Infectious Diseases, 2015; 47: 27–32

informa
healthcare

ORIGINAL ARTICLE

Fecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae in community setting in Casablanca

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Abstract

Background: The importance of community-acquired infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE) has been increasingly recognized in recent years. This study aimed to determine the prevalence of intestinal carriage of ESBL-PE in the community in Casablanca, Morocco. *Methods:* During 6 months (2013), 93 fecal samples were examined for ESBL-PE. Isolates expressing an ESBL phenotype were investigated for the presence of genes encoding β-lactamases and plasmid-mediated quinolone resistance. Conjugation experiments were done to determine the mobility of ESBL genes. *Results:* The prevalence of fecal carriage of ESBL-PE was 4.3% (4/93; 95% CI, 0.2–8.4). Klebsiella pneumoniae ($n = 2$), Enterobacter cloacae ($n = 2$), Escherichia coli ($n = 1$), and Serratia odorifera ($n = 1$) were the ESBL-producing species. Four (66.7%) of these isolates were multidrug-resistant. The $bla_{\text{SHV-12}}$ ($n = 5$) was the most frequent ESBL gene detected, followed by $bla_{\text{CTX-M-15}}$ ($n = 3$).The non-ESBL gene detected was $bla_{\text{TEM-1}}$ ($n = 5$). One isolate harbored the *qnrB1* variant. Results of conjugation experiments indicated that $bla_{\text{SHV-12}} + bla_{\text{TEM-1}} + qnrB1$ and $bla_{\text{CTX-M-15}} + bla_{\text{TEM-1}}$ genes were co-transferred and that these genes were carried by a conjugative plasmid of high molecular weight (125 kb). *Conclusion:* Our results show the importance of the intestinal tract as a reservoir for ESBL-PE in the community in Morocco.

Keywords: *ESBL, Enterobacteriaceae, fecal carriage, Casablanca city, community*

Introduction

The prevalence of resistance to extended-spectrum β-lactam antibiotics in Enterobacteriaceae has increased worldwide in recent years [1]. The predominant resistance mechanism is the production of extended-spectrum β-lactamases (ESBL). TEM- and SHV-type β-lactamases, mainly produced by Klebsiella pneumoniae, have spread throughout hospital settings, and CTX-M enzymes, mainly produced by Escherichia coli, have become predominant in the community [2,3]. The genes encoding these β-lactamases are often located on large plasmids that also encode genes for resistance to other antibiotics. Furthermore, there is an increasing tendency for pathogens to produce multiple β-lactamases [4,5].

ESBLs were initially associated with nosocomial outbreaks caused by single enzyme-producing strains, but recent studies have revealed more complex situations, with significant increases in the frequency of isolates from the community [6]. Digestive tract colonization is a prerequisite for infections with ESBL-producing microorganisms [7].

Fecal carriage of ESBL-producing isolates is now widely studied in hospitals but few studies have evaluated carriage in the community. While ESBL-producing Enterobacteriaceae (ESBL-PE) carriage often persists for years without disease, these bacteria can occasionally cause urinary tract and bloodstream infections in patients without discernible healthcare-associated risk factors [8]. Prevalence data on

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(Received 5 July 2014; accepted 25 August 2014)

ISSN 2374-4235 print/ISSN 2374-4243 online © 2014 Informa Healthcare
DOI: 10.3109/00365548.2014.961542

intestinal carriage of relevant antibiotic resistance genes and/or structures promoting gene expression are important to identify sources and hot spots of antibiotic resistance with relevance for human health.

This study aimed to estimate the prevalence of intestinal carriage of ESBL-PE in the population of Casablanca and to investigate its determinants, to contribute to understanding the epidemiology of these bacteria in Moroccan community settings.

Materials and methods

Setting and patient selection

From January to June 2013, a total of 93 nonduplicate fecal samples were recovered from randomly selected healthy humans in community settings (68 females and 25 males; age range 20–76 years) living in Casablanca, the largest city of Morocco.

Samples were from asymptomatic persons without previous exposure to antibiotic therapy, hospitals, or long-term care facilities for at least 3 months before sampling.

This study was approved by the internal ethics committee of the Pasteur Institute, Morocco. Written informed consent was obtained from each individual participating in the study.

Identification and screening protocol for ESBL-PE isolates in fecal samples

Samples were processed immediately after collection. A total of 0.5 g of each fecal sample was suspended in 5 ml of saline and aliquots of 200 µl were seeded on two MacConkey agar plates (Oxoid Ltd, Basingstoke, UK) supplemented with cefotaxime or ceftazidime (1 mg/L), respectively, and incubated at 37°C for 48 h [9]. These selective media permit the isolation of ESBL-producing bacteria.

Presumptive Enterobacteriaceae (oxidase-negative, facultative, aerobic, gram-negative rods) from subcultured ceftazidime- or cefotaxime-supplemented MacConkey agar plates were identified using the API 20 E system (bio-Merieux, Marcy L'Étoile, France). Isolates from the same patient exhibiting different colonial morphotypes were also studied.

ESBL production was screened by double disk with a synergy test and agar diffusion test between a central amoxicillin/clavulanic acid disk (20/10 µg) and a third-generation cephalosporin (cefotaxime 30 µg and ceftazidime 30 µg), placed at a distance of 30 mm (center to center) as described previously [10]. The standard strains Escherichia coli ATCC 25922 and Klebsiella pneumoniae ATCC 700603 were used as negative and positive controls of ESBL production, respectively.

Antimicrobial susceptibility testing

Antimicrobial susceptibility was determined by the disk diffusion method on Mueller-Hinton (MH) agar plates (Bio-Rad, Marnes-la-Coquette, France) as recommended by the Clinical and Laboratory Standards Institute (CLSI) [11]. The following antimicrobial agents (Bio-Rad) were tested: amoxicillin (10 µg), amoxicillin/clavulanic acid (20/10 µg), ticarcillin (75 µg), cephalothin (30 µg), cefoxitin (30 µg), cefotaxime (30 µg), ceftazidime (30 µg), imipenem (10 µg), ertapenem (10 µg), nalidixic acid (30 µg), ciprofloxacin (5 µg), norfloxacin (10 µg), gentamicin (10 µg), tobramycin (10 µg), amikacin (30 µg) and trimethoprim/sulfamethoxazole (1.25/23.75 µg).

Preparation of DNA template for PCR

Total DNA was extracted by suspending a few colonies of overnight culture of Enterobacteriaceae isolates growing on Luria Bertani agar (Bio-Rad) in 500 µl of DNase- and RNase-free water (Invitrogen, Paisley, UK). The suspension was boiled at 100°C for 10 min in a thermal block (Polystat 5, Bioblock Scientific, France), then centrifuged at 19 000 *g* for 5 min. An aliquot of 1 µl of the supernatant was used as DNA template for PCR.

Detection of β-lactamase-encoding genes and plasmid-mediated quinolone resistance genes

All ESBL-producing strains were screened by PCR for *qnr* genes (*qnrA*, *qnrB*, and *qnrS*) and for the following β-lactamase-encoding genes: $bla_{\text{CTX-M}}$ phylogenetic lineage groups 1, 2, and 9, bla_{TEM}, bla_{SHV}, bla_{GES}, bla_{PER}, and bla_{VEB}, as described previously [12]. All primers are shown in Table I.

Amplification reactions were performed in a volume of 50 µl containing, 2 µl of DNA template, 2.5 mM $MgCl_2$, 0.4 µM of each forward and reverse primer, 100 µM of each dNTP, and 2 units of *Taq* DNA polymerase (Promega, Madison, WI, USA) in 1 × PCR buffer provided by the manufacturer.

Cycling parameters included 5 min of denaturation at 95°C, followed by 30 cycles of denaturation (95°C for 1 min), annealing (60°C for 1 min for CTX-M, PER, VEB, SHV, and *qnr*; 52°C for 1 min for TEM), and extension (72°C for 1 min), ending with a final extension period of 72°C for 7 min.

The known β-lactamase-producing strains *E. coli* U2A1790 (CTX-M-1), *E. coli* U2A1799 (CTX-M-9), *Salmonella* sp. U2A2145 (CTX-M-2), *Salmonella* sp. U2A1446 (TEM-1 and SHV-12), and the strains harboring plasmid-mediated quinolone resistance *E. coli* U2A2118 (*qnrA1*), *E. coli* U2A2119 (*qnrB1*), *E. coli* U2A2120 (*qnrS1*) were

Table I. Primers sets used for PCR amplification and sequencing.

Gene	Primer	Primer sequence (5′3′)	Expected amplicon size (bp)
$bla_{\text{CTX-M group 1}}$	CTX-M1 (+)	GGTTAAAAAATCACTGCGTC	863
	CTX-M1 (–)	TTGGTGACGATTTTAGCCGC	
$bla_{\text{CTX-M group 2}}$	CTX-M2 (+)	ATGATGACTCAGAGCATTCG	865
	CTX-M2 (–)	TGGGTTACGATTTTCGCCGC	
$bla_{\text{CTX-M group 9}}$	CTX-M9 (+)	ATGGTGACAAAGAGAGTGCA	869
	CTX-M9 (–)	CCCTTCGGCGATGATTCTC	
bla_{TEM}	a-216	ATAAAATTCTTGAAGACGAAA	1079
	a-217	GACAGTTACCAATGCTTAATCA	
bla_{SHV}	Os-5	CGCCGGGTTATTCTTATTTGTCGC	795
	Os-6	CGCCGGGTTATTCTTATTTGTCGC	
bla_{PER}	per (+)	CCTGACGATCTGGAACCTTT	716
	per (–)	GCAACCTGCGCAAT(GA)ATAGC	
bla_{VEB}	veb (+)	ATTTCCCGATGCAAAGCGT	542
	veb (–)	TTATTCCGGAAGTCCCTGT	
qnrA	qnrA (+)	TTCTCACGCCAGGATTTGAG	571
	qnrA (–)	TGCCAGGCACAGATCTTGAC	
qnrB	qnrB (+)	TGGCGAAAAAAATT(GA)ACAGAA	594
	qnrB (–)	GAGCAACGA(TC)GCCTGGTAG	
qnrS	qnrS (+)	GACGTGCTAACTTGCGTGAT	388
	qnrS (–)	AACACCTCGACTTAAGTCTGA	

used as positive controls. *E. coli* $K_{12}J_5$ strain was used as a negative control.

PCR products were detected on 1.5% agarose gel (FMC Bioproduct, Rockland, ME, USA) after ethidium bromide staining and UV illumination, photographed with an Olympus digital camera, and analyzed using the Digi-Doc-it software (UVP, Upland, CA, USA).

Sequencing of resistance genes

All amplified products obtained were sequenced to validate their identities. Both strands of the purified amplicons were sequenced with a Genetic Analyzer 3130x1 sequencer (Applied Biosystems, Foster City, CA, USA), with the same primers used for PCR amplification. The nucleotide and deduced protein sequences were analyzed with software available over the Internet at the National Center for Biotechnology Information website (www.ncbi.nlm.nih.gov).

Conjugation experiments and plasmid analysis

Conjugation assays were performed using a broth mating method with an azide-resistant mutant of *E. coli* $K_{12}J_5$ as the recipient strain. The transconjugants were selected on MH agar containing azide (200 μg/ml) and ceftazidime (1 μg/ml) (Bio-Rad), and incubated for 18–24 h at 37°C. If not successful at the first attempt, mating experiments were repeated up to three times.

The putative transconjugants were tested for their susceptibility to all 16 antibiotics to identify transferable antibiotic resistance determinants.

Plasmid DNA extraction from donors and transconjugants was performed using a plasmid midi prep kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The sizes of plasmids were estimated by electrophoresis on 0.7% agarose gels using plasmids from *E. coli* V517 (53.7, 7.2, 5.6, 5.1, 3.9, 3, 2.7, and 2.1 kb) and Salmonella ordonez (127.5 kb) as the standard markers [13].

Results

In total, nine Enterobacteriaceae isolates resistant to third-generation cephalosporins were recovered, of which six produced ESBL and were identified as K. pneumoniae ($n = 2$), Ent. cloacae ($n = 2$), E. coli ($n = 1$), and Serratia odorifera ($n = 1$) (Table II). These isolates were recovered from 4 fecal samples (4.3% of the 93 collected specimens) from 1 male aged 20 years and 3 females aged 21, 22, and 23 years, respectively.

Five of six isolates (83.3%) were resistant to nalidixic acid and three (50%) were resistant to ciprofloxacin and norfloxacin. Co-trimoxazole and cefoxitin resistance was observed in four (66.6%) and two isolates (33.3%), respectively. Only one strain (E20) (16.6%) was resistant to the aminoglycosides tested (tobramycin, gentamicin, and amikacin). All isolates were susceptible to imipenem and

Table II. Characteristics of the ESBL-PE isolates collected in Moroccan community.

Code	Date of isolation	Sex/age (years)	Species	β-Lactamase	*qnr*	Resistance to antibiotics
E20	31/01/2013	M/20	Ent. cloacae	CTX-M-15, TEM-1	–	AMX, AMC, TIC, CF, FOX, CTX, CAZ, NA, CIP, NOR, SXT, AN, TM, GM
TcE20	–	–	E. coli	CTX-M-15, TEM-1		AMX, AMC, TIC, CF, CTX, CAZ
E13	14/02/2013	F/23	Ent. cloacae	CTX-M-15, SHV-12, TEM-1	–	AMX, AMC, CF, CTX, CAZ, NA, CIP, NOR
K13	14/02/2013	F/23	K. pneumoniae	CTX-M-15, SHV-12, TEM-1	–	AMX, AMC, TIC, CF, CTX, CAZ, NA, SXT
SA1	27/02/2013	F/21	S. odorifera	SHV-12, TEM-1	–	AMX, AMC, TIC, CF, CTX, CAZ, NA, SXT
SA2	27/02/2013	F/21	E. coli	SHV-12, TEM-1	*qnrB1*	AMX, AMC, TIC, CTX, CAZ, NA, CIP, NOR, SXT
TcSA2	–	–	E. coli	SHV-12, TEM-1	*qnrB1*	AMX, AMC, TIC, CF, CTX, CAZ, NA, SXT
K132	13/03/2013	F/22	K. pneumoniae	SHV-12	–	AMX, AMC, TIC, CF, FOX, CTX, CAZ

AMC, amoxicillin/clavulanic acid; AMX, amoxicillin; AN, amikacin; CAZ, ceftazidime; CF, cephalothin; CIP, ciprofloxacin; CTX, cefotaxime; ESBL-PE, extended-spectrum beta-lactamase-producing Enterobacteriaceae; F, female; FOX, cefoxitin; GM, gentamicin; M, male; NA, nalidixic acid; NOR, norfloxacin; SXT, trimethoprim/sulfamethoxazole; Tc, transconjugant; TIC, ticarcillin; TM, tobramycin.

ertapenem. Four ESBL-producing isolates were multiresistant (resistant to three or more antibiotic classes) (Table II).

The results of ESBL-encoding gene detection by PCR revealed that the strains studied harbored a diversity of β-lactamases, namely SHV, CTX-M, and TEM (Table II). Further analysis of the bla_{TEM}, bla_{SHV}, and bla_{CTX-M} sequences identified the respective subgroups TEM-1 ($n = 4$), SHV-12 ($n = 5$), and CTX-M-15 ($n = 3$). No amplicons were obtained for the other two tested CTX-M subgroups (Table II). bla_{PER} and bla_{VEB} were not detected in any of the isolates.

The bla_{SHV-12} and the bla_{TEM} genes were detected in all isolates except in one Ent. cloacae strain (E20) and one K. pneumoniae strain (K132). The $bla_{CTX-M-15}$ gene was found in two E. cloacae strains (E20 and E13) and one K. pneumoniae strain (K13) (Table II).

All combinations of *bla* genes detected are shown in Table II. Of the five bla_{SHV-12} isolates, four also harbored bla_{TEM-1} and two had $bla_{CTX-M-15}$. It is interesting to note that three β-lactamase genes, bla_{SHV}, bla_{TEM}, and bla_{CTX-M}, were co-expressed in *K. pneumoniae* (K13) and *Ent. cloacae* (E13) isolates.

Only one ESBL-producing isolate (*E. coli* SA2) was positive for the *qnr* gene. This was found to be the *qnrB1*allele.

Conjugation experiments were carried out for four ESBL producers (E20, E13, SA2, and SA1), but transfer of this phenotype to the recipient sodium azide-resistant *E. coli* $K_{12}J_5$ was successful in only two isolates (E20 and SA2). All transconjugants were resistant to amoxicillin, amoxicillin-clavulanic acid, cephalothin, cefotaxime, and ceftazidime. Sulfamethaxazole and nalidixic acid resistance were co-transferred in the TcSA2 (Table II).

The E20 isolate successfully transferred the $bla_{CTX-M-15}$ and bla_{TEM-1} genes to the *E. coli* $K_{12}J_5$ recipient strain. The SA2 isolate successfully transferred the bla_{SHV-12}, bla_{TEM-1}, and *qnrB1* genes. The analysis of the plasmid content of donor strains and their transconjugants detected a plasmid of ~125 kb in all isolates. The SA2 isolate contained another plasmid of 7 kb.

Discussion

In Morocco, several studies demonstrate a wide dissemination of ESBLs in the environment, in clinical and community settings, especially in community-acquired urinary tract infections [12,14]. Most urinary and intra-abdominal infections with E. coli and K. pneumoniae are endogenous. However, there are no data on fecal carriage of ESBL-PE by healthy individuals. To our knowledge, this is the first study reporting the prevalence of fecal carriage of ESBL-producing bacteria in a Moroccan community.

We found a fecal carriage prevalence of 4.3%. This finding may not be representative of the whole country since the current study was conducted only in one city of Morocco. Despite this and despite the low number of ESBL-producing isolates included in our study, these data suggest that bacteria colonizing healthy persons constitute a reservoir of ESBL genes that could further evolve nosocomially and/or be responsible for future epidemic situations.

The presence of carriers in the community could increase the risk that other individuals will become carriers due to human-to-human transmission or through the environment [15], enriching the

resistance gene pool and thus facilitating the acquisition of resistance mechanisms by susceptible bacteria [16]. In addition, the admission of carriers harboring resistant bacteria to hospitals increases the risk of infection for other hospitalized patients [17].

Our ESBL-PE exhibited multiple resistances to cephalosporins, fluoroquinolones, and co-trimoxazole, a phenomenon favored by selection pressure from antibiotics. The diversity of ESBL-PE reflects interspecies dissemination of resistance genes in the community. This could be related to the fact that ESBL genes are clustered with other resistant determinants on the same genetic mobile elements such as plasmids, transposons or integrons. Plasmid analysis revealed that the transconjugants harbored large plasmids of about 125 kb.

An important finding in the present study is that SHV-12 is the most frequent β-lactamase. This might suggest that SHV enzymes could spread and dominate in the community setting as CTX-M enzymes do presently. SHV-12 was the only ESBL enzyme found in chickens and other animal foods in Morocco [18], indicating that foods could be the source of acquisition of the resistant isolates harboring this enzyme in the community. Further studies are required to obtain more detailed knowledge of the epidemiology of the SHV enzymes in the community, a probably underestimated aspect as a consequence of the worldwide CTX-M explosion [19].

Two of our isolates simultaneously produced two different ESBLs, CTX-M-15 and SHV-12. These findings indicated that, in our setting, the SHV-12 and CTX-M-15 alleles were carried by large conjugative plasmids which are exchanged by lateral gene transfer among the Enterobacteriaceae isolates. Most previous studies have found plasmids ranging from 7 to 200 kb in association with CTX-M-15 and SHV-12 [20,21].

Among the five ESBL-producing isolates with reduced susceptibility to quinolones, only one carried the *qnrB1* gene, while the *qnrB* gene was the most prevalent in community-acquired urinary tract infections in Morocco [12]. The *qnrB* genes and ESBL genes, especially $bla_{\text{CTX-M}}$, are mostly located on the same plasmid and thus passed on together between different enterobacterial species [22,23].

Conclusion

The results of this study reinforce the relevance of the human commensal flora as reservoir of clinically relevant antibiotic resistance genes ($bla_{\text{CTX-M}}$, bla_{SHV} or bla_{TEM}) and plasmids. Therefore, surveillance and control of the community reservoir are extremely important to detect microorganisms with the potential to cause pandemics in the future. It is also important to identify the risk factors associated with fecal carriage of ESBL-PE in asymptomatic Moroccan people, to develop effective management strategies for carriers.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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