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REVIEW

Extended-spectrum β-lactamase-producing organisms

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Summary Extended-spectrum β-lactamases (ESBLs), which hydrolyse extended-spectrum cephalosporins and are inhibited by clavulanic acid, are spreading among Enterobacteriaceae. The CTX-M enzymes are replacing SHV and TEM enzymes as the prevalent type of ESBLs, principally in community-acquired infections caused by *Escherichia coli*. Associated infectious syndromes include mainly urinary tract infections, and secondly bloodstream and intra-abdominal infections, and may be serious enough to warrant hospitalisation. Affected patients commonly have various underlying risk factors. This is also observed in hospital-acquired infections. The rates of ESBL-expression among nosocomial Enterobacteriaceae isolates, particularly *Klebsiella pneumoniae*, have risen substantially in several countries. The hospital epidemiology of these infections is often complex; multiple clonal strains causing focal outbreaks may co-exist with sporadic ones. Relevant infection-control measures should focus on reducing patient-to-patient transmission via the inanimate environment, hospital personnel, and medical equipment. Wise use of antibiotics is also essential. The available therapeutic options for the treatment of ESBL-associated infections are limited by drug resistance conferred by the ESBLs, along with frequently observed co-resistance to various antibiotic classes, including cephamycins, fluoroquinolones, aminoglycosides, tetracyclines, and trimethoprim/sulfamethoxazole. Relevant clinical data regarding the effectiveness of different regimens for ESBL-associated infections are limited. Although certain cephalosporins may appear active in vitro, associated clinical outcomes are often suboptimal. β-Lactam/β-lactamase inhibitor combinations may be of value, but the supporting evidence is weak. Carbapenems are regarded as the agents of choice,

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and may be more effective than fluoroquinolones for serious infections. Tigecycline and polymyxins have substantial antimicrobial activity against ESBL-producing Enterobacteriaceae, and, along with fosfomycin, merit further evaluation.

Introduction

The main mechanism of bacterial resistance to the β-lactam class of antibiotics consists of the production of β-lactamases, which are hydrolytic enzymes with the ability to inactivate these antibiotics before they reach the penicillin-binding proteins located at the cytoplasmic membrane. The extended-spectrum β-lactamases (ESBLs) are classified in the molecular (Ambler) class A and functional (Bush–Jacoby–Medeiros) group 2be; they are characterised by the ability to hydrolyse an oxyimino-β-lactam at a rate ≥10% of that for benzylpenicillin along with inhibition by clavulanic acid.[1,2] The presence of ESBLs in various members of the Enterobacteriaceae family, particularly *Klebsiella pneumoniae* and *Escherichia coli*, is of great microbiological and clinical importance. ESBLs are also found in non-fermentative Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[3]

The ESBL enzymes were initially recognised in clinical isolates in the 1980s; they derived mainly from the TEM or SHV types of β-lactamases, by point mutations in the parent enzymes which did not possess extended-spectrum β-lactam substrate activity.[3] The CTX-M type of ESBLs is becoming increasingly more prevalent, particularly in *E. coli* and *K. pneumoniae*.[4,5] More than 50 enzymes of the latter type have so far been identified, which can be divided into five main groups on the basis of amino acid changes (CTX-M1, CTX-M2, CTX-M8, CTX-M9 and CTX-M25, respectively).[6] The origin of some of these enzymes has been traced to chromosomally encoded enzymes of the *Kluyvera* spp. of environmental bacteria. The relevant genes are thought to have been mobilised into conjugative plasmids and thus transferred to pathogenic bacteria.[6] Additional clinically relevant types of ESBLs include mainly the VEB, PER, GES, TLA, IBC, SFO-1, BES-1 and BEL-1 types.[3]

Global epidemiology

The rate of ESBL production among Enterobacteriaceae varies worldwide. In a recent study based on the Tigecycline Evaluation and Surveillance Trial (TEST) global surveillance database, the rate of ESBL production was highest among the *K. pneumoniae* isolates collected in Latin America, followed by Asia/Pacific Rim, Europe, and North America (44.0%, 22.4%, 13.3% and 7.5%, respectively).[7] The same ranking order between the different geographical regions was observed regarding the prevalence of ESBLs among the *E. coli* isolates, although the corresponding rates were lower (13.5%, 12.0%, 7.6%, and 2.2%, respectively).[7] It should be mentioned that the above data refer to isolates related to hospital-acquired infections obtained from various clinical specimens.

Detailed data derived from the TEST database regarding the prevalence of ESBL production among Enterobacteriaceae isolates in Europe have recently been presented.[8] According to these data that refer to 22 European countries for the period of 2004 to 2007, the rate of ESBL production among 515 *K. pneumoniae* isolates and 794 *E. coli* isolates was 15.5% and 9.8%, respectively. Marked differences were observed in the country-specific data; the highest rate of ESBL production was noted in Greece, while the lowest was noted in Denmark. Relevant data collected by the European Antimicrobial Resistance Surveillance System (EARSS Annual Report 2007. Bilthoven. The Netherlands. ISBN:978-90-6960-214-1. available at: http://www.rivm.nl/earss/) regarding resistance rates to third-generation cephalosporins of *K. pneumoniae* and *E. coli* clinical isolates collected in 31 European countries are consistent with those of the TEST database.

Particular attention should be paid to the increasing prevalence of the CTX-M type ESBLs worldwide.[6] This can be attributed to the spread of CTX-M genes among bacterial species by plasmids or other mobile genetic elements, as well as to the clonal expansion of epidemic strains carrying these genes.[5] The prevalence of specific types or groups of CTX-M ESBLs has acquired endemic proportions in many countries. Among European countries, relevant examples include CTX-M-1 enzymes in Italy, CTX-M-9 and CTX-M-14 enzymes in Spain, CTX-M-3 enzymes in Poland, and CTX-M-15

enzymes in the UK.[5,6,9] Notably, the CTX-M-15 ESBLs exhibit a nearly worldwide distribution.[5] Nevertheless CTX-M enzymes have rarely been found responsible for ESBL production among clinical isolates collected in the USA. However, a recent study highlights the increasing prevalence of CTX-M type ESBLs in a large US institution.[10]

Laboratory detection

In the microbiological laboratory, detection of ESBLs can be done with phenotypic or genotypic tests. The phenotypic tests are routinely used in clinical diagnostic laboratories, whereas the genotypic tests are mainly used in reference or research laboratories.

The phenotypic tests for ESBL detection involve screening and confirmatory steps. The screening step consists of testing for resistance to cefpodoxime (which is hydrolysed by all TEM, SHV, and CTX-M types of ESBLs), cefotaxime, ceftazidime, ceftriaxone, or aztreonam.[11] The confirmatory step is based on the demonstration of synergy between the above agents and clavulanic acid.[11] Several methods including the double disc synergy test, the combination disc method, or specific ESBL Etests can be used in this regard.[11,12] Poor sensitivity of these tests may be observed when the evaluated ESBL-producing isolate additionally produces a β-lactamase not inhibited by clavulanic acid, such as an AmpC β-lactamase or metallo-β-lactamase.[12] Methods to overcome this limitation include the use of cefepime, which is a weak substrate for most AmpC β-lactamases, the use of chromogenic agar, cloxacillin-containing agar, or the addition of EDTA to inactivate metallo-β-lactamases.[11]

The above-mentioned principles for the detection of ESBLs by phenotypic methods have been incorporated in most commercial semi-automated bacterial identification and antimicrobial susceptibility testing systems. However, their performance in this regard is variable and their accuracy appears to be lower compared with the conventional phenotypic methods.[12]

The genotypic tests for the detection of ESBLs primarily consist of polymerase chain reaction-based amplification of the specific genes. Regarding the TEM and SHV type ESBLs, additional molecular techniques, such as sequencing or restriction fragment length polymorphism, are required for the identification of specific point mutations that differentiate these enzymes from parent enzymes without ESBL activity.[9] Although technically challenging, the genotypic methods have the advantage of identification of the specific type of ESBL present in a micro-organism, which may be particularly useful for epidemiological purposes.[9] Moreover, they can detect low-level resistance, and can be performed without prior culture of the microbiological specimen.

Clinical relevance and impact of ESBL-associated infections

It is increasingly being recognised that the production of ESBLs is not relevant to nosocomial infections only, but is becoming an important public health issue also with regard to infections acquired in the community. Community-onset ESBL-associated infections are principally caused by *E. coli* producing CTX-M type ESBLs.[9] Urinary tract infections constitute the main clinical syndrome observed in this setting. Bloodstream infections may also be observed, mainly of urinary or biliary tract origin.

Community-acquired ESBL-associated infections typically affect patients with various complicating factors. A relevant case—control study identified various risk factors for community-acquired infection by ESBL-producing *E. coli*, including increased age, female sex, diabetes mellitus, recurrent urinary tract infection, previous instrumentation of the urinary tract, follow-up in outpatient clinic, and previous receipt of aminopenicillins, cephalosporins, or fluoroquinolones.[13] Such findings raise the question whether community-onset ESBL-associated infections are mainly healthcare-associated. However, reports of truly community-acquired infections are increasing, while clusters of cases in the community, particularly among members of the same family, may be observed.[14] Additionally, faecal carriage of ESBLs has been reported in a considerable percentage of healthy individuals residing in the community.[15–17] Potential transmission of ESBL-producing organisms from animal sources to humans through the food chain or patient-to-patient transmission of these organisms might contribute to the dissemination of ESBLs in the community, but these issues require further study.[16]

ESBL-associated infections observed in hospitalised patients represent either serious community-acquired infections requiring hospital admission or infections acquired during hospitalisation. The degree that community-acquired infections contribute to the isolation of ESBL-producing organisms in hospitalised patients appears to be increasing.[18] Furthermore, infection or colonisation of residents in long-term care facilities by ESBL-producing organisms may provide a means for the dissemination of ESBLs between the community and hospitals.

In this respect, the incidence of colonisation by ESBL-producing organisms of residents in long-term care facilities appears to be substantially increasing, although relevant data are limited.[19]

Regarding hospital-acquired infections caused by ESBL-producing organisms, the majority of relevant studies refer to *K. pneumoniae*.[9,14] Clinical syndromes observed in this setting include respiratory tract and wound infections, in addition to urinary tract, bloodstream, and intra-abdominal ones.[9] Risk factors for infection or colonisation of hospitalised patients by ESBL-producing organisms are similar to those referring to other common nosocomial micro-organisms.[20] Specifically, increasing length of hospital or intensive care unit (ICU) stay, greater severity of clinical status, insertion of various types of indwelling catheters, performance of certain types of invasive procedures or surgical interventions, receipt of renal replacement therapy or mechanical ventilatory support have all been associated with the isolation of ESBL-producing organisms from hospitalised patients.[3,21] The use of antibiotics, particularly of oxyimino-β-lactams or fluoroquinolones, constitutes an important additional risk factor.[3]

Studies assessing the epidemiology of hospital-acquired ESBL-associated infections have often recognised a complex pattern.[18] Specifically, epidemic strains may co-exist with sporadic ones,[20] while multiple predominant clones may also be observed.[18] Furthermore, the same types of ESBLs may be identified in clonally unrelated isolates, or, conversely, isolates with the same clonal origin may encode different types of ESBLs.[14] These observations are attributed to horizontal spread of ESBL genes through mobile genetic elements.[15]

The clinical impact of ESBL-associated infections has mainly been studied in hospitalised patients, especially those with bloodstream infections. In this respect, it has been found that bloodstream infections by ESBL-producing Enterobacteriaceae isolates compared with non-producing isolates is associated with a delay in the institution of appropriate antimicrobial therapy, as empirically instituted antibiotics may be inactive.[22] The above factor is thought to be mainly responsible for the increased mortality related to ESBL production in *K. pneumoniae* or *E. coli* bloodstream infections.[22]

Hospital infection control

The general aspects of hospital infection control for ESBL-producing Enterobacteriaceae are similar to those applied for other common nosocomial Gram-negative organisms.[14,23] Specifically, infection control measures should focus on preventing the main modes of patient-to-patient transmission of ESBL-producing organisms in the hospital setting, which include transmission via colonisation of the inanimate environment, the hands of healthcare personnel, and of medical equipment.[14]

The identification of patients colonised with ESBL-producing organisms can be done with surveillance cultures of gastrointestinal tract specimens, particularly with rectal swabs.[14] It has been shown that a substantial percentage of patients who develop nosocomial ESBL-associated infections have preceding colonisation of the gastrointestinal tract. However, the identification of ESBL producers among commensal Enterobacteriaceae is technically demanding and requires the use of selective culture media. Whether a strategy of selective decontamination of the gastrointestinal tract of patients found to be colonised with ESBL-producing organisms is effective in terms of infection control remains a controversial issue.[14] Although effective decolonisation may reduce the likelihood of subsequent infection by these organisms, as well as horizontal spread to neighbouring patients, increased resistance rates of nosocomial ESBL-producing Enterobacteriaceae isolates to agents commonly used in this regard, such as neomycin and norfloxacin, limit the utility of this approach. Moreover, the use of microbiologically active agents, such as polymyxins, may carry the risk of selection for Gram-negative organisms resistant to this class of agents, which is often used as a last resort option for infections by highly resistant isolates.[24]

It should be mentioned that the selection of proper antibiotic therapy is a key factor relating to the effectiveness of infection control. Specifically, limiting the institutional use of third generation cephalosporins has been shown to aid towards the reduction of the prevalence of ESBL-producing organisms.[25] Use of fluoroquinolones may contribute to the selection of ESBL producers, because determinants of fluoroquinolone resistance are often carried in the same mobile genetic elements as ESBL genes.[15] Some studies have suggested that substitution of cephalosporins for piperacillin/tazobactam may be useful in limiting the nosocomial isolation rates of ESBL-producing organisms.[25,26] However, consideration should be given in preventing the emergence of Gram-negative organisms with advanced antimicrobial drug resistance.[27]

Treatment

Associated antimicrobial drug resistance patterns

ESBLs hydrolyse penicillins, cephalosporins (with the exception of cephamycins), and aztreonam.[14]

However, the degree of hydrolytic activity against the above substrates may considerably differ for different types of ESBLs. Typically, the TEM and SHV type ESBLs have greater hydrolytic activity for ceftazidime than cefotaxime, in contrast to the CTX-M type ESBLs.[6,14] Consequently, ESBL-producing organisms may appear susceptible to some of the above agents in vitro. The Clinical and Laboratory Standards Institute (CLSI) recommends that ESBL-producing *E. coli*, *K. pneumoniae*, *Klebsiella oxytoca* and *P. mirabilis* should be reported as resistant to penicillins, true cephalosporins and aztreonam, regardless of the in-vitro susceptibility data. The level of in-vitro antimicrobial drug resistance conferred by the presence of ESBLs to β-lactam/β-lactamase inhibitor combinations is variable.[14] Relevant minimum inhibitory concentrations can be in the susceptible range. An inoculum effect regarding the in-vitro susceptibility of ESBL-producing isolates to agents that are hydrolysed by the ESBLs, including β-lactam/β-lactamase inhibitor combinations, has also been found. However, clinical relevance of this phenomenon has not been firmly established, as it may represent simply a laboratory artefact.[21]

An important factor that limits the array of active antibiotics 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 trimethoprim/sulfamethoxazole.[9]

Cephalosporins

Relatively few studies have assessed clinically cephalosporin treatment for infections caused by ESBL-producing organisms, with an agent of this class showing activity in vitro against the causative organism. In a small relevant clinical trial, clinical success rates were similar in seven patients with CTX-M-producing *E. coli* bacteraemia treated with ceftazidime compared with eight such patients treated with imipenem/cilastatin (86% compared with 88%, respectively).[28] Likewise, a retrospective study did not find significant differences in the clinical outcome of 44 ICU hospitalised patients with TEM-24-producing *Enterobacter aerogenes* infections, treated with cefepime-based versus carbapenem-based therapy.[29] However, the microbiological outcome was inferior in the cefepime group. Moreover, in the context of a randomised trial evaluating patients with nosocomial pneumonia, cefepime treatment tended to be associated with worse outcome compared with imipenem/cilastatin regarding the subgroup of patients infected with ESBL-producing organisms.[30] Additional studies, although small, have reported suboptimal effectiveness of cephalosporins for the treatment of ESBL-producing Enterobacteriaceae, even if in-vitro antimicrobial activity is shown.[31,32] Thus, most experts argue against cephalosporin use as treatment of choice for ESBL-associated infections.

β-Lactams/β-lactamase inhibitor combinations

The degree of inhibitory activity of β-lactamase inhibitors against the hydrolysis of β-lactams by the ESBL enzymes may vary by the type of inhibitor as well as by the type of ESBL. In this respect, tazobactam has been found to be more potent compared with clavulanic acid against certain CTX-M type ESBLs,[33] while both of the above agents appear to be more potent than sulbactam in inhibiting TEM and SHV type ESBLs.[34]

The available clinical evidence regarding the utility of β-lactam/β-lactamase inhibitor combinations for the treatment of ESBL-associated infections is rather limited. Specifically, favourable patient outcomes have been related to piperacillin/tazobactam treatment in some small studies, although such findings have not been consistently reproduced.[26,35] One pharmacokinetic/pharmacodynamic modelling study concluded that the probability of pharmacodynamic target attainment against infections caused by ESBL-producing *E. coli* and *K. pneumoniae* is lower for piperacillin/tazobactam than cefepime if conventional dosing regimens are used.[36] Moreover, increasing resistance rates of ESBL Enterobacteriaceae to piperacillin/tazobactam may limit the potential therapeutic utility of this agent.[26] Last but not least, it should be mentioned that amoxicillin/clavulanate may have considerable antimicrobial activity against Enterobacteriaceae organisms isolated in the community, and it may constitute an effective therapeutic option for community-acquired urinary tract infections caused by ESBL-producing isolates.[13,37]

Cephamycins

The cephamycins, mainly including cefoxitin, cefotetan, and cefmetazole, do not by definition constitute substrates for hydrolysis by the ESBL enzymes. However, co-resistance to these agents in ESBL-producing Enterobacteriaceae may be observed, mainly due to porin loss or concomitant expression of AmpC β-lactamases. Clinical data

regarding the potential value of cephamycins for the treatment of ESBL-associated infections are scarce. Specifically, a small retrospective study evaluated treatment with flomoxef, which is grouped along with latamoxef in the related oxacephem class of β-lactams, or a carbapenem for a total of 27 patients with *K. pneumoniae* bacteraemia. Difference in mortality between the two treatment groups was not evident.[38] However, additional reports have noted that emergence of resistance to cephamycins may be observed during therapy with agents, and even co-resistance to carbapenems also.[14,39]

Carbapenems

Carbapenems are considered to be the treatment of choice against serious ESBL-associated infections.[9] This is mainly because they are not inactivated by these enzymes in vitro, and have demonstrated adequate effectiveness for the treatment of serious Gram-negative infections at various body sites. However, specific data for their clinical use against ESBL-associated infections are rather limited, although generally supportive of their effectiveness.[30,32,35,40] A multicentre prospective cohort study that evaluated 85 cases of *K. pneumoniae* bacteraemia demonstrated that use of a carbapenem in the initial five-day period of the infection was a factor independently associated with lower mortality.[41] In addition, in a small clinical trial, ertapenem use for the treatment of 20 patients with early-onset ventilator-associated pneumoniae caused by ESBL-producing Enterobacteriaceae resulted in a rather favourable overall clinical success rate of 80%.[42]

Fluoroquinolones

As mentioned above, ESBL-producing organisms may carry resistance determinants that confer low- or high-level resistance to fluoroquinolones. Potential resistance to fluoroquinolones may relate to suboptimal patient outcomes when these agents are elected as empirical therapy for infections caused by ESBL-producing organisms. There are some concerns also regarding the effectiveness of fluoroquinolones for the treatment of serious ESBL-associated infections caused by fluoroquinolone-susceptible isolates, compared with carbapenems. Studies that have provided relevant data — albeit only for a small number of patients — are summarised in Table I.[35,40,41,43,44] Regarding the findings of the two largest relevant studies, which both address *K. pneumoniae* bacteraemia, one study favoured the use of carbapenems over fluoroquinolones, whereas the other found similar effectiveness with both these antibiotic classes.[41,44]

Tigecycline

Tigecycline, a derivative of minocycline, is the first member of the glycylcycline class of antibiotics available for clinical use. It has the property to evade common mechanisms of resistance to tetracyclines expressed in Gram-negative and Gram-positive bacteria.[45] Detailed data on the antimicrobial activity of tigecycline against ESBL-producing Enterobacteriaceae, as reported in a recent systematic review of the literature, are summarised in Table II.[46] Specifically, excellent activity of tigecycline has been shown against ESBL-producing *E. coli* isolates. Additionally, substantial antimicrobial activity of tigecycline has been demonstrated against ESBL-producing *K. pneumoniae* isolates, although this depends on the interpretive breakpoints of susceptibility elected. Data regarding the antimicrobial activity of tigecycline against other ESBL-producing Enterobacteriaceae organisms are rather limited.

Clinical data regarding the effectiveness of tigecycline for the treatment of infections caused by ESBL-producing organisms are yet limited.[46] Further, consideration of the pharmacokinetic and pharmacodynamic parameters of this agent casts doubt on the potential effectiveness of tigecycline for the treatment of specific infectious syndromes, such as urinary tract and bloodstream infections.[45] In this respect, only a fraction of 10—15% of the tigecycline dose appears to be excreted as active, unchanged drug in the urine. Achievable serum concentrations of this agent may also be inadequate (due to extensive tissue drug distribution) for substantial antimicrobial activity to be exerted against pathogenic micro-organisms circulating in the bloodstream with minimum inhibitory concentrations close to the susceptibility breakpoint.

Considerations for further research

The re-evaluation of earlier-used antimicrobial agents, that have had low clinical use in recent decades, for potential antimicrobial activity and clinical effectiveness against today's resistant micro-organisms may provide a temporary solution to the problem of spreading and advancing bacterial drug resistance. Agents that may be useful for the treatment of ESBL-associated infections include polymyxins, fosfomycin, nitrofurantoin,

Table I Clinical outcome in patients with infections caused by ESBL-producing Enterobacteriaceae treated with fluoroquinolones, carbapenems, or other agents showing in-vitro activity

Study	Study design	Patient characteristics	Outcome	Specific agents: *n*/*N* (%)		
				Fluoroquinolones	Carbapenems	Other antibiotics
Kim *et al.* (2002)[43]	Retrospective cohort study	Adult patients with ESBL *K. pneumoniae* bacteraemia	Mortality	Ciprofloxacin[a]: 1/3 (33)	Imipenem: 2/12 (17)	Aminoglycosides[a]: 2/4 (50)
Burgess *et al.* (2003)[35]	Retrospective cohort study	Cases with infections by ESBL-producing organisms (*E. coli*, *K. pneumoniae*, *K. oxytoca*)	Clinical failure	Fluoroquinolones[a]: 0/3 (0)	Carbapenems[a]: 0/3 (0)	Piperacillin/tazobactam[a]: 1/3 (33)
Endimiani *et al.* (2004)[40]	Retrospective cohort study	Patients with TEM-52 ESBL-producing *K. pneumoniae* bacteraemia	Clinical failure	Ciprofloxacin[a,b]: 2/7 (29)	Carbapenems[a,b]: 3/11 (27) [imipenem: 2/10 (20); meropenem: 1/1 (100)]	Aminoglycosides[a,b]: 0/2 (0)
Kang *et al.* (2004)[44]	Retrospective cohort study	Patients with ESBL-producing *E. coli* or *K. pneumoniae* bacteraemia	30-day mortality	Ciprofloxacin[c]: 3/29 (10)	Carbapenems[c]: 8/62 (12.9)	NR
Paterson *et al.* (2004)[41]	Prospective multicentre cohort study	Patients aged >6 years with ESBL-producing *K. pneumoniae*	Mortality	Ciprofloxacin[a]: 4/11 (36)	Carbapenems[a]: 1/27 (4) [imipenem: 1/24 (4); meropenem: 0/3 (0)]	Cephalosporins[a]: 2/5 (50); β-lactam/β-lactamase inhibitor[a]: 2/4 (50)

ESBL, extended-spectrum β-lactamase; NR, not specifically reported.
[a] Representing therapy as the only microbiologically active agents.
[b] Patients who received adequate treatment and dose for ≥7 days.
[c] Definitive therapy.

Table II Cumulative susceptibility to tigecycline of ESBL-producing Enterobacteriaceae isolates identified in different studies[a]

Micro-organisms	No. of studies	Susceptibility, % (no. of isolates)	
		FDA criteria[b]	EUCAST criteria[b]
E. coli	16	99.8% (1636)	99.7% (737)
Klebsiella spp.	17	92.3% (2030)	72.3% (1284)
Enterobacter spp.	4	91.3% (69)	77.6% (49)

[a] Adapted from Kelesidis *et al.*[46]
[b] Food and Drug Administration (FDA) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints of susceptibility: minimum inhibitory concentrations $\leq$2 and $\leq$1 mg/L, respectively.

and temocillin. Furthermore, combining available cephalosporins with β-lactamase inhibitors could enhance the effectiveness of the former agents against ESBL-associated infections.

With regard to polymyxins (of which colistin and polymyxin B are currently available for clinical use), these have retained excellent antimicrobial activity against ESBL-producing organisms.[47] However, reported clinical use of these agents for the treatment of such infections is scarce, since they are typically reserved for the treatment of infections caused by Gram-negative bacteria with more advanced resistance patterns.[23]

Fosfomycin can also have good antimicrobial activity against ESBL-producing Enterobacteriaceae.[48] Despite concerns that increasing use of this agent may lead to resistance development, resistance rates among urinary tract isolates have remained low.[49] Moreover, a recent study revealed high effectiveness of fosfomycin in the treatment of community-acquired lower urinary tract infection caused by ESBL-producing *E. coli*.[13] The potential value of this drug for the treatment of systemic infections — of origin other than the urinary tract — is of marked interest.[49] With regard to nitrofurantoin, this agent may also be effective in the treatment of ESBL-associated uncomplicated urinary tract infections, but this could be limited by co-resistance to this agent of ESBL-producing organisms.[50]

β-Lactamases viewed from a clinical perspective

Clinicians involved in the treatment of infectious diseases may be puzzled by the continuous expansion of knowledge concerning β-lactamases, since new enzymes with potentially varying properties are increasingly being recognised. From a clinical standpoint, translating and grouping the complex microbiological information into therapeutically meaningful categories might facilitate the choice of appropriate therapy. In this regard, the need for a pragmatic new definition for ESBLs has been emphasised.[51] In fact, re-definition of the ESBLs to include enzymes of different classes of β-lactamases that confer resistance to extended-spectrum cephalosporins has recently been proposed.[52]

Conclusion

The increasing prevalence and shifting epidemiology of ESBL-producing organisms, particularly of *K. pneumoniae* and *E. coli*, render the infections caused by these pathogenic micro-organisms an important public health problem. The resistance to extended-spectrum β-lactams, which by definition these enzymes confer, along with frequently observed co-resistance to other antibiotics renders ineffective many of the regimens traditionally used for the empirical therapy of various types of associated infections. This may be of particular importance for community-acquired infections, since options for oral antibiotic therapy against ESBL-producing organisms appear to be limited. Regarding nosocomial infections caused by these organisms, carbapenems appear as the most reliable therapeutic agents. Further research is required on appropriate strategies to limit the emergence and spread of resistant organisms, both in the community and the hospital settings, as well as to evaluate the available therapeutic agents and identify new ones.

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References

1. Bush K, Jacoby GA, Medeiros AA. A functional classification scheme for beta-lactamases and its correlation with molecular structure. *Antimicrob Agents Chemother* 1995; **39**:1211—1233.

2. Ambler RP, Meadway RJ. Chemical structure of bacterial penicillinases. *Nature* 1969;**222**:24—26.
3. Jacoby GA, Munoz-Price LS. The new beta-lactamases. *N Engl J Med* 2005;**352**:380—391.
4. Jones CH, Tuckman M, Keeney D, Ruzin A, Bradford PA. Characterization and sequence analysis of extended spectrum β-lactamase encoding genes from *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* isolates collected during tigecycline phase 3 clinical trials. *Antimicrob Agents Chemother* 2009;**53**:465—475.
5. Livermore DM, Canton R, Gniadkowski M, *et al*. CTX-M: changing the face of ESBLs in Europe. *J Antimicrob Chemother* 2007;**59**:165—174.
6. Bonnet R. Growing group of extended-spectrum beta-lactamases: the CTX-M enzymes. *Antimicrob Agents Chemother* 2004;**48**:1—14.
7. Reinert RR, Low DE, Rossi F, Zhang X, Wattal C, Dowzicky MJ. Antimicrobial susceptibility among organisms from the Asia/Pacific Rim, Europe and Latin and North America collected as part of TEST and the in vitro activity of tigecycline. *J Antimicrob Chemother* 2007;**60**:1018—1029.
8. Hackel M, Badal R, Bouchillon S, *et al*. Extended-spectrum beta-lactamase production in Europe. In: Abstracts of the 18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Barcelona, Spain, 2008.
9. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis* 2008;**8**:159—166.
10. Lewis 2nd JS, Herrera M, Wickes B, Patterson JE, Jorgensen JH. First report of the emergence of CTX-M-type extended-spectrum beta-lactamases (ESBLs) as the predominant ESBL isolated in a U.S. health care system. *Antimicrob Agents Chemother* 2007;**51**:4015—4021.
11. Drieux L, Brossier F, Sougakoff W, Jarlier V. Phenotypic detection of extended-spectrum beta-lactamase production in Enterobacteriaceae: review and bench guide. *Clin Microbiol Infect* 2008;**14**(Suppl. 1):90—103.
12. Wiegand I, Geiss HK, Mack D, Sturenburg E, Seifert H. Detection of extended-spectrum beta-lactamases among Enterobacteriaceae by use of semiautomated microbiology systems and manual detection procedures. *J Clin Microbiol* 2007;**45**:1167—1174.
13. Rodriguez-Bano J, Alcala JC, Cisneros JM, *et al*. Community infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Arch Intern Med* 2008;**168**: 1897—1902.
14. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev* 2005;**18**: 657—686.
15. Canton R, Novais A, Valverde A, *et al*. Prevalence and spread of extended-spectrum beta-lactamase-producing Enterobacteriaceae in Europe. *Clin Microbiol Infect* 2008; **14**(Suppl. 1):144—153.
16. Rodriguez-Bano J, Lopez-Cerero L, Navarro MD, Diaz de Alba P, Pascual A. Faecal carriage of extended-spectrum beta-lactamase-producing *Escherichia coli*: prevalence, risk factors and molecular epidemiology. *J Antimicrob Chemother* 2008;**62**:1142—1149.
17. Falagas ME, Karageorgopoulos DE. Clinical Microbiology and Infectious Diseases (ECCMID) — 18th European Congress. Drug resistance among Gram-negative and Gram-positive bacteria. *IDrugs* 2008;**11**:409—411.
18. Valverde A, Coque TM, Garcia-San Miguel L, Baquero F, Canton R. Complex molecular epidemiology of extended-spectrum beta-lactamases in *Klebsiella pneumoniae*: a long-term perspective from a single institution in Madrid. *J Antimicrob Chemother* 2008;**61**:64—72.
19. Nicolas-Chanoine MH, Jarlier V. Extended-spectrum beta-lactamases in long-term-care facilities. *Clin Microbiol Infect* 2008;**14**(Suppl. 1):111—116.
20. Rodriguez-Bano J, Navarro MD, Romero L, *et al*. Clinical and molecular epidemiology of extended-spectrum beta-lactamase-producing *Escherichia coli* as a cause of nosocomial infection or colonization: implications for control. *Clin Infect Dis* 2006;**42**:37—45.
21. Pfaller MA, Segreti J. Overview of the epidemiological profile and laboratory detection of extended-spectrum beta-lactamases. *Clin Infect Dis* 2006;**42**(Suppl. 4):S153—S163.
22. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007;**60**:913—920.
23. Karageorgopoulos DE, Falagas ME. Current control and treatment of multidrug-resistant *Acinetobacter baumannii* infections. *Lancet Infect Dis* 2008;**8**:751—762.
24. Matthaiou DK, Michalopoulos A, Rafailidis PI, *et al*. Risk factors associated with the isolation of colistin-resistant gram-negative bacteria: a matched case—control study. *Crit Care Med* 2008;**36**:807—811.
25. Kim JY, Sohn JW, Park DW, Yoon YK, Kim YM, Kim MJ. Control of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* using a computer-assisted management program to restrict third-generation cephalosporin use. *J Antimicrob Chemother* 2008;**62**:416—421.
26. Peterson LR. Antibiotic policy and prescribing strategies for therapy of extended-spectrum beta-lactamase-producing Enterobacteriaceae: the role of piperacillin-tazobactam. *Clin Microbiol Infect* 2008;**14**(Suppl. 1):181—184.
27. Falagas ME, Rafailidis PI, Kofteridis D, *et al*. Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infections: a matched case control study. *J Antimicrob Chemother* 2007;**60**:1124—1130.
28. Bin C, Hui W, Renyuan Z, *et al*. Outcome of cephalosporin treatment of bacteremia due to CTX-M-type extended-spectrum beta-lactamase-producing *Escherichia coli*. *Diagn Microbiol Infect Dis* 2006;**56**:351—357.
29. Goethaert K, Van Looveren M, Lammens C, *et al*. High-dose cefepime as an alternative treatment for infections caused by TEM-24 ESBL-producing *Enterobacter aerogenes* in severely-ill patients. *Clin Microbiol Infect* 2006;**12**:56—62.
30. Zanetti G, Bally F, Greub G, *et al*. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. *Antimicrob Agents Chemother* 2003;**47**:3442—3447.
31. Paterson DL, Ko WC, Von Gottberg A, *et al*. Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum beta-lactamases: implications for the clinical microbiology laboratory. *J Clin Microbiol* 2001;**39**:2206—2212.
32. Wong-Beringer A, Hindler J, Loeloff M, *et al*. Molecular correlation for the treatment outcomes in bloodstream infections caused by *Escherichia coli* and *Klebsiella pneumoniae* with reduced susceptibility to ceftazidime. *Clin Infect Dis* 2002;**34**:135—146.
33. Bush K, Macalintal C, Rasmussen BA, Lee VJ, Yang Y. Kinetic interactions of tazobactam with beta-lactamases from all major structural classes. *Antimicrob Agents Chemother* 1993;**37**:851—858.
34. Payne DJ, Cramp R, Winstanley DJ, Knowles DJ. Comparative activities of clavulanic acid, sulbactam, and tazobactam against clinically important beta-lactamases. *Antimicrob Agents Chemother* 1994;**38**:767—772.

35. Burgess DS, Hall 2nd RG, Lewis 2nd JS, Jorgensen JH, Patterson JE. Clinical and microbiologic analysis of a hospital's extended-spectrum beta-lactamase-producing isolates over a 2-year period. *Pharmacotherapy* 2003;**23**: 1232—1237.
36. Ambrose PG, Bhavnani SM, Jones RN. Pharmacokinetics-pharmacodynamics of cefepime and piperacillin-tazobactam against *Escherichia coli* and *Klebsiella pneumoniae* strains producing extended-spectrum beta-lactamases: report from the ARREST program. *Antimicrob Agents Chemother* 2003; **47**:1643—1646.
37. Falagas ME, Polemis M, Alexiou VG, Marini-Mastrogiannaki A, Kremastinou J, Vatopoulos AC. Antimicrobial resistance of *Esherichia coli* urinary isolates from primary care patients in Greece. *Med Sci Monit* 2008;**14**: CR75—CR79.
38. Lee CH, Su LH, Tang YF, Liu JW. Treatment of ESBL-producing *Klebsiella pneumoniae* bacteraemia with carbapenems or flomoxef: a retrospective study and laboratory analysis of the isolates. *J Antimicrob Chemother* 2006;**58**:1074—1077.
39. Lee CH, Chu C, Liu JW, Chen YS, Chiu CJ, Su LH. Collateral damage of flomoxef therapy: in vivo development of porin deficiency and acquisition of blaDHA-1 leading to ertapenem resistance in a clinical isolate of *Klebsiella pneumoniae* producing CTX-M-3 and SHV-5 beta-lactamases. *J Antimicrob Chemother* 2007;**60**:410—413.
40. Endimiani A, Luzzaro F, Perilli M, *et al*. Bacteremia due to *Klebsiella pneumoniae* isolates producing the TEM-52 extended-spectrum beta-lactamase: treatment outcome of patients receiving imipenem or ciprofloxacin. *Clin Infect Dis* 2004;**38**:243—251.
41. Paterson DL, Ko WC, Von Gottberg A, *et al*. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum beta-lactamases. *Clin Infect Dis* 2004;**39**:31—37.
42. Bassetti M, Righi E, Fasce R, *et al*. Efficacy of ertapenem in the treatment of early ventilator-associated pneumonia caused by extended-spectrum beta-lactamase-producing organisms in an intensive care unit. *J Antimicrob Chemother* 2007;**60**:433—435.
43. Kim BN, Woo JH, Kim MN, Ryu J, Kim YS. Clinical implications of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* bacteraemia. *J Hosp Infect* 2002; **52**:99—106.
44. Kang CI, Kim SH, Park WB, *et al*. Bloodstream infections due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy. *Antimicrob Agents Chemother* 2004;**48**: 4574—4581.
45. Falagas ME, Karageorgopoulos DE, Dimopoulos G. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of tigecycline. *Curr Drug Metab* 2009;**10**: 13—21.
46. Kelesidis T, Karageorgopoulos DE, Kelesidis I, Falagas ME. Tigecycline for the treatment of multidrug-resistant Enterobacteriaceae: a systematic review of the evidence from microbiological and clinical studies. *J Antimicrob Chemother* 2008;**62**:895—904.
47. Gales AC, Jones RN, Sader HS. Global assessment of the antimicrobial activity of polymyxin B against 54 731 clinical isolates of Gram-negative bacilli: report from the SENTRY antimicrobial surveillance programme (2001—2004). *Clin Microbiol Infect* 2006;**12**:315—321.
48. Falagas ME, Kanellopoulou MD, Karageorgopoulos DE, *et al*. Antimicrobial susceptibility of multidrug-resistant Gram negative bacteria to fosfomycin. *Eur J Clin Microbiol Infect Dis* 2008;**27**:439—443.
49. Falagas ME, Giannopoulou KP, Kokolakis GN, Rafailidis PI. Fosfomycin: use beyond urinary tract and gastrointestinal infections. *Clin Infect Dis* 2008;**46**:1069—1077.
50. Garau J. Other antimicrobials of interest in the era of extended-spectrum beta-lactamases: fosfomycin, nitrofurantoin and tigecycline. *Clin Microbiol Infect* 2008;**14** (Suppl. 1):198—202.
51. Livermore DM. Defining an extended-spectrum beta-lactamase. *Clin Microbiol Infect* 2008;**14**(Suppl. 1):3—10.
52. Giske CG, Sundsfjord AS, Kahlmeter G, *et al*. Redefining extended-spectrum beta-lactamases: balancing science and clinical need. *J Antimicrob Chemother* 2009;**63**:1—4.