Clinical Management of Infections Caused by Enterobacteriaceae that Express Extended-Spectrum β-Lactamase and AmpC Enzymes

Patrick N. A. Harris, BSc, MBBS, MRCP, DTM&H, FRACP, FRCPA[1]

[1] Infection and Immunity Theme, University of Queensland Centre for Clinical Research, Brisbane, Queensland, Australia

Semin Respir Crit Care Med 2015;36:56–73.

Address for correspondence Patrick N. A. Harris, BSc, MBBS, MRCP, DTM&H, FRACP, FRCPA, University of Queensland Centre for Clinical Research (UQCCR), Building 71/918, Royal Brisbane and Women's Hospital Campus, Herston, Queensland 4029, Australia (e-mail: p.harris@uq.edu.au).

Abstract

The production of β-lactamase is the principal mechanism by which gram-negative bacteria resist the action of β-lactam antibiotics. In recent decades, there has been an alarming explosion in the diversity, global dissemination, host range, and spectrum of activity of β-lactamases. This has been most clearly reflected by the marked increase in infections caused by bacteria that express extended-spectrum β-lactamases (ESBLs). Some bacterial species possess chromosomally encoded broad-spectrum cephalosporinases (AmpC) that may be expressed at high level by mutational loss of regulatory genes and are intrinsic in some common Enterobacteriaceae, such as *Enterobacter* spp. Recently, high-level AmpC production has also been seen in new species such as *Escherichia coli* via plasmid acquisition. ESBL and AmpC producers present challenges to susceptibility testing and the selection of appropriate antimicrobial therapy. This review describes the current global epidemiology of ESBL producers, examines reported risk factors for infections caused by gram-negative bacteria that express ESBL or AmpC enzymes, and discusses the options for antimicrobial therapy, including "re-discovered" older antibiotics and novel agents in development.

Keywords
- Enterobacteriaceae
- extended-spectrum β-lactamase
- AmpC
- therapy

It is thought that β-lactamase enzymes have evolved in bacteria over many millions of years as a protective mechanism against naturally occurring compounds produced by other microorganisms.[1–3] Environmental bacteria found in underground caverns, isolated from the outside world for more than 4 million years, show extensive resistance to commercial antibiotics, including penicillins and cephalosporins mediated by hydrolyzing β-lactamases.[4] As such, bacterial resistance to β-lactam antibiotics may be nothing "new." Even before penicillin had been used to treat clinical infections, Abraham and Chain in 1940 observed a substance produced by *Escherichia coli* (then named *Bacillus coli*) that would reduce the inhibitory effect of penicillin on *Staphylococcus aureus*.[5] Although not known at that time, this was the first scientific description of β-lactamase activity, in this case the low-level AmpC activity seen in *E. coli*.[6] However, it is clear that the diversity, distribution, host range, and prevalence of β-lactamases have expanded dramatically since the introduction of widespread commercial use of antibiotics.[7]

Extended-Spectrum β-Lactamases

Production of β-lactamase is the primary mechanism by which gram-negative bacteria express resistance to β-lactams—our most useful and effective antibiotics (see ►**Fig. 1**). When first recognized, most β-lactamase enzymes showed narrow spectrum activity. For instance, TEM-1 in *E. coli* or SHV-1 in *Klebsiella pneumoniae* are both able to effectively hydrolyze ampicillin, yet most other β-lactam classes remain unaffected to any clinically significant degree (unless these enzymes become expressed at very high levels). In response to the increasing prevalence of these β-lactamases in gram-negative bacteria and their spread to other new host species

Issue Theme Antimicrobial Resistance: Management of Superbugs; Guest Editor, David L. Paterson, MBBS, PhD, FRACP, FRCPA

DOI http://dx.doi.org/10.1055/s-0034-1398387.
ISSN 1069-3424.

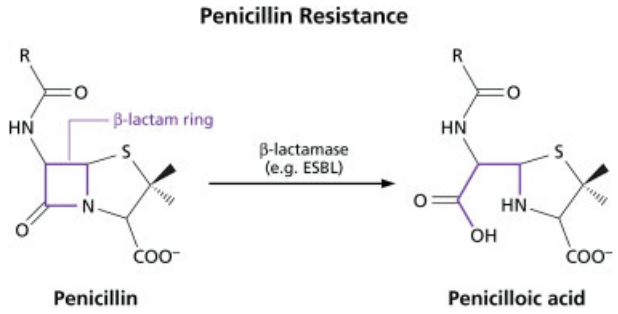

Fig. 1 Hydrolysis of β-lactam antibiotics by β-lactamase enzymes.

(e.g., *Haemophilus influenzae* or *Neisseria gonorrhoeae*), third-generation cephalosporins (such as ceftriaxone or cefotaxime) were developed and showed stability to the effects of these narrow spectrum β-lactamases. As such, these agents became "workhorse" antibiotics in many hospitals, with a spectrum of activity that covered common pathogens implicated in many infectious syndromes. However, within a few years of their introduction into clinical use a bacterial isolate showing transmissible resistance to third-generation cephalosporins, a key feature of "extended-spectrum" β-lactamase (ESBL) activity, was described in a nosocomial *K. pneumoniae* isolate following a point mutation in its "parent" β-lactamase.[8] There are now more than 1,300 unique β-lactamase types described[7] (see www.lahey.org/Studies for a comprehensive list), many of which possess activity against "expanded-spectrum" cephalosporins—a term used to include third-generation (e.g., ceftriaxone, cefotaxime, ceftazidime) and fourth-generation (e.g., cefepime) cephalosporins, as well as novel antistaphylococcal agents such as ceftaroline.[9] ESBLs also typically render bacteria resistant to monobactams such as aztreonam.

Classification of β-Lactamases

Several classification schemes for β-lactamases have been proposed over the years, but two main systems have predominated. The Bush–Jacoby–Medeiros functional classification scheme defines three main groups of β-lactamase enzymes according to their substrate and inhibitor profiles: group 1 cephalosporinases not inhibited well by clavulanate; group 2 enzymes with penicillinase, cephalosporinase, and broad-spectrum β-lactamase activity generally inhibited by β-lactamase inhibitors; and group 3 metallo-β-lactamase that hydrolyze penicillins, cephalosporins, and carbapenems that are poorly inhibited by most β-lactamase inhibitors.[10] This scheme also incorporates several subcategories that have evolved over the years with the discovery of new β-lactamase types.[7] The Ambler classification scheme relies upon amino acid sequences of β-lactamase types and includes four categories: types A, C, and D with a serine residues at the active site and class B metalloenzymes with a Zn^{2+} cofactor[11] (see ►**Table 1**).

Although these schemes have been helpful in categorizing β-lactamase types, they have several drawbacks. The nomenclature can seem impenetrable to the nonspecialist and has evolved significant complexity to accommodate the expanding variety of β-lactamase types.[7,12] Some β-lactamases do not fit neatly into the category definitions. As a result, the clinical applicability of these schemes, in terms of determining therapy, defining infection control responses or policy decisions, may be obscure. The narrow definition of an ESBL suggests an Ambler class A type, clavulanate-inhibited, Bush–Jacoby group 2be ("e" standing for "extended spectrum") enzyme that can hydrolyze an oxyimino-cephalosporin at a rate at least 10% of that for benzylpenicillin. Yet many other enzymes, such as OXA-type cephalosporinase or carbapenemase, plasmid-mediated AmpC, metallo-β-lactamases, or KPC-type carbapenemases all share some activity in common with ESBLs, and lead to key resistance patterns such as resistance to expanded spectrum cephalosporins. Such β-lactamase types are not considered as "true" or "classical" ESBLs, yet have equal or greater consequences for infection control and therapeutic decision making. A simplified nomenclature has been proposed, whereby the term ESBL applies to any broad-spectrum β-lactamase with a suffix to suggest underlying mechanisms (e.g., using $ESBL_{CARBA}$ for a KPC-type carbapenemase, $ESBL_{M\text{-}C}$ for a "miscellaneous" plasmid AmpC type, or $ESBL_{CARBA\text{-}D}$ for OXA-type carbapenemase). This nomenclature is yet to find widespread use or acceptance.[13,14]

The Problem with AmpC

In addition to ESBL-type enzymes, Ambler class C (Bush–Jacoby group 1) enzymes may also effectively hydrolyze third-generation cephalosporins. These enzymes have been recognized since the 1960s and were termed AmpC-type β-lactamases—a nomenclature that remains today. Many gram-negative species contain chromosomally located genes encoding and regulating AmpC. Yet, in several species AmpC is only expressed at clinically insignificant levels (e.g., *E. coli, Shigella* spp.), and do not alter the effect of β-lactams, unless their expression is upregulated by mutations in promoter regions.[15] In some species, AmpC production is controlled by transcription factors that respond to changes in cell-wall cycling pathways under the influence of β-lactam exposure, leading to marked increases in AmpC levels—so-called inducible expression.[16] Inducible *ampC* genes are usually chromosomally located and are intrinsic to certain species: particularly *Enterobacter cloacae, Enterobacter aerogenes, Serratia marcescens, Citrobacter freundii, Providencia* spp., and *Morganella morganii*. These species have been informally labeled as the "ESCPM" or "SPACE" organisms.[17,18] However, there is no clear definition for the term; it can include variable species (such as *Proteus vulgaris* or *P. penneri*, which have a weakly inducible cephalosporinase, but of a class A type[19]) and underestimates the variability in AmpC expression in each species and the clinical consequences of this. It should also be noted that nonfermenters such as *Pseudomonas aeruginosa* also possess inducible AmpC enzymes with homology to those seen in Enterobacteriaceae.[20] There are several other additional species that possess AmpC-type enzymes, with variation in the levels of expression and subsequent clinical significance.[6] Nevertheless, the "ESCPM"

Table 1 Key β-lactamase enzymes that mediate resistance in Enterobacteriaceae

Ambler classification	Bush–Jacoby classification	Structure and function	Genetics	Common species	Common examples
Class A	Group 2 (2be includes "classical" ESBLs)	Contain serine residues at active site. Key feature of ESBL producers is resistance to third-generation cephalosporins (e.g., ceftriaxone) and monobactams, but not cephamycins. Inhibited by clavulanate or tazobactam in vitro (except KPC)	ESBLs arise from mutations in "parent" narrow-spectrum β-lactamase. Highly transmissible on mobile genetic elements (e.g., plasmids) often carrying multiple resistance determinants	ESBLs most common in *E. coli*, *Klebsiella* spp., and *Proteus* spp. but have been described in most Enterobacteriaceae and *Pseudomonas* spp. KPC seen in *Klebsiella pneumoniae*	ESBLs: TEM and SHV variants, CTX-M Carbapenemase: KPC
Class B	Group 3	Contain metal ions (e.g., Zn^{2+}). Carbapenemase activity, not inhibited by clavulanate/tazobactam. Aztreonam not hydrolyzed	Highly transmissible on plasmids carrying multiple other resistance determinants	*E. coli*, *Klebsiella* spp. But described in many Enterobacteriaceae	Carbapenemase: IMP, NDM (Often called "metallo-β-lactamases")
Class C	Group 1	Contain serine residues at active site. Also known as "AmpC" enzymes. Broad cephalosporinase activity including hydrolysis of third-generation cephalosporins and cephamycins, but cefepime usually stable. Not inhibited well by clavulanate, and only limited tazobactam effect	Chromosomally encoded in several species, and may be inducible by exposure to β-lactams. Expression regulated by complex systems; mutations in key regulatory genes can lead to "derepression" and high-level AmpC production. Increasing plasmid transmission seen	*Enterobacter cloacae*, *E. aerogenes*, *Serratia marcescens*, *Citrobacter freundii*, *Providencia* spp. and *Morganella morganii* all contain inducible AmpC enzymes. Plasmid mediated AmpC increasing in *E. coli*, *Klebsiella* spp.	Cephalosporinase: CMY, DHA, ACT
Class D	Group 2d	Contain serine residues at active site. Oxacillinases that may have carbapenemase activity. Only weakly inhibited by clavulanate	May be acquired or naturally occurring chromosomal genes. May be co-located on plasmids with other β-lactamases (e.g., OXA-48 and CTX-M-15)	Increasingly described in Enterobacteriaceae (e.g., *K. pneumoniae* and OXA-48)	Carbapenemase: OXA-types

Abbreviation: ESBLs, extended-spectrum β-lactamases.

term can be useful in encapsulating a complex issue in shorthand, but one should be mindful of its limitations.

Chromosomally encoded AmpC enzymes in the species listed earlier render them intrinsically resistant to some narrow spectrum β-lactams and early generation cephalosporins. Under exposure to β-lactam antibiotics, the action of regulatory elements (particularly AmpR, which represses AmpC expression in the absence of an inducer) is altered and *ampC* expression can occur at significant levels.[21] For instance, the AmpR protein found in *C. freundii* downregulates the expression of AmpC by 2.5-fold in the absence of an inducing agent, but when exposed to a β-lactam inducer, AmpC expression increases to 10- to 200-fold.[22] This process is now understood to be linked to cell-wall recycling involving a complex interaction of peptidoglycan breakdown products, penicillin-binding proteins, the *ampC* gene and its regulators (such as AmpR), enzymes involved in recycling muropeptidases (such as AmpD), and other modulating elements such as the permease AmpG (see ►**Fig. 2**).[23–25] This phenomenon is of key importance to antibiotics such as ampicillin, amoxicillin–clavulanate, and first-generation cephalosporins. The "ESCPM" species are intrinsically resistant to these agents—to the extent that susceptibility may call the species identification into question. However, once β-lactam exposure ceases, AmpC levels usually return to baseline. If mutations occur in genes that contribute to the regulation of *ampC* transcription, AmpC can become constitutively hyper-expressed.[6,26] Such AmpC hyper-producers (sometimes termed "de-repressed mutants") demonstrate additional resistance to third-generation cephalosporins, cephamycins (e.g., cefoxitin), new anti-staphylococcal cephalosporins such as ceftaroline,[9] anti-pseudomonal penicillins (such as piperacillin and ticarcillin), and their β-lactamase inhibitor combinations.[6,27] These variants occur spontaneously at a frequency of $\sim 10^{-6}$ to 10^{-8} of the bacterial

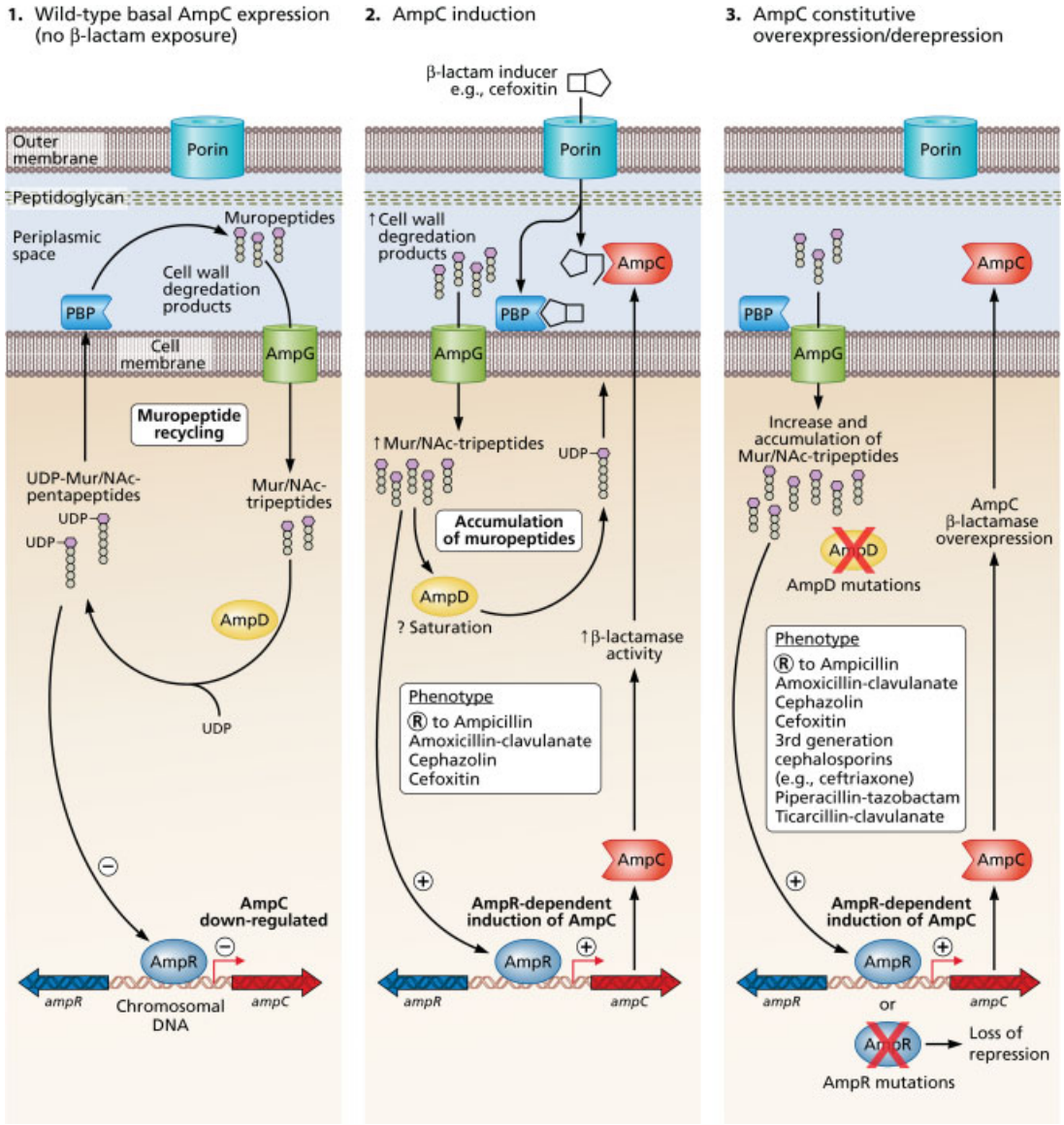

Fig. 2 Resistance mediated by inducible AmpC and AmpC overexpression. (**1**) In the absence of inducing β-lactams, basal AmpC levels are low. Normal peptidoglycan recycling involves the transport of muropeptides across the inner cell membrane by AmpG permease, following which, 1,6-anhydro-MurNAc-tripeptides or pentapeptide species are formed, with levels regulated by AmpD, and recycled to form UDP-MurNAc-pentapeptide which is incorporated back into the cell wall. UDP-MurNAc-pentapeptides bind to the AmpR regulatory unit which, under these conditions, predominates and is inhibitory to the expression of the *ampC* gene. (**2**) Under the influence of a strongly inducing β-lactam, cytosolic levels of 1,6-anhydro-MurNAc-tripeptides or pentapeptides increase; under such conditions, UDP-MurNAc-pentapeptides are displaced from AmpR causing promotion of *ampC* expression; phenotypic resistance to strong inducers that remain labile to AmpC is seen but weak inducers or inducers that are stable to AmpC remain effective. (**3**) Spontaneous mutations in regulatory elements (such as AmpD) occur at a rate of 1 in 10^6 to 10^8 cells and may be selected during antibiotic therapy. Under such circumstances, 1,6-anhydro-MurNAc-peptides accumulate in the cytoplasm resulting in AmpR-mediated overexpression of AmpC; mutations in AmpR may also cause a similar phenotype. Such AmpC hyperproduction can occur in the absence of an inducing agent and mediates resistance to many β-lactams. Please note, this diagram has been simplified for clarity—more detail can be found elsewhere.[17,24,221,222]

population[23] and may be selected rapidly following β-lactam therapy and predispose to clinical failure.[27]

Plasmid-Mediated AmpC

While AmpC is usually chromosomally encoded, we now increasingly see *ampC* genes mobilized on plasmids, which can easily transfer between species. The first transmissible cephamycinase (CMY-1) was identified in a *K. pneumoniae* isolate from a patient in South Korea in 1989.[28] Plasmid-mediated AmpC is now becoming increasingly common as a cause of resistance in *Klebsiella* and *E. coli*.[29–32] Such isolates can be identified from nosocomial, community onset, and healthcare-associated infections and may be associated with high mortality.[33] Like ESBL producers, isolates with plasmid AmpC may also frequently be resistant to other agents such as quinolones or trimethoprim–sulphamethoxazole.[34] In the laboratory, they can give a phenotype similar to an ESBL producer (with resistance to third-generation cephalosporins) but fail to demonstrate synergy with clavulanate (the standard test to phenotypically confirm an ESBL) and

also show resistance to cefoxitin.[31] However, other mechanisms (such as outer membrane protein permeability changes) may confer cefoxitin resistance.[35] Several inhibitors have been proposed to help confirm AmpC production (such as boronic acid[36] or cloxacillin[31]), but the sensitivity and specificity of such tests have been variable and are not routinely used. This can cause substantial difficulty for the clinical microbiologist in knowing which agents to recommend to clinicians for isolates with resistance to key β-lactams, such as third-generation cephalosporins, without immediately defaulting to carbapenems (given the implications for antimicrobial stewardship). Furthermore, plasmid-mediated AmpC can coexist with ESBL enzymes in the same host, making phenotypic interpretation even less reliable.[29]

Plasmid AmpC genes are usually noninducible, as they lack the genetic apparatus to regulate expression, but there have been reports of plasmid-mediated inducible AmpC spreading into new hosts[37]—raising the alarming prospect of making it impossible to predict emergent AmpC-mediated resistance by species identification alone. Furthermore, there have been increasing reports of extended-spectrum AmpC β-lactamases, which have developed the ability to inactivate cefepime.[38]

Current Epidemiology

The incidence of infection or colonization with ESBL-producing organisms has dramatically increased in recent years.[39] A recent WHO report on Antimicrobial Resistance Surveillance reported high levels of resistance to third-generation cephalosporins; rates >50% for *E. coli* were reported from at least one country in five of six regions and in six of six regions for *K. pneumoniae*.[40] In some areas, ESBL-positive strains have not simply replaced wild-type ESBL-negative strains, but have added to the overall burden of *E. coli* infection.[41] There is significant geographical variation in the burden of ESBL-producing Enterobacteriaceae across the world, although limited data prevent forming an accurate and comprehensive assessment, a key weakness identified by the WHO.[40] The Centers for Disease Control and Prevention have estimated that 23% of *K. pneumoniae* and 14% of *E. coli* are ESBL producers and have been associated with 26,000 infections and 1,700 deaths annually in the United States.[42] In Australia, rates of resistance are relatively low; a national survey in 2012 suggested that 4.2% of community *E. coli* isolates were resistant to third-generation cephalosporins, but prevalence is increasing.[43] A recent review of published literature reported the rate of *E. coli* non-susceptibility to third-generation cephalosporins in Latin America to range between 11 to 25% and 45 to 52% for *K. pneumoniae*.[44] The Study for Monitoring Antimicrobial Resistance Trends (SMART) has tracked the susceptibility patterns of gram-negative bacteria identified from intra-abdominal infections since 2002. Of >1,700 isolates from patients with appendicitis in 39 countries from 2008 to 2010, the rates of ESBL positivity were highest for countries in the Asia-Pacific region (but excluding India) at 28%, lowest in Europe (4.4%) compared with a global average of 16.3%.[45] In a study of >3,000 *E. coli* isolated from intra-abdominal infections across Europe from 2008 to 2009, 11% were found to be ESBL producers.[46] ESBL rates as high as 67.1% in *E. coli* have been reported from the SMART program in India.[47]

Although a large number of acquired genes can confer antibiotic resistance in gram-negative bacteria, only a relatively small number of these tend to dominate. Across the Asian-Pacific region and the United States, *E. coli* or *Klebsiella* spp. with resistance to third-generation cephalosporins have most frequently acquired $bla_{\text{CTX-M}}$ type ESBLs.[48,49] A highly successful pathogenic clone of *E. coli*, known as sequence type 131 (ST131), which also frequently harbors CTX-M–type ESBL,[50,51] has rapidly disseminated globally following a relatively recent evolutionary divergence and demonstrates numerous adaptive responses (including point mutations, recombination events, and acquisition of mobile genetic elements) that have contributed to its prevalence.[52]

E. coli containing ESBLs, particularly CTX-M types, have been increasingly seen from community isolates.[39,53–56] Residency of a long-term care facility has been recognized as a key risk factor for community acquisition of ESBL producers.[57,58] In low-prevalence countries, such as Australia, travel to a region with high endemicity for resistance, especially with healthcare exposure, has emerged as a key risk factor for subsequent infection with an ESBL producer.[59] Travel to India has been associated with a high prevalence of colonization; 37.4% of returned travelers in Spain presenting with diarrhea symptoms tested positive for ESBL-producing *E. coli*.[60] Gut colonization with CTX-M–producing *E. coli* was seen in 6% of >3,000 individuals tested from the community in Germany, highlighting the reservoir of resistance that may exist in the population.[61] Following infection, fecal carriage of ESBL-producing *E. coli* can frequently persist for up to 12 months,[62] with a median duration of 6.6 months in one study.[63] The risk for subsequent infection with an expanded-spectrum cephalosporin-resistant *E. coli* appears to be significantly increased for up to 6 months following exposure.[59]

Clinical Risk Factors and Outcomes

Several studies have attempted to define risk factors for infection with ESBL or AmpC producers, primarily to aid selection of appropriate empirical therapy. Prior antibiotic use has emerged as a key influence upon the risk for infection by an ESBL producer. An international multicenter prospective observational study examined 455 consecutive bacteremia events caused by *K. pneumoniae*, 18.7% of which were ESBL producers.[64] Prior use of a β-lactam containing an oxyimino group (particularly third-generation cephalosporins), even after adjusting for confounders, was associated with bacteremia caused by an ESBL-producing *K. pneumoniae* (relative risk (RR), 3.9; 95% confidence interval [CI], 1.1–13.8).[64] It is worth noting that the great majority (96.5%) of infections by ESBL-producing *Klebsiella* were nosocomially acquired in this study, contrasting the current increasing incidence of community-acquired ESBL-producing *E. coli*.[65,66]

Kang et al examined factors associated with bacteremia caused by ESBL-producing *K. pneumoniae*; risks included the

presence of a catheter, a recent invasive procedure, or broad-spectrum antibiotic use.[67] Similar findings were reported by Tumbarello et al, where prior antibiotic use, increasing age, and length of hospitalization were risk factors for bloodstream infection with ESBL-producing *K. pneumoniae*.[68] In a Korean study, by examining risk factors for community-acquired ESBL *E. coli* bacteremia, a decision-tree analysis suggested that empirical coverage for ESBL producers should be used in patients with septic shock, hepatobiliary infection, and healthcare-associated infections.[69] Among ICU patients, risk of subsequent infection in patients with prior colonization with ESBL-producing Enterobacteriaceae was associated with referral from a medical ward, nursing home, or rehabilitation center; fluoroquinolone use; and the use of extracorporeal membrane oxygenation.[70] Prior use of third-generation cephalosporins appears to be a consistent risk factor for subsequent infection by an ESBL producer.[66,71,72] There is equal risk with other antibiotic exposures, including carbapenems,[73] β-lactam/β-lactamase inhibitors (BLBLIs) and quinolones.[74,75] Risk-prediction models have been developed and can prove useful in predicting community-onset ESBL infections, especially when combined with local epidemiology.[76] However, such scoring systems require careful validation, as their performance can vary between hospital locations.[77]

Infections caused by ESBL producers have had a significant clinical impact and may be associated with adverse outcomes such as increased mortality,[72,78,79] length of hospital stay,[66,80–83] and healthcare-related costs,[81,83] particularly when associated with inadequate initial antimicrobial therapy.[84]

Treatment

There is a significant evidence gap between our understanding of basic biology of ESBL- and AmpC-producing bacteria and the clinical application of this information. Despite many hundreds of studies reporting on resistant gram negatives, the majority of studies focus on laboratory, epidemiological, or infection-control aspects of these bacteria—only a handful provide reliable insight into optimal therapy. There have been several notable but relatively small observational studies reporting treatment outcomes for ESBL or AmpC producers. While these have been invaluable to our limited evidence-base, we have been lacking adequately powered, well-designed, international prospective studies in this area. Particularly, there has never been a randomized controlled trial reported that specifically addresses these questions, which is unfortunate given the significance and scale of the problem, but not a surprise given the realities of clinical research.

It would seem intuitive that selecting appropriate initial empirical therapy is important in patients with bacteremia, and becomes increasingly difficult when the incidence of resistance is high. Choosing inappropriate empirical antibiotic therapy for bacteremia caused by ESBL-producing *E. coli* or *Klebsiella* has been associated with increased mortality in some studies,[85] especially in nonurinary infections or with multidrug resistant isolates.[86] However, this has not been a universal finding, with several studies showing no significant impact of inappropriate empirical therapy on mortality.[67,87–91] A meta-analysis of 16 studies suggested increased mortality in bacteremia caused by ESBL producers (RR, 1.85; 95% CI, 1.39–2.47), which increased with delayed therapy (RR, 5.56; 95% CI, 2.9–10.5), although only 1 study controlled for confounders.[92]

Expanded-Spectrum Cephalosporins for ESBL and AmpC Producers

Soon after the recognition of ESBLs emerging as a concern, clinical failures in patients treated with third-generation cephalosporins for infections caused by ESBL producers were reported, even when breakpoints used at that time suggested susceptibility.[93,94] This phenomenon was also supported by animal studies.[95] Observational studies suggested that treatment with cephalosporins of bloodstream infection caused by ESBL producers was associated with poorer outcome when compared with non-ESBL strains in children[72] and adults.[96] Empirical therapy with ceftriaxone in patients with pyelonephritis, found subsequently to be caused by ESBL-producing *E. coli*, was associated with delayed resolution of symptoms, less likelihood of microbiological resolution at 5 days and longer hospital admissions.[82]

Given the concern that bacteria could harbor ESBLs that would not be detected by the higher breakpoints for cephalosporins used at the time, the use of third-generation cephalosporins for ESBL producers (even if susceptible) was discouraged. Regulatory authorities issued guidance that laboratories should report all ESBL-containing *E. coli* and *Klebsiella* spp. as resistant to all penicillins, all cephalosporins, and aztreonam, regardless of susceptibility results.[97] Although less supported by evidence, most laboratories extended such guidance to include all other non-carbapenem β-lactams, including inhibitor combination agents. Although this was an understandable response to the challenges faced at the time, it had the unintended consequence of directing clinicians to use carbapenems increasingly frequently for ESBL-related infections, even in relatively uncomplicated disease like cystitis.

In recent years, the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) have lowered the susceptibility breakpoints for third- and fourth-generation cephalosporins against Enterobacteriaceae, without the need for additional testing. For ESBL production, unless for infection control or surveillance purposes.[98,99] This still begs the question of whether any known ESBL producer which tests susceptible to an agent, against which the enzyme has potential activity, can be safely used clinically. For instance, CTX-M producers may retain susceptibility to ceftazidime; yet whether this would be safe drug to use for a serious infection remains unclear, largely due to the presence of pronounced inoculum effects and limited clinical data.[100] In theory (at least), given the revised standards, susceptibility should be read as reported and therapeutic options provided as such.[101] In this way, the current guidance has the implicit message that clinicians should worry less about the

underlying resistance mechanism when selecting therapy. However, there remains concern that drugs that may act as substrates for ESBLs should still be avoided for therapy, even if susceptibility is demonstrated.[102]

Emergent resistance during therapy with third-generation cephalosporins for AmpC-producing Enterobacteriaceae has been a major concern. A key study from 1991 by Chow et al reported outcomes for patients with bloodstream infections caused by *Enterobacter* spp. In those treated with a third-generation cephalosporin, 19% experienced relapsed bacteremia and resistance mediated by high level of AmpC, despite initial susceptibility.[103] This phenomenon has been replicated in larger cohorts, although a lower risk of clinical failure has been reported with other AmpC-producing species.[104,105] When emergent resistance occurs, it has been associated with higher mortality and healthcare-associated costs.[106] As a result, the use of third-generation cephalosporins for the treatment of significant infections caused by AmpC producers such as *Enterobacter* spp. has been strongly discouraged, except perhaps in simple infections (such as uncomplicated urinary tract infection [UTI]), where a rapid bactericidal effect can be achieved before selection for hyper-producing mutants can occur.[107] Poor outcomes have also been reported for plasmid AmpC-producing *K. pneumoniae* treated with third-generation cephalosporins; although such studies often are small, retrospective and report mortality rates unadjusted for comorbidity.[108]

Cefepime for AmpC and ESBL Producers

Cefepime is the only expanded spectrum cephalosporin with stability to AmpC β-lactamase and retains in vitro activity to species such as *E. cloacae*, including constitutively AmpC derepressed strains.[109] Recent retrospective studies would suggest that cefepime is effective for infections caused by AmpC-producing Enterobacteriaceae. Comparing patients paired by propensity score matching given either meropenem or cefepime, there were no differences in 30-day mortality (odds ratio [OR], 0.63; 95% CI, 0.23–2.11) or length of hospital stay (RR, 0.96; 95% CI, 0.79–1.26), although this study included only 64 patients.[110] In a large series of over 300 patients with *Enterobacter* bacteremia, mortality was similar for patients treated with meropenem or cefepime after adjustment for comorbidity and propensity score matching.[111]

However, the picture is complicated by the fact that *Enterobacter*, *Citrobacter*, and *Serratia* spp. can frequently acquire additional ESBLs,[112] to which cefepime is not stable, thus elevating minimum inhibitory concentrations (MICs).[113] Clinical failures from isolates with MICs at or above the previous CLSI breakpoint of 8μg/mL treated with cefepime have been shown to be associated with an increased risk of mortality, especially with a dosing regimen of 1 g 12 hourly.[114] ESBLs expressed in AmpC producers may be difficult to reliably detect and discriminate from chromosomal AmpC with routine laboratory methods. Cefepime may also be subject to significant inoculum effects with ESBL producers.[115] Eightfold or greater increases in MIC values were observed with several cephalosporins, including cefepime, when tested against a variety of Enterobacteriaceae at inocula 100-fold higher than standard—a phenomenon not seen with carbapenems.[116] Similarly, cefepime was prone to significant inoculum effects when tested against *K. pneumoniae* containing plasmid-mediated AmpC β-lactamase.[117] Resistance to cefepime in *Enterobacter* has also been described to develop by the overexpression of an altered AmpC enzyme or porin mutations.[118]

Treatment of ESBL-producing *Klebsiella* or *E. coli* with cefepime is controversial. Cefepime, like other cephalosporins, demonstrates marked inoculum effects in vitro when tested against ESBL producers.[100] Some small case series have reported a role for cefepime, although clinical failures were observed.[119] In a retrospective study that compared cefepime to a carbapenem for the treatment of bacteremia caused by susceptible ESBL producers, cefepime was independently associated with an increased 30-day mortality on multivariate analysis (OR, 9.9; 95% CI, 2.8–31.9).[120] A nonsignificant trend toward increased mortality was also seen for cefepime when used as empirical therapy for bacteremia caused by ESBL producers (OR, 1.66; 95% CI, 0.71–3.87).[121]

It has been suggested that standard dosing of cefepime should be effective for ESBL producers that demonstrate an MIC for cefepime of $\leq$2 mg/L (CLSI) or $\leq$1 mg/L (EUCAST), but higher or more frequent dosing would be required for an MIC between 4 and 8 mg/L.[122] It should be noted that the method of susceptibility testing for cefepime against ESBL producers may provide variable results; lack of concordance between gold standard agar dilution and Vitek2 microbroth dilution methods have been reported and could lead to major interpretative errors, especially when lowered breakpoints are used.[123]

Cephamycins

Although rarely used in many countries, cephamycins (such as cefoxitin, flomoxef, and cefmetazole) remain stable to hydrolysis by ESBLs, but are susceptible to AmpC enzymes. Cefoxitin was effective in a murine model of UTI caused by CTX-M-15–producing *E. coli*, when compared with a carbapenem.[124] A small study from Japan compared cefmetazole to meropenem for the treatment UTI caused by ESBL-producing Enterobacteriaceae and showed no differences in clinical or microbiological cure rates or adverse events.[125] However, for dialysis patients with ESBL *K. pneumoniae* bacteremia and high acuity of illness, use of flomoxef was independently associated with mortality (OR, 3.52; 95% CI, 1.19–58.17).[126]

Carbapenems

Carbapenems have long been considered the first-line treatment option for significant infections caused by ESBL or AmpC producers. Carbapenems are generally stable to hydrolysis by ESBLs or AmpC. They are less affected by inoculum effects in vitro[117] and in animal models.[95] They demonstrate excellent pharmacodynamic exposure in vitro. Monte Carlo simulation of carbapenems against 133 ESBL-producing isolates showed that the bactericidal cumulative fraction of response (defined as $\geq$40% of the proportion of the dosing interval for which free drug levels were above the MIC) was

achieved for 96.3% of isolates against ertapenem and >99% for imipenem and meropenem.[127]

Several observational studies have demonstrated that carbapenems are associated with improved outcome when compared with cephalosporins or other alternatives for bloodstream infections caused by ESBL producers.[71,90,128–131] However, superiority has never been demonstrated in a randomized trial.

Ertapenem, a carbapenem lacking activity against *Pseudomonas*, has been increasingly used for directed therapy against ESBL and AmpC producers. Testing both ertapenem and meropenem against ESBL-producing *E. coli* or *Klebsiella* with a range of MICs in an animal model showed that both drugs had similar efficacy when MICs were low, but meropenem had greater efficacy against isolates with ertapenem MICs $\geq$ 2 μg/mL.[132] Ertapenem achieved clinical success in 80% of patients with ventilator-associated pneumonia caused by ESBL producers, although this study only enrolled 20 patients and lacked any control group.[133] Similarly, a clinical success rate of 78% and microbiological cure rate of 92% were seen in a series of patients treated with ertapenem for a variety of infections caused by ESBL producers, although this study also had only 50 evaluable patients and no comparison group.[134] Favorable clinical response rates of up to 96% have been reported in its use against ESBL bacteremia.[135] When ertapenem was compared with carbapenems (such as meropenem) for the treatment of bacteremia caused by ESBL-producing Enterobacteriaceae in a cohort of 261 patients, no difference in mortality was seen even after controlling for the propensity to receive ertapenem (OR, 0.50; 95% CI, 0.12–2.1).[129] Other studies of ESBL bacteremia have also shown an equivalent mortality between ertapenem and other carbapenems.[136]

Although most studies have concentrated on *Klebsiella* and *E. coli*, being the most common ESBL producers, some studies have examined treatment options for other ESBL-producing species. Huang et al[137] assessed the 14-day survival of 54 adult patients with bacteremia caused by ESBL producers other than *E. coli* or *Klebsiella* spp. (including intrinsic AmpC producers such as *E. cloacae* or *C. freundii*) and compared carbapenem to noncarbapenem therapy. Although improved survival (90.9%, 20/22) was seen with carbapenems compared with noncarbapenems (71.9%, 23/32), with ciprofloxacin as the main alternative choice, this difference was not statistically significant.[127] As with many small retrospective cohorts, such studies may be underpowered to detect true differences in treatment regimens.

The treatment options for inducible AmpC-producing Enterobacteriaceae that also express ESBLs are limited. Among 31 patients with ESBL-producing *E. cloacae*, all (8/8) patients who received a carbapenem survived, whereas 38.9% died when given a noncarbapenem ($p = 0.06$).[138] In a study that compared patients treated for bacteremia caused by ceftriaxone nonsusceptible *E. cloacae*, with or without ESBL production, carbapenems were associated with lower mortality in the ESBL group when compared with those treated by noncarbapenem β-lactam (5/53, 9.4% vs. 13/44, 29.5%; $p = 0.01$), although the difference was not significant in a multivariate analysis; breakthrough bacteremia was more common in the noncarbapenem β-lactam group (18/31, 58% vs. 3/31, 9.6%; $p < 0.001$).[139]

However, emergent carbapenem resistance has been described during carbapenem therapy, leading to clinical failure. In a patient with pneumonia caused by a CTX-M–producing *K. pneumoniae* treated with ertapenem, carbapenem resistance developed via the loss of a porin.[140] Carbapenem resistance in Enterobacteriaceae may occur either by the acquisition of a carbapenemase, hyperproduction of AmpC, or an ESBL combined with porin mutations or via efflux pumps.[118,141–143] Resistance to ertapenem has also been described by chromosomal AmpC mutations that allow carbapenemase activity,[144] especially when combined with loss of outer membrane proteins.[145]

β-Lactam/β-Lactamase Inhibitor Combinations

By definition, ESBLs (Ambler class A enzymes) are inhibited by clavulanate and tazobactam. Indeed, phenotypic confirmation of an ESBL in *E. coli*, *Klebsiella* spp., and *Proteus mirabilis* relies upon this phenomenon.[98,146] These inhibitors act as suicide substrates by irreversibly binding to β-lactamase enzymes.[147] Despite this inhibition, the currently available BLBLI agents (such as amoxicillin–clavulanate, piperacillin–tazobactam, ampicillin–sulbactam, cefoperazone–sulbactam, and ticarcillin–clavulanate) have generally been avoided for infections caused by ESBL producers in favor of carabapenems.[148]

In general, piperacillin–tazobactam has retained good in vitro activity against ESBL producers, especially for *E. coli*, although *K. pneumoniae* are often less susceptible.[149,150] MICs for BLBLIs tested against ESBL producers may tend to cluster around susceptibility breakpoints, so a single dilution change (within the margin of error) can alter the categorization. BLBLIs, especially piperacillin–tazobactam, may also be subject to significant inoculum effects in vitro.[100,115] Although piperacillin–tazobactam exhibits significant MIC elevations against ESBL producers tested using a high inoculum, this phenomenon is less marked than that observed with expanded-spectrum cephalopsorins.[116] Inoculum effects are not universal to all BLBLIs. In time-kill studies of amoxicillin–clavulanate, bactericidal killing of ESBL-producing *E. coli* was maintained over 24 hours in the presence of a high inoculum, in contrast to piperacillin–tazobactam.[151] However, an inoculum effect was also seen for piperacillin–tazobactam against non-ESBL strains, which suggests that the effect is more likely a property of the drug rather than related to β-lactamase activity alone. The significance of the inoculum effect has been debated and has been argued to represent a laboratory phenomenon of limited clinical significance.[152] However, some animal models appear to reproduce the effect.[153] In a murine model of pneumonia caused by ESBL-producing *K. pneumoniae* at higher inoculum, 100% of mice died with piperacillin–tazobactam treatment, in contrast to 100% survival with meropenem.[154] However, in animal models at standard inocula, piperacillin–tazobactam appeared to be efficacious against ESBL-producing *K. pneumoniae*, whereas ceftazidime was not; although imipenem was the most effective agent.[155]

Another theoretical concern relating to the use of BLBLIs for ESBL producers is the co-location of other β-lactamase types on acquired plasmids, some of which may be poorly inhibited (such as plasmid AmpC or OXA-1). Bacteria may overexpress other non-ESBL "parent" enzymes that can overcome β-lactamase activity.[156,157] Resistance may also occur by the development of inhibitor-resistant enzymes, porin mutations, or efflux pumps.[158] It should be noted that BLBLIs have been used for many years against isolates with narrow spectrum β-lactamases, even in critical infections, without clear concerns over loss of efficacy.

However, there were early reports of clinical failure with piperacillin–tazobactam against ESBL producers.[159,160] There were concerns over the reliability of tazobactam to inhibit some ESBL variants or if expression occurs at high levels[156,161] and limited experience with the use of BLBLIs for this indication. As a result, a view was formed that these agents could not be relied upon.[148]

In recent years, clinical evidence has accumulated that may support the use of BLBLIs in the treatment of infections caused by ESBL producers. Piperacillin–tazobactam was effective in treating a small series of patients with UTI caused by ESBL producers, as well as 90% of infections from other sites, provided the MIC was $\leq$16 μg/mL.[162] In a small study from Thailand, a predictor of mortality in patients with bloodstream infection caused by ESBL-producing *E. coli* or *Klebsiella* was failure to receive either a carbapenem or BLBLI for empirical therapy (93 vs. 43%; $p = 0.002$), although all patients switched to carbapenem therapy once susceptibility was determined.[163] After adjustment for confounders, no association between empirical use of piperacillin–tazobactam and increased mortality was found in a study of 114 patients from Korea with bacteremia caused by ESBL-producing *E. coli* or *K. pneumoniae* (OR, 0.55; 95% CI, 0.16–1.88).[164] In a large study of 387 ESBL *E. coli* bacteremia cases, piperacillin–tazobactam was associated with lower mortality when compared with carbapenems, provided treatment was adequate.[165]

Much of the current evidence to support the use of BLBLIs has been derived form a large Spanish cohort of patients with bacteremia caused by ESBL-producing *E. coli*. A post hoc analysis of six prospective studies compared BLBLI treatment with carbapenems and found no differences in mortality for empirical (hazard ratio [HR], 1.14; 95% CI, 0.29–4.40) or definitive therapy (HR, 0.76; 95% CI, 0.28–2.07).[166] However, for nonurinary infection, an MIC $\leq$2 mg/L to piperacillin–tazobactam appears to be predictive of better outcome.[167] A larger international observational study, including 656 patients, has recently been reported and also suggests noninferiority for BLBLIs used for ESBL bloodstream infection in comparison to carbapenems, with an adjusted HR for 30-day mortality of 0.97 (95% CI, 0.48–2.03).[168]

Optimized dosing of piperacillin–tazobactam to reach therapeutic drug targets may be necessary in critically ill patients,[169] who frequently demonstrate altered pharmacokinetics through variations in key variables such as renal clearance, increased capillary permeability, hypoalbuminemia and increased volumes of distribution.[170] Continuous infusions of β-lactams may improve outcomes in critically ill patients.[171]

BLBLIs such as piperacillin–tazobactam may offer a carbapenem-sparing "step-down" option once susceptibility is proven—especially if the MIC is low and the burden of infection has been reduced.[150] This seems most reliable for urinary infections. However, further evidence is required to allow confidence in efficacy for a wider set of clinical circumstances. An international randomized-controlled trial registered with www.clinicaltrials.gov that compares piperacillin–tazobactam with meropenem for the definitive treatment of bloodstream infections caused by ceftriaxone nonsusceptible *E. coli* or *Klebsiella* spp. is currently recruiting (Trial registration number NCT02176122).

BLBLIs for AmpC Producers

AmpC enzymes are generally poorly inhibited by clavulanate or tazobactam, although the concentration of tazobactam needed to inhibit AmpC β-lactamase is much lower than for clavulanate.[172] Clavulanate is a powerful inducer of AmpC and poorly inhibits its activity, and so may antagonize the activity of ticarcillin when used in combination against isolates with inducible β-lactamase.[147] Conversely, tazobactam is much less potent inducer of AmpC.[147] However, once again, the clinical efficacy of drugs such as piperacillin–tazobactam against AmpC producers is controversial. Isolates with derepressed AmpC frequently demonstrate high MIC values to piperacillin–tazobactam. It is a curiosity that the AmpC enzyme produced by *M. morganii* is well inhibited by tazobactam, even when highly expressed.[173,174] However, no clinical studies exist to corroborate efficacy in significant *M. morganii* infections.

Clinical studies to assess the efficacy of piperacillin–tazobactam in serious infections caused by AmpC producers are limited. Many laboratories do not report piperacillin–tazobactam susceptibility results for AmpC producers such as *Enterobacter* spp., over concerns of clinical failure and emergent resistance. This practice is somewhat extrapolated from the poor outcomes seen with third-generation cephalosporins.[103] However, piperacillin–tazobactam was not associated with the emergence of cephalosporin resistance in the treatment of *Enterobacter* bacteremia (RR, 1.1; 95% CI, 0.4–2.7) in contrast to third-generation cephalosporins (RR, 3.3; 95% CI, 1.8–6.0).[104] In another study that examined 377 *Enterobacter* bacteremia events in adults, the only factor independently associated with a reduction in 30-day mortality was the early use of piperacillin–tazobactam.[175] However, piperacillin–tazobactam use may still cause selection pressure for isolates with derepressed AmpC. The risk of isolating a resistant *Enterobacter* following piperacillin–tazobactam or broad-spectrum cephalosporin was equal in one study (2% in both groups, RR = 1.02; $p = 0.95$).[176]

Fosfomycin

Fosfomycin has been used for many years in some countries as a single-dose treatment for uncomplicated UTIs caused by *E. coli*. It has a bactericidal effect by inhibiting cell wall

synthesis.[177] There has been renewed interest in its use against urinary infections caused by ESBL- or plasmid AmpC-producing *E. coli* or *K. pneumoniae*, as it demonstrates excellent in vitro activity against such strains.[177–183] Although only a handful of clinical studies have examined fosfomycin for the treatment of UTI caused by ESBL-producing *E. coli*, clinical response rates of >78% have been reported.[184] In a prospective observational study from Turkey, oral fosfomycin (given alternate days for 3 doses) was compared with carbapenems (given for 14 days) for ESBL *E. coli* causing lower UTIs in 47 patients, with complicating factors such as catheterization or urological surgery, but no signs of pyelonephritis.[185] Clinical and microbiological success rates were similar in both the fosfomycin and carbapenem groups, with significant cost savings seen and no adverse effects reported in those given fosfomycin.[185] It achieves high concentrations in prostate tissue and may be a useful prophylactic antibiotic before transrectal prostate biopsy or for treatment of prostatitis caused by resistant gram-negative bacteria.[186] Increased use of fosfomycin has been associated with a rising burden of resistance. In Spain, the incidence of fosfomycin resistance in ESBL-producing *E. coli* has increased from 0% in 2005 to 14.4% in 2011.[187] Rates of resistance remain low, but high-level resistance can occur via single-step mutations,[188] or may be acquired on plasmids.[189] It should be noted that studies of fosfomycin resistance require attention to the methods used. Resistance can be overestimated by disk diffusion or microbroth dilution susceptibility testing, when compared with a reference agar dilution.[178]

Data regarding the use of fosfomycin outside the urinary tract are sparse. In a murine model of ESBL-producing *E. coli* implant infections that compared combinations of fosfomycin, tigecycline, gentamicin, and colistin, fosfomycin was the only single agent able to eradicate biofilm in a small number of cases (17%) and, when combined with colistin, had the highest cure rate (8/12, 67%) and was superior to fosfomycin alone.[190] Intravenous formulations of fosfomycin are available in some countries. It has been used successfully as salvage therapy in combination with meropenem for refractory Lemierre syndrome, bacteremia and cerebral abscesses caused by ESBL-producing *K. pneumoniae*.[191] In a literature review of available evidence that examined 62 studies involving 1,604 patients with various infections treated with fosfomycin alone or in combination, an overall cure rate of 81.1% was reported.[192]

Tigecycline

Tigecycline, a first in class glycylcyline, has activity against most ESBL- and AmpC-producing Enterobacteriaceae.[193] It should be noted that tigecycline has limited penetration into the urinary tract and may not be effective at this location, although successful treatment has been reported.[194] It may also achieve poor serum levels because of a very large volume of distribution, which may limit effectiveness in bacteremia. Breakthrough infections have been reported.[195] However, it has been used successfully as salvage therapy for a complex infection caused by a carbapenem-resistant, ESBL-producing *K. pneumoniae*.[196] A recent meta-analysis has suggested excess mortality for tigecycline,[197] limiting enthusiasm for its use in serious infections when alternatives exist.

Mecillinam and Pivmecillinam

Mecillinam is an amidinopenicillin with a wide spectrum of gram-negative activity. There has been interest in its use against resistant Enterobacteriaceae since the 1970s.[198] It appears to act by binding penicillin-binding protein-2 to inhibit cell wall synthesis. However, given the poor oral bioavailability of this drug, the prodrug pivmecillinam has been developed and is approved for the use against uncomplicated UTIs. It is now included in the Infectious Disease Society of America (IDSA) guidelines for the treatment of cystitis, although there are concerns that it has inferior efficacy for pyelonephritis when compared with other agents.[199] However, (piv)mecillinam has the advantage of retaining activity against ESBL and plasmid AmpC-producing *E. coli*,[200,201] even if expressing multiple β-lactamase types.[202] In a series of 100 ESBL-producing *E. coli* isolated from patients with (predominantly community acquired) UTI, 85% demonstrated susceptibility to pivmecillinam.[183] Against *E. coli* strains that expressed various β-lactamase types, it showed excellent activity when compared with other penicillins against isolates that contained TEM, IRT, and AmpC producers.[203,204] The combination with clavulanate may also enhance its activity and mitigate against inoculum effects.[201] In a small study of patients with lower UTI caused by ESBL-producing *E. coli* or *K. pneumoniae*, patients treated with pivmecillinam achieved good clinical responses (8/8) but low (2/8) bacteriological cure rates (defined as $<10^3$ CFU/mL at 30-day follow-up). The drug is not approved for use in the United States and has not been widely used outside European countries, but deserves greater attention in an era of increasing community-acquired gram-negative resistance. It has also been suggested that, although resistance to pivmecillinam may develop by mutations in the genes affecting the bacterial elongation process, the risk for clonal spread is low and may be associated with limited epidemiological fitness.[205]

Temocillin

Temocillin is a carboxypenicillin derivative of ticarcillin, which has been modified to improve stability to AmpC and ESBL enzymes, although it has less activity against *Pseudomonas* spp., gram positives, and anaerobes. Having initially received little market interest, it was withdrawn from the United Kingdom, but continued to be used in Belgium for infections caused by resistant Enterobacteriaceae,[206] and it has now been relaunched.[207] It demonstrated in vitro efficacy against 88% of 846 isolates with ESBL or AmpC phenotypes or *K. oxytoca* K1 hyperproducers,[207] and >90% of multiresistant ESBL-producing *E. coli*.[206] However, temocillin efficacy may be affected by porin mutations and is not stable to OXA-48 and NDM-1 carbapenemases. It achieves excellent levels in the urine and may be a useful agent for infections at this site, although clinical data are limited. One study reported outcome for 92 adults treated with temocillin, mainly for urinary or bloodstream infections caused by ESBL or derepressed AmpC producers.[208] Good clinical (86%) and microbiological

(84%) cure rates were observed, especially when dosed at 2 g twice daily (clinical cure rate 97%, 36/37 patients with ESBLs or AmpC); a low risk of *C. difficile* (2%) also seems an advantage.[208] Further prospective studies of temocillin as a carbapenem-sparing option for ESBL or AmpC producers would be of interest, especially in nonurinary infections.

Nitrofurantoin

Although nitrofurantoin is only effective in the context of uncomplicated UTIs, a significant proportion of ESBL-producing *E. coli* retain susceptibility to this agent, especially when community acquired.[55,183,209] In a retrospective study of 75 patients treated with nitrofurantoin for uncomplicated UTI caused by ESBL-producing *E. coli*, clinical and microbiological success rates of 69 and 68%, respectively, were reported, although there was no control group.[210]

Other Agents

Although ESBL producers are frequently multidrug resistant, they may still demonstrate susceptibility to other standard antimicrobials such as trimethoprim–sulphamethoxazole, quinolones, or aminoglycosides (especially amikacin). Some of these agents have limitations in terms of toxicity (e.g., amikacin) and there are few published studies examining the clinical efficacy against ESBL producers, especially for critical infections. These may be reasonable alternatives for less complex infections, especially where oral options are limited. However, coresistance to agents such as quinolones is very common in ESBL producers.[56] Some studies have shown inferiority of quinolones in comparison to carbapenems, even when susceptible in vitro.[85,211] Although not widely used, sitafloxacin (a quinolone) showed excellent in vitro efficacy against ESBL-producing *E. coli* or *K. pneumoniae* from Japan, even when strains showed resistance to levofloxacin.[179]

New Agents in Development

Ceftolozane is a novel oxyimino-aminothiazole cephalosporin, which has additional activity against *P. aeruginosa* in comparison to ceftazidime or cefepime, but may be inactivated by ESBL or AmpC enzymes. However, in combination with tazobactam, it has demonstrated greater in vitro activity against almost 3,000 gram-negative isolates from U.S. and European patients with pneumonia, including ESBL- and AmpC-producing Enterobacteriaceae, when compared with current cephalosporins and piperacillin–tazobactam.[212] It even maintained reasonable activity against Enterobacteriaceae with multidrug or extensive drug-resistant phenotypes.[212] It is currently being evaluated in phase III trials in combination with tazobactam.[213]

There has been a renewed interest in developing novel β-lactamase inhibitor compounds.[214] One of the most promising is Avibactam, a new non-β-lactam inhibitor of β-lactamase that shows efficacy against class A, C, and some class D enzymes. Coformulations with ceftazidime, ceftaroline, and aztreonam are currently under investigation. It has been shown to retain its effect against extend-spectrum AmpC variants.[215] It also has limited ability to induce the expression of AmpC.[216] In vitro, when combined with ceftazidime, it showed broad-spectrum efficacy against a large series of clinical isolates from the United States.[217] Several trials are currently underway, including phase I, II, and III studies, for various combinations of avibactam with β-lactams or monobactams.[214]

Summary

Gram-negative bacteria that express ESBL or AmpC enzymes are an increasing problem. We lack high-quality evidence to definitively inform treatment decisions, but an increasing body of observational studies can provide some guidance. To date, no studies have demonstrated superiority of any agent over carbapenems to treat serious infections caused by ESBL or AmpC producers. However, overuse of carbapenems is likely to be driving increased selection pressure for carbapenem resistance—a new threat that is rapidly emerging on a global scale.[40,218–220] Carbapenem-sparing options should be increasingly considered in less critical infections and in targeted circumstances. BLBLIs such as piperacillin–tazobactam are probably effective treatment for ESBL producers when susceptibility is proven, especially in urinary or biliary tract infections or when the MIC is low. Efficacy in critical or complex infections remains uncertain—a proposed trial may go some way to answering this question. Amoxicillin–clavulanate is also likely to be a reasonable choice for urinary infections caused by susceptible ESBL producers. Although theoretical concerns have limited the use of piperacillin–tazobactam against AmpC producers, several observational studies have not indicated a strong signal for high failure rates. Cefepime is stable to AmpC derepressed isolates and some recent clinical studies suggest that it is effective against AmpC producers causing bacteremia, but efficacy against ESBL producers is unreliable. There also remains a reasonable selection of uncommon antibiotics to treat less critical infections, such as fosfomycin, pivmecillinam, or temocillin, but clinical experience is limited and some of these drugs are not widely available outside specific countries. Some novel BLBLI agents are in development, and we await larger clinical trials with interest.

Conflict of Interest
None.

References

1 Fevre C, Jbel M, Passet V, Weill FX, Grimont PA, Brisse S. Six groups of the OXY beta-Lactamase evolved over millions of years in Klebsiella oxytoca. Antimicrob Agents Chemother 2005;49(8): 3453–3462
2 Hall BG, Barlow M. Structure-based phylogenies of the serine beta-lactamases. J Mol Evol 2003;57(3):255–260
3 Hall BG, Salipante SJ, Barlow M. The metallo-beta-lactamases fall into two distinct phylogenetic groups. J Mol Evol 2003;57(3): 249–254
4 Bhullar K, Waglechner N, Pawlowski A, et al. Antibiotic resistance is prevalent in an isolated cave microbiome. PLoS ONE 2012;7(4): e34953

5 Abraham EP, Chain E. An enzyme from bacteria able to destroy penicillin. Nature 1940;146(3713):837
6 Jacoby GA. AmpC beta-lactamases. Clin Microbiol Rev 2009; 22(1):161–182
7 Bush K. Proliferation and significance of clinically relevant β-lactamases. Ann N Y Acad Sci 2013;1277:84–90
8 Knothe H, Shah P, Krcmery V, Antal M, Mitsuhashi S. Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of Klebsiella pneumoniae and Serratia marcescens. Infection 1983;11(6):315–317
9 Mushtaq S, Livermore DM. AmpC induction by ceftaroline. J Antimicrob Chemother 2010;65(3):586–588
10 Bush K, Jacoby GA, Medeiros AA. A functional classification scheme for beta-lactamases and its correlation with molecular structure. Antimicrob Agents Chemother 1995;39(6):1211–1233
11 Ambler RP. The structure of beta-lactamases. Philos Trans R Soc Lond B Biol Sci 1980;289(1036):321–331
12 Lee JH, Bae IK, Lee SH. New definitions of extended-spectrum β-lactamase conferring worldwide emerging antibiotic resistance. Med Res Rev 2012;32(1):216–232
13 Giske CG, Sundsfjord AS, Kahlmeter G, et al. Redefining extended-spectrum beta-lactamases: balancing science and clinical need. J Antimicrob Chemother 2009;63(1):1–4
14 Bush K, Jacoby GA, Amicosante G, et al. Comment on: Redefining extended-spectrum beta-lactamases: balancing science and clinical need. J Antimicrob Chemother 2009;64(1):212–213, author reply 213–215
15 Corvec S, Prodhomme A, Giraudeau C, Dauvergne S, Reynaud A, Caroff N. Most Escherichia coli strains overproducing chromosomal AmpC beta-lactamase belong to phylogenetic group A. J Antimicrob Chemother 2007;60(4):872–876
16 Jacobs C, Frère J-M, Normark S. Cytosolic intermediates for cell wall biosynthesis and degradation control inducible β-lactam resistance in gram-negative bacteria. Cell 1997;88(6): 823–832
17 Macdougall C. Beyond susceptible and resistant, Part I: Treatment of infections due to gram-negative organisms with inducible β-lactamases. J Pediatr Pharmacol Ther 2011;16(1):23–30
18 Harris PN, Ferguson JK. Antibiotic therapy for inducible AmpC β-lactamase-producing Gram-negative bacilli: what are the alternatives to carbapenems, quinolones and aminoglycosides? Int J Antimicrob Agents 2012;40(4):297–305
19 Livermore DM. beta-Lactamases in laboratory and clinical resistance. Clin Microbiol Rev 1995;8(4):557–584
20 Lodge JM, Minchin SD, Piddock LJ, Busby SJ. Cloning, sequencing and analysis of the structural gene and regulatory region of the Pseudomonas aeruginosa chromosomal ampC beta-lactamase. Biochem J 1990;272(3):627–631
21 Lindberg F, Normark S. Common mechanism of ampC beta-lactamase induction in enterobacteria: regulation of the cloned Enterobacter cloacae P99 beta-lactamase gene. J Bacteriol 1987; 169(2):758–763
22 Lindberg F, Westman L, Normark S. Regulatory components in Citrobacter freundii ampC beta-lactamase induction. Proc Natl Acad Sci U S A 1985;82(14):4620–4624
23 Korfmann G, Sanders CC. ampG is essential for high-level expression of AmpC beta-lactamase in Enterobacter cloacae. Antimicrob Agents Chemother 1989;33(11):1946–1951
24 Mark BL, Vocadlo DJ, Oliver A. Providing β-lactams a helping hand: targeting the AmpC β-lactamase induction pathway. Future Microbiol 2011;6(12):1415–1427
25 Johnson JW, Fisher JF, Mobashery S. Bacterial cell-wall recycling. Ann N Y Acad Sci 2013;1277(1):54–75
26 Kaneko K, Okamoto R, Nakano R, Kawakami S, Inoue M. Gene mutations responsible for overexpression of AmpC beta-lactamase in some clinical isolates of Enterobacter cloacae. J Clin Microbiol 2005;43(6):2955–2958
27 Sanders WE Jr, Sanders CC. Enterobacter spp.: pathogens poised to flourish at the turn of the century. Clin Microbiol Rev 1997; 10(2):220–241
28 Bauernfeind A, Chong Y, Schweighart S. Extended broad spectrum beta-lactamase in Klebsiella pneumoniae including resistance to cephamycins. Infection 1989;17(5):316–321
29 Alvarez M, Tran JH, Chow N, Jacoby GA. Epidemiology of conjugative plasmid-mediated AmpC beta-lactamases in the United States. Antimicrob Agents Chemother 2004;48(2):533–537
30 Sidjabat HE, Seah KY, Coleman L, et al. Expansive spread of IncI1 plasmids carrying blaCMY-2 amongst Escherichia coli. Int J Antimicrob Agents 2014;44(3):203–208
31 Reuland EA, Hays JP, de Jongh DM, et al. Detection and occurrence of plasmid-mediated AmpC in highly resistant gram-negative rods. PLoS ONE 2014;9(3):e91396
32 Freitas F, Machado E, Ribeiro TG, Novais Â, Peixe L. Long-term dissemination of acquired AmpC β-lactamases among Klebsiella spp. and Escherichia coli in Portuguese clinical settings. Eur J Clin Microbiol Infect Dis 2014;33(4):551–558
33 Rodríguez-Baño J, Miró E, Villar M, et al. Colonisation and infection due to Enterobacteriaceae producing plasmid-mediated AmpC β-lactamases. J Infect 2012;64(2):176–183
34 Gude MJ, Seral C, Sáenz Y, et al. Molecular epidemiology, resistance profiles and clinical features in clinical plasmid-mediated AmpC-producing Enterobacteriaceae. Int J Med Microbiol 2013; 303(8):553–557
35 Hanson ND. AmpC beta-lactamases: what do we need to know for the future? J Antimicrob Chemother 2003;52(1):2–4
36 Jeong SH, Song W, Park MJ, et al. Boronic acid disk tests for identification of extended-spectrum beta-lactamase production in clinical isolates of Enterobacteriaceae producing chromosomal AmpC beta-lactamases. Int J Antimicrob Agents 2008;31(5): 467–471
37 Miriagou V, Tzouvelekis LS, Villa L, et al. CMY-13, a novel inducible cephalosporinase encoded by an Escherichia coli plasmid. Antimicrob Agents Chemother 2004;48(8):3172–3174
38 Rodríguez-Martínez JM, Fernández-Echauri P, Fernández-Cuenca F, Diaz de Alba P, Briales A, Pascual A. Genetic characterization of an extended-spectrum AmpC cephalosporinase with hydrolysing activity against fourth-generation cephalosporins in a clinical isolate of Enterobacter aerogenes selected in vivo. J Antimicrob Chemother 2012;67(1):64–68
39 Denisuik AJ, Lagacé-Wiens PR, Pitout JD, et al; Canadian Antimicrobial Resistance Alliance. Molecular epidemiology of extended-spectrum β-lactamase-, AmpC β-lactamase- and carbapenemase-producing Escherichia coli and Klebsiella pneumoniae isolated from Canadian hospitals over a 5 year period: CANWARD 2007-11. J Antimicrob Chemother 2013;68(Suppl 1):i57–i65
40 World Health Organisation. Antimicrobial Resistance Global Report on Surveillance. Geneva: WHO; 2014
41 Ho PL, Chow KH, Lai EL, Lau EH, Cheng VC. Extended-spectrum-β-lactamase-positive Escherichia coli mainly adds to, rather than replaces, extended-spectrum-β-lactamase-negative E. coli in causing bacteraemia in Hong Kong, 2000-10. J Antimicrob Chemother 2012;67(3):778–780
42 Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States: U.S. Department of Health and Human Services; 2013
43 Turnidge J, Gottlieb T, Mitchell D, et al. Gram-Negative Survey 2012 Antimicrobial Susceptibility Report: Australian Group for Antimicrobial Resistance (AGAR); 2013
44 Guzmán-Blanco M, Labarca JA, Villegas MV, Gotuzzo E; Latin America Working Group on Bacterial Resistance. Extended spectrum β-lactamase producers among nosocomial Enterobacteriaceae in Latin America. Braz J Infect Dis 2014;18(4):421–433
45 Lob SH, Badal RE, Bouchillon SK, Hawser SP, Hackel MA, Hoban DJ. Epidemiology and susceptibility of Gram-negative appendicitis

pathogens: SMART 2008-2010. Surg Infect (Larchmt) 2013;14(2): 203–208
46 Hawser SP, Bouchillon SK, Lascols C, et al. Susceptibility of European Escherichia coli clinical isolates from intra-abdominal infections, extended-spectrum β-lactamase occurrence, resistance distribution, and molecular characterization of ertapenem-resistant isolates (SMART 2008-2009). Clin Microbiol Infect 2012;18(3):253–259
47 Chen YH, Hsueh PR, Badal RE, et al. Antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region according to currently established susceptibility interpretive criteria. J Infect 2011;62(4):280–291
48 Ginn AN, Wiklendt AM, Zong Z, et al. Prediction of major antibiotic resistance in Escherichia coli and Klebsiella pneumoniae in Singapore, USA and China using a limited set of gene targets. Int J Antimicrob Agents 2014;43(6):563–565
49 Sheng WH, Badal RE, Hsueh PR; SMART Program. Distribution of extended-spectrum β-lactamases, AmpC β-lactamases, and carbapenemases among Enterobacteriaceae isolates causing intra-abdominal infections in the Asia-Pacific region: results of the study for Monitoring Antimicrobial Resistance Trends (SMART). Antimicrob Agents Chemother 2013;57(7):2981–2988
50 Pitout JD. Infections with extended-spectrum beta-lactamase-producing enterobacteriaceae: changing epidemiology and drug treatment choices. Drugs 2010;70(3):313–333
51 Chen LF, Freeman JT, Nicholson B, et al. Widespread dissemination of CTX-M-15 genotype extended-spectrum-β-lactamase-producing enterobacteriaceae among patients presenting to community hospitals in the southeastern United States. Antimicrob Agents Chemother 2014;58(2):1200–1202
52 Petty NK, Ben Zakour NL, Stanton-Cook M, et al. Global dissemination of a multidrug resistant Escherichia coli clone. Proc Natl Acad Sci U S A 2014;111(15):5694–5699
53 Rodríguez-Baño J, Navarro MD, Romero L, et al. Bacteremia due to extended-spectrum beta -lactamase-producing Escherichia coli in the CTX-M era: a new clinical challenge. Clin Infect Dis 2006; 43(11):1407–1414
54 Doi Y, Adams J, O'Keefe A, Quereshi Z, Ewan L, Paterson DL. Community-acquired extended-spectrum beta-lactamase producers, United States. Emerg Infect Dis 2007;13(7):1121–1123
55 Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum β-lactamase-producing Escherichia coli infection in the United States. Clin Infect Dis 2013;56(5):641–648
56 Ben-Ami R, Rodríguez-Baño J, Arslan H, et al. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in nonhospitalized patients. Clin Infect Dis 2009;49(5):682–690
57 Ben-Ami R, Schwaber MJ, Navon-Venezia S, et al. Influx of extended-spectrum beta-lactamase-producing enterobacteriaceae into the hospital. Clin Infect Dis 2006;42(7):925–934
58 Stuart RL, Kotsanas D, Webb B, et al. Prevalence of antimicrobial-resistant organisms in residential aged care facilities. Med J Aust 2011;195(9):530–533
59 Rogers BA, Ingram PR, Runnegar N, et al; Australasian Society for Infectious Diseases Clinical Research Network. Community-onset Escherichia coli infection resistant to expanded-spectrum cephalosporins in low-prevalence countries. Antimicrob Agents Chemother 2014;58(4):2126–2134
60 Solé M, Pitart C, Oliveira I, et al. Extended spectrum β-lactamase-producing Escherichia coli faecal carriage in Spanish travellers returning from tropical and subtropical countries. Clin Microbiol Infect 2014
61 Valenza G, Nickel S, Pfeifer Y, et al. Extended-spectrum-β-lactamase-producing Escherichia coli as intestinal colonizers in the German community. Antimicrob Agents Chemother 2014;58(2): 1228–1230
62 Titelman E, Hasan CM, Iversen A, et al. Faecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae is common 12 months after infection and is related to strain factors. Clin Microbiol Infect 2014;20(8):O508–O515
63 Birgand G, Armand-Lefevre L, Lolom I, Ruppe E, Andremont A, Lucet JC. Duration of colonization by extended-spectrum β-lactamase-producing Enterobacteriaceae after hospital discharge. Am J Infect Control 2013;41(5):443–447
64 Paterson DL, Ko WC, Von Gottberg A, et al. International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial Infections. Ann Intern Med 2004;140(1):26–32
65 Rodríguez-Baño J, Navarro MD, Romero L, et al. Epidemiology and clinical features of infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in nonhospitalized patients. J Clin Microbiol 2004;42(3):1089–1094
66 Fan NC, Chen HH, Chen CL, et al. Rise of community-onset urinary tract infection caused by extended-spectrum β-lactamase-producing Escherichia coli in children. J Microbiol Immunol Infect 2014;47(5):399–405
67 Kang CI, Kim SH, Kim DM, et al. Risk factors for and clinical outcomes of bloodstream infections caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae. Infect Control Hosp Epidemiol 2004;25(10):860–867
68 Tumbarello M, Spanu T, Sanguinetti M, et al. Bloodstream infections caused by extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae: risk factors, molecular epidemiology, and clinical outcome. Antimicrob Agents Chemother 2006;50(2): 498–504
69 Park YS, Bae IK, Kim J, et al. Risk factors and molecular epidemiology of community-onset extended-spectrum β-lactamase-producing Escherichia coli bacteremia. Yonsei Med J 2014;55(2): 467–475
70 Vodovar D, Marcadé G, Rousseau H, et al. Predictive factors for extended-spectrum beta-lactamase producing Enterobacteriaceae causing infection among intensive care unit patients with prior colonization. Infection 2014;42(4):743–748
71 Du B, Long Y, Liu H, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bloodstream infection: risk factors and clinical outcome. Intensive Care Med 2002;28(12):1718–1723
72 Kim YK, Pai H, Lee HJ, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in children: epidemiology and clinical outcome. Antimicrob Agents Chemother 2002;46(5):1481–1491
73 Martínez JA, Aguilar J, Almela M, et al. Prior use of carbapenems may be a significant risk factor for extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella spp. in patients with bacteraemia. J Antimicrob Chemother 2006;58(5): 1082–1085
74 Freeman JT, McBride SJ, Nisbet MS, et al. Bloodstream infection with extended-spectrum beta-lactamase-producing Enterobacteriaceae at a tertiary care hospital in New Zealand: risk factors and outcomes. Int J Infect Dis 2012;16(5):e371–e374
75 Wener KM, Schechner V, Gold HS, Wright SB, Carmeli Y. Treatment with fluoroquinolones or with beta-lactam-beta-lactamase inhibitor combinations is a risk factor for isolation of extended-spectrum-beta-lactamase-producing Klebsiella species in hospitalized patients. Antimicrob Agents Chemother 2010;54(5): 2010–2016
76 Johnson SW, Anderson DJ, May DB, Drew RH. Utility of a clinical risk factor scoring model in predicting infection with extended-spectrum β-lactamase-producing enterobacteriaceae on hospital admission. Infect Control Hosp Epidemiol 2013;34(4):385–392
77 Slekovec C, Bertrand X, Leroy J, Faller JP, Talon D, Hocquet D. Identifying patients harboring extended-spectrum-β-lactamase-producing Enterobacteriaceae on hospital admission is not that

simple. Antimicrob Agents Chemother 2012;56(4):2218–2219, author reply 2220
78 Ha YE, Kang CI, Cha MK, et al. Epidemiology and clinical outcomes of bloodstream infections caused by extended-spectrum β-lactamase-producing Escherichia coli in patients with cancer. Int J Antimicrob Agents 2013;42(5):403–409
79 Kang CI, Chung DR, Ko KS, Peck KR, Song JH; Korean Network for Study of Infectious Diseases. Risk factors for infection and treatment outcome of extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae bacteremia in patients with hematologic malignancy. Ann Hematol 2012;91(1): 115–121
80 Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. Clin Infect Dis 2001;32(8):1162–1171
81 MacVane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum β-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. J Hosp Med 2014; 9(4):232–238
82 Lee S, Song Y, Cho SH, Kwon KT. Impact of extended-spectrum beta-lactamase on acute pyelonephritis treated with empirical ceftriaxone. Microb Drug Resist 2014;20(1):39–44
83 Stewardson A, Fankhauser C, De Angelis G, et al. Burden of bloodstream infection caused by extended-spectrum β-lactamase-producing enterobacteriaceae determined using multistate modeling at a Swiss University Hospital and a nationwide predictive model. Infect Control Hosp Epidemiol 2013;34(2):133–143
84 Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. Antimicrob Agents Chemother 2010;54(10): 4085–4091
85 Tumbarello M, Sanguinetti M, Montuori E, et al. Predictors of mortality in patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae: importance of inadequate initial antimicrobial treatment. Antimicrob Agents Chemother 2007;51(6):1987–1994
86 Hyle EP, Lipworth AD, Zaoutis TE, Nachamkin I, Bilker WB, Lautenbach E. Impact of inadequate initial antimicrobial therapy on mortality in infections due to extended-spectrum beta-lactamase-producing enterobacteriaceae: variability by site of infection. Arch Intern Med 2005;165(12):1375–1380
87 Apisarnthanarak A, Mundy LM. Prevalence, treatment, and outcome of infection due to extended-spectrum Beta-lactamase-producing microorganisms. Infect Control Hosp Epidemiol 2006; 27(3):326–327
88 To KK, Lo WU, Chan JF, Tse H, Cheng VC, Ho PL. Clinical outcome of extended-spectrum beta-lactamase-producing Escherichia coli bacteremia in an area with high endemicity. Int J Infect Dis 2013; 17(2):e120–e124
89 Frakking FN, Rottier WC, Dorigo-Zetsma JW, et al. Appropriateness of empirical treatment and outcome in bacteremia caused by extended-spectrum-β-lactamase-producing bacteria. Antimicrob Agents Chemother 2013;57(7):3092–3099
90 Wu UI, Chen WC, Yang CS, et al. Ertapenem in the treatment of bacteremia caused by extended-spectrum beta-lactamase-producing Escherichia coli: a propensity score analysis. Int J Infect Dis 2012;16(1):e47–e52
91 Chaubey VP, Pitout JD, Dalton B, et al. Clinical outcome of empiric antimicrobial therapy of bacteremia due to extended-spectrum beta-lactamase producing Escherichia coli and Klebsiella pneumoniae. BMC Res Notes 2010;3:116
92 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(5):913–920
93 Smith CE, Tillman BS, Howell AW, Longfield RN, Jorgensen JH. Failure of ceftazidime-amikacin therapy for bacteremia and meningitis due to Klebsiella pneumoniae producing an extended-spectrum beta-lactamase. Antimicrob Agents Chemother 1990;34(6):1290–1293
94 Karas JA, Pillay DG, Muckart D, Sturm AW. Treatment failure due to extended spectrum beta-lactamase. J Antimicrob Chemother 1996;37(1):203–204
95 Rice LB, Yao JD, Klimm K, Eliopoulos GM, Moellering RC Jr. Efficacy of different beta-lactams against an extended-spectrum beta-lactamase-producing Klebsiella pneumoniae strain in the rat intra-abdominal abscess model. Antimicrob Agents Chemother 1991;35(6):1243–1244
96 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(6):2206–2212
97 National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing; Tenth Informational Supplement (Aerobic Dilution) M100–S10. Wayne, PA: NCCLS; 2000
98 Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty Third Informational Supplement. CLSI Document M100–S23. Wayne, PA: CLSI; 2013
99 European Committee on Antimicrobial Susceptibility Testing. Breakpoint Tables for Interpretation of MICs and Zone Diameters Version 3.1; 2013. Available at: http://www.eucast.org
100 Kang CI, Cha MK, Kim SH, et al. Extended-spectrum cephalosporins and the inoculum effect in tests with CTX-M-type extended-spectrum β-lactamase-producing Escherichia coli: potential clinical implications of the revised CLSI interpretive criteria. Int J Antimicrob Agents 2014;43(5):456–459
101 Leclercq R, Cantón R, Brown DF, et al. EUCAST expert rules in antimicrobial susceptibility testing. Clin Microbiol Infect 2013; 19(2):141–160
102 Livermore DM, Andrews JM, Hawkey PM, et al. Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly? J Antimicrob Chemother 2012;67(7): 1569–1577
103 Chow JW, Fine MJ, Shlaes DM, et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 1991;115(8):585–590
104 Kaye KS, Cosgrove S, Harris A, Eliopoulos GM, Carmeli Y. Risk factors for emergence of resistance to broad-spectrum cephalosporins among Enterobacter spp. Antimicrob Agents Chemother 2001;45(9):2628–2630
105 Choi SH, Lee JE, Park SJ, et al. Emergence of antibiotic resistance during therapy for infections caused by Enterobacteriaceae producing AmpC beta-lactamase: implications for antibiotic use. Antimicrob Agents Chemother 2008;52(3):995–1000
106 Cosgrove SE, Kaye KS, Eliopoulous GM, Carmeli Y. Health and economic outcomes of the emergence of third-generation cephalosporin resistance in Enterobacter species. Arch Intern Med 2002;162(2):185–190
107 Livermore DM, Brown DF, Quinn JP, Carmeli Y, Paterson DL, Yu VL. Should third-generation cephalosporins be avoided against AmpC-inducible Enterobacteriaceae? Clin Microbiol Infect 2004;10(1):84–85
108 Pai H, Kang CI, Byeon JH, et al. Epidemiology and clinical features of bloodstream infections caused by AmpC-type-beta-lactamase-producing Klebsiella pneumoniae. Antimicrob Agents Chemother 2004;48(10):3720–3728
109 Sanders WE Jr, Tenney JH, Kessler RE. Efficacy of cefepime in the treatment of infections due to multiply resistant Enterobacter species. Clin Infect Dis 1996;23(3):454–461

110 Tamma PD, Girdwood SC, Gopaul R, et al. The use of cefepime for treating AmpC β-lactamase-producing Enterobacteriaceae. Clin Infect Dis 2013;57(6):781–788

111 Siedner MJ, Galar A, Guzmán-Suarez BB, et al. Cefepime vs other antibacterial agents for the treatment of Enterobacter species bacteremia. Clin Infect Dis 2014;58(11):1554–1563

112 Choi SH, Lee JE, Park SJ, et al. Prevalence, microbiology, and clinical characteristics of extended-spectrum beta-lactamase-producing Enterobacter spp., Serratia marcescens, Citrobacter freundii, and Morganella morganii in Korea. Eur J Clin Microbiol Infect Dis 2007;26(8):557–561

113 Gottlieb T, Wolfson C. Comparison of the MICs of cefepime for extended-spectrum beta-lactamase-producing and non-extended-spectrum beta-lactamase-producing strains of Enterobacter cloacae. J Antimicrob Chemother 2000;46(2):330–331

114 Bhat SV, Peleg AY, Lodise TP Jr, et al. Failure of current cefepime breakpoints to predict clinical outcomes of bacteremia caused by gram-negative organisms. Antimicrob Agents Chemother 2007; 51(12):4390–4395

115 Burgess DS, Hall RG II. In vitro killing of parenteral beta-lactams against standard and high inocula of extended-spectrum beta-lactamase and non-ESBL producing Klebsiella pneumoniae. Diagn Microbiol Infect Dis 2004;49(1):41–46

116 Thomson KS, Moland ES. Cefepime, piperacillin-tazobactam, and the inoculum effect in tests with extended-spectrum beta-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2001;45(12):3548–3554

117 Kang CI, Pai H, Kim SH, et al. Cefepime and the inoculum effect in tests with Klebsiella pneumoniae producing plasmid-mediated AmpC-type beta-lactamase. J Antimicrob Chemother 2004;54(6): 1130–1133

118 Fernández-Cuenca F, Rodríguez-Martínez JM, Martínez-Martínez L, Pascual A. In vivo selection of Enterobacter aerogenes with reduced susceptibility to cefepime and carbapenems associated with decreased expression of a 40 kDa outer membrane protein and hyperproduction of AmpC beta-lactamase. Int J Antimicrob Agents 2006;27(6):549–552

119 Labombardi VJ, Rojtman A, Tran K. Use of cefepime for the treatment of infections caused by extended spectrum beta-lactamase-producing Klebsiella pneumoniae and Escherichia coli. Diagn Microbiol Infect Dis 2006;56(3):313–315

120 Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing Enterobacteriaceae: MIC matters. Clin Infect Dis 2013;56(4):488–495

121 Chopra T, Marchaim D, Veltman J, et al. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-β-lactamase-producing Klebsiella pneumoniae and Escherichia coli. Antimicrob Agents Chemother 2012;56(7):3936–3942

122 Nguyen HM, Shier KL, Graber CJ. Determining a clinical framework for use of cefepime and β-lactam/β-lactamase inhibitors in the treatment of infections caused by extended-spectrum-β-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother 2014;69(4):871–880

123 Rhodes NJ, Richardson CL, Heraty R, et al. Unacceptably high error rates in Vitek 2 testing of cefepime susceptibility in extended spectrum? lactamase producing *Escherichia coli*. Antimicrob Agents Chemother 2014;58(7):3757–3761

124 Lepeule R, Ruppé E, Le P, et al. Cefoxitin as an alternative to carbapenems in a murine model of urinary tract infection due to Escherichia coli harboring CTX-M-15-type extended-spectrum β-lactamase. Antimicrob Agents Chemother 2012;56(3): 1376–1381

125 Doi A, Shimada T, Harada S, Iwata K, Kamiya T. The efficacy of cefmetazole against pyelonephritis caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. Int J Infect Dis 2013;17(3):e159–e163

126 Yang CC, Li SH, Chuang FR, et al. Discrepancy between effects of carbapenems and flomoxef in treating nosocomial hemodialysis access-related bacteremia secondary to extended spectrum beta-lactamase producing Klebsiella pneumoniae in patients on maintenance hemodialysis. BMC Infect Dis 2012;12:206

127 Kiffer CR, Kuti JL, Eagye KJ, Mendes C, Nicolau DP. Pharmacodynamic profiling of imipenem, meropenem and ertapenem against clinical isolates of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella spp. from Brazil. Int J Antimicrob Agents 2006;28(4):340–344

128 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(1): 31–37

129 Collins VL, Marchaim D, Pogue JM, et al. Efficacy of ertapenem for treatment of bloodstream infections caused by extended-spectrum-β-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2012;56(4):2173–2177

130 Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis 2008;8(3):159–166

131 Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis. J Antimicrob Chemother 2012;67(12):2793–2803

132 DeRyke CA, Banevicius MA, Fan HW, Nicolau DP. Bactericidal activities of meropenem and ertapenem against extended-spectrum-beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in a neutropenic mouse thigh model. Antimicrob Agents Chemother 2007;51(4):1481–1486

133 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(2): 433–435

134 Fong JJ, Rosé L, Radigan EA. Clinical outcomes with ertapenem as a first-line treatment option of infections caused by extended-spectrum β-lactamase producing gram-negative bacteria. Ann Pharmacother 2012;46(3):347–352

135 Lye DC, Wijaya L, Chan J, Teng CP, Leo YS. Ertapenem for treatment of extended-spectrum beta-lactamase-producing and multidrug-resistant gram-negative bacteraemia. Ann Acad Med Singapore 2008;37(10):831–834

136 Lee NY, Huang WH, Tsui KC, Hsueh PR, Ko WC. Carbapenem therapy for bacteremia due to extended-spectrum β-lactamase-producing Escherichia coli or Klebsiella pneumoniae. Diagn Microbiol Infect Dis 2011;70(1):150–153

137 Huang SS, Lee MH, Leu HS. Bacteremia due to extended-spectrum beta-lactamase-producing Enterobacteriaceae other than Escherichia coli and Klebsiella. J Microbiol Immunol Infect 2006; 39:496–502

138 Qureshi ZA, Paterson DL, Pakstis DL, et al. Risk factors and outcome of extended-spectrum β-lactamase-producing Enterobacter cloacae bloodstream infections. Int J Antimicrob Agents 2011;37(1):26–32

139 Lee CC, Lee NY, Yan JJ, et al. Bacteremia due to extended-spectrum-beta-lactamase-producing Enterobacter cloacae: role of carbapenem therapy. Antimicrob Agents Chemother 2010; 54(9):3551–3556

140 Elliott E, Brink AJ, van Greune J, et al. In vivo development of ertapenem resistance in a patient with pneumonia caused by Klebsiella pneumoniae with an extended-spectrum beta-lactamase. Clin Infect Dis 2006;42(11):e95–e98

141 Szabó D, Silveira F, Hujer AM, et al. Outer membrane protein changes and efflux pump expression together may confer resistance to ertapenem in Enterobacter cloacae. Antimicrob Agents Chemother 2006;50(8):2833–2835

142 Suh B, Bae IK, Kim J, Jeong SH, Yong D, Lee K. Outbreak of meropenem-resistant Serratia marcescens comediated by chromosomal AmpC beta-lactamase overproduction and outer membrane protein loss. Antimicrob Agents Chemother 2010;54(12): 5057–5061
143 Skurnik D, Lasocki S, Bremont S, et al. Development of ertapenem resistance in a patient with mediastinitis caused by Klebsiella pneumoniae producing an extended-spectrum beta-lactamase. J Med Microbiol 2010;59(Pt 1):115–119
144 Guillon H, Tande D, Mammeri H. Emergence of ertapenem resistance in an Escherichia coli clinical isolate producing extended-spectrum beta-lactamase AmpC. Antimicrob Agents Chemother 2011;55(9):4443–4446
145 Mammeri H, Nordmann P, Berkani A, Eb F. Contribution of extended-spectrum AmpC (ESAC) beta-lactamases to carbapenem resistance in Escherichia coli. FEMS Microbiol Lett 2008; 282(2):238–240
146 European Committee on Antimicrobial Susceptibility Testing. EUCAST Guidelines for Detection of Resistance Mechanisms and Specific Resistances of Clinical and/or Epidemiological Importance. 2012. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/ (Accessed June 2014)
147 Lister PD. Beta-lactamase inhibitor combinations with extended-spectrum penicillins: factors influencing antibacterial activity against enterobacteriaceae and Pseudomonas aeruginosa. Pharmacotherapy 2000;20(9, Pt 2):213S–218S, discussion 224S–228S
148 Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev 2005;18(4):657–686
149 Pagani L, Migliavacca R, Luzzaro F, et al. Comparative activity of piperacillin/tazobactam against clinical isolates of extended-spectrum beta-lactamase-producing Enterobacteriaceae. Chemotherapy 1998;44(6):377–384
150 Canoui E, Tankovic J, Bige N, Alves M, Offenstadt G. Which proportion of extended-spectrum beta-lactamase producing strains could be treated by non-carbapenem beta-lactams? Med Mal Infect 2014;44(5):235–237
151 López-Cerero L, Picón E, Morillo C, et al. Comparative assessment of inoculum effects on the antimicrobial activity of amoxycillin-clavulanate and piperacillin-tazobactam with extended-spectrum beta-lactamase-producing and extended-spectrum beta-lactamase-non-producing Escherichia coli isolates. Clin Microbiol Infect 2010;16(2):132–136
152 Craig WA, Bhavnani SM, Ambrose PG. The inoculum effect: fact or artifact? Diagn Microbiol Infect Dis 2004;50(4):229–230
153 Docobo-Pérez F, López-Cerero L, López-Rojas R, et al. Inoculum effect on the efficacies of amoxicillin-clavulanate, piperacillin-tazobactam, and imipenem against extended-spectrum β-lactamase (ESBL)-producing and non-ESBL-producing Escherichia coli in an experimental murine sepsis model. Antimicrob Agents Chemother 2013;57(5):2109–2113
154 Harada Y, Morinaga Y, Kaku N, et al. In vitro and in vivo activities of piperacillin-tazobactam and meropenem at different inoculum sizes of ESBL-producing Klebsiella pneumoniae. Clin Microbiol Infect 2014;20(11):831–839 [epub ahead of print]
155 Thauvin-Eliopoulos C, Tripodi MF, Moellering RC Jr, Eliopoulos GM. Efficacies of piperacillin-tazobactam and cefepime in rats with experimental intra-abdominal abscesses due to an extended-spectrum beta-lactamase-producing strain of Klebsiella pneumoniae. Antimicrob Agents Chemother 1997;41(5): 1053–1057
156 Akhan S, Coskunkan F, Tansel O, Vahaboglu H. Conjugative resistance to tazobactam plus piperacillin among extended-spectrum beta-lactamase-producing nosocomial Klebsiella pneumoniae. Scand J Infect Dis 2001;33(7):512–515
157 Perez F, Bonomo RA. Can we really use ß-lactam/ß-lactam inhibitor combinations for the treatment of infections caused by extended-spectrum ß-lactamase-producing bacteria? Clin Infect Dis 2012;54(2):175–177
158 Livermore DM, Hope R, Mushtaq S, Warner M. Orthodox and unorthodox clavulanate combinations against extended-spectrum beta-lactamase producers. Clin Microbiol Infect 2008;14 (Suppl 1):189–193
159 Paterson DL, Singh N, Gayowski T, Marino IR. Fatal infection due to extended-spectrum beta-lactamase-producing Escherichia coli: implications for antibiotic choice for spontaneous bacterial peritonitis. Clin Infect Dis 1999;28(3):683–684
160 Zimhony O, Chmelnitsky I, Bardenstein R, et al. Endocarditis caused by extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae: emergence of resistance to ciprofloxacin and piperacillin-tazobactam during treatment despite initial susceptibility. Antimicrob Agents Chemother 2006;50(9):3179–3182
161 Essack SY. Treatment options for extended-spectrum beta-lactamase-producers. FEMS Microbiol Lett 2000;190(2):181–184
162 Gavin PJ, Suseno MT, Thomson RB Jr, et al. Clinical correlation of the CLSI susceptibility breakpoint for piperacillin- tazobactam against extended-spectrum-beta-lactamase-producing Escherichia coli and Klebsiella species. Antimicrob Agents Chemother 2006;50(6):2244–2247
163 Apisarnthanarak A, Kiratisin P, Saifon P, Kitphati R, Dejsirilert S, Mundy LM. Risk factors for and outcomes of healthcare-associated infection due to extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae in Thailand. Infect Control Hosp Epidemiol 2007;28(7):873–876
164 Kang CI, Park SY, Chung DR, Peck KR, Song JH. Piperacillin-tazobactam as an initial empirical therapy of bacteremia caused by extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae. J Infect 2012;64(5):533–534
165 Peralta G, Lamelo M, Alvarez-García P, et al; SEMI-BLEE STUDY GROUP. Impact of empirical treatment in extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella spp. bacteremia. A multicentric cohort study. BMC Infect Dis 2012; 12:245
166 Rodríguez-Baño J, Navarro MD, Retamar P, Picón E, Pascual Á; Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing Escherichia coli: a post hoc analysis of prospective cohorts. Clin Infect Dis 2012;54(2):167–174
167 Retamar P, López-Cerero L, Muniain MA, Pascual Á, Rodríguez-Baño J; ESBL-REIPI/GEIH Group. Impact of the MIC of piperacillin-tazobactam on the outcome of patients with bacteremia due to extended-spectrum-β-lactamase-producing Escherichia coli. Antimicrob Agents Chemother 2013;57(7):3402–3404
168 Gutiérrez-Gutiérrez B, Salamanca E, Pérez-Galera S, et al. Assessment of Beta-Lactam/Beta-Lactamase Inhibitor Combinations for the Treatment of Bacteraemia Due to Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae: The INCREMENT Project. Washington, DC: ICAAC; 2014
169 Felton TW, Roberts JA, Lodise TP, et al. Individualization of piperacillin dosing for critically ill patients: dosing software to optimize antimicrobial therapy. Antimicrob Agents Chemother 2014;58(7):4094–4102
170 Carlier M, Carrette S, Roberts JA, et al. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care 2013;17(3):R84
171 Dulhunty JM, Roberts JA, Davis JS, et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. Clin Infect Dis 2013;56(2): 236–244
172 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(4): 851–858

173 Akova M, Yang Y, Livermore DM. Interactions of tazobactam and clavulanate with inducibly- and constitutively-expressed Class I beta-lactamases. J Antimicrob Chemother 1990;25(2):199–208

174 Power P, Galleni M, Ayala JA, Gutkind G. Biochemical and molecular characterization of three new variants of AmpC beta-lactamases from Morganella morganii. Antimicrob Agents Chemother 2006;50(3):962–967

175 Marcos M, Iñurrieta A, Soriano A, et al. Effect of antimicrobial therapy on mortality in 377 episodes of Enterobacter spp. bacteraemia. J Antimicrob Chemother 2008;62(2):397–403

176 Schwaber MJ, Graham CS, Sands BE, Gold HS, Carmeli Y. Treatment with a broad-spectrum cephalosporin versus piperacillin-tazobactam and the risk for isolation of broad-spectrum cephalosporin-resistant Enterobacter species. Antimicrob Agents Chemother 2003;47(6):1882–1886

177 Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect Dis 2010; 10(1):43–50

178 de Cueto M, López L, Hernández JR, Morillo C, Pascual A. In vitro activity of fosfomycin against extended-spectrum-beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: comparison of susceptibility testing procedures. Antimicrob Agents Chemother 2006;50(1):368–370

179 Nakamura T, Komatsu M, Yamasaki K, et al. Susceptibility of various oral antibacterial agents against extended spectrum β-lactamase producing Escherichia coli and Klebsiella pneumoniae. J Infect Chemother 2014;20(1):48–51

180 Morfín-Otero R, Mendoza-Olazarán S, Silva-Sánchez J, et al. Characterization of Enterobacteriaceae isolates obtained from a tertiary care hospital in Mexico, which produces extended-spectrum β-lactamase. Microb Drug Resist 2013;19(5):378–383

181 Gupta V, Rani H, Singla N, Kaistha N, Chander J. Determination of Extended-Spectrum β-Lactamases and AmpC Production in Uropathogenic Isolates of Escherichia coli and Susceptibility to Fosfomycin. J Lab Physicians 2013;5(2):90–93

182 Hutley EJ, Chand MA, Hounsome G, Kelsey MC. Fosfomycin: an oral agent for urinary infection caused by extended spectrum beta-lactamase producing organisms. J Infect 2010;60(4): 308–309

183 Auer S, Wojna A, Hell M. Oral treatment options for ambulatory patients with urinary tract infections caused by extended-spectrum-beta-lactamase-producing Escherichia coli. Antimicrob Agents Chemother 2010;54(9):4006–4008

184 Wilson DT, May DB. Potential role of fosfomycin in the treatment of community-acquired lower urinary tract infections caused by extended-spectrum β-lactamase-producing Escherichia coli. Am J Ther 2013;20(6):685–690

185 Senol S, Tasbakan M, Pullukcu H, et al. Carbapenem versus fosfomycin tromethanol in the treatment of extended-spectrum beta-lactamase-producing Escherichia coli-related complicated lower urinary tract infection. J Chemother 2010;22(5):355–357

186 Gardiner BJ, Mahony AA, Ellis AG, et al. Is fosfomycin a potential treatment alternative for multidrug-resistant gram-negative prostatitis? Clin Infect Dis 2014;58(4):e101–e105

187 Rodríguez-Avial C, Rodríguez-Avial I, Hernández E, Picazo JJ. Increasing prevalence of fosfomycin resistance in extended-spectrum-beta-lactamase-producing Escherichia coli urinary isolates (2005-2009-2011) [in Spanish]. Rev Esp Quimioter 2013;26(1):43–46

188 Ellington MJ, Livermore DM, Pitt TL, Hall LM, Woodford N. Mutators among CTX-M beta-lactamase-producing Escherichia coli and risk for the emergence of fosfomycin resistance. J Antimicrob Chemother 2006;58(4):848–852

189 Lee SY, Park YJ, Yu JK, et al. Prevalence of acquired fosfomycin resistance among extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae clinical isolates in Korea and IS26-composite transposon surrounding fosA3. J Antimicrob Chemother 2012;67(12):2843–2847

190 Corvec S, Furustrand Tafin U, Betrisey B, Borens O, Trampuz A. Activities of fosfomycin, tigecycline, colistin, and gentamicin against extended-spectrum-β-lactamase-producing Escherichia coli in a foreign-body infection model. Antimicrob Agents Chemother 2013;57(3):1421–1427

191 Lee WS, Wang FD, Shieh YH, Teng SO, Ou TY. Lemierre syndrome complicating multiple brain abscesses caused by extended-spectrum β-lactamase-producing Klebsiella pneumoniae cured by fosfomycin and meropenem combination therapy. J Microbiol Immunol Infect 2012;45(1):72–74

192 Falagas ME, Giannopoulou KP, Kokolakis GN, Rafailidis PI. Fosfomycin: use beyond urinary tract and gastrointestinal infections. Clin Infect Dis 2008;46(7):1069–1077

193 Silva-Sanchez J, Reyna-Flores F, Velazquez-Meza ME, Rojas-Moreno T, Benitez-Diaz A, Sanchez-Perez A; Study Group. In vitro activity of tigecycline against extended-spectrum β-lactamase-producing Enterobacteriaceae and MRSA clinical isolates from Mexico: a multicentric study. Diagn Microbiol Infect Dis 2011; 70(2):270–273

194 Geerlings SE, van Donselaar-van der Pant KA, Keur I. Successful treatment with tigecycline of two patients with complicated urinary tract infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. J Antimicrob Chemother 2010;65(9):2048–2049

195 Cho SY, Kang CI, Chung DR, Peck KR, Song JH, Jang JH. Breakthrough bacteremia due to extended-spectrum-β-lactamase-producing Klebsiella pneumoniae during combination therapy with colistin and tigecycline. Antimicrob Agents Chemother 2012;56(9):4994–4995, author reply 4996

196 Chen PL, Yan JJ, Wu CJ, et al. Salvage therapy with tigecycline for recurrent infection caused by ertapenem-resistant extended-spectrum β-lactamase-producing Klebsiella pneumoniae. Diagn Microbiol Infect Dis 2010;68(3):312–314

197 Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis 2012;54(12):1699–1709

198 Neu HC. Mecillinam—an amidino penicillin which acts synergistically with other β-lactam compounds. J Antimicrob Chemother 1977;3(Suppl B):43–52

199 Gupta K, Hooton TM, Naber KG, et al; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52(5):e103–e120

200 Brenwald NP, Andrews J, Fraise AP. Activity of mecillinam against AmpC beta-lactamase-producing Escherichia coli. J Antimicrob Chemother 2006;58(1):223–224

201 Lampri N, Galani I, Poulakou G, et al. Mecillinam/clavulanate combination: a possible option for the treatment of community-acquired uncomplicated urinary tract infections caused by extended-spectrum β-lactamase-producing Escherichia coli. J Antimicrob Chemother 2012;67(10):2424–2428

202 Wootton M, Walsh TR, Macfarlane L, Howe RA. Activity of mecillinam against Escherichia coli resistant to third-generation cephalosporins. J Antimicrob Chemother 2010;65(1):79–81

203 Sougakoff W, Jarlier V. Comparative potency of mecillinam and other β-lactam antibiotics against Escherichia coli strains producing different β-lactamases. J Antimicrob Chemother 2000;46 (Suppl 1):9–14

204 Titelman E, Iversen A, Kalin M, Giske CG. Efficacy of pivmecillinam for treatment of lower urinary tract infection caused by extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae. Microb Drug Resist 2012;18(2):189–192

205 Poulsen HO, Johansson A, Granholm S, Kahlmeter G, Sundqvist M. High genetic diversity of nitrofurantoin- or mecillinam-resistant Escherichia coli indicates low propensity for clonal spread. J Antimicrob Chemother 2013;68(9):1974–1977
206 Rodriguez-Villalobos H, Malaviolle V, Frankard J, de Mendonça R, Nonhoff C, Struelens MJ. In vitro activity of temocillin against extended spectrum beta-lactamase-producing Escherichia coli. J Antimicrob Chemother 2006;57(4):771–774
207 Livermore DM, Hope R, Fagan EJ, Warner M, Woodford N, Potz N. Activity of temocillin against prevalent ESBL- and AmpC-producing Enterobacteriaceae from south-east England. J Antimicrob Chemother 2006;57(5):1012–1014
208 Balakrishnan I, Awad-El-Kariem FM, Aali A, et al. Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother 2011;66(11):2628–2631
209 Fournier D, Chirouze C, Leroy J, et al. Alternatives to carbapenems in ESBL-producing Escherichia coli infections. Med Mal Infect 2013;43(2):62–66
210 Tasbakan MI, Pullukcu H, Sipahi OR, Yamazhan T, Ulusoy S. Nitrofurantoin in the treatment of extended-spectrum β-lactamase-producing Escherichia coli-related lower urinary tract infection. Int J Antimicrob Agents 2012;40(6):554–556
211 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(2):243–251
212 Farrell DJ, Sader HS, Flamm RK, Jones RN. Ceftolozane/tazobactam activity tested against Gram-negative bacterial isolates from hospitalised patients with pneumonia in US and European medical centres (2012). Int J Antimicrob Agents 2014;43(6):533–539
213 Zhanel GG, Chung P, Adam H, et al. Ceftolozane/tazobactam: a novel cephalosporin/β-lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. Drugs 2014;74(1):31–51
214 Drawz SM, Papp-Wallace KM, Bonomo RA. New β-lactamase inhibitors: a therapeutic renaissance in an MDR world. Antimicrob Agents Chemother 2014;58(4):1835–1846
215 Porres-Osante N, Dupont H, Torres C, Ammenouche N, de Champs C, Mammeri H. Avibactam activity against extended-spectrum AmpC β-lactamases. J Antimicrob Chemother 2014;69(6):1715–1716
216 Miossec C, Claudon M, Levasseur P, Black MT. The β-lactamase inhibitor avibactam (NXL104) does not induce ampC β-lactamase in Enterobacter cloacae. Infect Drug Resist 2013;6:235–240
217 Flamm RK, Farrell DJ, Sader HS, Jones RN. Ceftazidime/avibactam activity tested against Gram-negative bacteria isolated from bloodstream, pneumonia, intra-abdominal and urinary tract infections in US medical centres (2012). J Antimicrob Chemother 2014;69(6):1589–1598
218 Glasner C, Albiger B, Buist G, et al; European Survey on Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) Working Group. Carbapenemase-producing Enterobacteriaceae in Europe: a survey among national experts from 39 countries, February 2013. Euro Surveill 2013;18(28):20525
219 Molton JS, Tambyah PA, Ang BS, Ling ML, Fisher DA. The global spread of healthcare-associated multidrug-resistant bacteria: a perspective from Asia. Clin Infect Dis 2013;56(9):1310–1318
220 Nordmann P, Dortet L, Poirel L. Carbapenem resistance in Enterobacteriaceae: here is the storm!. Trends Mol Med 2012;18(5):263–272
221 Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant Pseudomonas aeruginosa: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. Clin Microbiol Rev 2009;22(4):582–610
222 Zeng X, Lin J. Beta-lactamase induction and cell wall metabolism in Gram-negative bacteria. Front Microbiol 2013;4:128