

Prevalence and Antimicrobial Susceptibility Pattern of Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae in the United Arab Emirates

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Key Words

Antimicrobial resistance · Enterobacteriaceae · *Escherichia coli* · *Klebsiella pneumoniae* · Extended spectrum β-lactamase

Abstract

Objective: To investigate the prevalence and antibiotic susceptibility pattern of extended-spectrum β-lactamases (ESBL)-producing *Enterobacteriaceae* among patients in the United Arab Emirates. **Materials and Methods:** A total of 130 *Enterobacteriaceae* comprising of *Escherichia coli* (n = 83), *Klebsiella pneumoniae* (n = 45) and *Klebsiella oxytoca* (n = 2) was studied. Of these 130 isolates, 64 were from urine. ESBL screening was by disc diffusion and confirmatory tests for ESBL phenotype were conducted using BD Phoenix™ ESBL System and cephalosporin/clavulanate combination discs. Susceptibility to a panel of antibiotics was evaluated. **Results:** Of the 130 isolates, 53 (41%) were identified as having ESBL phenotype; of these, 32 (60%) were *E. coli*, 20 (36%) *K. pneumoniae* and 2 (4%) *K. oxytoca*. ESBL phenotype was seen in 100% of endotracheal tubes isolates, 20 (31%) from urine, 7 (58%) from blood and 4 (80%) from catheter tips. Amikacin susceptibility was 100%. Over 90% of ESBL isolates showed resistance to aztreonam and cephalosporins. All *Klebsiella* isolates were carbapenem sensitive. One ESBL isolate showed intermediate resistance to imipenem and meropenem (both

MIC 8 μg/ml), cefotetan (MIC 32 μg/ml) and piperacillin/tazobactam (MIC 32 μg/ml). MIC for the carbapenems was lower in non-ESBL isolates (0.034 μg/ml) than ESBL isolates (0.071 μg/ml). Resistance to gentamicin, ciprofloxacin and piperacillin/tazobactam was higher in ESBL than non-ESBL isolates (p < 0.05). **Conclusion:** A high prevalence of ESBL-producing bacteria exists among in-patients in the United Arab Emirates. Amikacin and carbapenems remain the most effective drugs, but the presence of carbapenem-resistant ESBL-producing *E. coli* and occurrence of multidrug resistance are of concern. Continued surveillance and judicious antibiotic usage are recommended.

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Introduction

The upward trend in the prevalence of pathogens producing extended-spectrum β-lactamases (ESBL) is of increasing clinical concern. Infections with these ESBL-producing organisms continue to be associated with higher rates of mortality, morbidity and health care costs. ESBL arise as a result of mutations in the TEM-1, TEM-2, or SHV-1 genes which are commonly found in the *Enterobacteriaceae* family [1]. The mutation causes an alteration of their amino acid configuration making these enzymes capable of hydrolyzing a wider spectrum of

β -lactam antibiotics including penicillins, oxyiminocephalosporins, such as cefotaxime (CTX), ceftazidime (CAZ), and ceftriaxone, as well as monobactams, e.g. aztreonam. However, these plasmid-mediated enzymes have no detectable activity against carbapenems and their activity is inhibited by clavulanic acid (CA) [1, 2]. Although ESBLs occur predominantly in *Klebsiella* species and *Escherichia coli*, they have also been described in other genera of the Enterobacteriaceae, family including *Citrobacter*, *Serratia*, *Proteus*, *Salmonella*, and *Enterobacter* [1, 2]. Additionally, other types of ESBL such as CTX-M and OXA type enzymes have now been described [1, 3, 4]. ESBL-producing strains often exhibit a multi-drug-resistant phenotype, including resistance to aminoglycosides and fluoroquinolones, further limiting the therapeutic options available to the clinician [5, 6].

The first description of ESBL-producing organisms was reported in 1983 [7] and since then reports from Europe, the USA and the Far East have confirmed the role of ESBL-producing organisms in nosocomial infections [1]. However, the prevalence of ESBL among clinical isolates varies among geographic areas with low rates of 3–8% in Sweden, Japan and Singapore to much higher prevalence rates reported from Portugal: 34%, Latin America: 30–60%, and Turkey: 58% [1, 8, 9]. This study presents the first reported data describing the prevalence and antibiotic susceptibility pattern of ESBL-producing *Enterobacteriaceae* among patients in the United Arab Emirates (UAE).

Materials and Methods

Bacterial Strains

The study was carried out at the Microbiology Laboratory, Al-Qassimi Hospital, Sharjah, United Arab Emirates from April 2005 to May 2006. Specimens/isolates were obtained from in-patients in six general hospitals in the UAE. Duplicate isolates from the same patient was not allowed, hence only one isolate was accepted per episode of infection. A total of 130 Enterobacteriaceae comprising *E. coli*: 83, *Klebsiella pneumoniae*: 45, and *Klebsiella oxytoca*: 2 isolated during the collection period were included in the study. Of the 130 isolates, 64 were from urine and the proportion obtained from different specimen types are listed in table 1. Identification of isolates was done based on cultural characteristics and reactions in standard biochemical tests.

Detection of ESBL

In keeping with the Clinical and Laboratory Standards Institute (CLSI) recommended guidelines [10], screening for ESBL was performed by disc diffusion using CAZ and cefpodoxime; confirmatory tests for ESBL phenotype were carried out using BD Phoenix™ ESBL Automated System (Becton, Dickinson, Md., USA) and cephalosporin/clavulanate combination discs. These

Table 1. Number of *Enterobacteriaceae* isolated from different specimen types

Specimen	Isolates
Urine	64
Blood	12
Pus	12
High vaginal swab	10
Sputum	9
Wound	7
Endotracheal tubes/secretion	6
Catheter tip	5
Ear/eye secretions	3
Cerebral spinal fluid	1
Umbilical cord	1
Total	130

tests were applied to all 130 isolates. The Phoenix™ ESBL test used fixed concentrations of the following drugs or drug combinations: cefpodoxime, CAZ, CAZ plus CA, CTX plus CA, and ceftriaxone plus CA. The isolates were subcultured on MacConkey agar to obtain a pure culture from which a 0.5 McFarland suspension was obtained and tested according to the manufacturer-provided protocol. Phenotypic confirmation with antibiotic disks containing a combination of cephalosporin plus CA in conjunction with a corresponding cephalosporin disc alone was carried out and interpreted according to CLSI guidelines [10]. Discs used were CAZ (30 μ g), CAZ plus CA (CAZ/CA, 30/10 μ g), CTX (30 μ g) and CTX plus CA (CTX/CA, 30/10 μ g) all obtained from Becton Dickinson, USA. Briefly, isolates were subcultured on MacConkey agar and 0.5 McFarland standard prepared from the pure colonies was inoculated on Muller Hinton agar plates. Cephalosporin discs (CAZ and CTX) and cephalosporin with CA discs (CAZ/CA and CTX/CA) were applied on the inoculated plates and incubated in ambient air at 35°C for 16 to 18 h. Following incubation, the diameter of the zones of inhibition was measured and a ≥ 5 -mm increase in the zone of inhibition for the CAZ/CLA and CTX/CLA-containing disc versus the corresponding CAZ or CTX disc was considered positive for ESBL.

Antibiotics Susceptibility

The susceptibility of the isolates to a panel of antibiotics was evaluated using Vitek I (bioMérieux, Vitek Inc, Hazelwood, Mo., USA), BD Phoenix™ and Etest (AB Biodisk, Solna, Sweden). The antibiotic susceptibility of the isolates to the following agents was tested: amikacin, aztreonam, ciprofloxacin, gentamicin, cefotetan, cefuroxime, ceftriaxone, CAZ, CTX, imipenem, meropenem and piperacillin/tazobactam. *E. coli* ATCC 25922 was used as a negative control. The tests for the automated Vitek I and BD Phoenix system were carried out following manufacturer-recommended protocol. The Vitek cards for identification (GNI) and susceptibility testing (GNS-203, GNS108) were used. For the Etest, isolates were subcultured on MacConkey agar to obtain a pure culture. A 0.5 McFarland suspension was prepared from the pure culture and used to inoculate Muller Hinton agar plate prior

Table 2. Distribution of ESBL and non-ESBL producers among *E. coli* and *Klebsiella* spp. isolates

Isolate	ESBL	Non-ESBL
<i>E. coli</i> (n = 83)	32 (39%)	51 (61%)
<i>K. pneumoniae</i> (n = 45)	19 (42%)	26 (58%)
<i>K. oxytoca</i> (n = 2)	2 (100%)	0 (0%)

to application of Etest strips. Following incubation in inverted position at 35°C for 16–20 h, the MIC level was read and interpreted in accordance with CLSI guidelines.

Results

With the exception of one *E. coli* isolate, there was 100% agreement between the two confirmatory tests for ESBL detection. This isolate was determined to be ESBL positive by BD Phoenix and CTX +/- CLAV but non-ESBL by CAZ +/- CLAV. Of the 130 isolates, 53 (41%) were identified as having ESBL phenotype, of which 32 (60%) were *E. coli*, 19 (36%) *K. pneumoniae* and 2 (4%) *K. oxytoca*. The two *K. oxytoca* isolates were ESBL producers. The proportion of ESBL phenotypes for each microorganism is given in table 2. All six isolates obtained from endotracheal tubes showed ESBL phenotype. Additionally, 20/64 (31%) of isolates obtained from urine specimens, 7/12 (58%) from blood and 4/5 (80%) from catheter tips were found to be ESBL producers. In contrast, no ESBL-positive strain was obtained from high vaginal swab.

There was 100% susceptibility to amikacin. Of the 53 ESBL-producing isolates, 48 (90%) showed resistance to aztreonam (MIC ≥ 64 $\mu\text{g/ml}$) and cephalosporins with only two ESBL isolates being sensitive to CAZ (MIC ≥ 1 $\mu\text{g/ml}$) by all testing methods. With the exception of one non-ESBL *K. pneumoniae* and one ESBL *E. coli* isolates both with MIC > 32 $\mu\text{g/ml}$, all other isolates were sensitive to cefotetan. All *K. pneumoniae* and *K. oxytoca* isolates were sensitive to imipenem and meropenem. However, two *E. coli* isolates (one ESBL and one non-ESBL) were resistant to these drugs. The ESBL isolate which showed intermediate resistance to imipenem and meropenem (MIC by Etest: 8 $\mu\text{g/ml}$ for both drugs) also showed intermediate resistance to cefotetan (MIC 32 $\mu\text{g/ml}$) and piperacillin/tazobactam (MIC 32 $\mu\text{g/ml}$). Overall, the MIC for the carbapenems was lower in non-ESBL isolates compared with ESBL isolates (0.034 vs. 0.071 $\mu\text{g/ml}$, respectively).

A significantly higher proportion of ESBL-producing isolates compared to non-ESBL producers were found to be resistant to gentamicin (67 vs. 6%), ciprofloxacin (38 vs. 19%) and piperacillin/tazobactam (25 vs. 2.8%); $p < 0.05$.

Discussion

The presence of ESBL enables certain Gram-negative bacteria to inactivate extended-spectrum (third-generation) cephalosporins, broad-spectrum penicillins and monobactams but do not affect the cephamycins or carbapenems. As the presence of these enzymes significantly impacts the efficacy of β -lactam therapy, there is a need for clinical laboratories to accurately recognize ESBL producers so as to better support therapy and provide accurate prevalence data. The findings presented here indicate that there is a high prevalence of ESBL-producing Enterobacteriaceae circulating among hospitalized patients in the UAE. Global reports have shown that considerable differences exist in the occurrence and proportion of ESBL-producing isolates in different countries [1, 8, 9, 11–16]. In Europe, a large-scale survey of intensive care units found that the prevalence of ESBL in *Klebsiella* ranged from a low of 3% in Sweden to as high as 34% in Portugal [8]. Higher figures of 30–60% have been reported for the South American countries of Brazil, Venezuela and Colombia [11–13]. In Asia, National Surveys have indicated the presence of ESBLs in 5–8% of *E. coli* isolates from Korea, Japan, Malaysia and Singapore with higher rates of up to 24% for other Asian countries [1, 9]. ESBL production in *Klebsiella* have also been reported to be as low as 5% in Japan and Australia with higher rates of 20–50% in other parts of the continent [1, 9, 14]. In the Arabian Gulf region, 7.5% of Enterobacteriaceae and *Pseudomonas* isolated over a 1-year period in Kuwait were reported as being ESBL producers using the VITEK 2 system [15]. Thus, comparative to other surveys, the finding of 41% ESBL producers in this study is on the higher end of the spectrum. A predominance of either *K. pneumoniae* or *E. coli* has often been reported among the ESBL isolates identified in different geographical regions. A prevalence of ESBL-producing *K. pneumoniae* versus ESBL-producing *E. coli* (70 vs. 28.6%) has been reported in Pakistan [16], and in Italy a 2003 nationwide survey found that the most prevalent ESBL-positive species among hospitalized patients was *E. coli*, a switch from the predominance of *K. pneumoniae* in 1999 [17]. In contrast to these other reports, equal proportions of *K. pneumo-*

niae and *E. coli* were identified among the ESBL-producing isolates in our setting. Similar to other reports [18], the majority of Enterobacteriaceae isolates were from urine specimens, indicating the need for active screening of urine cultures for ESBL producers. Indeed, the detection of ESBL producers in urine has been described as representing an epidemiologic marker of colonization and potential for transfer between patients [1]. However, as high proportions of isolates obtained from other sources were found to be ESBL producers, it is imperative that active screening of Enterobacteriaceae isolates from all specimen types should be adopted to address the high prevalence rate of ESBL isolates. Unfortunately, many clinical microbiological laboratories still face significant problems with ESBL screening and identification as ESBL pathogens can present with variations in the in vitro pattern of resistance to β -lactam agents. Proficiency-testing studies performed by the World Health Organization and the Centers for Disease Control have raised concerns about the current ability of many clinical laboratories to detect ESBL-producing microorganisms [19, 20]. Some enzymes (TEM-3 and SHV-2) confer high levels of resistance to cephalosporins, whereas others, such as TEM-7 and TEM-12, confer low levels of resistance, which possibly makes it even more difficult to detect them through the susceptibility tests routinely used in microbiology laboratories. In this study, the CLSI protocol was applied with satisfactory results thus indicating that this approach of screening and phenotypic confirmation integrating both automated and manual methods is applicable in our setting and useful for incorporation into routine microbiological testing.

The antimicrobial susceptibility results show that amikacin, imipenem and meropenem were the most effective antibiotics against the ESBL producers. Although carbapenems are widely regarded as the drugs of choice for treatment of infection caused by ESBL-producing organisms, production of β -lactamases capable of hydrolyzing carbapenems has been reported in Enterobacteriaceae mostly in *Enterobacter* spp. and *Serratia* spp. [21, 22]. Carbapenem resistance also arises from the production of large quantities of chromosomal and plasmid-mediated cephalosporinases combined with decreased drug permeability through the outer membrane [23]. In *E. coli*, although the first report of carbapenem resistance appeared in 1999 [24], the occurrence remains a rare phenomenon and only a few cases of carbapenem-resistant *E. coli* strains have been documented in the literature [23]. We identified an ESBL-producing *E. coli* isolate which was resistant to the carbapenems, piperacillin-

tazobactam and cefotetan. It has been suggested that such low-level resistance to imipenem may arise from AmpC hyperproduction and loss of porins [23–25]. There is also the potential role of variants of the original ESBL enzymes such as CTX-M β -lactamases and even efflux changes giving rise to carbapenem resistance [20]. New findings indicate that the spread of CTX-M type ESBLs, especially in *E. coli*, may provide a favorable background for selection of carbapenem resistance [26]. While this study was aimed at determining the prevalence of ESBL isolates in our setting, we also recognize the need for the molecular characterization of these isolates, particularly in light of our findings. Although we have not carried out the molecular characterization of this carbapenem-resistant *E. coli*, the finding of such resistant isolate in our setting is a serious cause for concern, indicative of the need for more aggressive surveillance and evaluation of the molecular epidemiology and characterization of ESBL isolates in the UAE. Hence, we are embarking on further work to determine the molecular characterization of ESBL-producing isolates circulating in the UAE.

ESBL-producing organisms often show cross-resistance with non- β -lactam antibiotics, such as aminoglycosides and quinolones, resulting in limitation of therapeutic options. A significantly higher level of resistance to ciprofloxacin, gentamicin and piperacillin-tazobactam was demonstrable in the ESBL-producing isolates, indicating their limited use in the treatment of infections due to these pathogens. This co-resistance arises probably because these plasmid-mediated enzymes are transferable between bacterial species and are also capable of incorporating genetic material coding for resistance to other antibiotics. Indeed plasmid-mediated quinolone resistance has been reported in *K. pneumoniae* and *E. coli*, associated with acquisition of the *qnr* gene [27]. Tazobactam is an inhibitory compound which is expected to hinder the activity of ESBL. However, the usefulness of β -lactam/ β -lactamase inhibitor combinations for the treatment of infections caused by ESBL-producing organisms remains vague and failures have been reported. Our findings echo these concerns as 25% of ESBL isolates exhibited resistance to piperacillin-tazobactam.

Conclusion

This study shows a high prevalence of ESBL in hospitalized patients in the UAE occurring in equal proportion among *E. coli* and *K. pneumoniae* isolates. Amikacin and carbapenems remain the most useful drugs for treat-

ment of ESBL infections. However, the findings of a carbapenem-resistant ESBL-producing *E. coli* isolate as well as the occurrence of multidrug resistance are of major concern. Large surveys, continued surveillance by clinical

microbiology laboratories, judicious use of antimicrobial agents as well as implementation of infection control measures are recommended if the frequency of ESBL isolates is to be reduced in this setting.

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