Clinical management of infections caused by multidrug-resistant *Enterobacteriaceae*

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Abstract: *Enterobacteriaceae* showing resistance to cephalosporins due to extended-spectrum β -lactamases (ESBLs) or plasmid-mediated AmpC enzymes, and those producing carbapenemases have spread worldwide during the last decades. Many of these isolates are also resistant to other first-line agents such as fluoroquinolones or aminoglycosides, leaving few available options for therapy. Thus, older drugs such as colistin and fosfomycin are being increasingly used. Infections caused by these bacteria are associated with increased morbidity and mortality compared with those caused by their susceptible counterparts. Most of the evidence supporting the present recommendations is from *in vitro* data, animal studies, and observational studies. While carbapenems are considered the drugs of choice for ESBL and AmpC producers, recent data suggest that certain alternatives may be suitable for some types of infections. Combined therapy seems superior to monotherapy in the treatment of invasive infections caused by carbapenemase-producing *Enterobacteriaceae*. Optimization of dosage according to pharmacokinetics/pharmacodynamics data is important for the treatment of infections caused by isolates with borderline minimum inhibitory concentration due to low-level resistance mechanisms. The increasing frequency and the rapid spread of multidrug resistance among the *Enterobacteriaceae* is a true and complex public health problem.

Introduction

The traditional first-line available options for treating serious infections caused by enterobacteria include penicillins, cephalosporins, monobactams, carbapenems, fluorquinolones, and in certain situations, aminoglycosides. The frequency of resistance to these first-line agents has been rising worldwide during the last decades [Paterson 2006; Rhomberg and Jones 2009; Houghton *et al.* 2010; Nordmann, *et al.* 2011] and now reach high proportions in many areas of the world.

Thus, recent reports from the Study for Monitoring Antimicrobial Resistance Trends (SMART) showed a prevalence of resistance to cephalosporins mediated by extended-spectrum β -lactamases (ESBL) production in *Escherichia coli* and *Klebsiella pneumoniae* of 17.6% and 38.9% respectively in Europe; 8.5% and 8.8% in the USA [Hoban *et al.* 2012]; and 40.8% and 21.5% in the Asia-Pacific region [Hsueh 2012]; the prevalence of ESBL production in *E. coli* was 23.6% in South America [Hawser *et al.* 2012]. Also, data from the Meropenem Yearly

Susceptibility Test information Collection (MYSTIC) project showed that the prevalence of ESBL in Europe and the USA respectively in 2007 was 3.9% and 7.5% for *E. coli* and 7.2% and 23.3% for *Klebsiella* spp. [Jones *et al.* 2008; Turner, 2009].

Plasmid-mediated AmpCs are increasingly found as a cause of cephalosporin resistance in *Enterobacteriaceae* in many areas of the world, although their frequency is heterogeneous according to the geographical area, for *E. coli* the prevalence ranging from 0.6% in Spain and 1.3% in Canada to 2% in Japan or China [Ding *et al.* 2008; Simner *et al.* 2011; Miró *et al.* 2012; Matsumura *et al.* 2012;]. As regards ciprofloxacin and amikacin, data from SMART studies in 2007 showed a prevalence of susceptibility of 15.4% and 88.5% for *E. coli*, and 24.5% and 72.8% for *K. pneumoniae* [Hoban *et al.* 2010]. In one study in ICU patients from Canada, plasmid-mediated AmpC-producing *E. coli* were less frequently multidrug resistant than ESBL producers [Baudry *et al.* 2008].

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Within Europe, the most recent data from European Antimicrobial Resistance Surveillance (EARSS; <http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net>), which includes data from blood isolates, showed a prevalence of resistance to third-generation cephalosporin in *E. coli* and *K. pneumoniae* of 8.5% and 27.5% respectively; to quinolones and aminoglycosides resistance in *E. coli* of 20.7% and 8.7%; and to carbapenems, quinolones, and aminoglycosides in *K. pneumoniae* of 0.8%, 28.5%, and 23.1% respectively.

Main mechanisms for multidrug resistance in enterobacteria

Resistance to β -lactams in enterobacteria is mainly (but not exclusively) caused by intrinsic and acquired β -lactamases. Two systems classify these enzymes, one based on the molecular structure and the other in their function [Ambler, 1980; Bush and Jacoby, 2010]. The most important plasmid-mediated β -lactamases produced by multidrug-resistant enterobacteria are shown in Table 1.

Molecular class A β -lactamases can be chromosomal or plasmid mediated and predominantly inactive penicillin. The ESBLs derive from class A β -lactamases, are plasmid mediated, and their spectrum includes all penicillins and cephalosporins (with the exception of cephamycins) and aztreonam; they are typically inhibited by β -lactamase inhibitors. There are three main ESBL groups: TEM and SHV, which are

frequently more active against ceftazidime than cefotaxime and were predominant during the 1980s and 1990s; and CTX-M, which are more active against cefotaxime, have rapidly spread worldwide since the late 1990s, and are now the most frequent ESBLs worldwide [Canton and Coque, 2006]. Many non- β -lactam agents are frequently useless against ESBL-producing organisms, either because the plasmids carrying the ESBL gene also harbour genes encoding resistance to other drug classes (quinolones, aminoglycosides and trimethoprim sulfamethoxazole) or because of epidemiological association with resistance to other agents (quinolones) [Paterson and Bonomo, 2005]. The so-called *K. pneumoniae* carbapenemases (KPCs) are also class A enzymes that extend their hydrolytic activity to the carbapenems [Tzouveleakis *et al.* 2012]. KPC-producing *K. pneumoniae* have become an important problem as a cause of nosocomial outbreaks in some geographical areas. Class B enzymes are metallo β -lactamases (MLBs) that can readily inactivate penicillins, cephalosporins, and carbapenems; monobactams are not affected. There are several types of MLBs, such as IMP, VIM, and NDM, among others. MLBs are now endemic in different parts of the world [Psichogiou *et al.* 2008; Tato *et al.* 2009; Tzouveleakis *et al.* 2012]. Class C β -lactamases are constitutively present in the chromosome of several enterobacteria as *Enterobacter* spp., *Citrobacter freundii* and *Serratia marcescens* [Jacoby, 2009]; moreover, class C β -lactamase genes can be present in transferable plasmids.

Table 1. Summary of relevant, emerging broad-spectrum, plasmid-mediated β -lactamases in *Enterobacteriaceae*.

Molecular class	Enzymes	Spectrum	Epidemiology
A	Extended-spectrum β -lactamases (TEM, SHV, CTX-M, others)	Penicillins, cephalosporins (except cefamycins), aztreonam. Inhibited by β -lactamase inhibitors	Worldwide spread. Community and nosocomial infections. Predominantly in <i>Escherichia coli</i> , <i>Klebsiella</i> , <i>Salmonella</i> , <i>Enterobacter</i>
	KPC	Penicillins, cephalosporins, aztreonam, carbapenems. Inhibited by β -lactamase inhibitors	Mainly nosocomial outbreaks. Frequent in some areas of USA, Greece, Israel, Italy, etc.
B	Metallo β -lactamases (VIM, IMP, NDM, others)	Penicillins, cephalosporins and carbapenems. Monobactams are susceptible. Not inhibited by β -lactamase inhibitors	Worldwide spread. Nosocomial outbreaks and endemic situations
C	AmpC type (CMY-2, DHA-1, FOX-1, others)	Penicillins, cephalosporins (except cefepime), and monobactams. Not inhibited by β -lactamase inhibitors	Worldwide spread. Community and nosocomial infections
D	OXA (OXA-48, OXA-23, others)	Penicillin, aztreonam and carbapenems. Not inhibited by β -lactamase inhibitors	Nosocomial outbreak. Spread in Middle East, Mediterranean countries and Africa

These enzymes can confer resistance to penicillins and cephalosporins except cefepime and are not inhibited by β -lactamase inhibitors [Jacoby, 2009; Navarro *et al.* 2010]. Recently, a novel type of class C β -lactamases also showing activity against cefepime and denominated extended-spectrum AmpC (ESAC) β -lactamases has been described [Mammeri *et al.* 2008; Rodriguez-Martinez *et al.* 2012]. Class D β -lactamases include a heterogeneous group of β -lactamases also named oxacillinases for their efficient hydrolysis of oxacillin. These enzymes hydrolyze aztreonam and carbapenems. There are several types of class D β -lactamases; as regards the *Enterobacteriaceae*, the most important are OXA-48 and OXA-181 among others. Recently, OXA-48 has rapidly spread in several areas in different enterobacteria, and it appears to have the highest affinity for imipenem [Poirel *et al.* 2004]. OXA-48 is frequently coproduced with an ESBL.

Other mechanisms of resistance to β -lactams include porin loss, efflux pumps, and modified targets (penicillin-binding proteins [PBPs]); some of these mechanisms, particularly when combined with β -lactamases, may confer resistance to carbapenems [Bush *et al.* 1995; Hirsch and Tam, 2010; Patel and Bonomo, 2011].

Resistance to quinolones most commonly results from the accumulation of chromosomal mutations in DNA gyrase (*GyrA*) then in topoisomerase IV (*ParC*) [Hooper, 2000; Jacoby, 2005]. Also, decreased membrane permeability or an overexpression of efflux pump systems cause lower intracellular concentration of the drug, which is associated with decreased susceptibility [Ruiz, 2003]. In 1998, a plasmid-mediated mechanism conferring low-level resistance to quinolones was discovered [Martinez-Martinez *et al.* 1998]; currently several plasmid-mediated mechanisms have been identified: the Qnr proteins (which act by protecting the antibiotic target), the modified amino-glycoside acetyltransferase AAC(6')-Ib-cr, and the efflux pump QepA [Robicsek *et al.* 2006; Perichon *et al.* 2007; Yamane *et al.* 2007]. The association of different mechanisms of quinolone resistance (plasmidic and chromosomal) at the same isolate is common.

Resistance to aminoglycoside may be due to several mechanisms: enzymatic modification, inactivation, alteration of diffusion through the outer

membrane due to porin loss, mutations in the target of the antimicrobial by methylation of ribosomal RNA [Fritsche *et al.* 2008]. The most prevalent mechanism of resistance is enzymatic modification. There are three main types of aminoglycoside-modifying enzymes (AMEs): acetyltransferases (AAC), phosphotransferases (APH), and nucleotidyltransferases (ANT). The modified aminoglycoside is unable to bind to its target, the bacterial ribosome. Bifunctional AMEs have been described, including AAC(3)-Ib/AAC(6)-Ib [Dubois *et al.* 2002; Kim *et al.* 2007], AAC(6)/APH(2'')-Ia [Boehr *et al.* 2004], ANT(3'')-Ii/AAC(6)-IId [Kim *et al.* 2006], and AAC(6)-30/AAC(6)-Ib [Zhang *et al.* 2009]. Recently, a novel mechanism causing high-level resistance to all aminoglycosides has been described. This is mediated by a 16S rRNA methylase, which causes methylation of the aminoglycoside binding site [Galimand *et al.* 2003]. Several types of 16S rRNA methylase genes have been described up to now: *armA*, *rmtA*, *rmtB*, *rmtC*, *rmtD*, and *npmA* [Wu *et al.* 2009]. They have been found in isolates coproducing ESBLs or MLBs, contributing to their multidrug-resistant phenotypes [Doi and Arakawa, 2007].

Empirical therapy of multidrug-resistant *Enterobacteriaceae*

Infections caused by multidrug-resistant *Enterobacteriaceae* are associated with increased morbidity and mortality than those caused by their susceptible counterparts [Rodríguez-Bano and Pascual, 2008; Rottier *et al.* 2012]. This is mainly related to delay in providing active therapy, and also to the fact that some alternative drugs may not be as effective as first-line antibiotics.

Empirical antimicrobial therapy is very important for serious infections. Several studies demonstrated that inactive empirical therapy is independently associated with worse outcomes in patients with bacteraemia due to *Enterobacteriaceae* [Kang *et al.* 2005; Peralta *et al.* 2012; Retamar *et al.* 2012; Rodríguez-Baño *et al.* 2010]. The fact that antimicrobial resistance to first-line agents has been increasing makes the selection of empirical therapy more difficult [Livermore *et al.* 2008; Canton *et al.* 2012]. Clinicians must frequently face the dilemma between choosing one of those agents, which might not be active in some patients, or a drug with a very broad spectrum, knowing that this may further fuel the spread of resistance. For

Figure 1. Algorithm for clinical decisions. MDRE, multidrug-resistant enterobacteria; BLBLI, β -lactam/ β -lactamase inhibitor combination; ESBL, extended-spectrum β -lactamase.

such decisions a few factors must be considered in patients with infections potentially caused by *Enterobacteriaceae*, including individual risk factors, local epidemiology, and clinical severity. Figure 1 shows an algorithm for clinical decisions.

Development of a rapid test to detect the most important mechanisms of resistance is an important challenge but is critical to improve management because such a test would allow a reduction in treatment delay. It is beyond the scope of this review to address this issue.

Individual risk factors

There are several cohort and case–control studies reporting individual risk factors associated with infection or colonization by multidrug-resistant *Enterobacteriaceae*. Many of the risk factors are often common to different organisms and mechanisms of resistance, and thus their importance depends on the local prevalence [Cheong *et al.* 2012; Han *et al.* 2012; Kang *et al.* 2012; Park *et al.* 2012; Rodríguez-Baño *et al.* 2008; Rodríguez-Baño *et al.* 2010] (Table 2).

Risk factors for community-onset infections due to ESBL-producing *E. coli* were recently reviewed

Table 2. Individual risk factors for infections due to multidrug-resistant *Enterobacteriaceae* as identified in cohort and case–control studies (for references, see text).

Variable	Resistance mechanism
Urinary catheter	ESBLs
Previous antimicrobial therapy	ESBLs, AmpCs, carbapenemases
Diabetes mellitus	ESBLs
Malignancy	AmpCs
Recent hospitalization	ESBLs
Prolonged hospitalization	ESBLs, AmpCs, carbapenemases
Travel to high risk areas	ESBLs, carbapenemases
ESBL, extended-spectrum β -lactamase.	

[Rodríguez-Baño and Pascual, 2008] and include age, diabetes mellitus, previous hospital admission, residence in a long-term care facility, use of a urinary catheter, and previous use of aminopenicillins, cephalosporins, and fluoroquinolones. For nosocomial infections, prolonged hospitalization, invasive procedures, and previous

use of cephalosporins and fluoroquinolones have been consistently associated with infections caused by ESBL-producing *E. coli* or *Klebsiella* [Rodríguez-Baño and Pascual, 2008]. Although the data are much more limited, the risk factors seem to be quite similar for enterobacteria-producing plasmid AmpC [Pai *et al.* 2004; Rodríguez-Baño *et al.* 2012a]; also, solid-organ malignancy, connective tissue disease, and a recent history of surgery have been related to bacteraemic infections by AmpC-producing *E. coli* in one study [Park *et al.* 2012].

Data regarding the risk factors are still limited for carbapenemase-producing *Enterobacteriaceae*. Infections caused by KPC- or MBL-producing *K. pneumoniae* have been associated with severity of underlying disease, age, diabetes mellitus, ICU admission, mechanical ventilation, and exposure to cephalosporins, carbapenems, and fluoroquinolones [Gasink *et al.* 2009; Hussein *et al.* 2009; Moloudi *et al.* 2010; Zarkotou *et al.* 2010; Chitnis *et al.* 2012; Tuon *et al.* 2012].

Local epidemiology and recent travel

Resistance patterns observed for a particular strain represent the addition of intrinsic and acquired mechanisms of resistances [Navarro *et al.* 2010; Leclercq *et al.* 2011]. While the first are universal, the latter may be present only in some geographical areas, and their prevalence may be very heterogeneous in the areas where they are present; also, within a specific centre, only some wards may be affected. Therefore, efficient surveillance system together with updated and efficient reporting of the local epidemiology to clinicians is a very important contribution of the microbiology laboratories to the appropriate management of patients.

However, the continuous movements of people across international borders make it necessary to also consider immigration and travelling when evaluating the possibility of harbouring a resistant pathogen [van der Bij and Pitout, 2012]. In fact, recent travel to areas where these mechanisms of resistance (including ESBL and carbapenemases) are endemic has been shown to be an important risk factor; previous admission to a hospital in those areas further increases the risk [Laupland *et al.* 2008; Schwaber *et al.* 2008; Tangden *et al.* 2010; Nordmann *et al.* 2011; Patel and Bonomo, 2011; Rogers *et al.* 2011; Canton *et al.* 2012; van der Bij and Pitout, 2012].

Clinical severity

Clinical severity of systemic inflammatory response syndrome at the onset of infection is one of the most important predictors of mortality in *Enterobacteriaceae* invasive infections [Peralta *et al.* 2012]. Therefore, providing adequate antibiotic coverage is especially important in these situations and the use of broader spectrum antibiotics or combined therapy might be justified even in the absence of individual risk factors when a multidrug-resistant organism is to be considered according to the local epidemiology. Once the susceptibility data are available, the treatment regimen must be optimized and the spectrum reduced if possible to avoid the selection pressure of broader-spectrum agents. Examples of infectious disease syndromes that may be classified as severe infection include those involving the central nervous system, people presenting with severe sepsis or shock, hospital-acquired pneumonia, and necrotizing soft-tissue infections [Carmeli, 2008; Pitout, 2012].

Therapy of infections caused by *Enterobacteriaceae*-producing extended-spectrum β -lactamases

A summary of the available options for the treatment of these infections is shown in Table 3.

Carbapenems

Carbapenems are considered the drugs of choice for serious infections due to ESBL-producing bacteria, since they are usually associated with lower failure rates and better outcomes in observational studies [Endimiani *et al.* 2004; Bassetti *et al.* 2007; Rodríguez-Baño and Pascual 2008]. A recently published meta-analysis of observational studies found that mortality was lower in patients who received empirical or definitive therapy with carbapenem in comparison with other antibiotics, including cephalosporins, fluoroquinolones, and aminoglycosides, with the exception of non- β -lactam/ β -lactam inhibitor combinations [Vardakas *et al.* 2012]. Among carbapenems, most studies evaluated imipenem or meropenem. There is also some recent experience with ertapenem [Collins *et al.* 2012; Wu *et al.* 2012]; this antibiotic would be preferred for empirical therapy in community-acquired severe infections potentially caused by ESBL producers when coverage against *Pseudomonas aeruginosa* or *Acinetobacter baumannii* is not needed to avoid further selection pressure over these organisms [Nicolau *et al.* 2012], since ertapenem lacks

Table 3. Summary of options available for the treatment of multidrug-resistant enterobacteria. For references, see the text.

Mechanism of resistance	Antimicrobial	Comment
ESBL and plasmid AmpC producers	Carbapenems	Drugs of choice for severe infections
	β -lactam/ β -lactam inhibitors	ESBL: alternative to carbapenems if active <i>in vitro</i> . Data available mainly for urinary bacteremia due to <i>Escherichia coli</i> . AmpCs are not inhibited
	Cephalosporins	ESBL: potentially active for isolates with low MIC. Controversial
	Temocillin	AmpC: ceftazidime might be useful
	Fluoroquinolones	Potentially useful as definitive therapy
KPC, MLB, and OXA producers		Useful if <i>in vitro</i> active. Caution in case of isolates showing borderline MIC
	Aminoglycosides	Useful if active mainly for urinary tract infections
	Fosfomycin	Useful for cystitis
	Carbapenem	Potentially useful for isolates with low MIC (optimized dose). Probably worse than combination
	Aztreonam, cephalosporins	Aztreonam only for MLB or OXA-48 (without ESBL). Cephalosporins only for OXA-48 without ESBL. Potentially useful. Limited experience
	Colistin	Real efficacy is controversial. Optimized dosing might improve results
	Fosfomycin	Limited experience. To be used in combination
	Tigecycline	Limited experience. To be used in combination. Less efficacy expected in UTI
	Combinations	Better results in observational studies. Carbapenems should probably be included. A third drug may improve the results

ESBL, extended-spectrum β -lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration; MLB, metallo β -lactamase; OXA, oxacillinase; UTI, urinary tract infection.

significant activity against them. It may also be useful for outpatient parenteral therapy because of the convenience of once daily dosing. Resistance to ertapenem in ESBL producers during therapy may occur due to concurrent loss of porins and have been described for *Klebsiella* and *Enterobacter* [Elliott *et al.* 2006; Pitout, 2010; Skurnik *et al.* 2010] and also in *E. coli* during treatment with imipenem [Lartigue *et al.* 2007]. This, together with pharmacokinetics/pharmacodynamics (PK/PD) data caused some doubts about the breakpoints for ertapenem [Frei *et al.* 2008], which were subsequently lowered by the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST), as happened with all carbapenems. The use of a carbapenem with activity against *P. aeruginosa* such as imipenem, meropenem, or doripenem is recommended as empirical therapy in nosocomial infections potentially caused by ESBL producers [Rodriguez-Baño and Pascual, 2008].

Cephalosporins

The hydrolytic activity of ESBLs against cephalosporins is heterogeneous: while TEM and SHV

producers usually show lower minimum inhibitory concentrations (MICs) for cefotaxime than for ceftazidime or ceftazidime, the opposite occurs with CTX-M producers. However, it was seen early on that patients treated with cephalosporins showed an increased failure rate even if the MIC was in the susceptible range according to old breakpoints [Paterson *et al.* 2001]. Possible causes for this were inoculum effect, poor drug penetration to the site of infection, or insufficient dose. At that time, the CLSI recommended that all ESBL producers should be reported as resistant to cephalosporins irrespective of the MIC. However, the results from animal models suggested that cephalosporins would be efficacious provided the appropriate PK/PD target could be reached [Lee *et al.* 2007; MacGowan, 2008]. Also, a prospective cohort study showed good results with ceftazidime in the treatment of 22 consecutive patients with bacteraemia due to ESBL-producing *E. coli*, showing a MIC of ceftazidime of at least 8 mg/liter [Bin *et al.* 2006]. In a report of 43 patients with infections caused by ESBL-producing *Enterobacter aerogenes*, no significant differences in outcomes were observed between patients treated with carbapenems or ceftazidime [Goethaert *et al.* 2006]. Finally, in a

study comparing cefepime and imipenem for the treatment of nosocomial pneumonia, clinical response rates for a subset of 13 and 10 patients in whom the infection was caused by ESBL-producing organisms were 69% and 100% respectively; in all of these cases, the isolated organisms were susceptible to cefepime using newer CLSI breakpoints [Zanetti *et al.* 2003]. In 2010, the CLSI and EUCAST modified their recommendations in two ways: the breakpoints for cephalosporins in *Enterobacteriaceae* were lowered (isolates showing MIC $\leq$ 1 mg/liter are now considered susceptible according to EUCAST, while the CLSI breakpoints are $\leq$ 1 for cefotaxime, $\leq$ 4 for ceftazidime, and $\leq$ 8 for cefepime), and it was recommended that the clinical category should be reported as found irrespective of ESBL production. Such recommendations are controversial, and imply that an important proportion of ESBL producers, particularly isolates producing CTX-M enzymes, would be reported as susceptible to ceftazidime (and to a lesser extent to cefepime) [Rodríguez-Baño *et al.* 2012c]. A recent retrospective cohort study found that cefepime (particularly when the MIC was 1–8 mg/liter) was independently associated with increased mortality among patients with bacteraemia due to ESBL-producing *Enterobacteriaceae* compared with carbapenems [Lee *et al.* 2012]. In our opinion, there is still not enough information about the efficacy of active cephalosporins in the treatment of serious infections caused by ESBL producers, particularly for those from sources other than the urinary tract. From a practical point of view, neither cefotaxime nor ceftazidime can be safely used empirically if ESBL producers are a concern, since the ESBL produced cannot be predicted, but we think it may be reasonable to continue with a cephalosporin in patients with urinary tract sepsis who had been started empirically with one of them if the patient is responding and the MIC is low enough according to present breakpoints.

Finally, although cephamycins (cefoxitin, cefotetan) are usually active against ESBL-producing isolates, they are not considered a good option because of the possibility of *in vivo* selection of cephamycin-resistant impermeability mutants, especially when using cefoxitin [Pitout, 2010]. Flomoxef is a cephamycin with better *in vitro* activity against ESBL-producing *Enterobacteriaceae*; it showed similar mortality rates to carbapenem in a retrospective observational study including only 27 patients with

bacteraemia due to ESBL-producing *K. pneumonia* [Lee *et al.* 2006]. Obviously, more data would be needed before any conclusion can be drawn for this antibiotic.

β -lactam/ β -lactam inhibitors

β -lactamase inhibitors characteristically inhibit ESBL. Although hyperproduction of β -lactamases or additional resistance mechanisms may hamper the activity of these compounds, β -lactam/ β -lactamase inhibitor combinations (BLBLIs) such as amoxicillin–clavulanate or piperacillin–tazobactam remain active against a considerable proportion of ESBL-producing enterobacteria, particularly in some areas. However, the efficacy of these combinations for treating serious infections caused by ESBL-producing enterobacteria has long been controversial.

In a recently published *post hoc* analysis of prospective cohorts of patients with bloodstream infections due to ESBL-producing *E. coli*, empirical or definitive therapy with *in vitro* active BLBLIs showed similar results to carbapenems, after controlling for confounders [Rodríguez-Baño *et al.* 2012b]. These results suggest that amoxicillin–clavulanate and piperacillin–tazobactam are an alternative to carbapenems for treating patients with bloodstream infections due to susceptible ESBL-producing *E. coli* and would be particularly useful as definitive therapy as carbapenem-sparing agents. Since the study mainly includes patients with bacteraemia from the urinary and biliary tracts, the results may only apply to such infections. Also, a recent meta-analysis could not demonstrate superiority of carbapenems over BLBLIs [Vardakas *et al.* 2012].

As regards noninvasive infections, the efficacy of amoxicillin–clavulanate was analyzed in a prospective series of 37 patients with cystitis caused by ESBL-producing *E. coli*. The cure rate was 93% for susceptible isolates and was significantly lower for resistant strains. It was concluded that amoxicillin–clavulanate is useful for cystitis caused by isolates with MIC values in the susceptibility range (MIC $\leq$ 8 μ g/ml) [Rodríguez-Baño *et al.* 2008].

Other β -lactams

Temocillin is stable against ESBLs and AmpC β -lactamase mutants and has no activity against *P. aeruginosa*. It is administered intravenously and is available only in some countries. Although the

clinical experience in infections caused by such bacteria is limited, the available data suggest that it might also be a good alternative as a carbapenem-sparing agent [Balakrishnan *et al.* 2011].

Pivmecillinam is an oral drug approved for the treatment of acute uncomplicated cystitis in some countries. It has good activity against many ESBL producers. Clinical experience on the use of pivmecillinam for treatment by ESBL producers is anecdotal. A woman with relapsing pyelonephritis due to a CTX-M-producing *E. coli* was finally cured with a prolonged course of pivmecillinam [Nicolle and Mulvey, 2007]. Also, eight patients with lower urinary tract infections (UTIs) treated with pivmecillinam were cured, but bacteriuria persisted in six [Titelman *et al.* 2012].

Fluoroquinolones

Although fluoroquinolone resistance is frequent in ESBL producers, these drugs may be very convenient for definitive therapy in case of susceptible strains. In a recent meta-analysis, fluoroquinolones were associated with increased mortality compared with carbapenems for empirical therapy but not for definitive therapy [Vardakas *et al.* 2012]. In a study by Tumbarello and colleagues, 8 of 16 patients with bacteraemia due to ESBL-producing *Enterobacteriaceae* who were treated with ciprofloxacin died. In all these patients, the MIC of ciprofloxacin was 0.5–1 mg/liter, suggesting that even borderline MICs may be deleterious in these infections [Tumbarello *et al.* 2007]. Thus, it may be prudent to use another drug for isolates with these borderline MICs and if a quinolone is to be used, high doses are recommended.

Other antimicrobials

Fosfomycin is a phosphonic acid-derivate drug with bactericidal activity against *Enterobacteriaceae*. It has been shown to be useful for the treatment of uncomplicated UTIs [Falagas *et al.* 2010b]. Frequently it retains good *in vitro* activity against ESBL-producing *E. coli* and *K. pneumoniae* [de Cueto *et al.* 2006; Maraki *et al.* 2009; Falagas *et al.* 2010a]. Observational studies have shown that fosfomycin is effective for the treatment of lower UTIs due to ESBL-producing *Enterobacteriaceae* [Rodriguez-Baño *et al.* 2008; Senol *et al.* 2010] and is our preferred therapy for such infections. There is very limited experience in the use of intravenous fosfomycin for invasive infections.

The activity of aminoglycosides against ESBL producers is diverse according to geographical areas. Overall, amikacin is usually the most frequently active drug among these compounds [Pitout *et al.* 2008]. The efficacy and limitations of aminoglycosides against enterobacteria can be applied to ESBL producers [Vidal *et al.* 2007]. Kim and colleagues reported 15 cases of bacteraemia due to ESBL-producing *K. pneumoniae* and *E. coli* treated with active aminoglycosides in monotherapy; only seven had a sufficient clinical response [Kim *et al.* 2002]. We think that aminoglycosides, particularly amikacin, can probably be used in combination with other drugs for urinary tract sepsis in selected patients to avoid the overuse of carbapenems.

Nitrofurantoin is an agent approved for use in uncomplicated urinary infections, and is active against many ESBL producers. A recent retrospective report found a 69% clinical response rate in patients with lower UTIs due to ESBL-producing *E. coli* [Tasbakan *et al.* 2012], suggesting that it might be an alternative for such infections.

Tigecycline and colistin will be discussed in other sections in this review.

Therapy of infections caused by plasmid-mediated AmpC-producing *Enterobacteriaceae*

Carbapenems

Carbapenems, which are not affected by AmpC β -lactamases, have been shown to be efficacious in uncontrolled studies [Pai *et al.* 2004; Rodriguez-Baño *et al.* 2012a] and thus are rendered as the drugs of choice for serious infections caused by such enterobacteria-expressing enzymes. However, development of resistance to carbapenems during therapy due to porin loss has been repeatedly described in depressed chromosomal and plasmid-mediated AmpC producers [Jacoby, 2009]. Whether this may be avoided by using optimized doses or combinations is not well known.

Third-generation cephalosporins

It is well known that *in vitro* susceptibility in *Enterobacteriaceae* with inducible chromosomal AmpC may not correlate with clinical efficacy because of the risk of selecting β -lactamase derepressed mutants expressing high levels of AmpC. This phenomenon was well characterized for

Enterobacter spp. bloodstream infection during third-generation cephalosporin therapy [Chow *et al.* 1991; Choi *et al.* 2008], but is less so for other bacteria of the group such as *Serratia marcescens*, *Morganella morganii*, and *Citrobacter* spp. The risk for resistance emergency and therapeutic failure is probably highest for certain sites of infection associated with high-inoculum or diminished drug concentrations [Harris and Ferguson, 2012]. Therefore, third-generation cephalosporins (and monobactams) must be avoided to treat severe infections by these bacteria despite being susceptible *in vitro* [Jacoby, 2009; Navarro *et al.* 2010], but such concerns are probably less important for other sites of infections like the urinary tract [Harris and Ferguson, 2012].

Cefepime and ceftiprome

These are fourth-generation cephalosporins, which are little affected by these enzymes [Navarro *et al.* 2010]. There is more clinical experience with cefepime. Regardless the presence of β -lactamases, the effectiveness of cefepime for the treatment of patients with sepsis (especially in patients with neutropenia) was questioned in a meta-analysis which found higher mortality in patients treated with this antibiotic in comparison with other β -lactams [Yahav *et al.* 2007], although a subsequent study did not corroborate those results [Kim *et al.* 2010].

Cefepime shows inoculum effect *in vitro* (which means that it is less active at high bacterial inoculums) against plasmid-mediated AmpC-producing *K. pneumoniae* [Kang *et al.* 2004]. It has been shown to be effective in animal models [Vimont *et al.* 2007], even for porin-deficient, plasmid-mediated AmpC-producing *K. pneumoniae* [Pichardo *et al.* 2005]. Development of cefepime resistance *in vivo* has been described during cefepime therapy in infections caused by AmpC-expressing *Enterobacter aerogenes* [Barnaud *et al.* 2004; Rodriguez-Martinez *et al.* 2012]. Overall, cefepime would seem useful for the treatment of AmpC-producing *Enterobacteriaceae* but caution is needed for infections with a high inoculum or presenting with septic shock.

Other drugs

As stated before, temocillin is not efficiently hydrolyzed by AmpC β -lactamases [Livermore *et al.* 2006] and has shown clinical efficacy in an uncontrolled study [Balakrishnan *et al.* 2011] and might be an alternative for definite

therapy. Also, tigecycline has shown good *in vitro* activity against AmpC-hyperproducing *Enterobacteriaceae* [Hope *et al.* 2006; Conejo *et al.* 2008; Zhanel *et al.* 2009; Simner *et al.* 2011], but clinical experience is limited. Fluoroquinolones are a good alternative for susceptible isolates, especially for non-life-threatening infections such as urinary tract infection [Jacoby, 2009]; the cautions explained in the ESBL section would also apply here. Cotrimoxazole can also be used to treat certain infections by susceptible AmpC-producing bacteria [Harris and Ferguson 2012]. Colistin will be discussed in the next section.

Therapy of infections caused by carbapenemase-producing *Enterobacteriaceae*

Carbapenems are potent β -lactam antibiotics with a very broad spectrum and thus have been traditionally rendered as 'last-resort' antibiotics. However, carbapenems are now frontline antibiotics in many more clinical situations than before because of the emergence and spread of ESBL- and plasmid-mediated AmpC-producing *Enterobacteriaceae*. The emergence of transferable resistance to these antibiotics, which are now disseminating very rapidly, is a public health emergency because of the very limited commercially available antimicrobials showing activity against carbapenemase-producing Gram-negative bacteria [Tortola *et al.* 2005; Hirsch and Tam 2010; Carrer *et al.* 2010; Lascols *et al.* 2011; Nordmann *et al.* 2011; Patel and Bonomo 2011; Glupczynski *et al.* 2012]. This is due to the hydrolytic activity of these enzymes against β -lactams, but also to the fact that these organisms usually harbour resistance mechanisms affecting other classes of antibiotics (e.g. fluoroquinolones and aminoglycosides). We will discuss the main available therapeutic options against these bacteria, including polymyxins (colistin), fosfomycin, tigecycline, aminoglycosides, aztreonam (for MLB producers only), extended-spectrum cephalosporins (for OXA-48 producers only), carbapenems, and combination regimens. A summary of the potential options is shown in Table 3.

Polymyxins

Polymyxin B and polymyxin E (or colistin) are the members of this family used in clinical practice. Intravenous formulations of colistin and polymyxin B were mostly abandoned in the 1980s because of a reported high incidence of nephrotoxicity. Since then, they have almost

only been used for the treatment of lung infections in patients with cystic fibrosis [Falagas and Kasiakou, 2005; Landman *et al.* 2008]. Both have been reintroduced for clinical practice during the last decades, coinciding with the emergence of multidrug resistance among Gram-negative bacteria (initially nonfermenting Gram-negative pathogens and more recently *Enterobacteriaceae*) and the lack of new antibiotics to combat them.

Colistin is the most used and it is available in two commercial formulations: colistin sulfate and colistimethate sodium. Neither of these formulations is absorbed by the gastrointestinal tract after oral administration; in fact, colistin sulfate can be administered orally for bowel decontamination. Colistimethate sodium, which is less toxic than colistin sulfate, is available in parenteral formulations and can be administered intravenously, intramuscularly, or by nebulization. Usually the term 'colistin' refers to this parenteral presentation of colistimethate sodium.

Colistin is a bactericidal antibiotic with concentration-dependent activity. It targets the outer bacterial cell membrane: the polypeptidic ring binds the lipopolysaccharide through electrostatic interactions and displaces magnesium and calcium, while the fatty acid grass interacts with a lipid region of the lipopolysaccharide leading to increased permeability, leakage of cell contents, and inhibition of biological effects of endotoxin [Falagas and Kasiakou, 2005; Landman *et al.* 2008]. Colistin is active only against Gram-negative aerobic bacilli, including most *Enterobacteriaceae*, nonfermentative bacilli (e.g. *Acinetobacter* spp., *P. aeruginosa*, and *Stenotrophomonas maltophilia*), and other Gram-negative bacilli like *Haemophilus influenza*. Among the *Enterobacteriaceae*, *Proteus* spp., *Providencia* spp., *Serratia* spp., and *Edwardsiella* spp. are all resistant to colistin [Falagas and Kasiakou, 2005; Landman *et al.* 2008].

Colistin has been mainly used in the treatment of invasive infections caused by multidrug-resistant (particularly carbapenem-resistant) Gram-negative bacteria. The results of published studies are frequently difficult to analyze because of their limitations: there is a lack of randomized controlled trials, and many comparative observational studies failed to appropriately control for confounders. Whether the efficacy of colistin is noninferior to that of other antibiotics

(particularly β -lactams) is controversial, especially for lung infections [Paul *et al.* 2010; Florescu *et al.* 2012]. It has been claimed that the conventional dose of colistin (e.g. 1–2 million IU every 8 h) is insufficient to reach the targeted PK/PD parameters that predict efficacy, and that optimization of dosing would improve its efficacy [Michalopoulos *et al.* 2011; Yilmaz *et al.* 2012]. Recently, a colistin dosing schedule based on PK/PD models (including a loading dose of 9 million IU followed by 4.5 million IU every 12 h) has been tested in an uncontrolled study with apparently good efficacy and safety results [Dalfino *et al.* 2012]. Whether this new dosing regimen will solve the doubts about the efficacy and safety of colistin would obviously need more data.

Besides the intravenous route, colistin can be administered by inhalation, either alone or as adjunctive therapy. While there is experience in the treatment of patients with cystic fibrosis, the published experience in patients with ventilator-associated pneumonia is scarce. Although the idea is attractive, the results have not been as good as expected [Michalopoulos *et al.* 2008; Kofteridis *et al.* 2010].

Carbapenems

Carbapenemases confer a heterogeneous level of resistance to carbapenems according to the specific hydrolytic activity of each enzyme and the level of expression of the β -lactamase [Falagas *et al.* 2011; Daikos and Markogiannakis, 2011; Tzouvelekis *et al.* 2012]. Overall, KPCs usually present enough carbapenem-hydrolytic activity to be detected as resistant by using the new CLSI breakpoints. As for MLB producers, there is substantial heterogeneity in their carbapenemase enzymatic activity (e.g. high for VIM-2 and VIM-19 and low for VIM-1, VIM-5, IMP-4, NDM-1, and NDM-4); however, MICs of carbapenems for bacteria producing these are frequently higher due to additional resistance mechanisms [Tzouvelekis *et al.* 2012]. In addition, coexisting mechanisms of resistance (e.g. alteration in porins) can also be associated with increased MIC of carbapenems. The fact that some carbapenemase producers may show 'low MIC' of carbapenems has brought a similar controversy to that caused by cephalosporins and ESBL producers. While some authors considered that carbapenems may be used if MIC is low enough to reach the PK/PD target by using a conventional or optimized dose of carbapenems [Daikos and Markogiannakis, 2011], it can be

argued that the expression of the β -lactamase may increase during therapy or an additional mechanism of resistance may arise if killing of bacteria is not fast enough and causes therapeutic failure.

Clinical breakpoints of carbapenems for *Enterobacteriaceae* have been changed during recent years to be adapted to both PK/PD and available clinical data. At the time of writing this review, the EUCAST breakpoint for susceptibility is up to 2 mg/liter for imipenem and meropenem, 1 mg/liter for doripenem, and 0.5 mg/liter for ertapenem [EUCAST, 2012], while the values for CLSI are up to 1 mg/liter for imipenem, meropenem, and doripenem, and up to 0.25 mg/liter for ertapenem [CLSI, 2010]. Both institutions recommend reporting the clinical category as found irrespective of the production of carbapenemases. It is true that the majority, but certainly not all carbapenemase producers will be rendered resistant with these breakpoints, particularly when using the CLSI ones. However, carbapenems used in monotherapy for infections caused by KPC-producing *K. pneumoniae* have been associated with a high rate of clinical or microbiological failure [Weisenberg *et al.* 2009]. If a carbapenem is to be used against a carbapenemase-producing organism, optimizing the dose and administration to improve the probability of attaining the PK/PD target is probably very important [Falagas *et al.* 2011]. To do so, the use of high doses at shorter intervals, and the use of extended infusions (if the drug is stable for long enough, as is the case for meropenem and doripenem) must be considered [Dandekar *et al.* 2003; Daikos and Markogiannakis, 2011]. In a murine model of thigh infection by KPC-producing *K. pneumoniae* using doripenem at an equivalent dose of 1–2 g every 8 h by intravenous extended infusion (4 h), bacteriostatic activity was achieved against strains showing MICs as high as 8 and 16 mg/liter respectively [Bulik and Nicolau, 2010]. In humans, serum concentrations above 4 mg/liter can be reached for the whole time between doses when meropenem is administered at 2–3 g every 8 h in an extended infusion [Dandekar *et al.* 2003]. Whatever the case, more studies are needed to establish the efficacy of carbapenem monotherapy against carbapenemase-producing *Enterobacteriaceae* showing low MICs to these compounds.

A recent *in vitro* and animal model investigation showed that the combination of ertapenem and doripenem was more efficacious than a

carbapenem alone against KPC-producing *K. pneumoniae* [Bulik and Nicolau, 2011]. This is due to the high affinity of KPCs for ertapenem [Anderson *et al.* 2007], which blocks most KPC molecules and allows doripenem to kill the bacteria. Such an innovative approach would need to be studied in patients. Combined therapy including carbapenems and non- β -lactamic antibiotics will be discussed later.

Aztreonam and extended-spectrum cephalosporins

The MLB and some OXA-type enzymes show low hydrolytic activity against aztreonam [Falagas *et al.* 2011]. Additionally, OXA-48 and OXA-181 very weakly hydrolyze the extended-spectrum cephalosporins (e.g. ceftazidime). Thus, such antibiotics must be considered as options for these specific enzymes. However, there are two major limitations for their use. First, there are no published clinical data, and second, many of the *Enterobacteriaceae* isolates that produce MBLs or oxacillinases additionally carry ESBLs or other resistant determinants that confer resistance to aztreonam and extended-spectrum cephalosporins [Falagas *et al.* 2011; Shakil *et al.* 2011]. For isolates coexpressing ESBLs and MBLs, a combination of aztreonam with a β -lactamase inhibitor has been proposed [Shakil *et al.* 2011; Livermore *et al.* 2011a].

Other antimicrobials

Fosfomycin remains active against many carbapenemase-producing *Enterobacteriaceae*. However, the clinical experience is very limited. Fosfomycin has been intravenously administered to treat infections caused by carbapenem-resistant *K. pneumoniae* (2–4 g every 6 h) with good results in an uncontrolled study [Michalopoulos *et al.* 2010]. Since there is a concern that development of resistance to fosfomycin may occur during treatment, it seems prudent to use fosfomycin in combination with other agents for the treatment of invasive infections caused by carbapenemase-producing *Enterobacteriaceae* [Falagas *et al.* 2011]. Clinical studies of fosfomycin in monotherapy and combined with other drugs are awaited.

Tigecycline has a predominantly time-dependent bacteriostatic activity against *Enterobacteriaceae* (except *Proteus* spp., *Providencia* and *Morganella* which are intrinsically resistant) and other bacteria, including Gram positives and anaerobes; it shows *in vitro* activity against most

carbapenemase-producing *Enterobacteriaceae* [Kelesidis *et al.* 2008; Zhanel *et al.* 2009]. Tigecycline is approved for the treatment of complicated skin and soft tissues infection (diabetic foot infections are not included) and complicated intra-abdominal infections. Several published meta-analyses suggested that the mortality of patients treated with tigecycline was higher in comparison with a pool of different comparators used in the randomized trials [Yahav *et al.* 2011; Tasina *et al.* 2011; Prasad *et al.* 2012]. Thus, it is recommended that tigecycline is used only in situations in which other options are unsuitable; due to the paucity of options for the treatment of carbapenemase-producing enterobacteria, tigecycline is frequently considered in such infections. Some aspects related to the PK/PD properties of tigecycline need to be taken into account. Because only 22% of a tigecycline dose is excreted in urine, it is not expected to be useful for treating urinary tract infections; and because of its bacteriostatic activity, it is not suitable for central nervous system infections, endocarditis, or infections in patients with neutropenia. Also, its low blood levels do not make it an attractive drug for the treatment of vascular-related infections [Falagas *et al.* 2011]. Development of resistance was observed *in vitro* and *in vivo* in *K. pneumoniae* [Rodriguez-Avial *et al.* 2012] and *E. coli* [Stone *et al.* 2011]. Tigecycline has been used frequently in association with other drugs for the treatment of infections caused by extremely drug-resistant enterobacteria [Qureshi *et al.* 2012; Tumbarello *et al.* 2012].

Combination therapy

Combination therapy has recently focused a great interest in the treatment of infections caused by carbapenemase-producing *Enterobacteriaceae* for several reasons: the potential synergistic effect of some antimicrobial combinations, the increased probability of providing active initial therapy, and the possibility of preventing further resistance development [Falagas *et al.* 2011].

Two recent studies provide the best clinical data to date, suggesting that combination therapy is superior to monotherapy for these infections. In a retrospective cohort study including 125 patients with bloodstream infections caused by KPC-producing *K. pneumoniae*, the 30-day mortality rate was significantly lower in those receiving combined therapy with two or more drugs than in those receiving monotherapy

[Tumbarello *et al.* 2012]. Another observational study including 41 patients with bloodstream infection caused by similar organisms, combination therapy achieved better results than monotherapy [Qureshi *et al.* 2012]. In view of the clinical results, combined therapy is nowadays considered the treatment of choice for infections caused by KPC-producing enterobacteria. The best antimicrobial combinations remain unclear, particularly because some combinations might be antagonistic or increase toxicity. The role of carbapenems in the combination regimens against carbapenemase-producing *Enterobacteriaceae* may be relevant; furthermore, carbapenems must be considered as part of the combination not only for isolates with low MICs (≤ 4 mg/liter) but also for isolates showing higher values [Daikos and Markogiannakis, 2011; Pournaras *et al.* 2011; Qureshi *et al.* 2012; Tumbarello *et al.* 2012].

The use of colistin as part of the combination regimen without carbapenems has yielded heterogeneous results both in *in vitro* and *in vivo* studies. *In vitro* data studying the combination of colistin plus tigecycline were contradictory [Pournaras *et al.* 2011; Albur *et al.* 2012; Tumbarello *et al.* 2012]. There are some clinical data to support this combination but they are still insufficient [Qureshi *et al.* 2012; Cho *et al.* 2012]. Intravenous fosfomycin (fosfomycin sodium) has been used in combination with colistin, gentamicin and piperacillin/tazobactam with good results against carbapenem-resistant *K. pneumoniae* in critically ill patients [Michalopoulos *et al.* 2010]. Combinations of tigecycline with carbapenems have also shown good clinical efficacy in the treatment of bacteraemia due to KPC-producing *K. pneumoniae* [Qureshi *et al.* 2012]. A triple-drug regimen that included tigecycline, colistin, and meropenem was significantly linked to a reduced risk of death in patients with bloodstream infections caused by these bacteria in one study [Tumbarello *et al.* 2012].

In view of the available data, we recommend using combined therapy for invasive infections caused by carbapenemase producers, including imipenem or meropenem (optimized dose) at least if the isolate shows a MIC up to 4 mg/liter plus one or, in case of severe infection, two further *in vitro* active drugs. The following should be considered according to *in vitro* activity: aztreonam (for MLB producers), ceftazidime or cefepime (for those only producing OXA enzymes),

colistin, tigecycline, aminoglycosides, and fosfomycin. Carbapenem, colistin, and tigecycline would be our preferred option for severe infections caused by extremely drug-resistant KPC producers.

New antimicrobial agents

The development of new antimicrobial agents is urgent. However, only a few new agents have entered full clinical development; these include newer aminoglycosides, β -lactams, β -lactam inhibitors, and tetracycline derivatives with activity against enterobacteria [Bush, 2012].

Plazomicin (ACHN-490) is a new aminoglycoside within the class named neoglycosides [Aggen *et al.* 2010]. It is not affected by the aminoglycoside-modifying enzymes except for AAC(2'')-Ia, -Ib, and -Ic. Plazomicin has shown *in vitro* activity against multidrug-resistant enterobacteria, including isolates producing ESBLs, KPCs, and MLBs, except NDM-1 producers which may be resistant due to the production of 16S rRNA methylase [Endimiani *et al.* 2009; Livermore *et al.* 2011b; Galani *et al.* 2012] and has shown to be efficacious in animal models [Reyes *et al.* 2011].

New β -lactam/ β -lactamase inhibitor combinations are currently under development. Avibactam (formerly NXL104) is a novel non- β -lactam inhibitor of class A and C β -lactamases; it also shows activity against class D enzymes, albeit heterogeneous. Avibactam has shown good activity in *in vitro* and animal studies, and is currently entering phases II and III clinical trials in combination with ceftazidime or ceftaroline [Endimiani *et al.* 2011; Lucasti *et al.* 2011; Vazquez *et al.* 2011; Wiskirchen *et al.* 2011; Castanheira *et al.* 2012]. The results from a phase II study comparing ceftazidime avibactam with imipenem in complicated UTIs have been published. Favourable microbiological response was achieved in 70% and 71% of patients respectively. Of note, 85.7% of patients with a ceftazidime-resistant isolate showed a favourable response to ceftazidime–avibactam [Vazquez *et al.* 2012]. The combination of ceftolozane–tazobactam has demonstrated synergistic activity *in vitro* against many ESBL producers and AmpC producers; unfortunately, it is not active against KPC-producing enterobacteria [Titelman *et al.* 2011; Sader *et al.* 2011]. MK-7655 in combination with imipenem has been shown to be effective *in vitro* against a variety of

AmpC- and KPC-producing isolates [Hirsch *et al.* 2012].

Omadacycline (PTK0796) belongs to a new class of compounds, the aminomethylcyclines, which are semisynthetic derivatives of minocycline. It has *in vitro* activity against Gram-positive and Gram-negative bacteria. Omadacycline has completed phase I and II clinical trials [Maccone *et al.* 2003; Sutcliffe, 2011].

Conclusion and future prospects

There has been a rapid and worldwide spread of multidrug-resistant *Enterobacteriaceae*, causing infections both in hospitalized and (for some of such mechanisms) non-hospitalized patients. The decisions about therapy must be individualized according to the susceptibility profile and, if available, the resistance mechanism. There is clearly a need for rapid testing to detect the most important mechanisms of resistance, the development of new drugs, and better clinical studies investigating the efficacy and safety of old active drugs and combinations. Data from PK/PD models should be considered to optimize the use of drugs with borderline susceptibility.

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