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Infections with Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae

Changing Epidemiology and Drug Treatment Choices

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Abstract

Since 2000, *Escherichia coli* producing CTX-M enzymes (especially CTX-M-15) have emerged worldwide as important causes of community-onset urinary tract infections (UTIs) and bloodstream infections due to extended-spectrum β-lactamase (ESBL)-producing bacteria. Molecular epidemiology studies suggested 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 might in part play a role in the spread of this clone across different continents. Empirical antibacterial coverage for these resistant organisms should be considered in community patients presenting with sepsis involving the urinary tract especially if a patient recently travelled to a high-risk area. Infections due to ESBL-producing Enterobacteriaceae are associated with a delay in initiation of appropriate antibacterial therapy, which consequently prolongs hospital

stays and increases hospital costs. Failure to initiate appropriate antibacterial therapy from the start appears to be responsible for higher patient mortality. The carbapenems are widely regarded as the drugs of choice for the treatment of severe infections due to ESBL-producing Enterobacteriaceae, although comparative clinical trials are lacking. Agents that may be useful for the treatment of ESBL-associated UTIs include fosfomycin, nitrofurantoin and temocillin. If this emerging public health threat is ignored, it is possible that clinicians may be forced in the near future to use the carbapenems as the first choice for empirical treatment of serious infections associated with UTIs originating from the community.

The production of β-lactamases is the most important contributing factor to β-lactam resistance in Gram-negative bacteria.[1] β-Lactamases are bacterial enzymes that inactivate β-lactam antibacterials by hydrolysis, which results in ineffective compounds. β-Lactamases can differ from one another in their substrate profiles (i.e. the different types of antibacterials they can inactivate), inhibitor profile (i.e. which compounds inactivate them) and sequence homology (i.e. amino acid composition). At least 500 different types of β-lactamases, originating from clinical isolates, have been described and a website has been specifically created to monitor the latest developments (URL: http://www.lahey.org/studies/webt.htm).

Clinical isolates of Enterobacteriaceae and *Pseudomonas aeruginosa* producing the so-called 'newer β-lactamases' have been described from different parts of the world. These enzymes include plasmid-mediated cephamycinases, extended-spectrum β-lactamases (ESBLs), and carbapenem-hydrolysing enzymes or carbapenemases.[1]

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

Organisms producing SHV and TEM types of ESBLs have traditionally been responsible for serious nosocomial infections. Specific risk factors for acquisition of these bacteria identified previously 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 antibacterials.[2] The majority of the 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.[3] Infections caused by ESBL-producing bacteria are often associated with increased morbidity, mortality and healthcare-associated costs.[4,5]

ESBLs have been identified in various members of the Enterobacteriaceae as well as *P. aeruginosa*; however, *Klebsiella* spp. were mostly responsible for producing these enzymes during the 1980s and 1990s.[2] Interestingly, since 2000, *Escherichia coli* has emerged as an important organism responsible for producing ESBLs. While *Klebsiella* spp. were mostly involved in nosocomial infections, *E. coli* was more likely to cause community-onset infections.[6]

The most recent worldwide surveys of ESBL-producing Enterobacteriaceae are from the 'study for monitoring antimicrobial resistance trends' or SMART programme. The SMART programme monitors the activity of several antimicrobial agents against Gram-negative bacteria from intra-abdominal infections. This programme has been ongoing since 2002 in most regions of the world. The latest data regarding the prevalence of ESBLs in isolates collected during 2007 show some alarmingly high rates of ESBL-producing *E. coli* and *Klebsiella* spp. in certain areas of Asia. Rates as high as 55% were reported from China and a staggering 79% of *E. coli* collected in India were positive for ESBLs.[7,8] An interesting aspect of the data from India was that the ESBL prevalence was equally high among *E. coli* collected from the hospital and community settings.[8]

Phylogenetic analyses of *E. coli* have shown that isolates can be divided into four main phylogenetic groups, namely A, B1, B2 and D.[9] A possible link between phylogeny and virulence has been observed. Virulent isolates causing extraintestinal infections belong mainly to group B2 and, to a lesser extent, to group D, whereas most commensal strains belong to groups A and B1.[10] Studies have addressed an association of the presence of ESBLs in *E. coli* with specific phylogenetic groups and have shown that the prevalence of ESBLs was lower among isolates belonging to the B2 phylogenetic group, suggesting a trade-off between resistance and virulence.[11]

Organisms producing ESBLs are clinically relevant and have become important players among antimicrobial-resistant organisms. A report from the Infectious Diseases Society of America from 2006 has listed ESBL-producing *Klebsiella* spp. and *E. coli* as priority drug-resistant microbes to which new therapies are urgently needed.[12] The characteristics of bacteria (i.e. *Klebsiella* spp. and *E. coli*) that produce ESBLs are shown in table I.

Table I. The characteristics of bacteria that produce extended-spectrum β-lactamases (ESBLs)

Characteristic	*Escherichia coli*	*Klebsiella* spp.
Origin	Community-onset	Nosocomial
Type of ESBL	Ambler class A CTX-M (especially CTX-M-15)	Ambler class A SHV (especially SHV-2, -5, -12) TEM (especially TEM-3, -26, -51)
Type of infection	UTIs Intra-abdominal infections Primary bacteraemia	Primary bacteraemia Respiratory tract infections, Intra-abdominal infections Skin and soft tissue infections UTIs
Susceptibilities	Resistance to all penicillins and cephalosporins Susceptible to cephamycins, carbapenems and β-lactam/β-lactamase combinations Resistance also present to other classes of antibacterials, especially fluoroquinolones and cotrimoxazole	Resistance to all penicillins and cephalosporins Susceptible to cephamycins, carbapenems and β-lactam/-β-lactamase combinations Resistance also present to other classes of antibacterials, especially aminoglycosides and cotrimoxazole
Molecular epidemiology	Worldwide spread of clone ST131 that especially produce CTX-M-15 associated with IncFII plasmids	Most often clonal spread within a ward or institution Plasmid spread has also been described
Risk factors	Repeat UTIs and underlying renal pathology Previous antibacterials including cephalosporins and fluoroquinolones Previous hospitalization Residence in a nursing home Older age (male and female patients) Diabetes mellitus Underlying liver pathology International travel	Longer length of hospital stay Severity of illness (more severe, the higher risk) Longer time in the intensive care unit Intubations and mechanical ventilation Urinary or arterial catheterization Previous exposure to antibacterials (especially cephalosporins)

UTI = urinary tract infection.

1. The Changing Epidemiology of Infections due to Enterobacteriaceae that Produce ESBLs

1.1 The Emergence of CTX-Mβ-Lactamases

CTX-M β-lactamases (which stands for 'active on CefoTaXime, 1st isolated in Munich') were first reported from Japan in 1986[13] and during the 1990s occasional nosocomial outbreaks mostly due to CTX-M-2-producing Enterobacteriaceae were reported from South America (especially in Argentina).[14] However, since 2000 *E. coli* producing CTX-M enzymes have emerged worldwide as important causes of community-onset urinary tract infections (UTIs) and have been called 'the CTX-M pandemic'.[11,15] This phenomenon accelerated rapidly especially during the past 5 years and today organisms producing these enzymes are the most common type of ESBL found in most areas of the world.[16]

The CTX-M β-lactamases are encoded by genes that have been captured by mobile elements (such as IS*Ecp1*) from the chromosomes of the environmental bacteria called *Kluyvera* spp.[17] Several studies have reported the dissemination of bla_{CTX-M} genes associated with highly efficient mobile genetic elements. Genes encoding CTX-M β-lactamases have been associated with different genetic platforms, such as the insertion elements IS*Ecp1*, IS*CR1* or phage-related sequences that are often located on conjugative plasmids.[18] The insertion element IS*Ecp1* plays an important role in the expression and continuous spread of these β-lactamases.[19] The genes responsible for CTX-M β-lactamases are encoded by plasmids belonging to both narrow host-range types (IncFI, IncFII, IncHI2 and IncI) or broad host-range types (IncN, IncP-1-a, IncL/M and IncA/C).[20]

Although CTX-M enzymes also belong to the class A Ambler classification, they are not related to other ESBLs such as the TEM or SHV types. Currently, CTX-M β-lactamases includes more than 80 different enzymes that are clustered into six groups based on their amino acid identities and include the CTX-M-1, -2, -8, -9, -25 and -45 groups.[21] The members of these clusters exhibit >94% amino acid identity within each group and ≥90% amino acid identity between the different groups. CTX-M enzymes are more active against cefotaxime and ceftriaxone than against ceftazidime, but point mutations around the active site of some enzymes belonging to the CTX-M-1 and CTX-M-9 groups have increased their ability to hydrolyse ceftazidime significantly.[22]

Although Enterobacteriaceae producing CTX-M β-lactamases have been involved in hospital-acquired infections, *E. coli* producing these enzymes are more likely to be responsible for community-onset infections.[15] This is very different from infections caused by bacteria producing TEM- and SHV-derived ESBLs that are often limited to nosocomial outbreaks. Risk factors for acquiring community-onset infections due to CTX-M-producing *E. coli* include repeat UTIs, underlying renal pathology, previous antibacterials including cephalosporins and fluoroquinolones, previous hospitalization, residence in a nursing home, diabetes mellitus, underlying liver pathology and international travel.[23,24]

It is interesting to note that organisms producing specific CTX-Ms have been isolated from different countries: CTX-M-9 and CTX-M-14 are mostly present in Spain, CTX-M-14 in Canada and China, CTX-M-1 in Italy, CTX-M-3 in Poland, and CTX-M-2 in several South American countries, Japan and Israel, while CTX-M-15 has been described from all continents except Antarctica.[11,15,16] Additionally, surveys from several countries have illustrated the association of resistance genes of other antimicrobial classes (especially to the fluoroquinolones) among CTX-M-producing organisms.[11,15] Reports have also shown that CTX-M-15-producing *E. coli* are more likely to be multiresistant when compared with other CTX-M-producing isolates.[25]

1.2 Importance and Distribution of CTX-M-15-Producing *Escherichia coli*

Currently, the most widely distributed CTX-M enzyme on a worldwide basis is CTX-M-15, which was first detected in *E. coli* from India in 2001.[26] CTX-M-15 belongs to the CTX-M-1 cluster and is derived from CTX-M-3 by one amino acid substitution at position 240 (Asp→

Gly). This substitution confers increased catalytic activity to ceftazidime, and bacteria producing these enzymes often test resistant to this agent.[22] The mobilization and production of CTX-M-15 is also associated with the insertion element IS*Ecp1* that is located 49 bp upstream of $bla_{CTX\text{-}M\text{-}15}$.[26,27]

CTX-M-15 has often been associated with the co-production of other β-lactamases such as TEM-1, OXA-1 and the aminoglycoside-modifying enzyme, *aac*(6′)-*Ib-cr*.[28] *aac*(6′)-*Ib-cr* has the additional ability to acetylate fluoroquinolones with unprotected amino nitrogen on the piperazine ring such as norfloxacin and ciprofloxacin.[29] The production of CTX-M-15, TEM-1, OXA-1 and *aac*(6′)-*Ib-cr* has been linked to epidemic narrow host range IncFII plasmids, and is in part responsible for the resistance profile often noted with *E. coli* producing CTX-M-15.[20]

Multidrug-resistant CTX-M-15-producing *E. coli* is emerging worldwide, especially since 2003, as an important pathogen causing community-onset and hospital-acquired infections,[15] and has been reported from most countries in Europe,[30] some countries in Asia,[31] and Africa,[16] North America,[32,33] South America[34] and Australia[35] (figure 1).

CTX-M-15-producing *E. coli* is the most common type of ESBL in Europe and has been increasingly described in community isolates, particularly associated with infections in healthcare-associated patients.[36] The widespread dispersion of CTX-M-15 across Western and Eastern Europe (including the UK) has been associated with specific clones as well as the transfer of specific epidemic IncFII plasmids harbouring the $bla_{CTX\text{-}M\text{-}15}$ gene.[27,30,36]

CTX-M enzymes (most often CTX-M-14 and -27) have been described in Asia especially since the late 1990s and early 2000s; however, reports on the presence of CTX-M-5 outside the subcontinent (i.e. India and Pakistan) remain relatively scarce.[31] Reports from India indicate that CTX-M-15-producing *E. coli* is very common in the community as well as the hospital settings.[37,38] Therefore, it is possible that India represents a significant reservoir and source of CTX-M-15-producing *E. coli*. CTX-M-15 has also been reported from community and hospital isolates in the Middle East.[39]

In Africa, CTX-M-15-producing *E. coli* has been identified in Saharan (Algeria, Tunisia) and sub-Saharan countries including Cameroon, Tanzania and the Central African Republic.[40-43]

Fig. 1. Worldwide distribution of *Escherichia coli* that produce CTX-M-15 (grey shading).

In North America, the ESBL profiles differ considerably between the US and Canada. Until 2007, reports of CTX-M-producing strains were rare in the US, while TEM and SHV types were the dominant ESBLs in this country.[44,45] Lewis et al.[32] reported the first emergence of CTX-M-15 in Texas as the most common enzyme among other ESBLs. Castanheira et al.[46] performed a surveillance study of β-lactam resistance in Enterobacteriaceae recovered from US medical centres during the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) programme of 2007. CTX-M-encoding genes were detected in 38.8% of ESBL-positive isolates and were observed in 80.0% of the participating hospitals. In Canada, the largest outbreak involving CTX-M-15 occurred in multiple long-term care facilities in Toronto between 2000 and 2002,[28] and later its emergence was also reported in several studies from the Calgary Health Region.[25,47]

In South America, CTX-M-15 was first reported in 2004 among faecal *E. coli* isolates from Peru and Bolivia[48] and later in Colombia,[49] although South America is particularly dominated by CTX-M-2- and CTX-M-9-producing *E. coli*.[34]

A recent report from Sydney, NSW, Australia, has described CTX-M-15 as the dominant ESBL among clinical isolates of *E. coli* and *Klebsiella pneumoniae*, and CTX-M was present in a wide range of community isolates.[35]

1.3 Molecular Epidemiology of CTX-M-15-Producing *E. coli*

The molecular epidemiology of clinical CTX-M-15-producing *E. coli* on a countrywide or regional scale has been described from various continents and includes Russia,[50] UK,[51] India,[37] Spain,[52] Austria,[53] Italy,[54] Portugal,[55] France,[56] Canada,[25] US[32] and Sweden.[57] These studies included *E. coli* isolates collected from different parts of the respective countries, either as part of prospective surveillance studies over a specific period or acting as a reference laboratory for resistance isolates. Some of the reports describe some clonal similarity among the CTX-M-15 producers especially in those from Russia, Italy, Spain, Portugal, France, Sweden, UK and Canada. Interestingly, in the studies that used pulsed field gel electrophoresis for typing, the clonal relatedness among the isolates was most often less than 80% and therefore did not meet the 'possibly related (4–6 bands difference)' criteria of Tenover et al.[58] However, typing of CTX-M-15 *E. coli* from the Indian, Austrian and US studies demonstrated great diversity among the different isolates.

Molecular characterization of plasmids encoding CTX-M-15 from *E. coli* strains involved in outbreaks in different countries showed that they additionally carried other antibacterial resistance genes, such as $bla_{\text{OXA-1}}$, $bla_{\text{TEM-1}}$, *tetA*, *aac(6′)-Ib-cr* and *aac(3)-II*, and sometimes within a class 1 integron.[20,28,59] The $bla_{\text{CTX-M-15}}$ was located on closely related IncFII plasmids of various sizes (85–200 kb), transferability properties and replicon contents (FII or FII-FIA).[20] However, association with IncFI plasmids has also been noted.[60] Marcade et al.[61] reported that $bla_{\text{CTX-M-15}}$ was carried by FIA-FIB, FIA-FIB-FII and FIB-FII multireplicons. The diversity of such plasmids may be explained by the different recombinal events between IncFII plasmids with different variations in *copA*, which may alter their compatibility properties.[20]

1.4 Emergence of Multilocus Sequencing Typing Clone ST131 O25:H4 Producing CTX-M-15

An identical clone named ST131 has been identified using multilocus sequencing typing (MLST) among CTX-M-15-producing *E. coli* isolated during 2000–6 from several countries including Spain, France, Canada, Portugal, Switzerland, Lebanon, India, Kuwait and Korea.[62,63] MLST offers a more fundamental perspective of the population biology of a species, defining 'sequence types' (ST) based on polymorphisms within strongly conserved 'housekeeping' genes. Serogroup O25 is associated with clone ST131 and belongs to the highly virulent phylogenetic group B2 while harbouring multidrug-resistant IncFII plasmids. These two initial studies[62,63] showed that clone ST131 had

emerged independently in different parts of the world spanning three continents at the same time. Their findings suggested that the emergence of clone ST131 could be due to contaminated food/water sources and/or importation into various countries via returning travellers.

MLST is the most reliable method for the identification of clone ST131. This technique is the most suitable typing method for comparing data generated independently from different laboratories and therefore ideal for tracking antimicrobial-resistant bacteria on a worldwide basis.[64] Unfortunately, MLST is expensive, time consuming and not really suitable to track resistant clones in a rapid, real-time fashion. Methods for the rapid and easy identification of clone ST131 have recently been published and include repetitive-element polymerase chain reaction (PCR) typing schemes,[65,66] PCR for the *pabB* allele,[67] PCR for ST131-associated single nucleotide polymorphisms (SNPs) in *mdh* and *gyrB* combined with the O25b *rfb* allele,[68] and a triplex PCR that targeted the operon afa FM955459 and part of the CTX-M-15 gene.[69]

Clone ST131 producing CTX-M-15 has also recently been described in the UK,[70] Italy,[71] Turkey,[72] Croatia,[73] Japan,[74] the US[75] and Norway.[76] *E. coli* belonging to clone ST131 without CTX-M-producing β-lactamases has been isolated from stools of healthy volunteers in Paris, France[77] and among isolates causing UTIs in Canada.[68] CTX-M-15-producing *E. coli* belonging to clone ST131 have been identified in isolates recovered from the community,[78] hospital[79] and nursing home settings[80] and, interestingly, in a companion animal.[81]

Johnson and colleagues[68] recently gave some insight into the origin of clone ST131. They studied 199 cotrimoxazole-resistant and fluoroquinolone-resistant *E. coli* isolated from urine during 2002–4. They identified clone ST131 in 23% of isolates and nearly all were fluoroquinolone-resistant (i.e. 99%) but, notably, remained susceptible to cephalosporins (i.e. only 2% of clone ST131 in that study were resistant to the cephalosporins!). Therefore, it is possible that clone ST131 is common among fluoroquinolone-resistant *E. coli* and it seems that ST131 does not necessarily have to produce an ESBL.[68] This issue should be investigated by searching for clone ST131 among fluoroquinolone-resistant *E. coli* that were isolated in the mid- to late 1990s.

Why did CTX-M-15-producing *E. coli* emerge simultaneously in different continents as a cause of community-onset infections? Recent studies from Calgary, AB, Canada and Auckland, New Zealand shed some light on this intriguing question.[23,82,83] The publication from New Zealand describes a series of patients who presented to an Auckland hospital with community-onset genitourinary tract infections due to CTX-M-15-producing *E. coli* who had a history of travel to or recent emigration from the Indian subcontinent.[82] All the patients lacked the traditional risk factors associated with UTIs. The Canadian study demonstrated that travel to the Indian subcontinent (India, 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.[23] A follow-up study showed that this high risk of infection was mostly due to the acquisition of clone ST131 producing CTX-M-15.[83]

A different study from Calgary over an 8-year period (2000–7) showed that the *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. (i.e. 1 of 18 [5%] ESBL-producing *E. coli* isolated from blood between 2000 and 2003 was ST131 as opposed to 20 of 49 [41%] isolated between 2004 and 2007).[84] In this study, clone ST131 (as compared with other ESBL-producing *E. coli*) was more likely to be resistant to several antibacterials, more likely to produce the aminoglycoside-modifying enzyme *aac(6′)-Ib-cr*, and more likely to cause community-acquired infections and urosepsis.

These studies suggest that the sudden worldwide increase of CTX-M-15-producing *E. coli* is at least in part due to clone ST131. Since reports from India indicate that more than 70% of *E. coli* collected from the community are ESBL producers,[8] it is conceivable that foreign travel to high-risk areas such as the Indian subcontinent potentially plays an important role in spread

across different continents. Empirical antibacterial 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 high spreading capacity of CTX-M-15-producing *E. coli* includes two possible ways: the spread of an epidemic clone (such as ST131) with selective advantages (as multiple antibacterial resistance and enhanced virulence factors) between different hospitals, long-term care facilities and the community; or the horizontal transfer of plasmids or genes that carry *bla*CTX-M-15 alleles. The literature suggests that the spread of CTX-M-15 *E. coli* is mostly due to clone ST131 but plasmid transfer also seems to be important in certain places.

2. Economic Burden of Infections due to ESBL-Producing Enterobacteriaceae

The economic and clinical outcomes of infections due to ESBL-producing bacteria were evaluated in a recent matched-cohort study.[85] Twenty-one patients infected with ESBL-producing *E. coli* or *Klebsiella* spp. at sites other than the urinary tract were compared with 21 patients with non-ESBL infections matched for pathogen, patient age, co-morbid conditions, anatomical site of infection, hospital location, date of hospitalization and initial antimicrobials received. The two groups were well matched with respect to demographic and clinical characteristics, except that patients with ESBL-positive strains had been hospitalized for a longer period before onset of the infection (24 vs 11 days) and were more likely to have recently received antimicrobials (42.9% vs 4.8%). Patients infected with ESBL-producing strains had significantly higher infection-related hospital costs than did those with non-ESBL-producing strains ($US41 353 vs $US24 902 per patient, year of costing 2004), which was largely driven by a prolonged length of stay in the hospital. Patients with ESBL-producing strains required an additional length of stay of 9.7 days. In both groups, hospital bed costs accounted for approximately 55% of total costs, whereas antimicrobial costs represented only 2–3% of the total. Initial antimicrobial therapy was less likely to be successful in patients infected with the ESBL-positive strains (47.6% vs 85.7%), reflecting a difference in success rates for non-carbapenem β-lactams and fluoroquinolones. In contrast, treatment was successful in all patients who received a carbapenem, regardless of ESBL phenotype. Patients in whom initial antibacterial therapy failed were significantly more likely to receive sequential antibacterial therapy, thus increasing their length of stay and hospital costs.

Similar results were obtained in an earlier case-control study involving 33 patients infected with ESBL-producing *E. coli* or *K. pneumoniae* and 66 matched control individuals.[86] Patients with ESBL-producing strains had significantly greater median hospital charges than did those with non-ESBL-producing strains ($US66 590 vs $US22 231 per patient, year of costing 2000). On multivariate analysis, which controlled for APACHE II (Acute Physiology and Chronic Health Evaluation II) score and hospitalization duration before infection, ESBL-producing strains increased costs by an average of 1.71-fold relative to controls. Hospital stays were also 1.7 times longer after correction for APACHE II scores, although this difference largely disappeared when correction was also made for the duration of hospitalization before infection.

A larger case-control study compared 99 bacteraemic patients with ESBL-producing strains of *E. coli*, *Klebsiella* spp. or *Proteus* spp. with 99 control patients with bacteraemia caused by non-ESBL strains.[4] Patients with ESBL-positive strains had significantly higher average hospital costs ($US46 970 vs $US16 877 per patient, year of costing 2003), longer median hospital stays after the onset of bacteraemia (11 vs 5 days) and higher in-hospital mortality (35% vs 18%) compared with control individuals. After adjusting for potential confounding variables in multivariate analyses, ESBL production remained independently associated with increased hospital costs ($p = 0.003$), longer hospital stays ($p = 0.001$) and higher in-hospital mortality ($p = 0.008$). Moreover, patients with ESBL-positive strains were much more likely than control individuals

to have a delay of at least 48 hours until initiation of appropriate antimicrobial therapy (66% vs 7%).

The importance of selecting appropriate initial antimicrobial therapy to patient outcome is illustrated by a prospective study of 455 consecutive cases of *K. pneumoniae* at 12 hospitals in seven countries.[87] Eighty-five cases were caused by an ESBL-producing strain, and, of these, 20 patients (23.5%) died within 14 days of the first positive blood culture. Failure to administer an appropriate antibacterial with *in vitro* activity against the isolate within the first 5 days resulted in significantly higher mortality than treatment with an appropriate antibacterial (63.6% vs 14.1%). Patients who received a carbapenem – either alone or in combination with another antibacterial – during that 5-day period had 83% lower risk for 14-day mortality than did those who received non-carbapenem antibacterials. Moreover, on multivariate analysis carbapenem use was found to be independently associated with decreased mortality.

The impact of ESBL production on mortality from bacteraemia caused by Enterobacteriaceae had also been studied in a recent meta-analysis by Schwaber and Carmeli,[88] and they found a significantly increased rate of mortality in the ESBL group (pooled relative risk [RR] 1.85; 95% CI 1.39, 2.47). The same study demonstrated an increased RR for delayed effective therapy (pooled RR 5.36; 95% CI 2.73, 10.53). The increased mortality observed in patients with bloodstream infections can be contrasted with the findings of eight additional studies, all of which also included patients with types of infections other than bloodstream infections. Among those studies, increased mortality was found in only one, although a tendency toward a higher rate of mortality in the ESBL group could be observed in some of the studies. Six of seven studies found increased length of hospital stay for patients with extended-spectrum cephalosporin-resistant isolates, while increased cost was found in the three studies that considered this parameter.

The studies consistently show that infections due to ESBL-producing Enterobacteriaceae are associated with a delay in initiation of appropriate antimicrobial therapy, which consequently prolongs hospital stays and increases hospital costs.[89] More importantly, failure to initiate appropriate antimicrobial therapy from the start appears to be responsible for higher patient mortality.[90,91]

3. Treatment of Infections Caused by ESBL-Producing Enterobacteriaceae

3.1 Introduction

The presence of ESBLs complicates antimicrobial selection especially in patients with serious infections such as bacteraemia. The reason for this is that ESBL-producing bacteria are often multiresistant to various antimicrobials, and an interesting feature of CTX-M-producing isolates is the co-resistance to the fluoroquinolones.[15] Antimicrobials that are regularly used for empirical therapy of serious community-onset infections, such as the third-generation cephalosporins (e.g. cefotaxime and ceftriaxone), are often not effective against ESBL-producing bacteria.[87] This multiple drug resistance has major implications for selection of adequate empirical therapy regimens. Empirical therapy is prescribed at the time when an infection is clinically diagnosed while awaiting the results of cultures and antimicrobial susceptibility profiles. Multiple studies in a wide range of settings, clinical syndromes and organisms have shown that failure or delay in adequate therapy results in an adverse mortality outcome. This is also true of infections caused by ESBL-producing bacteria.[88] A major challenge when selecting an empirical regimen is to choose an agent that has adequate activity against the infecting organism(s). Empirical antimicrobial choices should be individualized based on institutional antibiograms that tend to be quite different from hospital to hospital, city to city and country to country.

The next issue surrounding the therapy of ESBL-producing infections is that even if an agent is selected that has *in vitro* activity against the bacteria (when tested in the laboratory), clinical *in vivo* efficacy in patients is not always guaranteed. Several studies have noted a reduction in clinical effect against ESBL-producing

bacteria with some β-lactam agents despite testing susceptible *in vitro*, while other studies have shown good clinical outcome with β-lactam/β-lactamase inhibitor combinations.[92] This is widely believed to occur as a result of the so-called inoculum effect that occurs when the minimum inhibitory concentration (MIC) of the antibacterial rises (i.e. the antibacterial loses activity) with the increasing size of the inoculum (or number) of bacteria tested. This has been described for cephalosporins, β-lactam/β-lactamase inhibitor combinations (e.g. piperacillin/tazobactam and less with amoxicillin/clavulanic acid[93]) and to a lesser extent with the fluoroquinolones.[94]

The cephamycins, including cefoxitin and cefotetan, are stable to hydrolysis by ESBL-producing Enterobacteriaceae and demonstrate susceptibility. However, there is a general reluctance to use these agents because of the relative ease by which some isolates may decrease the expression of outer membrane proteins, creating resistance to these agents during therapy.[95]

As a result of these major concerns, the carbapenems, including imipenem, meropenem, doripenem and ertapenem, have become widely recognized as the drug class of first choice for the treatment of serious infections due to ESBL-producing Enterobacteriaceae. This has occurred because these agents are highly stable to hydrolysis by ESBLs, their distribution into body tissues in high concentrations and there is a lack of the inoculum effect.[96] Potential drawbacks of their use include high cost, the necessity for the parenteral route of administration, and wide spectrum of activity that may promote infections with yeasts and bacteria with the potential selection of carbapenem-resistant variants.[97]

3.2 Susceptibility of Enterobacteriaceae that Produce ESBLs

ESBLs have the ability to hydrolyse and cause resistance to the majority of β-lactam antibacterials including the penicillins, cephalosporins and monobactams. The degree of hydrolytic activity against the third-generation cephalosporins may be different for the genotypes of ESBLs. For example, the TEM and SHV types of ESBLs sometimes have greater activity against ceftazidime than cefotaxime, while the majority of the CTX-M type of ESBLs have greater activity against cefotaxime and ceftriaxone.[2] Consequently, ESBL-producing organisms may appear susceptible *in vitro* to some of the cephalosporins. The Clinical and Laboratory Standards Institute (CLSI) from the US recommends that ESBL-producing *E. coli, K. pneumoniae, K. oxytoca* and *Proteus mirabilis* should be reported as resistant to penicillins, cephalosporins and monobactams regardless of the *in vitro* susceptibility data.[98] These guidelines include the fourth-generation cephalosporin cefepime that often tests sensitive against ESBL-producing bacteria. The CLSI has just published in 2010 new cephalosporin susceptibility breakpoints for Enterobacteriaceae.

An important factor that limits the array of active antimicrobials against ESBL-producing Enterobacteriaceae is the frequent co-expression of resistance by these organisms to classes of antimicrobial agents other than those hydrolysed by the ESBLs. This has been shown for fluoroquinolones, aminoglycosides, tetracyclines (excluding glycylcyclines) and cotrimoxazole.[2] Resistance to the carbapenems has only rarely been reported in isolated cases.[99] The rates of resistance of ESBL-producing *E. coli* and *Klebsiella* spp. to different non-β-lactam antimicrobial agents (excluding the β-lactam/β-lactamase inhibitor combinations) from different parts of the world are summarized in table II.[8,36,44,56,100-103]

3.3 Specific Agents for the Treatment of Infections Caused by ESBL-Producing Enterobacteriaceae

3.3.1 Carbapenems

The carbapenems are considered to be the treatment of choice against serious infections due to ESBL-producing bacteria.[96] Several studies have highlighted the clinical effectiveness and superior outcomes of serious infections treated with the carbapenems. Endimiani et al.[104] investigated 35 cases of bloodstream infections caused by TEM-52-producing *K. pneumoniae*. Twenty-eight cases were investigated with regard to response to treatment with ciprofloxacin or

Table II. Rates of resistance of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* spp. to different non-β-lactam antimicrobial agents (excluding the β-lactam/β-lactamase inhibitor combinations)

Antimicrobial agent	Nonsusceptibility (i.e. intermediate or resistance) [%]	Inoculum effect[a]
Piperacillin/tazobactam	0–53	Yes
Amoxicillin/clavulanic acid	37–>80	Yes[b]
Gentamicin	9–67	No
Tobramycin	14–72	No
Amikacin	5–27	No
Ciprofloxacin	62–>90	Yes
Cotrimoxazole	25–>90	No
Nitrofurantoin	6–29	?
Fosfomycin	1–9	?
Tigecycline	0–1	?
Temocillin	<10	?

a Inoculum effect occurs when the minimum inhibitory concentration of the antimicrobial rises with the increasing size of the inoculum of bacteria tested.

b The inoculum effect described with amoxicillin/clavulanic acid is less than with piperacillin/tazobactam.

? indicates unknown.

imipenem/cilastatin. Ten patients were treated with imipenem/cilastatin, two failed to respond, while in the ciprofloxacin group, five of seven patients failed to respond to therapy, although the bacteria were classified as susceptible to ciprofloxacin. The authors also noted an inoculum effect with ciprofloxacin.

In an international study involving 12 hospitals in seven countries over a period of 2 years, Paterson et al.[87] prospectively collected data on 455 episodes of *K. pneumoniae* bacteraemia, and 85 episodes were caused by ESBL-producing isolates. Treatment with a carbapenem, most often imipenem/cilastatin, was associated with significantly lower 14-day mortality than treatment with other *in vitro* active antibacterials. Several other studies are also supportive of the effectiveness of the carbapenems.[35,105] In addition, in a small clinical trial, the use of ertapenem for the treatment of 20 patients with early-onset ventilator-associated pneumonia caused by ESBL-producing Enterobacteriaceae resulted in a clinical success rate of 80%.[106]

It is important to note that development of resistance during therapy to ertapenem (due to the production of CTX-M-15 and the loss of porin OmpK36 in *K. pneumoniae*) and imipenem (due to CMY-2 and the loss of porins OmpF and OmpC in *E. coli*) has been described previously.[107,108] Resistance to ertapenem has been described in *Klebsiella* spp. and *Enterobacter* spp. due to the production of various types of ESBLs and AmpC β-lactamases as well as the concurrent loss of porins.[109,110]

3.3.2 Cephalosporins

The second- and third-generation cephalosporins are not considered to be options for the treatment of infections due to ESBL-producing bacteria. With infections due to ESBL-producing strains of Enterobacteriaceae, it is known that the MIC and therefore the time over the MIC for β-lactams will predict outcome. Therefore, pharmacodynamic modelling has been used to set breakpoints for ESBL-producing bacteria with β-lactams that are generally much lower than existing breakpoints.[111]

In a retrospective study of consecutive patients, those treated with imipenem/cilastatin for nosocomial bloodstream infection due to ESBL-producing *E. coli* or *K. pneumoniae* were significantly more likely to survive than were such patients treated with a third-generation cephalosporin.[112] Previous treatment with a third-generation cephalosporin was shown to be an independent risk factor for bloodstream infection caused by ESBL-producing bacteria. This observation led the investigators to conclude that

more cautious use of third-generation cephalosporins might even be important for preventing bacteraemia due to ESBL-producing *E. coli* or *K. pneumoniae*.

Infectious disease physicians have been contemplating if ceftazidime will be effective for the treatment of infections caused by CTX-M-producing organisms that show sufficient *in vitro* susceptibilities. Bin and colleagues[113] have tried to address this important issue. They performed a prospective observational study of 22 patients with CTX-M-producing *E. coli* bloodstream infections over a period of 3 years; seven patients were treated with ceftazidime, eight with imipenem/cilastatin and seven with cefoperazone/sulbactam. The patients had comparable demographic characteristics, and the treatment success ratios were similar between the three groups and none of the patients died. Some interesting findings of this study included that successful therapy in the three different groups was expedited with additional treatment modalities such as urinary drainage, mucolytics and drainage of abscesses, and patients with bacteraemia due to peritonitis failed to respond to therapy irrespective of the type of antibacterial used. The study suggests that patients infected with CTX-M-producing *E. coli* sensitive to ceftazidime can be successfully treated with this agent, although this needs to be confirmed with a randomized, blinded study.

Cefepime is a fourth-generation cephalosporin that shows improved activity (compared with other cephalosporins) against some bacteria that produce ESBLs. *In vitro* studies have confirmed that ESBL-producing organisms are generally susceptible to the antimicrobial action of cefepime,[114] suggesting that cefepime may be of clinical value for the treatment of some infections caused by bacterial strains that are resistant to third-generation cephalosporins. In addition to its *in vitro* activity, the pharmacokinetic-pharmacodynamic properties of cefepime appear to contribute to and support its bactericidal activity.[115] Zanetti et al.[116] reported on a randomized, controlled, multicentre trial comparing cefepime with imipenem for the treatment of nosocomial pneumonia in ICU patients. Although this was not designed as an ESBL-producing organism treatment study, a subgroup analysis revealed that among 23 patients with ESBL-producing infections, 4 of 13 cefepime-treated patients compared with none of ten imipenem/cilastatin-treated patients failed to respond to therapy as defined by clinical criteria. In all of these cases, the isolated organisms were susceptible to cefepime using CLSI breakpoints.

3.3.3 Cephamycins

The majority of clinicians avoid the use of cephamycins in the treatment of infections due to ESBL-producing bacteria because of *in vivo* selection of cephamycin-resistant impermeability mutants especially when using the older drugs such as cefoxitin.[95] However, Lee et al.[117] from Taiwan evaluated a new cephamycin, flomoxef, in a retrospective study and compared the clinical efficacy of this agent with that of the carbapenems meropenem and imipenem for the treatment of infections caused by ESBL-producing *K. pneumoniae*. They included 27 patients in this study and their results suggest that flomoxef was as clinically effective as the carbapenems. Unfortunately, this study lacked the power to discriminate real differences in outcome between the groups, but does provide insight into the possibility of using a cephamycin for infections caused by ESBL-producing bacteria.

3.3.4 β-Lactam/β-Lactamase Inhibitor Combinations

The available clinical evidence regarding the usefulness of β-lactam/β-lactamase inhibitor combinations for the treatment of infections due to ESBL-producing bacteria is limited. Tumbarello et al.[118] evaluated the treatment outcomes in 48 cases of infections caused by ESBL-producing bacteria compared with 99 control cases. The rate of treatment failure in the patients infected with ESBL producers was nearly twice that of the controls (31% vs 17%) and the 21-day mortality rates were 52% and 29%, respectively. Therapy that led to a successful outcome was observed with a carbapenem in 33% of the cases, an aminoglycoside in 22%, a fluoroquinolone in 17% and a β-lactam/β-lactamase inhibitor combination

(piperacillin/tazobactam) in 28% of cases. This study suggested a successful outcome could be expected when the *in vitro* testing indicated susceptibility to piperacillin/tazobactam.

Gavin et al.[119] reported a similar outcome when using piperacillin/tazobactam for infections due to ESBL-producing *E. coli* and *Klebsiella* spp. from seven medical centres across North America. The authors observed that meropenem therapy was successful in only two of four infections due to piperacillin/tazobactam-resistant isolates, illustrating that sometimes the carbapenems are not effective in the treatment of non-UTIs caused by ESBL-producing bacteria.

Recently, Rodríguez-Baño et al.[120] analysed the outcome of 43 episodes of *E. coli* bacteraemia caused by ESBL-producing isolates (most often producing CTX-M-14). Mortality was lower when patients were given a β-lactam/β-lactamase inhibitor or a carbapenem, compared with either a cephalosporin or fluoroquinolone (9% vs 35%; $p = 0.05$).

Another study by Rodríguez-Baño et al.[121] evaluated the use of amoxicillin/clavulanic acid in a series of 37 patients with cystitis caused by ESBL-producing *E. coli*. The overall cure rate was 84%; however, the effectiveness of this drug combination appeared to be significantly lower in a subgroup of patients infected with isolates having elevated MIC values to this drug. A case report has also been published that showed successful treatment with amoxicillin/clavulanic acid of UTI caused by an amoxicillin/clavulanic acid-resistant *E. coli*.[122]

Various authors have also reported ecological supporting evidence for the activity of β-lactam/β-lactamase inhibitor combinations against ESBL-producing bacteria, i.e. use of these agents as a replacement for extended-spectrum cephalosporins as part of a formulary strategy to, over a period, lower the prevalence of ESBL-producing Gram-negative bacilli in healthcare settings.[92] The change of antimicrobial agent prescribing habits to increase the use of β-lactam/β-lactamase inhibitor compounds that then led to a significant reduction of infections due to ESBL-producing Gram-negative bacteria, strongly suggests that these compounds have a useful ecological impact on the overall reduction of infections due to ESBL-producing bacteria.[92]

The existing data suggest that piperacillin/tazobactam may be a useful agent for the treatment of some infections with ESBL-producing pathogens. However, this potential recommendation must be interpreted cautiously, because it is based on a relatively small database of information. Definitive conclusions regarding the efficacy of piperacillin/tazobactam for the treatment of infections caused by bacteria that produce ESBLs must await large-scale, prospective, randomized clinical trials.

3.3.5 Aminoglycosides

Resistance to the aminoglycosides in ESBL-producing organisms has always been an issue for clinicians, since ESBLs are often located on large plasmids that harbour genes for resistance to other antimicrobial classes, especially gentamicin and tobramycin. Resistance to the aminoglycosides was exacerbated recently with the worldwide emergence of CTX-M-15-producing *E. coli* in the community setting. CTX-M-15 has often been associated with co-production of the aminoglycoside-modifying enzyme *aac*(6′)-*Ib-cr* that has the ability to inactivate tobramycin and amikacin.[29] Among the different aminoglycosides available in clinical practice, susceptibility to amikacin is highest among bacteria that produce ESBLs.[102] The limited success of aminoglycosides in treating bacteraemias caused by ESBL-producing *K. pneumoniae* has been demonstrated in a study from Korea.[123] Kim et al.[123] studied all cases of ESBL-producing *E. coli* and *K. pneumoniae* bacteraemia infections occurring in children at the Seoul National Children's Hospital. Of 36 infections caused by organisms that produce ESBLs, only 7 of 15 patients treated with appropriate aminoglycoside therapy had a sufficient clinical response.

3.3.6 Fluoroquinolones

Resistance to the fluoroquinolones has reached immense proportions in CTX-M-producing Enterobacteriaceae, with rates of resistance reported ranging from 55% to 100% from different areas of the world.[124] Therefore, the fluoroquinolones

have a very limited role in treating infection caused by ESBL-producing bacteria. However, the fluoroquinolones remain an option if the isolate tested is susceptible to these agents.[15]

3.3.7 Other Agents

Fosfomycin is a bactericidal antibacterial that acts as a cell-wall inhibitor by interfering with the first step in peptidoglycan biosynthesis. It has a broad spectrum of activity and resistance in clinical isolates is rare.[100] After many years of use, fosfomycin continues to be active against the most common uropathogens and there is a very low incidence of resistant strains in *E. coli* (about 2%). In a recent survey conducted in Spain, among the 428 ESBL-producing isolates studied, 417 (97.4%) were susceptible to fosfomycin (MIC ≤64 mg/L). The resistance rate of ESBL-positive *E. coli* to fosfomycin was 0.3%, whereas the resistance rate of ESBL-positive *K. pneumoniae* was 7.2%.[125] These results are similar to those described in previous reports of non-ESBL-producing isolates, confirming that fosfomycin retains its activity against ESBL-producing isolates, and that cross-resistance with other classes of antimicrobial agents is rare at present. Also, there were no differences in fosfomycin activity against strains expressing different types of ESBL.[125] Other recent surveys in other parts of the world confirm the activity of fosfomycin against ESBL-producing *E. coli*.[100] The use of fosfomycin has increased dramatically in certain countries and it has become the first choice for uncomplicated cystitis.[126] Unfortunately, very limited data are available about the use of fosfomycin for infections caused by ESBL-producing bacteria. A study by Rodríguez-Baño et al.[121] provided observational results for the successful treatment of cystitis with fosfomycin due to fosfomycin-susceptible ESBL-producing *E. coli*. Furthermore, susceptibility data suggest this agent might be a viable option to treat uncomplicated UTIs due to ESBL-producing bacteria. Unfortunately, a recent report from Spain described acquired resistance to fosfomycin in *E. coli* clone ST131.[127]

Nitrofurantoin is a synthetic nitrofuran antimicrobial agent that has been available in clinical practice for more than 50 years. It still has a role and continues to be prescribed, particularly in the ambulatory setting, for uncomplicated UTIs.[100] Susceptibility breakpoints are based on urinary concentrations of nitrofurantoin and have been correlated with eradication of bacteriuria in patients with UTIs. The rate of resistance to nitrofurantoin in 115 clinical isolates of *E. coli* that produce ESBLs from Spain was 29%;[103] however, resistance rates as low as 7% were reported from Canada.[83] Nitrofurantoin is restricted to treatment or prevention of uncomplicated cystitis; and is an option for the treatment of uncomplicated UTIs due to ESBL-producing bacteria. Because responses to this agent and infections caused by susceptible pathogens may be less satisfactory and require longer courses of therapy, nitrofurantoin is considered to be an alternative rather than a first-line therapeutic agent for this clinical syndrome.[100]

Tigecycline, a derivative of minocycline, is the first member of the glycylcycline class of antimicrobials available for clinical use. It has the property to evade common mechanisms of resistance to tetracyclines expressed in Gram-negative and Gram-positive bacteria.[128] Tigecycline has shown excellent activity against ESBL-producing *E. coli* isolates; especially those producing CTX-M enzymes.[101,102] Clinical data regarding the effectiveness of tigecycline against infections caused by ESBL-producing bacteria are rare at present, and the concentration of the drug in urine is not sufficient to treat UTIs.

Other agents such as temocillin, pivmecillinam and colistin show good *in vitro* activity against ESBL-producing bacteria.[129] However, clinical data on the use of these drugs for infections caused by ESBL-producing bacteria are not available at present. Temocillin, a derivative of ticarcillin, is resistant to hydrolysis by most ESBLs and to AmpC β-lactamases. It is also chemically stable, allowing administration by continuous infusion.[130] A recent *in vitro* study from Belgium[131] reported that temocillin was active against most AmpC- and ESBL-producing isolates, and a case report described successful treatment with temocillin of a spinal infection due to an ESBL-producing *K. pneumoniae*.[132]

A case report described a woman with relapsing pyelonephritis due to a CTX-M-producing *E. coli* who was cured with a prolonged course of oral pivmecillinam.[133]

4. Summary and Conclusions

Antimicrobial resistance is an important issue affecting public health and rapid detection in clinical laboratories is essential for the prompt recognition of antimicrobial-resistant organisms. Infection control practitioners and clinicians need the clinical laboratory to rapidly identify and characterize different types of resistant bacteria efficiently to minimize the spread of these bacteria and help to select more appropriate antibacterials. This is also true for ESBL-producing bacteria. It is clear that the epidemiology of ESBL-producing bacteria is becoming more complex with increasingly blurred limits between hospitals and the community. *E. coli* producing CTX-M β-lactamases (especially CTX-M-15) seem to be true community ESBL producers with different behaviour from *Klebsiella* spp. producing TEM- and SHV-derived ESBLs. These bacteria have become widely prevalent in the community setting in certain areas of the world and they are most likely being imported into the hospital setting.

Molecular epidemiology studies suggested 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 might play in part a role in the spread of this clone across different continents. Empirical antibacterial coverage for these resistant organisms should be considered in community patients presenting with sepsis involving the urinary tract, especially if a patient recently travelled to a high-risk area. 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. Internationally funded efforts should be undertaken to track and monitor the worldwide spread of ST131 *E. coli* producing CTX-M-β-lactamases within the hospital and community settings. If this emerging public health threat is ignored it is possible that clinicians may be forced to use the carbapenems as the first choice for the empirical

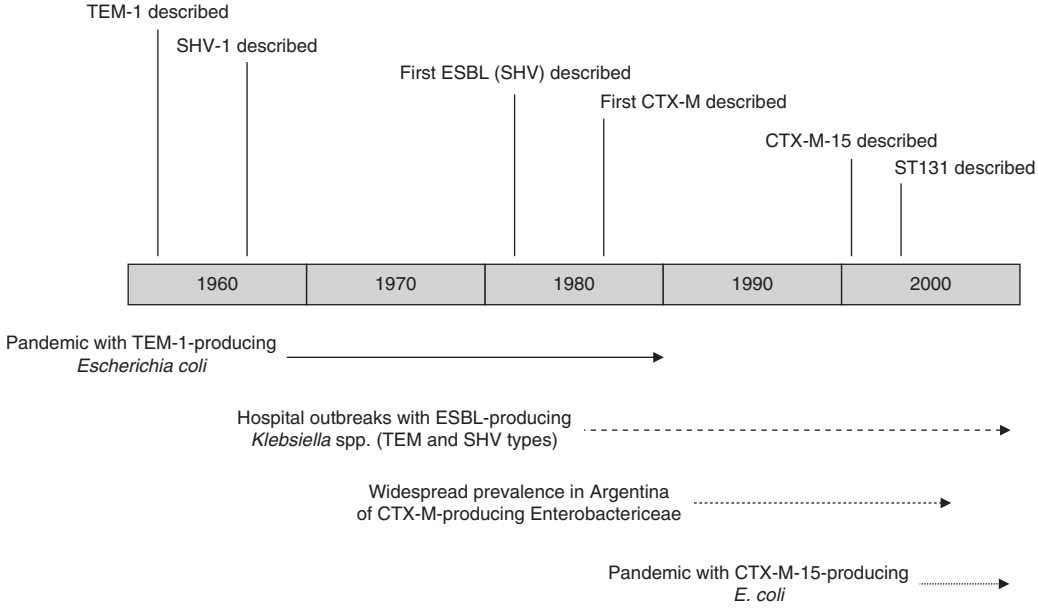

Fig. 2. Recent evolution of pandemics caused by bacteria that produce β-lactamases, especially extended-spectrum β-lactamases (ESBLs).

Table III. Antimicrobial agents for the treatment of Enterobacteriaceae that produce extended-spectrum β-lactamases

Type of infection	Origin	First-line therapy	Alternative therapy[a]
Systemic (primary bacteraemia, pneumonia, intra-abdominal sepsis, complicated UTI [urosepsis])	Community-onset	Ertapenem	Amikacin
Systemic (primary bacteraemia, pneumonia, intra-abdominal sepsis, complicated UTI [urosepsis])	Nosocomial	Imipenem/cilastatin or meropenem	Amikacin
Uncomplicated UTI	Community-onset	Fosfomycin[b]	Nitrofurantoin,[b] amoxicillin/clavulanic acid
Uncomplicated UTI	Nosocomial	Fosfomycin[b]	Nitrofurantoin,[b] amoxicillin/clavulanic acid

a It is appropriate to have the *in vitro* susceptibility test result available.

b Fosfomycin and nitrofurantoin are not reliably active against other non-*Escherichia coli* uropathogens.

UTI = urinary tract infection.

treatment of serious infections associated with UTIs that originate from the community. The recent evolution of pandemics caused by bacteria that produce different β-lactamases (especially ESBLs) is illustrated in figure 2.

The carbapenems are widely regarded as the drugs of choice for the treatment of severe infections due to ESBL-producing Enterobacteriaceae. It is reasonable to suggest the use of ertapenem for community-onset infections and imipenem/cilastatin, meropenem or doripenem for hospital-onset infections. Research is warranted to determine if significant clinical differences exist among the carbapenems and to define the optimal therapy of less severe infections due to ESBL-producing Enterobacteriaceae. Agents such as nitrofurantoin and fosfomycin show good *in vitro* activity against ESBL-producing bacteria and are options for the treatment of uncomplicated UTIs due to these multidrug-resistant bacteria. Antimicrobial options for the treatment of infections caused by Enterobacteriaceae that produce ESBLs are summarized in table III.

Future investigations should be undertaken to study the microbiological and ecological factors that make CTX-M-producing *E. coli* such successful pathogens. This will help to prevent future infections caused by these medically important pathogens.

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