

Fecal Carriage of Extended-Spectrum β -Lactamase Producing *Enterobacteriaceae*

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Asymptomatic colonization of the intestinal compartment with ESBL-producing *Enterobacteriaceae* isolates (ESBLE) has been described previously [1-4]. Higher prevalence of ESBL-producing *E. coli* fecal carriage has been reported in the nosocomial setting than in the community. Patients of medical units with high levels of antibiotic consumption have also shown higher rates of ESBL colonization. Similarly nursing homes and residents of health care or skilled care facilities, also have high rates of colonization with multi resistant pathogens, including ESBL producers, than that among true community patients or healthy volunteers [5,6]. Studies have shown that ESBL producing uropathogens have their reservoir in the digestive tract [6]. ESBL producing *E. coli* cause clinically significant hospital associated infections and are also known to cause community acquired infections due to selective pressure owing to widespread use of third generation cephalosporin. Community acquired infections due to ESBLE has been reported from studies from Europe and India [1,7]. Previous studies have documented 2-5 years of ESBL digestive carriage [1,7]. Finally hospitalization of carriers increases the risk of infection for other hospitalized patients via cross infection [8]. Patients with fecal carriage of ESBLE isolates have been investigated previously during nosocomial outbreaks, but the number of prospective longitudinal studies conducted in the community remains scarce. Previous studies have suggested that ESBL phenotypes in clinical isolates co vary with the percentage of healthy fecal carriers of ESBLE.

In Barcelona, Spain a study carried out in the stools revealed that the incidence of strains of *E. coli* producing ESBLs, in hospitalized patient was 7.5% while healthy volunteers showed a prevalence of 3.7% (4/108). Few retrospective studies have suggested foreign travel to countries with high prevalence of ESBLE as a risk factor for acquisition [9,10]. Moreover, the community can be a reservoir of ESBLs not yet detected in clinical isolates. Studies have reported a strong association between travel to Asia, Africa and Middle East with high risk of colonization with ESBLE (32% and 29% respectively). Gastroenteritis during travel has been strongly associated with acquisition of ESBLE, which may be due to exposure of contaminated food and water containing both diarrhoeagenic and ESBL producing *E. coli* strains. Prats et al. [11] studied stool samples during an outbreak of acute gastroenteritis involving >100 patients and found CTX-M-9 producing *E. coli* in 11 patients with same clone present in 7 patients. They concluded that common source exposure such as food and water was linked to dissemination of ESBL positive *E. coli* strains [11]. Person to person transfer of ESBLE has also been documented within travel groups or families. Prevalence of fecal carriage was found to be higher in patients with traveler's diarrhea when they visited countries outside Europe. Rates of fecal carriage of ESBLE in healthy individuals has been estimated to be 10% in Asia, 5.5% in Spain and 13.2 in Saudi Arabia [12].

Two studies describing the spread of community-acquired bacteria producing CTX-M β -lactamases have recently appeared from UK [13,14]. In one, ESBL-producing *Enterobacteriaceae* were detected from the fecal flora of community and hospital-based patients from York [13]. The second study from the UK was undertaken by Woodford et al. who investigated 291 CTX-M-producing *E. coli* from 42 centers [14]. The community isolates (24% of the 291) were mainly from

urines and produced CTX-M-15 associated with the mobile element ISEcp1 or CTX-M-9. The CTX-M enzymes usually have 4-16 fold more activity against cefotaxime than ceftazidime but some of them, such as CTX-M-15 and 19, also hydrolyze ceftazidime efficiently [15,16]. CTX-M15 was first described in India in 2001 and Indian population is a significant reservoir of CTX-M-15 [15]. ISEcp1 is seen with CTXM 14 and CTXM15 producing isolates [13]. Ability of ISEcp1 to mobilize and promote expression of CTX-M15 is a significant factor in rapid spread. The SENTRY and MYSTIC 2006 studies showed all Indian CTX-M to be CTX-M-15 type which is the only CTX-M type dominant in this region. A Spanish study from 2002 isolated *E. coli* producing CTX-M-14 β -lactamases from the urines of seven patients with UTIs who had never been admitted to a hospital [17]. High prevalence of CTX-M-15 has been reported in a Swedish study on fecal carriage of ESBLE in travelers. They also reported that all Indian ESBL isolates acquired by them were CTX-M-15.

The emergence of CTX-M type enzyme as the predominant ESBL *E. coli* in faecal carriers is not an isolated phenomenon [3,14,18,19]. Pitout [10] who found two closely related restriction patterns among 67 (77%) CTX-M-14 producers those were responsible for a community-wide clonal outbreak of UTIs during 2000 and 2001. However, studies from Spain and the UK, also using PFGE, showed that most *E. coli* producing CTX-M enzymes from the community were not clonally related. However, the UK study did suggest some evidence of genetic relatedness among strains producing CTX-M-15 [14]. *E. coli* producing CTX-M β -lactamases seem to be true community ESBL-producers and the current emergence and spread of these bacteria is intriguing but worrying. Several factors like plasmids, insertion sequence, transposon and integrons are involved in the mobilization of CTX-M gene [14,3].

It is also noteworthy that most of the CTX-M-15-producing strains were multiresistant to fluoroquinolones, trimethoprim, tetracycline and aminoglycosides [14]. ESBLs are often encoded by genes located on large plasmids and these also carry genes for resistance to other antimicrobial agents such as aminoglycosides, trimethoprim, sulphonamides, tetracyclines and chloramphenicol [20]. Multidrug resistance profiles involving non- β -lactamase antibiotics in ESBL-producing isolates may also contribute to the increase in colonization pressure. Fluoroquinolone resistance is becoming a common feature rather than an exception in ESBL-producing isolates. Recent studies

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Received November 15, 2012; **Accepted** November 19, 2012; **Published** November 21, 2012

Citation: Anil Kumar V, Babu R (2013) Fecal Carriage of Extended-Spectrum β -Lactamase Producing *Enterobacteriaceae*. J Med Microb Diagn 2: e119. doi:10.4172/2161-0703.1000e119

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have demonstrated co-transfer of the *qnr* determinant on ESBL-producing plasmids conferring resistance to nalidixic acid with reduced susceptibility to fluoroquinolones [21,22]. A population based study from Canada showed that ciprofloxacin resistance was independently associated with the presence of CTX-M β -lactamase and these strains commonly caused community onset urinary tract infections [23].

Among the SENTRY 2006 and MYSTIC 2006 clinical ESBL isolates from India fluoroquinolone resistance was 96% and 94% respectively. All CTX-M-15 ESBL isolates were resistant to fluoroquinolone. Other studies have also shown that all *E. coli* producing CTX-M-15 were resistant to ciprofloxacin [13]. Previous fluoroquinolone use has been demonstrated to be a risk factor for the acquisition of ESBL-producing isolates, particularly isolates producing the CTX-M-type enzymes in the community setting. Plasmid mediated Quinolone (*qnr*) resistance is on the rise, in fact *qnrB* plasmids was reported from Indian isolates carried blaCTX-M-15 and SHV-12 [24]. Other antimicrobial agents such as trimethoprim-co-trimoxazole or tetracyclines may also contribute to the acquisition of ESBL-producing isolates. Thus, very broad antibiotic resistance extending to multiple antibiotic classes is now a frequent characteristic of ESBL isolates.

In summary, asymptomatic colonization of the intestinal compartment with ESBL isolates, is considered a prerequisite for infection. This increase was associated with the predominance of ESBLs with CTX-M-type enzymes. The association of CTX-M β -lactamase-encoding genes with mobile elements such as *ISEcp1*, could explain the ease with which these enzymes are spreading among bacteria in the community setting. Travel to countries with high rates of ESBL has also been associated with intestinal colonization with these isolates. The importance of the detection of carriers of antimicrobial resistant bacteria has recently been highlighted not only in patient populations but also in healthy people [1-3]. The increase in the proportion of carriers in the community increases the risk that other individuals will become carriers as a consequence of human-to-human transmission of resistant bacteria or through the environment, enriching the resistance gene pool and thus facilitating the acquisition of resistance mechanisms by susceptible bacteria. Several investigations have illustrated those animals might represent a possible source for the dissemination of ESBL encoding genes to humans. The evidence of CTX-M-producing isolates in cattle, poultry, and dogs and cats is worrying since food-producing animals and domestic pets might act as reservoir for the acquisition of resistant organisms.

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