# INTRODUCTION

## Living with ESBLs

β-Lactams remain the most flexible antibiotic class, owing to their versatility and diversity in terms of chemical properties, antibacterial spectra and administration schedules. The major threat for these compounds is the ever-growing diversification and proliferation of β-lactamases. Among more than 350 different β-lactamases identified, almost one-third of them are able to hydrolyse broad-spectrum cephalosporins and aztreonam, although many of these are minor variants of a few major types.

Various definitions of extended-spectrum β-lactamases (ESBLs) have been in use over the past 20 years, some based on spectrum and inhibition, and others on evolutionary history. No definition is perfect but, in an attempt to be both comprehensive and pragmatic, a definition was proposed during the ESCMID conference, the proceedings of which are presented in this issue: 'an ESBL is any β-lactamase, ordinarily acquired and not inherent to a species, that can rapidly hydrolyse, or confer resistance to, oxyimino-cephalosporins (not carbapenems) or any β-lactamase mutant, within a family, that has an enhanced ability to do so' [D. Livermore].

ESBLs are clearly a matter for global concern but, like other bacterial resistance mechanisms, they evolve and spread differently in different settings. While clonal spread of strains of ESBL-producing *Escherichia coli* has been reported in some countries and care settings, in most countries it is mobile genetic elements encoding the ESBLs that are spreading among clonally unrelated strains. In Europe, CTX-M ESBLs, which began to disseminate clinically later than the classical TEM and SHV variants, are now spreading rapidly and are increasingly dominant. In contrast, ESBL producers in the USA still mainly have TEM and SHV mutant β-lactamases, and CTX-M types have only rarely been identified. In Latin America, or at least in Argentina, ESBLs are highly prevalent but belong to groups different from those prevalent in Europe and the USA. The high prevalence potentially can be attributed to many factors, e.g., uncontrolled use of broad-spectrum antibiotics, limited identification of ESBL-producing bacteria in microbiology laboratories due to economic constraints, and the likelihood of transmission among patients because of overcrowded hospitals and shortcomings of contact barriers and hand-washing procedures.

Initially found among hospitalised patients and in species more common in the intensive care setting (e.g., *Klebsiella pneumoniae* and *Enterobacter cloacae*), ESBLs are now commonly found in *E. coli* isolates from patients in nursing homes and long-term-care facilities, and even in patients with community-acquired infections. Although urinary tract infections are the most frequent primary site for community-acquired infections caused by ESBL-producing bacteria, 5–15% of community-acquired infections caused by ESBL-producing *E. coli* involve bacteraemia, and this figure continues to increase. Thus, protocols for the empirical treatment of community-acquired sepsis need to be revised, particularly in areas where *E. coli* strains with ESBLs are prevalent.

Antimicrobial susceptibility testing of third-generation cephalosporins is currently based on both breakpoints and screening tests to predict and confirm the presence of ESBLs. The growing number of species that are likely to produce ESBLs and the increasing number of different ESBLs tend to broaden the range of MIC values and degrees of synergy likely to be seen for ESBL producers, complicating ESBL detection methods. This situation mandates reassessment of susceptibility breakpoints of third-generation cephalosporins for Enterobacteriaceae on both sides of the Atlantic. Low cephalosporin breakpoints alone (as adopted by EUCAST) will facilitate detection of likely ESBL producers, but will not obviate the need for specific ESBL identification, since this is of epidemiological importance. Effective interpretive rules for in-vitro tests are urgently needed, since some ESBL producers appear to be susceptible to cephalosporins *in vitro* but have been associated with treatment failure and increased mortality. The CLSI recommends reporting ESBL-producing strains of *E. coli* and *Klebsiella* spp. as resistant to all penicillin, cephalosporin and monobactam antimicrobials (it provides no guidance concerning ESBLs in other species), but accepts results for β-lactam–β-lactamase inhibitor combinations as found. In fact, several clinical experiences with β-lactam–β-lactamase inhibitor combinations have been variable, and these com-

pounds are less active against organisms producing multiple ESBLs. Moreover, frank in-vitro resistance to them is increasing among ESBL producers.

Most notably in the case of clavulanate, whose good activity is critical in ESBL detection tests, the therapeutic potential is uncertain, partly because of difficult-to-protect penicillins in the marketed combinations and partly because of its potential antagonistic activities against cephalosporins through induction of AmpC synthesis.

Since the ESBL-producing organisms frequently also carry genes encoding resistance to other antibiotic classes, including quinolones, aminoglycosides, tetracyclines and antifolates, the therapeutic options are seriously reduced. The parenteral carbapenems are widely considered to be the most effective treatment for serious infections caused by ESBL producers. Imipenem and meropenem, which are active against both Enterobacteriaceae and non-fermentative Gram-negative bacilli, are licensed in Europe for many indications, covering almost all severe and nosocomial infections. Ertapenem, with limited activity against non-fermentative Gram-negative bacilli, has been licensed in the EU since 2002 for the treatment of intra-abdominal infections, community-acquired pneumonia, acute pelvic infections and soft-tissue infections associated with diabetic foot. Panipenem, with a spectrum similar to ertapenem, and biapenem, with in-vitro activity comparable to imipenem and meropenem, are available in Japan and South Korea, and several other carbapenems are under development, e.g., doripenem. Carbapenems with oral activity for community use, e.g., tebipenem, have demonstrated broad-spectrum antibacterial activity, including activity against ESBL producers, but their development looks uncertain.

While the spread of ESBLs is a driver for increasing use of carbapenems, the growing diffusion of carbapenem-hydrolysing enzymes among Enterobacteriaceae in some European countries mandates strict control over their use and careful monitoring of susceptibility trends.

In conclusion, laboratory findings and clinical experiences both show that the ESBL problem is rapidly evolving and increasing in severity, especially in Europe. New ESBLs, particularly the CTX-M types, are spreading. Producers are no longer confined to intensive care units, but are being isolated from community patients. *E. coli*, rather than *Klebsiella* spp., is becoming the main host. The challenge posed, which is a definite threat to the future of antimicrobial chemotherapy, must be seriously addressed by the laboratory, by the clinicians treating infected patients, by public health and infection control professionals, and by the pharmaceutical industry.

*G. Cornaglia, J. Garau and D. M. Livermore*
Organising Committee
ESCMID Conference on Extended-Spectrum
β-Lactamases