, particularly the broad-spectrum antibiotics, appears to be a major factor driving the emergence of these resistant bacteria [4,5]. The burden of diseases caused by these resistant bacteria in developing countries is poorly documented.

Extended-spectrum β-lactamases (ESBLs) capable of degrading the cephalosporins and monobactams are among the most important resistance determinants emerging in *Enterobacteriaceae* worldwide [6]. ESBLs are β-lactamases capable of conferring bacterial resistance to the penicillins, first-, second-, and third-generation cephalosporins and aztreonam by hydrolysis, excluding the cephamycins and carbapenems [7]. These enzymes hydrolyze extended-spectrum cephalosporins such as ceftazidime or cefotaxime as well as monobactams (aztreonam) and are inhibited by β-lactamase inhibitors. [8]. Although the prevalence and epidemiology of ESBLs have been well documented in the developed countries there is paucity of data on the prevalence of antibiotic resistance and ESBL-production in *Enterobacteriaceae* from the developing countries. It is conceivable that these resource-limited countries could harbor new clones of ESBLs with propensity to disseminate globally. Therefore, it is of utmost importance to investigate the existence of multidrug-resistant pathogens in the developing countries.

This study was undertaken to determine the point-prevalence of multidrug-resistant and ESBL-producing members of the family *Enterobacteriaceae* in a state teaching hospital in Lagos.

Materials and methodology

Bacterial isolates

One hundred and two consecutive clinically significant, non-repetitive isolates of the family *Enterobacteriaceae* recovered from samples of 102 patients attending Lagos State University Teaching Hospital (LASUTH), over a period of one month (October 2011), were studied. LASUTH is a state-owned 700-bedded teaching hospital with two intensive care units (ICUs), a dialysis unit, and an oncology unit. The demographic biodata of all patients as well as previous hospital admissions and travel history were documented.

Bacterial identification

The bacterial isolates were identified using VITEK-2 system (bioMérieux, Hazelwood, MO, USA). Isolates with low scores on VITEK-2 were subjected to further identification on VITEK MS (bioMerieux, Marcy-l'Etoile, France), a matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry system newly acquired in our Kuwait laboratory.

Susceptibility testing

The minimum inhibitory concentrations (MICs) of 16 antibiotics, amikacin, ampicillin, amoxicillin-clavulanic acid, aztreonam, cefepime, cefotaxime, ceftazidime, cefuroxime, ciprofloxacin, colistin, ertapenem, gentamicin, imipenem, meropenem, piperacillin—tazobactam, and tigecycline, were determined on Mueller-Hinton agar (Oxoid, Basingstoke, UK) using *E*-test (bioMerieux, France) according to manufacturer's protocol. Quality Control strain *Escherichia coli* ATCC 25922 was included in each run for media and potency controls. The results were interpreted according to the breakpoints and criteria recommended by the Clinical Laboratory Standard Institute (CLSI) [9].

Detection of extended-spectrum β-lactamase (ESBL)

The *E*-test ESBL method using cefotaxime (CT)/cefotaxime combined with clavulanic acid (CTL) and ceftazidime (TZ)/ceftazidime combined with clavulanic acid (TZL) (bioMerieux) were used for the phenotypic identification of the ESBL-producing strains according to the manufacturer's protocol.

Results

The ages of the 102 patients ranged from 5 months to 90 years (mean = 42.4 years); they were 52 females and 50 males. All patients were Nigerians of Southwestern region origin. Ninety-four (92.2%) were adults and eight (7.8%) pediatric patients. None gave history of previous travel outside the country or previous admission to other hospitals prior to the present hospital admission or visit.

One isolate per patient was studied. Of the 102 isolates, 43 (42.2%) were *E. coli*, 32 (31.4%) *K. pneumoniae*, 11 (10.8%) *Proteus mirabilis*, 10 (9.8%)

Enterobacter cloacae, 4 (3.9%) *Morganella morganii* and 2 (1.9%) *Citrobacter* spp. Out of these, 91 (89.2%) and 11 (10.8%) were from hospitalized and clinic patients, respectively.

Focus of infection

Sixty-six (64.7%) isolates were from urinary tract infections (UTI); 4 (3.9%) from blood stream infections and 20 (19.6%) from skin, soft tissue and surgical site infections. Other 6 (5.9%) isolates were from respiratory tract infections; 2 (2%) ear infections and 4 (3.9%) body fluids.

Antibiotic susceptibility

The MICs of the tested antibiotics are shown in Table 1. These results demonstrated remarkable high resistance rates to the β-lactam antibiotics, except the carbapenems and piperacillin—tazobactam. Colistin, imipenem, meropenem and tigecycline demonstrated excellent activities against all isolates with mean MIC_{90}s of 1.4, 0.88, 0.53 and 1.125 μg/ml, respectively. Amikacin and piperacillin—tazobactam also showed very good activities with MIC_{90}s that ranged between 2—16 and 2—12 μg/ml, respectively. Four (9.3%) of *E. coli* and 4 (12.5%) *K. pneumoniae* isolates were resistant to amoxicillin-clavulanic acid (MIC_{90}s = 4 and 12 μg/ml, respectively); mostly at low-levels with over half of the isolates requiring only 2 and 0.25 μg/ml for inhibition. Resistance rates of these two important pathogens to ampicillin (MIC_{90}s of > 256 μg/ml) were 74.4 and 100%, respectively, and to aztreonam (MIC_{90}s of 32 and >256 μg/ml) 72.1 and 78.1%, respectively. These isolates were also highly resistant to the cephalosporins including a fourth-generation cephalosporin, cefepime with MIC_{90}s of 32 and >256 μg/ml, respectively. The overall resistance rates were 34.9% and 37.5%, respectively. The MIC_{90}s of cefotaxime and ceftazidime were each >256 μg/ml, with resistance rates of 39.5% and 46.9%, respectively. The *P. mirabilis* isolates exhibited acceptable susceptibility ranges to all the antibiotics tested except ampicillin, aztreonam, and cefuroxime with resistance rates of 36.4, 27.3, and 36.4%, respectively. Resistance against ceftazidime was relatively high (18.2%). High resistance rates were also observed for *E. cloacae* against ampicillin (90%), aztreonam (80%), cefepime (70%), cefotaxime (80%), ceftazidime (60%), and cefuroxime (100%). It is noteworthy that one isolates each of *P. mirabilis* and *E. cloacae* had imipenem MIC of 8 μg/ml.

Prevalence of multidrug-resistant (MDR) isolates

Fifty-two (50.1%) of the isolates were multidrug-resistant (MDR). MDR is defined in this study as resistance to ≥3 classes of antibiotics. Twenty-eight (53.9%) of these were resistant to 3—4 classes of antibiotics and 24 (46.2%) to ≥5 classes. The most common MDR isolates were *E. coli* and *K. pneumoniae* accounting for 28 (53.9%) of 52 and 15 (28.9%), respectively. Six (60%) of 10 *E. cloacae* were resistant to more than three classes of antibiotics. The other isolates, *P. mirabilis*, *M. morganii* and *Citrobacter freundii*, were too small in number for any meaningful analysis.

Prevalence of ESBL-producing Enterobacteriaceae

Table 2 shows the point prevalence of ESBL-positive isolates. Out of the 102 isolates, 38 were ESBL producers, giving a point prevalence of 37.3%. Of these, 21 (55.3%) were *E. coli*, 12 (31.6%) *K. pneumoniae*, 3 (7.9%) *Proteus* spp., 1 (2.6%) *M. morganii* and 1 (2.6%) *C. freundii*. Thus, the overall prevalence of ESBL-producing *E. coli* was 20.6%, *K. pneumoniae* 11.8%, *Proteus* spp., 2.9%, *M. morganii* and *P. mirabilis* 1.0% each.

ESBL-producing isolates were multiply resistant to the cephalosporins (MIC90s = >256 μg/ml) ampicillin (MIC90s = >256 μg/ml), aztreonam (MIC90s = >256 μg/ml) and ciprofloxacin (MIC90s = >32 μg/ml). They were however susceptible to amikacin, colistin, imipenem, meropenem and tigecycline.

Discussion

According to a publication on behalf of the Infectious Diseases Society of America, ESBL-positive *E. coli* and *K. pneumoniae* are two of the organisms that are in need of urgent new therapies [10]. In our report, *E. coli* was the commonest etiological agent of nosocomial and community-acquired, complicated, and uncomplicated urinary tract infections (UTI) and bloodstream infections as in many parts of the world [11—13]. Until recently, this organism used to be the most susceptible member of the family *Enterobacteriaceae*.

Our data demonstrates very high prevalence rates of ampicillin-resistant *E. coli*, *E. cloacae*, and *M. morganii*. The carbapenems, except ertapenem, demonstrated excellent activities against all ESBL-producing and non-ESBL-producing isolates. Over

Table 1 Antimicrobial susceptibility pattern of the *Enterobacteriaceae* isolates in Lagos.

Bacteria/antibiotics	Minimum inhibitory concentrations of antibiotics (MICs; μg/ml)			No. (%) Resistant
	Range	MIC_{50}	MIC_{90}	
Escherichia coli (43)				
Amikacin	0.019—256	2	16	**3 (7.0)**
Ampicillin	0.002—>256	>256	>256	**32 (74.4)**
Amoxicillin-clavulanate	0.032—256	2	12	**4 (9.3)**
Aztreonam	0.064—>256	4	32	**31 (72.1)**
Cefepime	0.004—>256	0.05	32	**15 (34.9)**
Cefotaxime	0.094—>256	0.064	>256	**17 (39.5)**
Ceftazidime	0.004—>256	0.125	>256	**12 (27.9)**
Cefuroxime	0.05—>256	2	>256	**30 (69.8)**
Ciprofloxacin	0.002—>32	0.012	>32	**25 (58.1)**
Colistin	0.002—2	0.002	2	**1 (2.3)**
Ertapenem	0.012—8	0.0125	0.75	**7 (16.3)**
Gentamicin	0.064—>256	1	16	**9 (20.9)**
Imipenem	0.094—1.5	0.125	0.75	**0 (0)**
Meropenem	0.023—0.5	0.094	0.125	**0 (0)**
Piperacillin—tazobactam	0.008—>256	0.75	12	**4 (9.3)**
Tigecycline	0.06—2	0.5	1.5	**0 (0)**
Klebsiella pneumoniae (32)				
Amikacin	0.002—64	0.5	4	**1 (3.1)**
Ampicillin	4—>256	>256	>246	**31 (96.9)**
Amoxicillin-clavulanate	0.064—>256	0.25	16	**4 (12.5)**
Aztreonam	0.05—>256	0.75	>256	**25 (78.1)**
Cefepime	0.094—>256	0.5	>256	**12 (37.5)**
Cefotaxime	0.002—>256	1	>256	**15 (46.9)**
Ceftazidime	0.002—>256	0.75	32	**10 (31.3)**
Cefuroxime	0.094—>256	2	>256	**17 (53.5)**
Ciprofloxacin	0.002—>32	0.0125	>32	**14 (43.8)**
Colistin	0.002—2	0.064	1.5	**0 (0)**
Ertapenem	0.047—1.5	0.064	0.5	**3 (9.4)**
Gentamicin	0.125—>256	0.5	>256	**13 (40.6)**
Imipenem	0.094—1	0.125	0.25	**0 (0)**
Meropenem	0.023—0.75	0.047	1	**0 (0)**
Piperacillin—tazobactam	0.025—>256	0.5	8	**1 (3.1)**
Tigecycline	0.002—1.5	0.125	1	**0 (0)**
Proteus mirabilis (11)				
Amikacin	0.064—64	0.75	2	**0 (0)**
Ampicillin	0.002—>256	1	16	**4 (36.4)**
Amoxicillin-clavulanate	0.002—4	0.025	4	**0 (0)**
Aztreonam	0.0125—64	0.25	32	**3 (27.3)**
Cefepime	0.002—256	0.064	2	**1 (9.1)**
Cefotaxime	0.004—>256	0.094	2	**1 (9.1)**
Ceftazidime	0.002—8	0.125	32	**2 (18.2)**
Cefuroxime	0.002—>256	0.25	128	**4 (36.4)**
Ciprofloxacin	0.002—4	0.025	2	**1 (9.1)**
Colistin	0.025—1	0.125	1	**0 (0)**
Ertapenem	0.002—0.25	0.094	0.125	**0 (0)**
Gentamicin	0.064—4	0.064	2	**0 (0)**
Imipenem	0.002—8	0.064	1	**1 (9.1)**
Meropenem	0.002—1.5	0.023	0.5	**0 (0)**
Piperacillin—tazobactam	0.002—4	0.046	2	**0 (0)**
Tigecycline	0.064—2	0.125	1	**0 (0)**
Enterobacter cloacae (10)				
Amikacin	0.064—64	0.75	4	**0 (0)**

Table 1 (*Continued*)

Bacteria/antibiotics	Minimum inhibitory concentrations of antibiotics (MICs; μg/ml)			No. (%) Resistant
	Range	MIC_{50}	MIC_{90}	
Ampicillin	0.002—>256	2	64	**9 (90)**
Amoxicillin-clavulanate	0.002—32	0.025	128	**5 (50)**
Aztreonam	0.0125—>256	2	>256	**8 (80)**
Cefepime	0.002—256	0.5	256	**7 (70)**
Cefotaxime	0.004—>256	0.75	>256	**8 (80)**
Ceftazidime	0.002—8	0.125	32	**6 (60)**
Cefuroxime	0.002—>256	32	>256	**10 (100)**
Ciprofloxacin	0.002—4	0.025	1	**1 (10)**
Colistin	0.025—1	0.125	1	**0 (0)**
Ertapenem	0.002—0.5	0.094	0.5	**0 (0)**
Gentamicin	0.064—16	0.064	16	**2 (20)**
Imipenem	0.002—8	0.064	1	**1 (10)**
Meropenem	0.002—1.5	0.023	0.5	**0 (0)**
Piperacillin—tazobactam	0.002—4	0.046	8	**0 (0)**
Tigecycline	0.064—2	0.125	1	**0 (0)**

The others (*M. morganii* (4) and *Citrobacter* spp. (2)) are not included in the table.

90% of the isolates were inhibited at very low concentrations of these drugs. This information is crucial, as these agents are the recommended drugs of choice for treating infections caused by ESBL-positive *Enterobacteriaceae* and show excellent pharmacodynamic profiling against members of this family of organisms. Note worthily, our data shows that the activity of the carbapenems against ESBL-producing *Enterobacteriaceae* is not necessarily a class effect as there are some notable differences in activity among individual carbapenems as demonstrated by the fact that about 16% of *E. coli* and over 9% of *K. pneumoniae* were resistant to ertapenem. This observation supports the recommendation of the CLSI [9] to use ertapenem as screening drug to detect resistance to carbapenems in *Enterobacteriaceae* in order to avoid missing potential carbapenemase producers. However, it is possible that this low-level resistance to only ertapenem may be due to mechanisms other than carbapenemase-mediated resistance such as the presence of ESBL and reduced permeability because of porin loss.

Antibiotics with excellent activities against the *Enterobacteriaceae* isolates were colistin, tigecycline, amikacin and, to lesser extent, piperacillin—tazobactam. They remain alternatives for treatment of serious infections caused by members of the family *Enterobacteriaceae*. Colistin and tigecycline appear to be excellent alternatives for treating multidrug-resistant isolates including ESBL-positive strains. However, a cautionary note is the limitations of the use of these drugs such as inadequate serum level of tigecycline and toxicity of colistin. piperacillin—tazobactam is not recommended for treating serious infections caused by

Table 2 The prevalence of ESBL-producing isolates among the *Enterobacteriaceae*.

Bacteria (no. of isolate)	No. (%) of ESBL-positives	Proportion (%) of ESBL-positives ($n = 38$)	Overall prevalence (%) of ESBL-producers (38/102)
E. coli (43)	21 (48.8)	55.3	20.6
K. pneumoniae (32)	12 (37.5)	31.6	11.8
Proteus mirabilis (11)	3 (27.3)	7.9	2.9
E. cloacae (10)	1 (10)	2.6	1.0
M. morganii (4)	1 (25)	2.6	1.0
C. freundii (2)	0 (0)	0 (0)	0 (0)

ESBL-producing *Enterobacteriaceae* but has been recommended as a second choice for treating non-bloodstream *E. coli* infections [14].

Resistance of our isolates to the cephalosporins is unacceptably high, particularly resistance to cefepime, cefotaxime, and ceftazidime. These antimicrobials are potent life-saving drugs and finding many isolates with MIC_{90}s as high as >256 μg/ml is worrisome. It is conceivable that high resistance rates might have been driven by overuse of these drugs, particularly as they are often used as first-line drugs in this hospital. Obviously, this finding makes these drugs unreliable for empiric therapy in serious infections caused by *E. coli* and *K. pneumoniae*.

The high resistance rate to ciprofloxacin by *E. coli* and *K. pneumoniae* is certainly one of the highest reported in the literature. These rates are higher than those reported in the MYSTIC and SENTRY Surveillance programs [15] for Latin American, Northern European and Southern European countries, as well as some Western Pacific countries. This alarming phenomenon of high level resistance to ciprofloxacin in Lagos may be explained, in part, by the abuse of the drug by a large number of physicians in the country. Many doctors use ciprofloxacin to treat almost every fever with slightly raised ''H'' antibodies in Widal test that are often misinterpreted as typhoid fever. These observations, perhaps, is a tip of the iceberg. Another prevalence study over a longer period involving much larger number of isolates is being planned to confirm and extend our initial findings.

The point prevalence (37.3%) of ESBL-producing members of the family *Enterobacteriaceae* in our study was very high although studies from other centers in the country have found comparable and much higher prevalence rates ranging from 36.6% in Benin-City in the south [16] to 66.7% [17] in Kano in the north. However, these values, including our findings, should be compared with caution since the methods employed in the ESBL detection in all of these studies were dependent solely on phenotypic analysis. Nonetheless, we believe that the important message from our study and others is the demonstration of high prevalence of ESBL-producing *Enterobacteriaceae* in our hospitals.

Conclusion

In conclusion, our study demonstrated high prevalence rates of multidrug-resistant invasive isolates of *Enterobacteriaceae*, a high number of which were ESBL producers. Antibiotic stewardship and other preventive strategies are recommended to stem the spread of antibiotic resistance in *Enterobacteriaceae* in our hospital.

Conflict of interest statement

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