

Extended-spectrum β -lactamase-producing Enterobacteriaceae: an emerging public-health concern

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The medical community relies on clinical expertise and published guidelines to assist physicians with choices in empirical therapy for system-based infectious syndromes, such as community-acquired pneumonia and urinary-tract infections (UTIs). From the late 1990s, multidrug-resistant Enterobacteriaceae (mostly *Escherichia coli*) that produce extended-spectrum β lactamases (ESBLs), such as the CTX-M enzymes, have emerged within the community setting as an important cause of UTIs. Recent reports have also described ESBL-producing *E coli* as a cause of bloodstream infections associated with these community-onset UTIs. The carbapenems are widely regarded as the drugs of choice for the treatment of severe infections caused by ESBL-producing Enterobacteriaceae, although comparative clinical trials are scarce. Thus, more rapid diagnostic testing of ESBL-producing bacteria and the possible modification of guidelines for community-onset bacteraemia associated with UTIs are required.

Introduction

In Gram-negative pathogens, β -lactamase production remains the most important contributing factor to β -lactam resistance.¹ β lactamases are bacterial enzymes that inactivate β -lactam antibiotics by hydrolysis, which results in ineffective compounds. One group of β lactamases, extended-spectrum β lactamases (ESBLs), have the ability to hydrolyse and cause resistance to various types of the newer β -lactam antibiotics, including the expanded-spectrum (or third-generation) cephalosporins (eg, cefotaxime, ceftriaxone, ceftazidime) and monobactams (eg, aztreonam), but not the cephamycins (eg, cefoxitin and cefotetan) and carbapenems (eg, imipenem, meropenem, and ertapenem).² Organisms that produce ESBLs remain an important reason for therapy failure with cephalosporins and have serious consequences for infection control.³ That clinical microbiology laboratories detect and report ESBL-producing organisms is therefore important.

Most ESBLs can be divided into three groups: TEM, SHV, and CTX-M types.³ *Klebsiella pneumoniae* (figure) and *Escherichia coli* remain the major ESBL-producing organisms isolated worldwide, but these enzymes have also been identified in several other members of the Enterobacteriaceae family and in certain non-fermentors.⁴ A recent report from the Infectious Diseases Society of America listed ESBL-producing *Klebsiella* spp and *E coli* as one of the six drug-resistant microbes to which new therapies are urgently needed.⁵

Because of the increasing importance of multiresistant ESBL-producing *E coli* in the community, clinicians should be aware of the potential of treatment failures associated with serious infections caused by these bacteria. We review aspects of laboratory detection and treatment of infections caused by ESBL-producing bacteria.

Emergence in serious community-onset infections

Organisms that produce CTX-M enzymes have become the most prevalent type of ESBLs described during the

past 5 years, particularly from certain European and South American countries.⁶ The CTX-M β lactamases, now exceeding 50 different types, can be divided into five groups based on their aminoacid identities: CTX-M1, CTX-M2, CTX-M8, CTX-M9, and CTX-M25.⁷ Of note, organisms producing specific CTX-M enzymes have been isolated from different countries (table 1).^{6,8,9} The CTX-M enzymes originated from the *Kluyvera* spp of environmental bacteria, usually have greater activity against cefotaxime than ceftazidime (although certain types also inactivate ceftazidime), and are associated with mobile elements such as ISEcp1.¹⁰ The epidemiology of organisms producing CTX-M enzymes is very different from those that produce TEM-derived and SHV-derived ESBLs. CTX-M enzymes are not limited to nosocomial infections caused by *Klebsiella* spp, and their potential for spread beyond the hospital environment serves to exacerbate public-health concerns. *E coli* is most often

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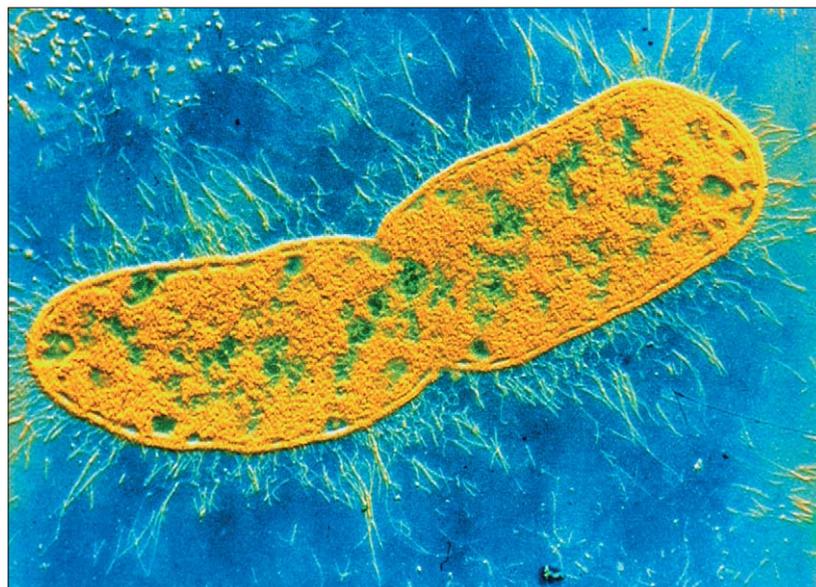


Figure: *Klebsiella pneumoniae*, an extended-spectrum β -lactamase-producing organism
False colour transmission electron micrograph (shadow technique) of *K pneumoniae*.

	Country
CTX-M1 ⁸	Italy
CTX-M2 ⁶	Israel, Argentina
CTX-M3 ⁸	Poland
CTX-M9 ⁸	Spain
CTX-M14 ^{6,9}	Spain, Canada, China
CTX-M15 ⁶	Worldwide

Table 1: Global distribution of the most common types of CTX-M β lactamases

responsible for producing CTX-M β lactamases and seems to be a true community ESBL pathogen.¹¹ The characteristics and risk factors of community-onset infections caused by ESBL-producing bacteria compared with nosocomial-onset infections are summarised in table 2.

Surveys since 2000 from several European countries (including Spain,¹² Italy,¹³ Greece,¹⁴ the UK,¹⁵ and Canada¹⁶) have shown an alarming trend of associated resistance to other classes of antimicrobial agents among ESBL-producing organisms isolated from community sites. These surveys show co-resistance to co-trimoxazole, tetracycline, gentamicin, and ciprofloxacin (up to 66% of isolates were resistant to ciprofloxacin in Canada¹⁶). These studies also showed that strains producing CTX-M enzymes were substantially more resistant to ciprofloxacin than strains lacking PCR evidence for *bla*_{CTX-M} genes.^{16,17}

Two recent reports from Israel and Spain have shown that CTX-M-producing *E coli* is an important cause of community-onset bloodstream infections.^{18,19} Ben Ami and colleagues¹⁸ from Tel-Aviv, Israel, investigated patients with community-onset, Gram-negative bacteraemia admitted to their hospital and found that 14% were caused by ESBL-producing organisms (most commonly CTX-M-producing *E coli*). These bacteria were multiresistant, with resistance to co-trimoxazole (64%), gentamicin (61%), and ciprofloxacin (64%) being reported. This study also found that nursing-home residents and men were at increased risk of bloodstream infections with ESBL-producing *E coli*. Rodriguez-Bano and colleagues¹⁹ reported 43 prospectively observed cases of ESBL-producing *E coli* bloodstream infections over a 4-year period in Seville, Spain. 51% had occurred within the community and were caused most often by CTX-M-producing isolates. These bacteria were also multiresistant with resistance to co-trimoxazole (64%), gentamicin (9%), and ciprofloxacin (68%) being reported. The most frequent origin of infection was the urinary tract, and empirical therapy with cephalosporins and fluoroquinolones was associated with higher mortality.¹⁹

Detection

The clinical laboratory acts as an early warning system, alerting the medical community to new resistance

mechanisms present in clinically important bacteria. The methods for detection of ESBLs can be broadly divided into two groups: phenotypic methods that use non-molecular techniques, which detect the ability of the ESBL enzymes to hydrolyse different cephalosporins; and genotypic methods, which use molecular techniques to detect the gene responsible for the production of the ESBL. Clinical diagnostic laboratories use mostly phenotypic methods because these tests are easy to do, are cost effective, and have been incorporated in most automated susceptibility systems, making them widely accessible.²⁰ However, phenotypic methods are not able to distinguish between the specific enzymes responsible for ESBL production (SHV, TEM, and CTX-M types). Several research or reference laboratories use genotypic methods for the identification of the specific gene responsible for the production of the ESBL, which have the additional ability to detect low-level resistance (ie, can be missed by phenotypic methods).²¹ Furthermore, molecular assays also have the potential to be done directly on clinical specimens without culturing the bacteria, with subsequent reduction of detection time.²² The detection of ESBL-producing bacteria in laboratories is a crucial step for appropriate management of patients, but genotypic identification of these enzymes provides essential information for infection prevention and control efforts, as well as the tracking of these organisms in surveillance systems.

The clinical diagnostic microbiology laboratory plays a crucial part in the detection and reporting of ESBL-producing bacteria, but many laboratories may not be fully aware of the importance of ESBL-producing organisms and the best phenotypic methods for detecting them.²³ The consequence has been several treatment failures in patients who received inappropriate antibiotics and outbreaks of multidrug-resistant, Gram-negative pathogens, which required expensive control efforts.³ Although there are several guidelines available for the phenotypic detection of ESBL-producing bacteria, this remains a contentious issue, and proficiency testing shows compliance varies widely across different parts of the world.⁴ A US study reported that only 8% of clinical laboratories from rural hospitals routinely screened for ESBL-producing organisms,²⁴ whereas a recent performance survey of 60 Italian laboratories misidentified up to 50% of known ESBL-producing isolates.²⁵

Phenotypic detection

The US Clinical and Laboratory Standards Institute (CLSI) and the UK Health Protection Agency (HPA) have published guidelines for ESBL detection in Enterobacteriaceae specifically for *E coli*, *Klebsiella* spp, and *Proteus* spp.^{26,27} The HPA guidelines also include other species, such as *Salmonella* spp. These guidelines are based on the principle that most ESBLs hydrolyse third-generation cephalosporins although they are

inhibited by clavulanate, and recommend initial screening with either 8 mg/L (CLSI) or 1 mg/L (HPA) of cefpodoxime, 1 mg/L each of cefotaxime, ceftazidime, ceftriaxone, or aztreonam, followed by confirmatory tests (including the E-test ESBL strips) with both cefotaxime and ceftazidime in combination with clavulanate at a concentration of 4 µg/mL. Automated systems that use similar detection principles have proved to be popular in clinical laboratories, especially those in North America and certain European countries.²⁸ If clinical laboratories adhere to the published guidelines for detecting ESBLs, the CLSI and HPA published methods show high sensitivity of up to 94% and specificity of 98% for detecting ESBLs in *E coli*, *Klebsiella* spp, and *Proteus* spp.²⁰

The phenotypic detection of ESBLs in bacteria other than *E coli*, *Klebsiella* spp, and *Proteus* spp remains a problematic and controversial issue.²³ The reason for this is that the clavulanate effect noticed with these ESBL-producing species is not always present in species such as enterobacter and citrobacter. This is because the clavulanate inhibition of ESBLs is often masked by other types of β lactamases, such as AmpC enzymes produced by *Enterobacter* spp. Several methods have been described, including modifications of double-disk method with cefepime,^{29,30} chromogenic agar,³¹ three-dimensional methods,³² and microdilution methods that use clavulanate with different β lactams (including fourth-generation cephalosporins, such as cefepime).³³ Unfortunately, most of these tests are technically demanding and difficult to interpret, which has limited their widespread use to detect ESBLs in bacteria such as *Enterobacter*, *Citrobacter*, and *Serratia* spp.

Genotypic detection

The determination of whether a specific ESBL present in a clinical isolate is related to TEM and SHV enzymes is a complicated process because point mutations around the active sites of the TEM and SHV sequences have led to aminoacid changes that increase the spectrum of activity of the parent enzymes, such as in TEM1, TEM2, and SHV1.² The molecular method commonly used is the PCR amplification of the *bla*_{TEM} and *bla*_{SHV} genes with oligonucleotide primers, followed by sequencing. Sequencing is essential to discriminate between the non-ESBL parent enzymes (eg, TEM1, TEM2, or SHV1) and different variants of TEM or SHV ESBLs (eg, TEM3, SHV2, etc).²

Several other molecular methods that do not use sequencing have been developed to characterise ESBLs and include PCR with RFLPs,³⁴ PCR with single-strand conformational polymorphism,³⁵ ligase chain reaction,³⁶ restriction site insertion PCR,³⁷ and real-time PCR.³⁸ However, the increasing number of additional subtypes within each ESBL family has placed strict limitations on these techniques with regard to their ability to cover the whole range of variants with different point mutations.

	Community onset	Hospital onset
Organism	<i>Escherichia coli</i>	<i>Klebsiella</i> spp (and others)
Type of ESBL	CTX-M (especially CTX-M15)	SHV (especially SHV2, SHV5) and TEM (especially TEM26, TEM51)
Infection	Most often UTIs, but also bacteraemia and gastroenteritis	Respiratory tract, intra-abdominal, and bloodstream infections
Susceptibilities	Resistance to all the penicillins and cephalosporins. High-level resistance to other classes of antibiotics, especially fluoroquinolones and co-trimoxazole	Resistance to all the penicillins and cephalosporins. High-level resistance to other classes of antibiotics, especially fluoroquinolones and co-trimoxazole
Molecular epidemiology	Most isolates often not clonally related, although clusters have been described in Canada, the UK, Italy, and Spain	Most often clonally related
Risk factors	Repeat UTIs and underlying renal pathology; previous antibiotics including cephalosporins and fluoroquinolones; previous hospitalisation; nursing-home residents; older men and women; diabetes mellitus; underlying liver pathology	Longer length of hospital stay; severity of illness (more severe, the higher the risk); longer time in the intensive-care unit; intubations and mechanical ventilation; urinary or arterial catheterisation; previous exposure to antibiotics (especially cephalosporins)

UTI=urinary-tract infection.

Table 2: Characteristics of infections caused by ESBL-producing bacteria

PCR amplification followed by nucleotide sequencing remains the gold standard for the identification of specific point mutation of *bla*_{TEM} or *bla*_{SHV} ESBL genes.³⁹ However, this is not always straightforward and cost effective because clinical isolates often have multiple copies of ESBL genes.

Genetic methods for detection of TEM and SHV types of ESBLs are thus complex and challenging because of the diversity of different point mutations that can cause an ESBL. The use of genetic methods to identify the different types of TEM and SHV ESBLs is mainly restricted to reference laboratories and to molecular surveillance studies. Hopefully, recent molecular developments, such as microarrays and rapid-cycle sequencing, will make genotypic detection more readily available and cost effective for diagnostic laboratories to identify these types of ESBLs in a real-time fashion.⁴⁰

The PCR amplification of CTX-M-specific products without sequencing, in an isolate that produces an ESBL, usually provides sufficient evidence that a *bla*_{CTX-M} gene is responsible for this phenotype. This is unlike TEM and SHV types of ESBLs. Several recent studies have described various molecular approaches for the rapid screening of ESBL-positive organisms for the presence of different *bla*_{CTX-M} genes. This involved a PCR assay that used four sets of primers to amplify group-specific CTX-M β-lactamase genes,⁴¹ amplification of a universal DNA fragment specific for most of the different groups of CTX-M β lactamases,⁴² duplex PCR,⁴³ multiplex PCR,⁴⁴ real-time PCR,⁴⁵ pyrosequencing,⁴⁶ and reverse-line hybridisation.⁴⁷ Molecular techniques undoubtedly have the potential to play an essential part in the laboratory setting for the screening, tracking, and monitoring of the spread of large numbers of organisms producing CTX-M enzymes from the community and hospital settings in real time.

Treatment of infections

Specific issues

The presence of ESBLs complicates the selection of antibiotics, particularly in patients with serious infections such as bacteraemia.³ The reason for this is that ESBL-producing bacteria are often multiresistant to various antibiotics, and CTX-M-producing isolates are co-resistant to the fluoroquinolones.¹¹ Antibiotics that are regularly used for empirical therapy of serious community-onset infections, such as the third-generation cephalosporins (eg, cefotaxime and ceftriaxone), are often not effective against ESBL-producing bacteria.⁴⁸ This multiple drug resistance has major implications for the selection of adequate empirical therapy regimens. Empirical therapy is prescribed at the time when an infection is clinically diagnosed, while the results of cultures and antimicrobial susceptibility profiles are awaited. 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, which is also true of infections caused by ESBL-producing bacteria.^{49,50} A major challenge when selecting an empirical regimen is to choose an agent that has adequate activity against the infecting organism(s). Empirical antibiotic choices should be individualised based on institutional antibiograms, which tend to be quite different from hospital to hospital, from city to city, and from country to country.

The next issue surrounding the therapy of ESBL-producing infections is that even if an agent is selected that has activity against the bacteria in vitro (when tested in the laboratory), clinical 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, whereas other studies have shown good clinical outcome with β -lactam- β -lactamase-inhibitor combinations.^{13,51} This is widely believed to occur as a result of the so-called inoculum effect that occurs when the minimum inhibitory concentration of the antibiotic rises (ie, the antibiotic loses activity) with the increasing size of the inoculum (or number) of bacteria tested.⁵² This effect has been described for cephalosporins, β -lactam- β -lactamase-inhibitor combinations (eg, piperacillin-tazobactam), and to a lesser extent with the quinolones.⁵³

The cephamycins, including cefoxitin and cefotetan, are stable to hydrolysis by ESBL-producing Enterobacteriaceae.³ 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, thus creating resistance to these agents during therapy.⁵⁴ No published data are available on the clinical efficacy of temocillin and newer agents such as tigecycline.

As a result of these major concerns, the carbapenems, including imipenem, meropenem, and ertapenem, have become widely recognised as the drug class of first choice

for the treatment of serious infections caused by ESBL-producing Enterobacteriaceae. These agents are highly stable to hydrolysis by ESBLs, are distributed into body tissues in high concentrations, and there is no inoculum effect.⁴⁸ 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.⁵⁵

Critical appraisal of clinical studies of antimicrobial therapies and infection outcomes

Despite their many theoretical advantages, carbapenems have not been subjected to specific prospective randomised clinical trials to compare their efficacy and outcome against other active agents for the treatment of infections caused by ESBL-producing Enterobacteriaceae. Several practical challenges exist with conduct of such trials and, as a result, the literature to date has been largely limited to observational analyses.⁴⁸ Our English-language Medline search to appraise the literature on antimicrobial therapy of ESBL-producing Enterobacteriaceae infections initially identified 547 articles. Titles were screened and abstracts were subsequently reviewed to select articles that assessed treatment and outcomes of an ESBL-producing Enterobacteriaceae infection. Bibliographies of selected articles and reviews were also screened to identify other reports. To assess potential efficacy differences among agents, we included only studies that had specific outcome details for ESBL-producing organisms and that reported an outcome(s) in association with an antimicrobial agent to which the organism was susceptible in vitro. Ten studies met the search criteria and are reviewed in detail (table 3).

Burgess and colleagues⁵⁶ reported on a retrospective clinical review of hospital inpatients with ESBL-producing *E coli* or *Klebsiella* spp infections at the University of Texas Health Science Center (San Antonio, TX, USA). 18 episodes of infections in 14 patients were treated with agents with in-vitro susceptibilities. The following regimens showed clinical cure: all four episodes treated with a carbapenem, two of three treated with piperacillin-tazobactam, all three treated with quinolones, and three of six treated with multiple non-carbapenem-containing drugs. Additionally, one episode of urinary-tract infection was successfully treated with nitrofurantoin and one bacteraemic patient was treated with amikacin. Given the small numbers of patients studied, multiple assessments of outcome for a given patient, and that investigator determination of outcome was not blinded to therapy, limited conclusions about therapy can be drawn from this study.

Endimiani and co-workers⁵⁷ did a retrospective review of 31 patients with *K pneumoniae* bacteraemia in L'Aquila, Italy. 21 episodes of infection with isolates that were susceptible to both imipenem and ciprofloxacin were

reported and 17 were assessed (ten patients were treated with imipenem and seven with ciprofloxacin). In the imipenem-treated cases, two were deemed to be non-responders and eight had complete responses. In the ciprofloxacin-treated cases, two were deemed to have had a partial response and five were classified as non-responders to therapy. Limitations of this study included the small numbers of patients studied, the potential bias in assessment of response to therapy, and that the adequacy of empirical therapy was not considered in the overall assessment of outcome.

Ho and colleagues⁵⁸ reported a case-control study of ESBL-producing *E coli* in Hong Kong. Case patients with an ESBL-producing *E coli* bacteraemia were matched 1:2 with controls that had a non-ESBL-producing *E coli* bacteraemia by use of four criteria (specialty, sex, age, and closest date to isolation of ESBL-positive *E coli*). During the 3-year study, 983 patients had an *E coli* bacteraemia, of which 7% were caused by ESBL-producing *E coli*. Inappropriate empirical therapy, as defined by an initial treatment to which the subsequent organism was not susceptible, occurred in 39 (80%) of 49 ESBL cases compared with six (6%) of 94 non-ESBL controls; crude mortality in cases was higher at 18% versus 7%. Of seven patients initially treated with ceftazidime, to which the organism was susceptible in vitro, three died. Specific data were not reported on the treatment and outcome of other patient subgroups.

Kim and colleagues⁵⁹ reported a retrospective hospital-based review at the Asan Medical Center (Seoul, Korea) and identified all cases of *K pneumoniae* bacteraemia among patients admitted during a 1-year period. Of 154 patients, 44 (29%) had infections with

ESBL-producing strains. 24 (55%) patients with ESBL-producing *K pneumoniae* bacteraemia infections were treated with inappropriate empirical antibiotic therapy before culture results were available, which was significantly higher than the 3% reported for non-ESBL producers ($p=0.001$). Of the 19 patients who received appropriate empirical therapy to which the isolate showed susceptibility in vitro, the case fatality was two of 12 in those treated with imipenem compared with three of six treated with other active agents (one of two with ciprofloxacin; two of four with aminoglycosides).

In another study from Korea, Kim and co-workers⁶⁰ 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 ESBL infections, only two of six patients treated empirically with expanded-spectrum cephalosporins to which the organisms showed sensitivities in vitro were deemed to have a sufficient clinical response to treatment. Seven of 15 patients treated with appropriate aminoglycoside therapy had a sufficient clinical response. Limitations included the small number of patients, that data for other agents were not reported in detail, and that investigators were not blinded for adjudication of outcome.

In a third report from Korea, Kang and colleagues⁶¹ studied 133 bacteraemic ESBL-producing *E coli* (67 patients) and *K pneumoniae* (66 patients) infections from Seoul National University Hospital, and assessed the effectiveness of empirical and definitive treatments on outcome. Of the eight patients treated with a cephalosporin to which the organism was susceptible in vitro, three were deemed to have treatment failure at 72 h and two died by 30 days of follow-up. Of particular

	Type of study	Organisms	Infection	Antimicrobial therapy	Conclusions	Limitations
Burgess et al ⁵⁶	Retrospective	<i>E coli</i> , <i>Klebsiella</i> spp	Various	Carbapenems, piperacillin-tazobactam, fluoroquinolones	Limited	Small number of patients; multiple assessments per patient; investigators not blinded
Endimiani et al ⁵⁷	Retrospective	<i>K pneumoniae</i>	Bacteraemia	Imipenem, ciprofloxacin	Good response with imipenem; poor response with ciprofloxacin	Small number of patients; potential for biases
Ho et al ⁵⁸	Case-control	<i>E coli</i>	Bacteraemia	Different empirical regimens	Higher crude mortality among ESBLs; poor response with ceftazidime	Specific data were not reported on treatment and outcome of patient subgroups
Kim et al ⁵⁹	Retrospective	<i>K pneumoniae</i>	Bacteraemia	Carbapenems, ciprofloxacin, aminoglycosides	Good outcome with carbapenems; limited numbers for ciprofloxacin and aminoglycosides	Small number of patients
Kim et al ⁶⁰	Observational	<i>E coli</i> , <i>K pneumoniae</i>	Bacteraemia	Empirical regimens with cephalosporins and aminoglycosides	Poor outcome with cephalosporins and aminoglycosides	Small number of patients; investigators not blinded
Kang et al ⁶¹	Observational	<i>E coli</i> , <i>K pneumoniae</i>	Bacteraemia	Various regimens (empirical and definitive)	Poor outcome with empirical cephalosporins; good outcome with ciprofloxacin and carbapenems	Observational study with conflicting results
Paterson et al ^{62,63}	Observational, multicentre	<i>K pneumoniae</i>	Bacteraemia	Various	Good outcome with carbapenems compared with non-carbapenem regimens	Small number of patients; effect of empirical therapy not reported
Zanetti et al ⁶⁴	Randomised controlled trial	Various	Nosocomial pneumonia	Imipenem vs cefepime	Superior outcome with imipenem	Small number of patients
Lee et al ⁶⁵	Retrospective	<i>K pneumoniae</i>	Various	Carbapenems, flomoxef	Flomoxef as effective as carbapenems	Small number of patients
Bin et al ⁶⁶	Observational	CTX-M-producing <i>E coli</i>	Bacteraemia	Imipenem, ceftazidime, cefoperazone-sulbactam	Outcomes were similar in the three groups	Small number of patients; observational study

Table 3: Clinical studies of antimicrobial therapies and outcomes of infections caused by ESBL-producing bacteria

interest in this study is that the investigators also assessed the effect of definitive therapy that they defined as that therapy given after culture results were available. They found that the 30-day mortality among 117 patients treated with carbapenems was eight (13%) of 62, with quinolones was three (10%) of 29, and with others was seven (27%) of 26. Furthermore, they also found no difference in mortality among patients who received appropriate or inappropriate antimicrobial therapy. This study underscores the importance of revising antimicrobial therapy once cultures are available, and argues that if the organism is susceptible, ciprofloxacin has similar efficacy in outcome to the carbapenems.

Paterson and colleagues^{62,63} have reported several different analyses from a single prospective observational study including 85 episodes of ESBL-producing *K pneumoniae* bacteraemia in 12 centres worldwide. In one analysis, they found that patients who received a carbapenem as monotherapy or in combination with other agents during the first 5 days after the first culture report showed a significantly lower 14-day mortality (two [5%] of 42) than those treated with non-carbapenem containing regimens (eight [28%] of 29; $p=0.012$).⁶³ One limitation of this study was that the investigators did not report whether a centre-related effect on outcome existed. They also did not explore empirical antibiotic therapies before blood culture results were obtained, and the study size was too small to allow a meaningful comparative efficacy assessment of different non-carbapenem agents.

Zanetti and colleagues⁶⁴ reported a multicentre randomised controlled trial comparing cefepime with imipenem for the treatment of nosocomial pneumonia in intensive-care-unit 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, four of 13 cefepime-treated patients versus none of ten imipenem-treated patients failed therapy, as defined by clinical criteria. In all of these cases, the isolated organisms were susceptible to cefepime by CLSI breakpoints.

In a retrospective study, Lee and co-workers⁶⁵ from Taiwan assessed the clinical efficacy of flomoxef (a cephamycin) compared 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 suggested 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.

Infectious diseases physicians have been contemplating whether ceftazidime will be effective for the treatment of infections caused by CTX-M-producing organisms that show sufficient susceptibilities in vitro. Bin and colleagues⁶⁶ tried to address this important issue in 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, and seven with cefoperazone-sulbactam. The patients had similar demographic characteristics and the treatment success ratios were similar between the three groups; none of the patients died. Some interesting findings of this study included that successful therapy in the three groups was expedited with additional treatment modalities such as urinary drainage, mucolytics, and drainage of abscesses, and patients with bacteraemia caused by peritonitis failed therapy irrespective of the type of antibiotic 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 blinded randomised study.

On the basis of these studies, we conclude that there are not enough comparative clinical data to determine the best treatment for infections caused by ESBL-producing bacteria. The carbapenems remain the first choice for treatment of serious bloodstream-associated infections, but quinolones might show similar outcomes if the isolate tested is susceptible.⁶¹ Unfortunately, resistance to this group is a major concern. Recent studies have explored the usefulness of alternative regimens (ie, flomoxef and ceftazidime for CTX-M-producing bacteria), but adequate clinical data are scarce.

Conclusions

Antibiotic 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 characterise different types of resistant bacteria efficiently to minimise the spread of these bacteria and help to select more appropriate antibiotics. This is particularly true for ESBL-producing bacteria. The epidemiology of ESBL-producing bacteria is becoming more complex with increasingly blurred boundaries between hospitals and the community. *E coli* that produce CTX-M β lactamases seem to be true community ESBL producers with different behaviours from *Klebsiella* spp, which produce TEM-derived 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.

A recent trend is the emergence of community-onset bloodstream infections caused by ESBL-producing bacteria, especially CTX-M-producing *E coli*. These infections are currently rare, but it is possible that, in the near future, clinicians will be regularly confronted with hospital types of bacteria causing infections in patients from the community, a scenario very similar to that of community-acquired methicillin-resistant *Staphylococcus*

Search strategy and selection criteria

Data for this Review were identified during March, 2007, by searches of Medline and references from relevant articles; many articles were also identified through searches of the extensive files of the authors. Search terms were "extended spectrum beta lactamase(s)" AND "treatment", "ESBLs" AND "treatment", "extended spectrum beta lactamase(s)" AND "detection", "ESBLs" AND "detection", "extended spectrum beta lactamase(s)" AND "laboratory detection", "ESBLs" AND "laboratory detection". Only English language papers were reviewed.

aureus (MRSA).⁶⁷ The carbapenems are widely regarded as the drugs of choice for the treatment of severe infections caused by ESBL-producing Enterobacteriaceae. The spread of *E coli* that produce CTX-M β lactamases will have important future implications for the empirical treatment of community-associated bloodstream infections, particularly in patients with associated urinary-tract infections, and therefore merits close monitoring with enhanced surveillance studies. Molecular methods for the detection of CTX-M β lactamases show potential to screen large numbers of these bacteria in a rapid fashion.

We recommend that internationally funded efforts should be undertaken to track and monitor the worldwide spread of *E coli* that produce CTX-M β lactamases within the hospital and community settings. If this emerging public-health threat is ignored, the medical community may be forced to use the carbapenems as the first choice for the empirical treatment of serious infections associated with urinary-tract infections that originate in the community.

Research is warranted to determine whether significant clinical differences exist among the carbapenems, and to define the best therapy of less severe infections caused by ESBL-producing Enterobacteriaceae. We also recommend that future investigations 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.

Conflicts of interest

JDDP and KBL have received previous research grants from Merck Frosst Ltd Canada, AstraZeneca Canada Inc, and Wyeth Pharmaceuticals Canada Ltd.

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