

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

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Abstract

Keywords

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

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.

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

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 <i>E. coli</i> , <i>Klebsiella</i> spp., and <i>Proteus</i> spp. but have been described in most Enterobacteriaceae and <i>Pseudomonas</i> spp. KPC seen in <i>Klebsiella pneumoniae</i>	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	<i>E. coli</i> , <i>Klebsiella</i> 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	<i>Enterobacter cloacae</i> , <i>E. aerogenes</i> , <i>Serratia marcescens</i> , <i>Citrobacter freundii</i> , <i>Providencia</i> spp. and <i>Morganella morganii</i> all contain inducible AmpC enzymes. Plasmid mediated AmpC increasing in <i>E. coli</i> , <i>Klebsiella</i> 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., <i>K. pneumoniae</i> 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 muropepti-

dases (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

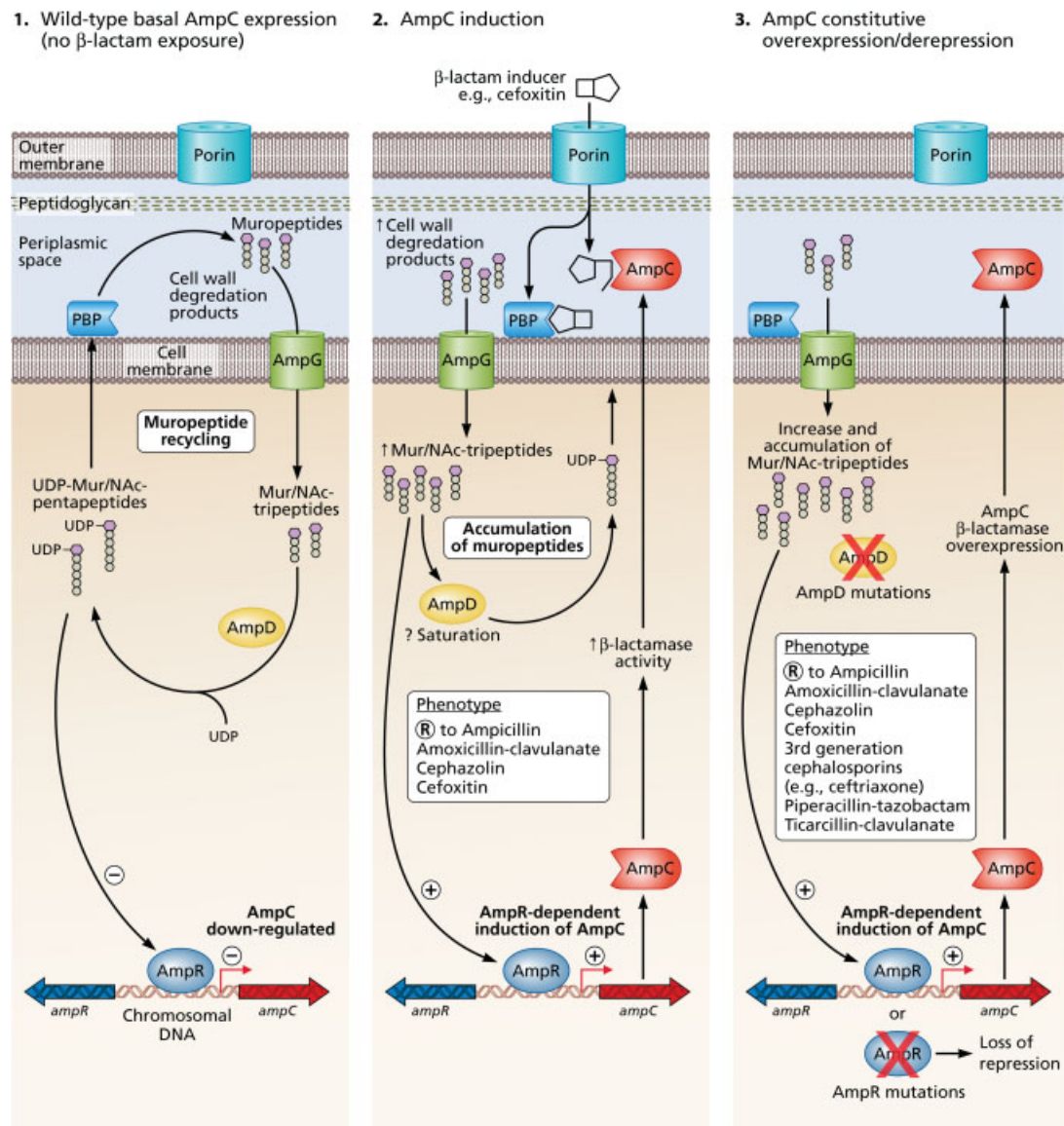


Fig. 2 Resistance mediated by inducible AmpC and AmpC overexpression. (1) In the absence of inducing β-lactams, basal AmpC levels are low. Normal peptidoglycan recycling involves the transport of muropeptides across the inner cell membrane by AmpG permease, following which, 1,6-anhydro-MurNAc-tripeptides 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}

population²³ 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 acid³⁶ or cloxacillin³¹), 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 hosts³⁷—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*_{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 children⁷² 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 8 μ g/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 ≤ 2 mg/L (CLSI) or ≤ 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

Cephameycins

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 vitro¹¹⁷ 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 ≥ 2 $\mu\text{g/mL}$.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 al¹³⁷ 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 carbapenems.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 cephalosporins.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 ≤ 16 $\mu\text{g/mL}$.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 BLBI 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 from a large Spanish cohort of patients with bacteremia caused by ESBL-producing *E. coli*. A post hoc analysis of six prospective studies compared BLBI 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 ≤ 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 non-inferiority 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 glycylcycline, 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 oxymino-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.

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