EXPERT REVIEWS

Clinical significance of extended-spectrum β-lactamases

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The spread of extended-spectrum β-lactamases (ESBLs) in nosocomial and community-acquired enterobacteria is an important challenge for clinicians as the therapeutic options for these organisms are limited. The emergence of ESBL-producing *Escherichia coli* in the community, associated with the spread of CTX-M ESBL, is one of the most significant epidemiologic changes in infectious diseases during recent years. The epidemiology of these infections is complex and combines the expansion of mobile genetic elements with clonal spread. Infections caused by ESBL producers are associated with increased mortality, length of stay and increased cost. An inadequate empirical therapy for serious infections caused by these organisms is independently associated with increased mortality. Carbapenems are the drugs of choice for serious infections caused by ESBL-producing organisms but their overuse is a cause of concern.

Keywords: antimicrobial therapy • β-lactamase • *Escherichia coli* • extended-spectrum β-lactamase • *Klebsiella pneumoniae* • mortality • risk factor

The potential options available for treating serious infections caused by enterobacteria include penicillins (with or without β-lactamase inhibitors), cephalosporins, aztreonam, carbapenems, fluoroquinolones and, in certain situations only, aminoglycosides and colistin. Recently, tigecycline has been added to the therapeutic arsenal for intra-abdominal and complicated soft-tissue infections. Most protocols have traditionally recommended keeping agents with the broadest spectrum in reserve, as a second or third option, as a way of limiting their use and preserving them. However, two facts seriously challenge this approach: first, the evidence that, in cases of severe infection, inadequate empirical therapy is associated with a worse outcome [1] and, second, the increasingly frequent resistance of Gram-negative bacilli to first-line agents [2]. As a consequence, a new paradigm has been put in place, which includes initiating broad-spectrum empirical therapy early on for patients with severe infections or those at risk of acquiring resistant organisms, but de-escalating to reduced-spectrum antimicrobials wherever possible, subject to the results of susceptibility tests [3]. In this context, there is an increased interest in assessing the clinical significance of different resistance mechanisms, particularly when they are associated with low-level or heterogeneous resistance.

Microbiology & epidemiology overview

Production of β-lactamase is the most frequent β-lactam resistance mechanism in Gram-negative organisms. In the varied and complex world of β-lactamases, extended-spectrum β-lactamases (ESBLs) have played a leading role in the clinical field in recent decades. Their importance resides in the fact that they significantly expand the spectrum of previous β-lactamases to include hydrolysis of all penicillins and cephalosporins (with the exception of cephamycins) and aztreonam. Moreover, non-β-lactam agents are frequently useless against ESBL-producing organisms, since the latter may also show resistance to aminoglycosides, trimethoprim–sulfamethoxazole and fluoroquinolones; as a result, many of these organisms become truly multidrug resistant [4]. Since some ESBLs show limited *in vitro* activity against certain cephalosporins (e.g., ESBLs from the TEM and SHV families are usually less active against cefotaxime, while many ESBLs from the CTX-M family are less active against ceftazidime) and are inhibited by β-lactamase inhibitors, such as clavulanic acid, tazobactam or sulbactam, it is useful from a clinical perspective to review the clinical efficacy of the less-affected cephalosporins and of β-lactam/β-lactamase inhibitor associations for infections caused by ESBL-producing organisms.

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Extended-spectrum β-lactamases are plasmid mediated and mainly found in Enterobacteriaceae. The most frequent ESBL-harboring organisms are *Escherichia coli* and *Klebsiella* spp., although, increasingly often, *Enterobacter*, *Serratia, Salmonella* and *Proteus* spp. are found to be ESBL producers [4]. The synergistic effect of β-lactamase inhibitors and cephalosporins is used for the phenotypic confirmation of ESBL production. Therefore, ESBLs are more difficult to detect in bacteria that express cephalosporin resistance through chromosomal inducible AmpC cephalosporinases, since these enzymes are not inhibited by β-lactamase inhibitors and obscure the synergistic effect of a β-lactamase inhibitor [4]. As a consequence, the prevalence of ESBLs in bacteria, such as *Enterobacter* or *Serratia* spp., may have been underestimated. In addition, plasmid-mediated AmpC-type enzymes are being increasingly found in *E. coli*, *Klebsiella pneumoniae* and other enterobacteria, which further undermines our ability to detect ESBL producers.

There are three main ESBL families: the TEM and SHV families, which derive from the non-ESBL TEM-1 and SHV-1 β-lactamases, are usually more active against ceftazidime than cefotaxime and were the predominant ESBLs in the 1980s and 1990s; the representatives of the CTX-M family derives from chromosomal cephalosporinases of *Kluyvera* spp. and are usually more active against cefotaxime than ceftazidime. It is worth noting how efficiently CTX-M enzymes have spread across the world since the late 1990s [5]. In most countries, with the notable exception of the USA, they are now the ESBLs most frequently found in clinical practice; although, a recent study reporting the predominance of CTX-M enzymes in Texas might indicate that this situation is either changing in the USA or that CTX-M have been previously under-reported [6]. CTX-M enzymes are mostly found in *E. coli* but they are increasingly being found in other enterobacteria, such as *Salmonella* spp., *Klebsiella*, *Enterobacter* and *Proteus* spp. [7]. CTX-M enzymes can be subdivided into five clusters: CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9 and CTX-M-25, each of which includes several specific enzymes. Other less-frequent ESBL families are PER, VEB, BES, GES, TLA, SFO, BEL and some enzymes from the OXA family; these enzymes are notable for their geographical diversity [8].

Extended-spectrum β-lactamase epidemiology is a complex equation integrating the epidemiologies of several strata [9]: those of the mobile genetic elements associated with the *bla* genes encoding the ESBL, the plasmids harboring them and the bacteria. From a bacterial perspective, ESBL-producing *K. pneumoniae* is a well-known cause of clonal outbreaks affecting healthcare facilities and behaves in a similar way to other multidrug-resistant nosocomial pathogens [10]. High-risk areas, such as intensive-care units (ICUs) and neonatal ICUs are the most frequently affected, although the organism may also cause infections in other wards and nursing homes. Until recently, outbreaks caused by ESBL-producing *K. pneumoniae* were predominantly due to TEM or SHV producers [4]. Colonized patients are usually the main reservoir, although some environmental reservoirs (e.g., thermometers, tapes, basins and oxygen-saturation probes) have been found occasionally [11,12]. The organism is predominantly spread via patient-to-patient transmission [13], probably through the hands of healthcare workers.

The spread of the CTX-M enzymes shows significant differences from this: they are mainly associated with *E. coli*, hospitalized patients affected are mainly in the medical services and many infections are community acquired [9]. The rapid worldwide spread of CTX-M-producing *E. coli* in the community setting is one of the most significant epidemiologic changes to recently occur in infectious diseases. In areas where these enzymes are endemic, the prevalence of fecal carriage by people not related to healthcare has increased in recent years [14–19]. Several data suggest that the acquisition of CTX-M-producing *E. coli* could be food related [20–22]. Initially, and in some areas even now, most ESBL-producing *E. coli* isolates were clonally unrelated [23,24]. $bla_{\text{CTX-M}}$ genes are linked to different successful mobile genetic elements, such as IS*Ecp*-1-like insertion sequences, a putative transposase named common region-1 and phage-related sequences [24]. However, clonal spread of certain CTX-M-producing isolates has been reported in some areas, indicating horizontal transmission as a way for the enzymes to spread. As a consequence of the intercontinental dissemination of one very successful *E. coli* clonal group producing CTX-M-15 (O25:H4-ST131) in countries from Europe (France, Switzerland and Spain), Asia (Lebanon and India) and North America (Canada) [25], CTX-M-15 now predominates in many countries. CTX-M-9 and CTX-M-14 are still predominant in many areas of Spain [26]. In addition, CTX-M-producing *E. coli* may also cause nosocomial infections [27,28].

In recent years, the clear-cut association of *E. coli* with CTX-M ESBLs, and of *K. pneumoniae* with SHV and TEM enzymes, has progressively become blurred, since CTX-M enzymes have also spread to *Enterobacter* spp. and *K. pneumoniae* [5,6,29,30]. In addition, complex multiclonal situations caused by *K. pneumoniae* have also been described [30,31]. Mixed situations, including both sporadic and epidemic clones of ESBL-producing *E. coli*, can be found in the hospital environment, suggesting that some cases may be imported from the community [27,32,33], while others are horizontally transmitted within the hospital [27].

Prevalence of ESBL-producing organisms

When reviewing data from surveillance studies, it should be taken into account that resistance to third-generation cephalosporins is not equivalent to ESBL production, since producers or hyperproducers of other β-lactamases may also show resistance to cefotaxime and ceftazidime. This is particularly important in the case of *Enterobacter* or *Serratia* spp., although data on *E. coli* or *Klebsiella* spp. based exclusively on cephalosporin resistance should also be considered with caution.

There are several multinational surveillance studies that give an idea of geographical differences in ESBL epidemiology. The most recent data from the Meropenem Yearly Susceptibility Test Information Collection project show that the prevalence of ESBL producers in Europe (in 2006) and the USA (in 2007), respectively, were: *E. coli*: 8.2 and 6.0%; *Klebsiella* spp.: 9.8 and 12%; and *Proteus mirabilis*: 1.4 and 0% [34,35]. Data from

the SENTRY antimicrobial surveillance program show much higher percentages for *E. coli* in several Asian countries, such as China (24.5%) and Singapore (11.3%) [36]. The Study for Monitoring Antimicrobial Resistance Trends project included isolates obtained from intra-abdominal samples. In the most recent study report (2004 data), the statistical figures for the prevalence of ESBLs in *E. coli*, *K. pneumoniae* and *Enterobacter* spp. were 2.8, 5.3 and 25.3%, respectively, in the USA; 6.4, 8.8, and 11.8% in Europe; 12.0, 27.6 and 31.1% in South America; 10.0, 27.4 and 17.8% in the Middle East and South Africa; and 19.6, 22.9 and 36.4% in the Asia–Pacific region [37]. To sum up, ESBLs are more prevalent now in Asia and South America than in Europe and the USA.

Even in Europe, there are differences. The European Antimicrobial Resistance Surveillance System study is a European surveillance project that includes invasive (blood) isolates from sentinel laboratories located throughout the continent; data are presented according to resistance patterns and not to the specific resistance mechanisms. In their 2006 report, the percentages of *E. coli* resistant to third-generation cephalosporins were: 25–50% in Turkey, Romania and Bulgaria; 10–25% in Israel and Cyprus; 5–10% in Spain, Portugal, Italy, the UK, Greece, Austria, the Czech Republic and Latvia; and 1–5% in most other countries. Data from most countries have shown a significant increase in the last 4–5 years. There are significant differences for *K. pneumoniae* aswell: percentages of resistance to third-generation cephalosporins are 25–50% in Italy, Turkey, Latvia, Poland, the Czech Republic, Israel and Cyprus; 10–25% in the UK, Germany and Lithuania; and lower percentages in other countries (data available at [201]).

Risk factors for infections caused by ESBL-producing enterobacteria

Risk factors have been examined in several studies. Some of these include different species. The information they provide is of interest, although it seems more appropriate to investigate their risk factors separately, since the epidemiologies of *E. coli*, *K. pneumoniae* and *Enterobacter* spp. are different. The selection of control patients may also have implications for results; selecting, as a control group, patients infected or colonized by non-ESBL-producing organisms has been shown to underestimate the magnitude of the risk factors [38], although it may also overestimate the magnitude of its association with previous antibiotic use with regard to studies in which the control group is chosen among patients without infection [39]. To gain a more comprehensive view of the risk factors involved, double case–control and case–double control studies have been performed [27,38,40,41].

With regard to *K. pneumoniae*, most studies found that previous antimicrobial use (specifically, oxyimino β-lactams or extended-spectrum cephalosporins) was an independent risk factor [38,42–46]. Other independent risk factors in some studies included length of hospital stay, central venous or urinary catheterization, other invasive procedures, diabetes mellitus or malignancy [38,42–47]. In neonatal units and other pediatric wards, length of hospital stay, exposure to cephalosporins and younger age were associated with ESBL-producing *K. pneumoniae* in studies using multivariate analysis [48–52]. Sometimes, specific risk factors could not be found [53].

In the case of ESBL-producing *E. coli*, we will briefly review the more recent studies as a reflection of the present epidemiologic situation at present. With regard to community-acquired infections, Pitout *et al.* performed a population-based laboratory surveillance study in Calgary (Canada) and found that CTX-M-producing *E. coli* in the community was more frequent in women and older patients [54]. The results of case–control studies are shown in Table 1 [40,55–60]. Despite the fact that the studies have different designs, previous exposure to fluoroquinolones or cephalosporins is consistently associated with ESBL-producing *E. coli* in the community. In the case of nosocomial infection, previous antibiotic use (particularly fluoroquinolones and oxyimino β-lactams) are also risk factors [27,28]. Two studies investigated the risk factors for bloodstream infections caused by ESBL-producing *E. coli*; severe underlying disease, nosocomial infection and urinary origin in the first study [61], and previous follow-up in outpatient clinic, urinary catheterization and exposure to fluoroquinolones and oxyimino β-lactams in the more recent one, were independently associated with ESBL-producing *E. coli* [41].

Features of infections caused by ESBL-producing organisms

Although there are dozens of microbiological studies on ESBLs, there are few that have studied clinical features and outcomes of infections caused by ESBL-producing organisms. Furthermore, many studies include different species of enterobacteria. Generally speaking, it can be assumed that ESBL-producing organisms cause infections in a similar way to their non-ESBL-producing counterparts; however, in an outbreak situation, ESBL-producing organisms may not substitute for susceptible ones, but are able by themselves to increase the total number of infections [62]. The frequency of each type of infection depends on the microorganism and the epidemiologic situation.

Klebsiella pneumoniae

In the case of ESBL-producing *K. pneumoniae*, Peña *et al.*, in one outbreak in a hospital in Barcelona, Spain, described 109 episodes of infections: 40 primary bacteremias, 28 surgical-site infections (including 18 postsurgical intra-abdominal infections, two of osteomyelitis and three of meningitis), 15 urinary tract infections (UTIs), 13 respiratory tract infections (five of pneumonia, all ICU patients) and two nonsurgical soft-tissue infections [63]. In another study, carried out in two hospitals in Pennsylvania (USA), UTIs predominated, followed by bloodstream and wound infections [64]. Garcia San Miguel *et al.* found no significant differences in the clinical features of 45 patients with infections caused by ESBL-producing *K. pneumoniae* when analyzed by type of ESBL produced (SHV in 25, TEM in five and CTX-M in 15 patients) [65]. In neonatal ICUs, primary bacteremia is usually the most frequent type of infection. The incidence of bacteremia among colonized patients was 9.5% in a study of neonates [66] and 8.5% in another study dealing with adults admitted to high-risk units [67]. We found

Table 1. Risk factors for community-acquired infection caused by extended-spectrum β-lactamase-producing *Escherichia coli*.

Country	Case definition	Number of cases	Control definition	Risk factors (multivariate analysis)	Ref.
Spain	Isolation of ESBL-EC	49	Outpatients without ESBL-EC	Age in male, diabetes mellitus, previous admission, fluoroquinolone	[55]
Spain	UTI by ESBL-EC	19	UTI by non-ESBL-EC (matched)	Oral cefuroxime	[56]
Israel	UTI by ESBL-EC or KP	128 (74 EC)	UTI by non-ESBL-EC or KP	Age > 60 years, male sex, cephalosporins, fluoroquinolones, previous admission, KP	[57]
Spain	Isolation of ESBL-EC	61	Non-ESBL-producing EC	Fluoroquinolones, urinary catheter	[58]
Thailand	I: Infections by ESBL-EC II: Infections by non-ESBL-EC	I: 46 II: 46	Patients without infection	I: diabetes, prior ESBL-EC, cephalosporins, fluoroquinolones, II: diabetes, stroke, diarrhea	[40]
New Zealand	Infections by ESBL-enterobacteria	107 (88 EC)	Non-ESBL enterobacteria	Residential care home, pulmonary disease	[59]
Spain	Isolation of ESBL-EC	122	Outpatients without ESBL-EC (multicenter)	Age > 60 years, female sex, diabetes mellitus, recurrent UTIs, invasive urinary procedure, aminopenicillins, fluoroquinolones, cephalosporins	[60]

EC: *Escherichia coli*; ESBL: Extended-spectrum β-lactamase; KP: *Klebsiella pneumoniae*; UTI: Urinary tract infection.

a 5.5% bacteremia rate for 161 colonized neonates in a successfully controlled outbreak in our own center [68]. The clinical features from several reports concerning bacteremia due to ESBL-producing *K. pneumoniae* in adults are summarized in Table 2 [43,45,62,69–71].

Escherichia coli

The recent emergence of ESBL-producing *E. coli* (particularly those producing CTX-M enzymes) as a significant community pathogen is a challenge for clinical investigators, since it is usually more difficult to investigate the clinical features and outcomes of community-acquired, rather than nosocomial infections, where patient charts are readily available for review. In Seville, Spain, 76% of 49 outpatients, from whom these organisms had been isolated, had a UTI, 22% had asymptomatic bacteriuria and 2% had acute cholangitis; 12% of the whole series were bacteremic [55]. A recent multicenter Spanish investigation studied 122 patients with community-acquired infections caused by ESBL-producing *E. coli*; 113 patients (92.6%) had a UTI, three had acute cholangitis, one had secondary peritonitis, one had cellulitis and one had pneumonia. Of the UTI patients, 73 had cystitis (59.8% of the whole series), 33 had asymptomatic bacteriuria (27%), five had pyelonephritis (4.1%) and two had prostatitis (1.6%). Seven patients (6%) were bacteremic (three with pyelonephritis, three with cholangitis and one with cellulitis) and 12 (10%) required hospitalization as a consequence of the infections. No one died [60].

Other studies have recently investigated the specific features of ESBL-producing *E. coli* as a cause of nosocomial infection in the context of the predominance of CTX-M enzymes [27,28,72]. Of all the patients from whom ESBL-producing *E. coli* were isolated, 68–78% were considered to have an infection, with UTIs and surgical site infections being the most frequent types [27,28]. The bacteremia rate was approximately 15–20% [27,72]. Curiously enough, and contrary to the usual situation with other resistant organisms, the percentage of ICU patients was lower than for other resistant organisms [27,28,73], probably reflecting the fact that the organism was community- and not hospital-acquired in many cases.

In addition, some studies have investigated the clinical features of patients with bloodstream infections caused by ESBL-producing *E. coli* [61,74–78]. The data are summarized in Table 3.

Other enterobacteria

There is very little information about the clinical features of infections caused by ESBL-producing Enterobacteriaceae other than *Klebsiella* spp. and *E. coli*. A few nosocomial outbreaks caused by *Salmonella* spp. have been described [79–83], all of them affecting pediatric wards. Most patients in these outbreaks suffered diarrhea and some were bacteremic. Endimiani *et al.* described the features of nine patients with bacteremia caused by ESBL-producing *P. mirabilis* [84]; the urinary tract was the source in four patients; three presented severe sepsis or septic shock and died as a consequence of the infection. Most series studying patients with infections caused by ESBL-producing *Enterobacter* spp. include other ESBL-producing microorganisms, such as *Klebsiella* spp. and *E. coli*. Manzur

et al. described the clinical features of seven patients affected by an outbreak caused by ESBL-producing *Enterobacter cloacae* in a cardiothoracic ICU [85]; four patients were considered to have an infection (three affecting the respiratory tract and one affecting the bloodstream) and two died.

Table 2. Clinical features of bloodstream infections caused by extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*.

Number of cases	Main sources (%)	Septic shock (%)	Crude mortality (%)	Ref.
49	Catheter (36) Unknown (28) Abdomen (6)	14	32	[62]
44	Primary (23) Biliary (29)		21	[69]
78	Pneumonia (26) Catheter (22) UTI (18)		27 (14 days)	[43]
60	Pancreatobiliary (38) Unknown (23) Peritonitis (17)	27	17	[45]
108	Pneumonia (41) Abdomen (21) Urinary tract (14) Catheter (11)	18	32 (15 days)	[70]
48	Unknown (54) Urinary tract (29) Respiratory (8)	15	25 (7 days) 52 (21 days)	[71]

Outcome of infections caused by ESBL-producing isolates

Comparison with non-ESBL-producing isolates

Whether the outcome of infections with ESBL-producing organisms is worse compared with non-ESBL-producing organisms is still a subject of debate, since studies investigating the association between ESBL and mortality or length of hospital stay have shown different results. Interpretation of these studies should bear in mind various methodological issues.

First, studies should be designed with sufficient power to be able to detect differences. It should be borne in mind that whenever 'no significant differences' between groups are found, the probability of considering the null hypothesis as true when it is actually false (β-error) should be calculated before interpreting the results as 'there is no difference between groups'. Alternatively, it should be simply stated that it was not possible to find significant differences (although they may exist). Schwaber and Carmeli, given an estimated 34% mortality rate in a cohort of patients with infections due to ESBL-producing organisms and a 20% mortality rate in a cohort with infections due to non-ESBL-producing organisms, and assuming less than 20% and less than 5% for β- and α-errors, respectively, and a 1:1 ratio, calculated that at least 171 patients should be included in each cohort [86] (an α-error occurs when the null hypothesis is considered false when it is actually true; to follow with the same example, to consider that the statement 'there is no difference between groups' is false, so that the existence of difference is implied, when actually there is not).

Second, confusion bias must be taken into account. Since variables that increase the risk of infection by ESBL-producing organisms may also be associated with outcome (e.g., severity of underlying disease and type of infection source), the effect of such variables needs to be controlled in the design and/or the analysis. Matched cohorts are frequently used as a way of controlling the baseline conditions in the design. However, caution should be taken to avoid overmatching, which makes real differences difficult to identify. Multivariate analysis should be used to control confusion bias in the analysis (and can also be used for matched cohorts). We are in agreement with other authors that presentation with severe sepsis or septic shock should be included in a multivariate analysis when investigating the outcome of resistant organisms and the impact of antimicrobial therapy [87].

If an infection due to an ESBL-producing organism is associated with a worse outcome, it should be related to one or both of the following: to an increase in virulence or to delay in appropriate therapy. With regard to virulence, several authors have investigated the virulence determinants expressed by different strains of ESBL-producing *E. coli*. These determinants are associated with the ability of the isolates to cause extraintestinal disease, although we are aware of no studies that have investigated the correlations between virulence factors and outcomes in patients with invasive infections. Recently, Lavigne *et al.* investigated the killing properties of CTX-M-producing *E. coli* in a nematode model and found that the ESBL producers in the study were less able than non-ESBL-producing isolates to kill nematodes, and this correlated with the presence of several virulence factors [88]. However, CTX-M-15-producing *E. coli* have been recently found to predominantly belong to virulent phylogenetic groups (mainly B2) and express virulence determinants [89]; in addition, representatives from the intercontinentally spread clone have been showed to be highly virulent in mice [90].

Concerning inappropriate therapy, it seems intuitive that the probability of prescribing appropriate empiric antimicrobials ought to be lower if the microorganism is multidrug resistant. In a meta-analysis of studies investigating the outcomes of bloodstream infections caused by ESBL- and non-ESBL-producing organisms, Schwaber and Carmeli found that ESBL-producing organisms were associated with a delay in effective therapy (pooled relative risk [RR]: 5.56; 95% confidence interval [CI]: 2.95–10.51) [86]. In certain situations (high-risk types of infection, debilitated patients and infections presenting with severe sepsis or septic shock), a delay in antimicrobial therapy certainly influences the outcome. However, the significance of a delay in appropriate

Table 3. Clinical features of bloodstream infections caused by extended-spectrum β-lactamase-producing *Escherichia coli*.

Country	Number of cases	Community acquired (%)	Main sources (%)	Septic shock	Crude mortality (%)	Ref.
China	50	20	Urinary (72) Biliary (10)		18	[61]
Turkey	53		Unknown (45) Urinary (24) Lung (15)		26	[74]
Spain	43	51	Urinary (46) Biliary (21) Primary (14)	19% severe sepsis or shock	21	[75]
China*	22	0	Biliary (36) Primary (27) Urinary (23)		0	[76]
Korea‡	38	100	Pancreatobiliary (45) Urinary (34)		21	[77]
UK	46	35	Urinary (56) Biliary (15)	50% hypotension	61	[78]

*Included only selected cases (those 'susceptible' to ceftazidime).
‡Included only community-acquired cases.

therapy is more difficult to detect in studies including mainly low-risk infections (e.g., UTIs without severe sepsis). Obviously, if a higher than usual frequency of appropriate empirical therapy in the ESBL group is found in any study, infections caused by ESBL producers would be less likely to be associated with a worse prognosis, a situation more likely to occur in recent studies, as clinicians are aware of the possibility of ESBL producers.

Finally, controversy exists about the outcome variable. Crude mortality is usually selected because it is an objective variable. Some part of the mortality, however, is not related to infection, causing a nondifferential classification bias that jeopardizes the possibility of finding differences. Infection-related mortality could be biased by subjectivity, so, for this reason, 14-day mortality is sometimes used as an alternative. However, infection-related mortality is not the only variable of interest related to outcome. Increased morbidity, length of hospital stay and cost are other variables to be taken into account.

To date, the only published meta-analysis showed that bloodstream infections caused by ESBL-producing isolates were significantly associated with increased mortality (RR: 1.85; 95% CI: 1.39–32.47) [86]. However, the authors mention that only one of the 16 studies used in the meta-analysis showed an adjusted RR; in this study, after adjusting for different variables using multivariate analysis, ESBL production was significantly associated with mortality, increased length of hospital stay and cost [91]. After the meta-analysis had been published, Melzer and Petersen reported the results of a cohort study including all patients with bacteremia due to *E. coli* [78]; ESBL production was associated with increased mortality after adjusting for age, gender, hypotension, nosocomial acquisition, length of ICU stay and site of infection (odds ratio: 3–57; 95% CI: 1.48–48.60). However, mortality in the ESBL group was much higher than usual (60.8%). We may conclude that invasive infections caused by ESBL-producing organisms tend to be associated with a worse outcome when compared with non-ESBL producers; however, this requires confirmation by adequately controlled and powered studies.

Outcome predictors in patients with infections caused by ESBL producers: impact of inadequate empirical antibiotic treatment

Several cohort studies have addressed the issue of the impact of inadequate empirical antibiotic treatment in patients with infections caused by ESBL producers. Some of them include several ESBL-producing enterobacteria; others are restricted to one species; some include different types of infections; others only bloodstream infections.

Two recent studies included different infections caused by ESBL producers and reached similar conclusions; Hyle *et al.* studied 187 patients with diverse infections caused by ESBL-producing *E. coli* or *K. pneumoniae* [64], where crude mortality was 17.1%. A delay in initiating adequate antimicrobial therapy was associated with increased mortality. Multivariate analysis revealed that inadequate initial antimicrobial therapy was an independent risk factor for mortality only in the case of nonurinary infections. Peña *et al.* studied 100 hospitalized patients with various infections caused by ESBL-producing *E. coli*; likewise, inadequate empirical antibiotic therapy was also an independent risk factor for mortality in nonurinary infections only [92].

More studies have been performed among bacteremic patients. Several recent studies have found that inadequate empirical antibiotic treatment was independently associated with mortality [93–95]. Other studies have investigated whether the antimicrobial used was associated with the outcome. Several authors reported

a worse outcome when cephalosporins were used [61,94,96,97] and a better outcome with carbapenems [75,84,94,98,99]. However, some reported series showed favorable results with cephalosporins in certain infections (mainly urinary or biliary infections) caused by ESBL-producing organisms with a low MIC against the cephalosporin [76,93]. We discuss the use of cephalosporins in infections caused by ESBL producers below.

Treatment options

Therapeutic decisions for infections caused by ESBL-producing organisms are complex, since local epidemiology (e.g., local prevalence of resistance to different agents among ESBL producers), community or nosocomial acquisition, individual risk factors for ESBLs, severity and site of infection, patient's features and ecological impact of antimicrobial use should all be taken into account.

Carbapenems

Carbapenems are the drug of choice for treating all types of severe infections caused by ESBL-producing organisms, since they are consistently associated with lower failure rates and better outcomes [4,75,84,94,98,99]. In areas where ESBL-producing *E. coli* are significant community pathogens, the empirical use of carbapenems is advisable in community-acquired urinary or intra-abdominal infections presenting with severe sepsis or septic shock in patients with risk factors for ESBLs (as reviewed previously). In the case of healthcare-associated infections, including those associated with long-term care facilities, local epidemiology data, individual risk factors and the severity of infection should be considered.

Of the carbapenems, ertapenem should be considered for community-acquired infection whenever it is not necessary to cover *Pseudomonas aeruginosa*; Frei *et al.* have proposed a pharmacokinetic/pharmacodynamic (PK/PD) breakpoint of 0.25 mg/l for ertapenem susceptibility in Gram-negative bacteria [100] (the Clinical and Laboratory Standards Institute breakpoint is 2 mg/l [101]); in a study involving a high number of isolates from a multicenter study in Spain, the MIC_{90} against ESBL-producing *E. coli* and *K. pneumoniae* was 0.125 and 0.25 mg/l, respectively [102]. The potential advantages of ertapenem are the avoidance of selection pressure over nonfermenters, such as *P. aeruginosa* or *Acinetobacter baumannii*, and, for nonhospitalized patients who need therapy with a carbapenem, the more convenient dosage (once daily, intravenously or intramuscularly). However, published experiences of treating ESBLs with ertapenem remain scarce [103–105] and reports have been made of development of ertapenem resistance in a case of infection due to an ESBL-producing *E. cloacae* after treatment with imipenem [106], and in one case of infection caused by an ESBL-producing *K. pneumoniae* during treatment with ertapenem [107]; in these cases, the MIC of ertapenem was 2 and 0.5 mg/l, respectively. In view of these MICs and the proposed PK/PD breakpoint, we recommend the use of imipenem or meropenem instead of ertapenem for isolates with a MIC more than 0.25 mg/l and in nosocomial infections, where it is usually necessary to cover *P. aeruginosa*.

The increasing prevalence of ESBLs, coupled with the emergence of ESBL-producing *E. coli* as a major community pathogen, are not only problems in themselves; they could also lead to overuse of carbapenems and possibly make it easier for carbapenem-hydrolizing enzymes, such as KPCs or metallo-β-lactamases, to spread. It makes sense, therefore, to think of alternatives.

Cephalosporins

With regard to cephalosporins, there is, in our opinion, no real controversy about their efficacy in the treatment of infections caused by ESBL producers. Animal model studies show that the pharmacodynamic target associated with efficacy is the same as in non-ESBL producers: that is, to maintain drug levels above the MIC for at least 50% of the time; the results of Monte Carlo simulations suggest that the probability of attaining the target at the usual doses was very low for all cephalosporins for organisms with a MIC of more than 8 mg/l, except for cefepime using 2 g every 12 h [108]. Based on these data, PK/PD breakpoints have been proposed [108,109]: ESBL-producing isolates should be regarded as nonsusceptible to cefotaxime or ceftriaxone where the MIC is greater than 1 mg/l; the breakpoint for cefepime would be 4–8 mg/l.

In our opinion, these points could be considered when thinking about carbapenem-sparing options in very specific circumstances (e.g., less-severe infections or UTIs because of the high urinary concentration of cephalosporins) but are of lesser interest when deciding on an empirical therapy. If an ESBL producer is the object of concern, neither cefotaxime nor ceftazidime can be safely used, since the isolate may produce a SHV or TEM ESBL (both very potent against ceftazidime) or a CTX-M (very potent against cefotaxime and some of them also against ceftazidime). Only cefepime (2 g every 12 h) might be an option but, even so, a significant percentage of isolates could show a MIC greater than 8 mg/l (52 and 22% of TEM- and CTX-M-producing *E. coli,* and 0 and 11% of CTX-M- and SHV-producing *K. pneumoniae*, respectively, in a multicenter Spanish study [Hernández JR, Unpublished Data]. CTX-M-15-producing *E. coli* isolates also frequently harbor OXA-1, which increases the hydrolytic activity against cefepime [110]. Moreover, porin loss in *K. pneumoniae* increases the MIC to most cephalosporins [111].

β-*lactam*/β-*lactamase inhibitor combinations*

Controversy exists regarding the efficacy of β-lactam/β-lactamase inhibitor combinations. ESBLs are inhibited by β-lactamase inhibitors but may show resistance to combinations because of other mechanisms (e.g., the production of inhibitor-resistant derivatives of TEM-1, TEM-2 and SHV-1 β-lactamases, the hyperproduction of class A β-lactamases, OXA β-lactamases, chromosomal or plasmidic class C β-lactamase and/or modified outer-membrane permeability). The percentage of resistant isolates is too high in some areas to recommend such combinations as empirical therapy, particularly among *Klebsiella* isolates [26,112]. The probability of attaining the PK/PD target with piperacillin/tazobactam has been shown to be low against ESBL producers (77% for *E. coli* and 48% for *K. pneumoniae*) using 3.375 mg every 4 h [113]. For cystitis caused by susceptible isolates, and

where oral alternatives are limited, oral amoxicillin/clavulanic acid has shown good results in an uncontrolled study [60]; unfortunately, resistance to this compound is frequent in some areas, such as the UK [114].

Other alternatives

Resistance to fluoroquinolones is very frequent among ESBL producers, particularly in some recent series on community-acquired ESBL-producing *E. coli* [24,54,55], precluding the use of these drugs in risk patients with pyelonephritis. Some studies have found inferior results with fluoroquinolones at standard doses in comparison with carbapenems [55,99], which might be due to the fact that the MICs in susceptible isolates are frequently higher than the proposed PK/PD breakpoint [100]. However, susceptible isolates causing UTIs may be treated with quinolones. Although ESBL-carrying plasmids may also harbor aminoglycoside-resistant determinants, the rate of resistance to these compounds is low for ESBL-producing *E. coli* in some areas [26]. In these areas, whenever a carbapenem is not used, aminoglycosides can be considered as part of an empirical combination regimen until susceptibility results are available for patients with certain conditions (e.g., urinary tract sepsis and low risk of renal insufficiency). Colistin is active against ESBL producers. Although renal toxicity of colistin is less frequent than previously thought [115], it is mainly reserved for carbapenem-resistant organisms. Published clinical experience with this antimicrobial is mostly limited to retrospective studies on infections caused by multidrug-resistant *A. baumannii* and *P. aeruginosa*, but is also being needed recently for the treatment of emergent carbapenem-resistant *K. pneumoniae* and *E. coli* due to the production of KPC or VIM β-lactamases [115,116]. Finally, tigecycline is a newer compound showing activity against ESBL producers [117]. It is not active against *P. aeruginosa* or Proteae, and has been approved in several countries for the treatment of complicated intra-abdominal and soft-tissue infections. It is concentrated in tissues but, due to low urinary levels, tigecycline cannot be considered an adequate choice for UTIs [118,119], despite some positive anecdotal experience reported [120]. In addition, caution has been advised with respect to the use of tigecycline for bloodstream infections due to *A. baumannii* (and possibly other organisms) due to low serum levels of tigecycline [121], although again some positive anecdotal experiences have been reported [122]. Clinical experience with tigecycline in infections caused by ESBL producers is lacking and awaited, since it might be an attractive alternative to carbapenems for infections other than UTIs [118]. Fosfomycin shows good *in vitro* activity against ESBL-producing *E. coli* [123] and the results of two uncontrolled studies of fosfomycin trometamol, showing cure rates of more than 90% in cystitis patients [60,124], suggest that it is the best choice for uncomplicated UTIs [125]. Nitrofurantoin could be an alternative, although it requires a longer treatment period and is less-well tolerated [125].

Expert commentary & five-year view

If the rate of spread of ESBL-producing enterobacteria, particularly of *E. coli*, continues to increase, the situation could turn into a public-health problem. These organisms are resistant to third-generation cephalosporins, among the most widely used antimicrobials in hospitals, which would not, therefore, be reliable in many situations. This may lead to overprescription of carbapenems, which, in a scenario of emerging carbapenemases, would make it easier for the enzymes to spread. In addition, as these isolates are frequently coresistant to fluoroquinolones and cotrimoxazole, the alternatives for UTIs will be further compromised. Fortunately, the increase in the prevalence of ESBL producers among *E. coli* in the community seems to be reaching a plateau in some areas, such as Spain [Campos J, Pers. Comm.].

Within hospitals, controlling the nosocomial transmission of ESBL-producing *Klebsiella* and *Enterobacter* spp. is crucial. Controlling the spread of *E. coli* is even more difficult, as many patients are colonized in the community and it is impossible to screen every patient admitted. In the community and hospitals, more studies are needed to characterize reservoirs for ESBL and the dynamics of transmission so that control measures can be implemented. Since fluoroquinolones and extended-spectrum cephalosporins seem to play an important role in the selection

Key issues

- Extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* and *Enterobacter* spp. cause predominantly healthcare-related infections; these may be epidemic.
- ESBL-producing *Escherichia coli* have emerged as a significant community pathogen in many areas of the world, along with the spread of CTX-M types of ESBL, which now predominate.
- Previous exposure to third-generation cephalosporins and fluoroquinolones are risk factors for infections caused by ESBL producers.
- Infections caused by ESBL producers are probably associated with increased mortality, length of hospital stay and cost.
- An inadequate empirical antibiotic therapy for invasive infections caused by ESBL producers is frequent and is associated with increased mortality, except in nonbacteremic urinary tract infections.
- Carbapenems are the empirical treatment of choice for patients with severe infections potentially caused by enterobacteria and/or at risk of ESBL. Nonsevere urosepsis in patients with a low risk of renal insufficiency could be treated with a cephalosporin (preferably cefepime) plus an aminoglycoside, pending susceptibility results.
- To avoid overuse of carbapenems, de-escalation strategies should be used once ESBL producers have been ruled out.
- Fosfomycin is the choice for patients with uncomplicated urinary tract infections potentially caused by ESBL-producing *E. coli*. Amoxicillin/clavulanic acid or nitrofurantoin are alternatives. Fluoroquinolones can be used for susceptible strains.

or coselection of these organisms, and secondarily facilitate their spread, prudent use of these antimicrobials is necessary in the community and in hospitals.

More studies investigating the efficacy and ecological consequences of β-lactam/β-lactamase inhibitors and the newer antimicrobial agents, such as ertapenem or tigecycline, are needed. In addition, the development of new antimicrobial agents with activity against organisms producing ESBLs (and other β-lactamases) is awaited. Finally, active programs for antibiotic use and control programs against resistant pathogens, to be developed by multidisciplinary teams, need to be implemented in every hospital. The diagnosis, epidemiology and treatment of these infections are complex matters and it cannot be expected that the problem be managed without highly specialized microbiologists and infectious-disease doctors.

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Website

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