

Recent changes in the epidemiology and management of extended-spectrum β -lactamase-producing Enterobacteriaceae

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F1000 Medicine Reports 2009, 1:84 (doi:10.3410/M1-84)

The electronic version of this article is the complete one and can be found at: <http://F1000.com/Reports/Medicine/content/1/84>

Abstract

Since 2000, *Escherichia coli* producing CTX-M enzymes (especially CTX-M-15) have emerged worldwide as important causes of community-onset urinary tract and blood stream infections due to extended-spectrum β -lactamase (ESBL) producing bacteria. Studies suggest that the sudden worldwide increase of CTX-M-15-producing *E. coli* is mostly due to a single clone named ST131 and that foreign travel to high-risk areas, such as the Indian subcontinent, play in part a role in the spread of this clone across different continents. Empiric antibiotic coverage for these resistant organisms should be considered in community patients presenting with sepsis involving the urinary tract, especially if a patient recently traveled to a high-risk area. If this emerging public health threat is ignored, it is possible that the medical community may be forced in the near future to use carbapenems as the first choice for the empirical treatment of serious infections associated with urinary tract infections originating in the community.

Introduction and context

The extended-spectrum β -lactamases (ESBLs) are a group of enzymes that have the ability to hydrolyze and cause resistance to the oxyimino-cephalosporins (cefotaxime, ceftazidime, ceftriaxone, cefuroxime, and cefepime) and monobactams (aztreonam), but not the cephamycins (cefoxitin and cefotetan) or carbapenems (imipenem, meropenem, doripenem, and ertapenem). These enzymes are inhibited by the so-called 'classical' β -lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam [1]. Most ESBLs belong to the class A Ambler classification system and include the SHV or TEM types that have evolved from parent enzymes (e.g., TEM-1, TEM-2, and SHV-1) due to point mutations around the active site of the β -lactamases. ESBLs are often located on large plasmids that also harbor genes for resistance to other antimicrobial classes and, therefore, will often exhibit multidrug-resistant phenotypes that include resistance to aminoglycosides and cotrimoxazole [1].

Although ESBLs have been identified in various bacteria, *Klebsiella* spp. producing SHV and TEM types of ESBLs were mostly responsible for serious nosocomial infections during the 1990s [1]. Specific risk factors included length of hospital stay, severity of illness, time in the intensive care unit (ICU), intubations and mechanical ventilation, urinary or arterial catheterization, and previous exposure to antibiotics. Most patients infected with ESBL-producing organisms have been admitted to ICUs, but infections can also occur in almost any other area of the hospital. These organisms are also isolated with increasing frequency from patients in extended-care facilities [2]. Infections caused by ESBL-producing bacteria are often associated with increased morbidity, mortality, and health care-associated costs [3,4]. Organisms producing ESBLs are clinically relevant and have become important players among antimicrobial resistant organisms. A report from IDSA (Infectious Diseases Society of America) from 2006 has listed ESBL-producing *Klebsiella* spp. and *Escherichia*

coli as priority drug-resistant microbes to which new therapies are urgently needed [5].

Recent advances

The CTX-M- β -lactamases and community onset infections

CTX-M- β -lactamases (which stands for 'active on Cefo-TaXime, first isolated in Munich') were first reported from Japan in 1986, and during the 1990s occasional nosocomial outbreaks mostly due to CTX-M-2-producing *Klebsiella pneumoniae* were reported from South America (especially Argentina) [6]. However, since 2000, *E. coli* producing CTX-M enzymes have emerged worldwide as important causes of community-onset urinary tract infections (UTIs) and bacteraemia, and this emergence has been referred to as 'the CTX-M pandemic' [7]. This is very different from infections caused by *Klebsiella* spp. producing TEM- and SHV-derived ESBLs, which are often limited to nosocomial outbreaks. The spread of CTX-M enzymes has accelerated rapidly, especially during the past 5 years, and today β -lactamases produced by *E. coli* are the most common types of ESBLs found in most areas of the world [8].

Risk factors for acquiring community-onset infections due to CTX-M-producing *E. coli* include repeat UTIs, underlying renal pathology, previous antibiotics (including cephalosporins and fluoroquinolones), previous hospitalization, residency in a nursing home, co-morbid conditions (especially diabetes mellitus and underlying liver pathology) and international travel [9].

Multidrug resistant CTX-M-15-producing *E. coli* were first detected in India during 2001 and have been emerging worldwide, especially since 2005, as important pathogens causing community-onset infections [7,8]. To date, CTX-M-15 enzymes are the most common and widely reported type of CTX-M enzyme and have been described in most countries, including Europe [10], Asia (especially India) [11], Africa [8], North America [12,13], South America [14], and Australia [15].

Emergence of multilocus sequencing typing clone O25:H4-ST131

An identical clone named ST131 has been identified using multilocus sequencing typing among CTX-M-15-producing *E. coli* isolated during 2000 to 2006 from several countries, including Spain, France, Canada, Portugal, Switzerland, Lebanon, India, Kuwait, and Korea [16,17]. Serogroup O25 is associated with this clone. Clone ST131 belongs to the highly virulent phylogenetic group B2 and harbors multidrug-resistant IncFII (incompatibility group FII) plasmids. These initial studies showed that clone ST131 had emerged independently in different parts of the world, spanning three

continents at the same time, suggesting that the emergence of clone ST131 could be due to either the ingestion of contaminated food/water sources or importation into various countries via returning travelers or both.

Clone ST131 producing CTX-M-15 has also recently been described in the UK [18], Italy [19], Turkey [20], Croatia [21], and Japan [22]. CTX-M-15-producing *E. coli* belonging to clone ST131 have been identified in isolates recovered from the community [23], hospitals [24], and nursing homes settings [25] and, interestingly, also in companion animals (such as dogs) [26].

Why did CTX-M-15-producing *E. coli* emerge simultaneously in different continents as a cause of community-onset infections? Recent studies from Calgary, Canada and Auckland, New Zealand shed some light on this intriguing question. The publication from New Zealand describes a series of patients that presented to an Auckland hospital with community-onset genitourinary tract infections due to CTX-M-15-producing *E. coli* that had a history of travel to, or recent emigration from, the Indian subcontinent [27]. All the patients lacked the traditional risk factors associated with UTIs.

A Canadian study demonstrated that travel to the Indian subcontinent (i.e., India and Pakistan), Africa, and the Middle East was associated with a high risk of UTI (including urosepsis) with an ESBL-producing *E. coli* in returning travellers [28]. A follow-up study showed that this high risk of infection was mostly due to the acquisition of clone ST131 producing CTX-M-15 [29].

A different study from Calgary over an 8-year period (2000-2007) showed that *E. coli* clone ST131 producing CTX-M-15 has emerged as an important cause of community-onset bacteraemia during the later part of the study period; 1 of 18 (5%) of ESBL-producing *E. coli* isolated from blood between 2000 and 2003 were ST131 as opposed to 20 of 49 (41%) isolated between 2004 and 2007 [30]. In this study, clone ST131 (as compared to other ESBL-producing *E. coli*) was more likely to be resistant to several antibiotics, more likely to produce the aminoglycoside-modifying enzyme *aac(6')-Ib-cr*, and more likely to cause community-acquired infections and urosepsis. This increase of clone ST131 was also noted in urine samples from different medical centers in Canada.

Implications for clinical practice

These studies suggest that the sudden worldwide increase of CTX-M-15-producing *E. coli* is due, at least in part, to clone ST131 and that foreign travel to high-risk areas

such as the Indian subcontinent potentially play an important role in its spread across different continents. Empiric antibiotic coverage for these resistant organisms should be considered in community patients presenting with sepsis involving the urinary and biliary tracts, especially in areas with a high prevalence of ESBL-producing *E. coli*.

The carbapenems such as imipenem, meropenem, and ertapenem remain the first choice for treatment of serious infections due to ESBL-producing bacteria. However, it seems that the quinolones and aminoglycosides might show comparable outcomes if the isolate tested is susceptible to these agents. Unfortunately, resistance to these groups is a major concern. Recent studies have explored the usefulness of alternative regimens (such as a new cephamycin and ceftazidime for CTX-Ms) but sufficient clinical data are lacking.

There is a serious need to monitor the spread of this multidrug resistant clone throughout the world and there are methods available for the rapid and easy identification of clone ST131, including repetitive-element polymerase chain reaction (PCR) typing schemes [31,32], PCR for the *pabB* allele [33], PCR for ST131-associated single-nucleotide polymorphisms in *mdh* and *gyrB* combined with the O25b *rfb* allele [34] and a triplex PCR that targets the operon *afa* FM955459 and part of the CTX-M-15 gene [35]. If this emerging public health threat is ignored, it is possible that the medical community may be forced to use the carbapenems as the first choice for the empirical treatment of serious infections associated with UTIs that originate from the community.

Abbreviations

CTX-M, active on CefoTaXime, first isolated in Munich; ESBL, extended-spectrum β -lactamase; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; IncFII, incompatibility group FII; PCR, polymerase chain reaction; UTI, urinary tract infection.

Competing interests

The author declares that he has no competing interests.

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