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REVIEW

Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing *Enterobacteriaceae*

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SUMMARY Therapy of invasive infections due to multidrug-resistant *Enterobacteriaceae* (MDR-E) is challenging, and some of the few active drugs are not available in many countries. For extended-spectrum β-lactamase and AmpC producers, carbapenems are the drugs of choice, but alternatives are needed because the rate of carbapenem resistance is rising. Potential active drugs include classic and newer β-lactam–β-lactamase inhibitor combinations, cephamycins, temocillin, aminoglycosides, tigecycline, fosfomycin, and, rarely, fluoroquinolones or trimethoprim-sulfamethoxazole. These drugs might be considered in some specific situations. AmpC producers are resistant to cephamycins, but cefepime is an option. In the case of carbapenemase-producing *Enterobacteriaceae* (CPE), only some "second-line" drugs, such as polymyxins, tigecycline, aminoglycosides, and fosfomycin, may be active; double carbapenems can also be considered in specific situations. Combination therapy is associated with better outcomes for high-risk patients, such as those in septic shock or with pneumonia. Ceftazidime-avibactam was recently approved and is active against KPC and OXA-48 producers; the available experience

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is scarce but promising, although development of resistance is a concern. New drugs active against some CPE isolates are in different stages of development, including meropenem-vaborbactam, imipenem-relebactam, plazomicin, cefiderocol, eravacycline, and aztreonam-avibactam. Overall, therapy of MDR-E infection must be individualized according to the susceptibility profile, type, and severity of infection and the features of the patient.

KEYWORDS multidrug resistance, antimicrobial therapy, extended-spectrum β-lactamases, carbapenemases, bloodstream infections, mortality

INTRODUCTION

The emergence and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Enterobacteriaceae* have become a public health problem in recent decades (1). *Enterobacteriaceae* are common pathogens and common causes of different types of community- and hospital-acquired infections, so antimicrobial resistance in these bacteria has significant potential impacts on antibiotic use and patient outcomes. Treatment of infections caused by MDR and XDR *Enterobacteriaceae* is challenging, with limited antimicrobials available and limited evidence of their efficacy. The previous paradigm, with a specific drug serving as the drug of choice across most clinical situations, no longer holds. Meanwhile, an increasing body of knowledge suggests that therapy can be individualized in accordance with the source and severity of infection and the susceptibility profile of the bacteria, among other factors. In order to help physicians make decisions for treatment of infections caused by MDR and XDR *Enterobacteriaceae*, a review of the available data is necessary.

The objective of this article is to review the potential therapeutic options for the treatment of infections due to extended-spectrum-β-lactamase (ESBL)-, AmpC-, and carbapenemase-producing *Enterobacteriaceae*. This review includes mainly clinical studies, prioritizing controlled studies when available, and includes noncomparative studies only when these provide information relevant to specific populations. *In vitro* and animal studies are also included only if considered necessary in the absence of clinical studies. The target infections are invasive ones, such as hospital-acquired pneumonia (HAP), complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), and any bacteremic infection. MDR has been defined for epidemiological purposes as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories, and XDR has been defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories (2). Here, however, we consider the most important MDR and XDR *Enterobacteriaceae* with specific mechanisms of resistance, such as those that produce ESBLs, AmpC β-lactamases, and carbapenemases, which are typically MDR according to the above criteria because of the β-lactamases produced but are also frequently resistant to some non-β-lactam antibiotics and so represent a therapeutic challenge. Also, most studies refer to bacteria that produce these mechanisms of resistance.

Readers should be aware that randomized controlled trials (RCT) are scarce in this field. Most available clinical studies are observational in design (frequently retrospective cohort studies) or are case series and anecdotal reports. RCT data on specific syndromes, based on MDR *Enterobacteriaceae* analyzed *post hoc*, are also considered. However, many studies suffer from important limitations, including potential selection and information biases as well as a lack of adequate control for confounding. Lack of statistical power is also a major consideration in studies not finding differences in efficacy between compared drugs.

Information is stratified into empirical and targeted therapy categories wherever possible. Nonetheless, decisions about empirical therapy should be made in accordance with local rates for the pathogens considered, together with individual risk factors and infection severity. Because of important differences in local epidemiology, rules about when empirical therapy against specific resistant bacteria should be started cannot be generalized.

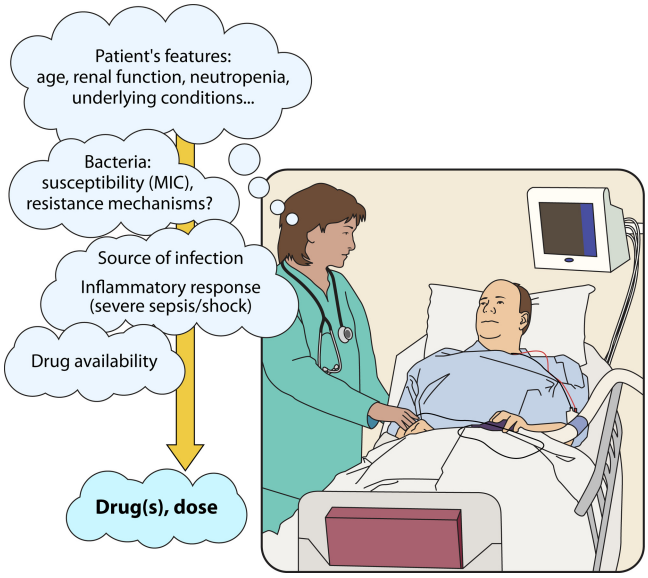

FIG 1 Aspects to be considered in the decision-making process for antimicrobial therapy of patients with infections due to ESBL-, AmpC-, or carbapenemase-producing *Enterobacteriaceae*.

The use of one or another drug may depend on the results of susceptibility testing. While this is beyond the objective of this review, it should be noted that the determination of the MIC for some antimicrobials may not be fully reliable, depending on the methods used; also, a ± 1 dilution variability in MIC determination is accepted. Finally, the breakpoints for susceptibility recommended by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee for Antimicrobal Susceptibility Testing (EUCAST) differ for some antimicrobials.

Finally, while it is taken for granted that the general principles for the management of infectious diseases apply, the paramount importance of these principles cannot be stressed enough and include support therapy when needed, rapid and effective source control whenever possible, and consideration of patient characteristics (immunosuppression, renal function, etc.), the severity of systemic inflammatory response syndrome, and the source of infection for the selection of an antimicrobial regimen (Figure 1).

THERAPY AGAINST ESBL- AND AmpC-PRODUCING *ENTEROBACTERIACEAE*

Both ESBL and AmpC producers are typically resistant to some or all cephalosporins, but they exhibit some differences, as follows. ESBLs are inhibited by β-lactam inhibitors and do not hydrolyze cephamycins, while AmpC enzymes are not inhibited by classic β-lactam inhibitors and confer resistance to cephamycins but do not efficiently hydrolyze cefepime (3–5). ESBLs are typically encoded by plasmid-borne genes (3, 4), whereas AmpC can be encoded by plasmid genes or be produced as a result of derepression of chromosomal genes in some *Enterobacteriaceae* (typically *Enterobacter* spp., *Serratia marcescens*, *Citrobacter freundii*, *Providencia* spp., and *Morganella morganii*). The latter will test as susceptible to cephalosporins if AmpC production is not derepressed, but resistance can develop while on treatment with these drugs (5). Finally, chromosomally encoded AmpC can be overproduced in *Escherichia coli* (5). Since some laboratories do not routinely identify the specific mechanism of resistance to cephalosporins, as this is not recommended for the purpose of treatment decisions by CLSI or EUCAST (but only for epidemiological reasons) and the type of cephalosporinase cannot always be differentiated phenotypically, both ESBL and AmpC producers are reviewed here. Most available information concerns ESBL-producing *Enterobacteriaceae* (ESBL-E); potentially active drugs against these bacteria are reviewed in Table 1.

TABLE 1 Summary of positive and negative aspects and dosing of potentially useful drugs in the treatment of infections with ESBL- and AmpC-producing *Enterobacteriaceae*[b]

Drug	Positive aspects	Negative aspects	Dosing (for adults with normal renal function) and comments
Meropenem, imipenem, doripenem	Reference drugs, usually active	Ecological impact; less experience with doripenem	Standard dosing is recommended
Ertapenem	Not active against *P. aeruginosa*[a]; usually active; convenient for outpatient therapy and deescalation from other carbapenems	Ecological impact if CPE endemicity/outbreak; doubts in cases of septic shock (insufficient dosing?); anecdotal failures described with development of resistance (porin loss)	1 g/day in most situations; for septic shock or high-inoculum infections with borderline MIC isolates, use other alternatives or increase dose to 2 g/day
Piperacillin-tazobactam	Probably noninferior to carbapenems in UTI and biliary tract infections	False susceptibility with some automated systems; inoculum effect (unrelated to ESBLs); heterogeneous resistance rates (5 to 30% among ESBL producers, higher among AmpC producers); doubts in cases of septic shock, pneumonia (CLSI susceptibility breakpoint too high)?	4.5 g every 8 h (extended infusion) or every 6 h
Amoxicillin-clavulanic acid	No inoculum effect; probably noninferior to carbapenems in UTI and biliary tract infections; not active against *P. aeruginosa*[a]; convenient for oral switch	Not available for i.v. use in many countries; heterogeneous resistance rates, usually >40% among ESBL producers; AmpC producers are resistant	Intravenous, 2.2 g/8 h; oral, at least 1.250 g/8 h for UTI
Ceftolozane-tazobactam	Areas with large proportions of susceptible isolates	Reserve drug for MDR *P. aeruginosa* infection; scarce experience so far; 10–30% resistance rates among ESBL producers, lower rates in AmpC producers	1.5 g/8h; approved for cUTI and cIAI (with metronidazole); consider 3 g/8 h for pneumonia
Ceftazidime-avibactam	Large proportion of susceptible isolates	Reserve drug for KPC- or OXA-48-producing *Enterobacteriaceae*	2.5 g/8 h; approved for cUTI and cIAI (with metronidazole); in Europe, also approved for HAP in case of limited options
Cefotaxime, ceftriaxone, ceftazidime, cefepime	Some ESBL-E may be susceptible; cefepime is usually active against AmpC producers	Most isolates are resistant (except to cefepime in the case of AmpC producers); inoculum effect; ecological impact; clinical data are scarce and contradictory	If used, high doses are recommended (cefotaxime, 1 g/6 h to 2 g/8 h; ceftazidime or cefepime, 2 g/8 h)
Cefoxitin, cefotetan, cefmetazole, moxalactam, flomoxef	Not active against *P. aeruginosa*[a]; areas with large proportions of susceptible isolates (ESBL producers); probably useful against UTI for stable patients	AmpC producers are resistant; inoculum effect; observational studies with contradictory results; anecdotally described development of resistance during therapy	High doses; close follow-up needed
Temocillin	Active against ESBL and AmpC producers; not active against *P. aeruginosa*[a]	Not available in many countries; comparative studies are lacking	Probably 2 g every 8 h
Gentamicin, tobramycin, amikacin	Active against many ESBL and AmpC producers; useful for UTI	Nephrotoxicity; less efficacious in non-UTI infections; heterogeneous resistance rates	Standard dosing (see Table 2); may be considered empirically as carbapenem-sparing agents (in monotherapy or in combination with a lower-spectrum β-lactam) until microbiological data are available
Tigecycline	Active against most ESBL and AmpC producers; not active against *P. aeruginosa*[a]	FDA and EMA warnings for use only if other options are unavailable/unsuitable; probably not a good option for UTI or HAP	100-mg loading dose, 50 mg/12 h; may be an alternative in cIAI
Fosfomycin (i.v.)	Noninferior to piperacillin-tazobactam in cUTI (pending publication of data)	Not available in many countries; scant experience; risk of emergence of resistant subpopulations with monotherapy	4 g/6 h to 6–8 g/8 h
Ciprofloxacin, levofloxacin	Potentially useful for fully susceptible isolates; convenient for oral switch	Ecological impact; most isolates are resistant; failures for isolates with MICs of 0.5–1 mg/liter have been described	For i.v. ciprofloxacin, 400 mg/8–12 h; for oral ciprofloxacin, 500–700 mg/12 h; for levofloxacin (i.v., oral), 750 mg/24 h
Trimethoprim-sulfamethoxazole	Convenient for oral switch	Most isolates are resistant; scant published experience	i.v. or oral, 160/800 mg/8–12 h

[a]Considered a positive aspect in terms of antimicrobial stewardship purposes (avoiding selective pressure on *P. aeruginosa*).
[b]CPE, carbapenemase-producing *Enterobacteriaceae*; i.v., intravenous.

Carbapenems

Carbapenems have traditionally been considered the drugs of choice for infections caused by enterobacteria producing ESBL and AmpC enzymes (3–5) because they are not affected by these resistance mechanisms. Furthermore, in the case of ESBL-E, they have been associated with lower failure rates than those for other drugs, mostly cephalosporins and fluoroquinolones. A meta-analysis that included 21 observational studies of bacteremic infections caused by ESBL-E up to January 2012 showed that mortality rates for patients who had received empirical or definitive treatment with carbapenems were lower than those for patients treated with cephalosporins, fluoroquinolones, or aminoglycosides; the differences were not significant for β-lactam–β-lactamase inhibitor (BLBLI) combinations (6). Note that many of the studies included in the meta-analysis had significant limitations, including a lack of control for confounding, and it was not always clear whether bacteria were susceptible to the noncarbapenem drugs used. There is very little published experience involving children. A small retrospective study in South Korea included children with ESBL-E UTI treated with carbapenems (4 patients) or "other drugs" (23 patients) and those who switched from a carbapenem to another drug (15 patients); the "other drugs" were cefotaxime, piperacillin-tazobactam, and amikacin (7). All patients were cured, and times to defervescence were similar. Studies comparing carbapenems to specific drugs are reviewed in specific subsections.

Regarding *Enterobacteriaceae* harboring chromosomal bla_{AmpC}, a recent meta-analysis that included studies with limitations did not find that carbapenems were clearly superior to fluoroquinolones, cefepime, or BLBLIs. In most studies reviewed, 20 to 35% of isolates included showed the derepressed AmpC phenotype (8). The data for plasmid-mediated AmpC producers are scarce.

In summary, the available data still suggest that carbapenems are the reference drugs for treatment of these infections. Nonetheless, the same assumption probably contributed to the significant worldwide increase in the consumption of carbapenems (9), which may be partly linked to the subsequent spread of carbapenem resistance. It is therefore important to take a closer look at potential alternative drugs.

Among carbapenems, most published articles have tended to focus on imipenem and meropenem (3, 6, 10). With respect to other group 2 carbapenems, a *post hoc* analysis of patients with infections due to ESBL-E included in an RCT comparing doripenem and other drugs against cUTI, cIAI, and HAP analyzed the outcomes of those receiving doripenem (25 patients) or comparators (levofloxacin, imipenem, and piperacillin-tazobactam) (29 patients); the efficacies were similar, but the numbers involved were clearly very limited (11).

Ertapenem is the only group 1 carbapenem, does not have clinically relevant activity against *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, and may exert lower selection pressure for resistance on these bacteria than that with other carbapenems (12); such a potential ecological advantage would be lost in environments with high rates of carbapenem-resistant *Enterobacteriaceae* (CRE) (13), for which the selection pressure would be similar or even higher. Five observational studies were found comparing ertapenem with other carbapenems in bloodstream infections (BSI) due to ESBL producers. There were no significant differences in terms of prognosis for either empirical or targeted therapy (14–18). In one study, however, subgroup analyses of patients who presented with severe sepsis or septic shock showed a trend toward increased mortality with ertapenem (18). A potential explanation for this would be the lower probability of attaining the pharmacokinetic-pharmacodynamic (PK-PD) target in these patients by using the standard dose of 1 g daily. The most common source of infection in all these studies was UTI, and patients with HAP were underrepresented. This is relevant because the probability of PK-PD target attainment with ertapenem has been shown to be low for patients with early-onset ventilator-associated pneumonia (VAP) and hypoalbuminemia (19). A noncomparative study analyzed 20 patients with VAP caused by ESBL-E (mostly *Klebsiella pneumoniae*), and clinical and microbiological

success rates were 80% and 75%, respectively (20). An open, single-center RCT compared deescalation to ertapenem versus continuation with a group 2 carbapenem, including imipenem, meropenem, doripenem, or biapenem, in patients with infections due to ESBL-E (32 and 34 patients, respectively) (21); 40% had a UTI and 16% had HAP. Overall, 50% of patients were bacteremic, and the ESBL-E was *Klebsiella pneumoniae* in 32% of cases. There were no significant differences in clinical cure (94% with ertapenem and 79% with other carbapenems), microbiological eradication (100% and 96%, respectively), or mortality (9% and 29%, respectively). With respect to children, data from two noncomparative studies of UTI due to ESBL-E gave promising results (22, 23). Ertapenem is also suitable for outpatient parenteral antimicrobial therapy (OPAT); experience so far comes from uncontrolled studies showing good results (24–27) and one study comparing it with oral fosfomycin (discussed below) (28).

Results from *in vitro* models suggest that regrowth occurs in isolates with a MIC of 1 mg/liter (intermediate susceptibility) exposed to ertapenem (29) and that resistant subpopulations of ESBL-producing *E. coli* may emerge during therapy at 1 g/day, while a dose of 1.5 to 2 g/day shows better bacterial killing (30). Contrary to expectations, extended infusions or fractionated dosing showed no benefits. Development of resistance to ertapenem (31–33) and other carbapenems (34) during or after treatment with ertapenem has been described anecdotally, mostly as a consequence of porin loss in complex infections. In any case, caution may be needed in using ertapenem for high-inoculum infections with inadequate source control or that are impossible to control/remove. In such circumstances, the use of a higher dose or an alternative drug would seem reasonable.

Classic BLBLIs

ESBLs are inhibited by β-lactam inhibitors (3, 4), and classic BLBLIs, such as amoxicillin-clavulanic acid, ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-sulbactam, and cefoperazone-sulbactam, are active against ESBL producers in the absence of other mechanisms of resistance. Nonetheless, β-lactamase hyperproduction and coproduction of plasmid-mediated AmpC enzymes, among other factors, can affect inhibitor activity. BLBLI resistance rates in ESBL producers show important geographical differences and are high in some areas (35–37). Furthermore, some automated systems may fail to detect resistance to piperacillin-tazobactam, as described for isolates coproducing CTX-M-15 and OXA-1 (38).

There have been concerns about the efficacy of BLBLIs against infections due to susceptible ESBL producers (3), even though similar concerns do not exist for *Enterobacteriaceae* producing other β-lactamases, such as TEM-1 or SHV-1. The arguments for such concerns include the inoculum effect with piperacillin-tazobactam. This effect, however, also occurs with non-ESBL-E organisms and is therefore not related to ESBL production (39). Animal model studies have suggested that the activity of piperacillin-tazobactam against ESBL producers depends, as expected, on the level of exposure and that use of low doses (3.375 g every 6 h) is insufficient (40–42), but they have also confirmed *in vivo* that a higher inoculum is associated with lower efficacy (43, 44). It should be noted that amoxicillin-clavulanic acid is not affected by the inoculum effect *in vitro* or *in vivo* (39, 43). Finally, some anecdotal failures with piperacillin-tazobactam have been described (45).

In regard to comparative clinical studies, a *post hoc* analysis of several prospective Spanish cohorts of patients with bacteremia caused by ESBL-producing *E. coli* did not find that *in vitro*-active BLBLIs (piperacillin-tazobactam and amoxicillin-clavulanic acid) had a deleterious impact on mortality or length of stay compared to that with carbapenems for either empirical or targeted therapy (46). The study included specific definitions for exposure, and control for confounding variables was performed by multivariate analysis with use of a propensity score for receiving BLBLI. For interpretation purposes, the following important aspects of this study should be considered: only *E. coli* cases were included, the source of the BSI was the biliary or urinary tract in more than half of patients, high doses of piperacillin-tazobactam were used (mainly 4.5 g

every 6 h), and the MIC of piperacillin-tazobactam was ≤4 mg/liter for 65% of patients treated with this antibiotic. Two meta-analyses published in 2015, one including all pathogens (47) and the other restricted to ESBL producers (6), did not find superiority of carbapenems over BLBLIs. However, a later study in the United States that included patients with BSI due to ESBL producers, mostly *K. pneumoniae*, found higher mortality with empirical piperacillin-tazobactam than with carbapenems after controlling for confounders (48). In that study, only patients receiving a carbapenem as definitive treatment were included; those who continued with piperacillin-tazobactam as definitive treatment (who were probably doing well) were excluded, which may have caused a selection bias. The most frequent dosage of piperacillin-tazobactam was 3.375 g every 6 h, and the MIC of piperacillin-tazobactam was ≤4 mg/liter for only 40% of isolates. A small study including only patients with *Proteus mirabilis* BSI found higher mortality for patients treated with piperacillin-tazobactam, but there was no control for confounders (49). Several other studies in which carbapenems did not show superiority over BLBLIs in patients with BSI were performed later (50–53). Two of these deserve further comment. One was an analysis of the international retrospective cohort INCREMENT, which compared 170 and 195 patients treated empirically with BLBLIs and carbapenems, respectively, and 92 and 509 patients treated with the respective definitive therapies (51). In the overall and subgroup analyses, BLBLIs did not show higher rates of mortality or clinical failure than those with carbapenems. The other was also a retrospective international cohort study (BICAR), performed with neutropenic patients and including 48 and 126 patients treated empirically with a BLBLI (mostly piperacillin-tazobactam) and a carbapenem, respectively; the patient numbers for targeted therapy were 17 and 234, respectively. Thirty-day mortality rates were 20.8% and 13.4% for empirical BLBLIs and carbapenems, respectively, and 5.8% and 15.8% for the respective targeted therapies (53). Treatment with a BLBLI was not shown to be associated with worse outcomes than those with carbapenems in multivariate analysis or after propensity score matching of patients. Other studies that included only UTI showed similar results (54, 55). An open randomized controlled trial performed in 3 hospitals compared the efficacies of piperacillin-tazobactam (4.5 g every 6 h) and ertapenem (1 g per day) in patients with UTI due to ESBL-E (56). Patients with obstruction of the urinary tract or prostatitis were excluded. Thirty-three patients were included in each arm; 27% and 21%, respectively, were bacteremic and 24 and 33%, respectively, had septic shock. The rates of clinical success, microbiological success, and mortality were 94%, 97%, and 6%, respectively, with piperacillin-tazobactam and 97%, 97%, and 6%, respectively, with ertapenem.

It is possible that not all BLBLIs are equally effective, with differences due to the inhibitory capacity of the β-lactamase inhibitor or to the activity of the β-lactam. There are nevertheless very few comparative data for different BLBLIs. As shown above, piperacillin-tazobactam, but not amoxicillin-clavulanic acid, shows reduced activity at high inoculum concentrations both *in vivo* and *in vitro* (39, 43). In the Spanish *post hoc* analysis of prospective cohorts of patients with BSI due to ESBL-producing *E. coli*, the 30-day mortality rate was 11.4% with piperacillin-tazobactam (4/35 patients) and 8.1% with amoxicillin-clavulanic acid (3/37 patients) (46). For susceptible isolates, the MIC distributions with piperacillin-tazobactam were extremely wide, with 10, 8, 4, 6, and 7 isolates showing MICs of ≤1, 2, 4, 8, and 16 mg/liter, respectively, while all isolates showed a MIC of 4 or 8 mg/liter with amoxicillin-clavulanic acid. A subsequent analysis showed differences in mortality according to the MIC of piperacillin-tazobactam (0/18 patients for isolates with MICs of ≤2 mg/liter and 36.8% for isolates with MICs of >2 mg/liter; relative risk [RR] = 0.13; 95% confidence interval [CI] for RR, 0.01 to 0.98) (57); note that all mortality was in patients with sources other than the urinary tract. A randomized controlled study (MERINO trial) comparing piperacillin-tazobactam with meropenem for the treatment of cephalosporin-resistant *Enterobacteriaceae* is recruiting at the time of this writing (58). Data for other BLBLIs, such as ampicillin-sulbactam, are lacking.

The above data strongly suggest that, in many situations, BLBLIs are suitable alternatives to carbapenems for the treatment of many invasive infections caused by ESBL producers if the intended BLBLI is active *in vitro*. The data are more solid for cUTI and biliary tract infections, including bacteremia. We still recommend a carbapenem for patients with high-inoculum infections (for example, undrained abscesses or pneumonia) or for patients with septic shock, for whom there are few available data. The recommended dosage for piperacillin-tazobactam is 4.5 g every 6 h, or possibly 4.5 g every 8 h if administered by extended infusion (59). Also, amoxicillin-clavulanate seems to be a good option for susceptible isolates in countries where this drug is available for intravenous administration. There are too few data on other BLBLIs to provide recommendations.

In regard to organisms harboring chromosomally carried bla_{AmpC} genes, a meta-analysis of BSI caused by *Enterobacter*, *Citrobacter*, and *Serratia* species showed that treatment with piperacillin-tazobactam was not associated with increased mortality compared to that with carbapenems (8). A retrospective cohort study studied 165 patients with BSI due to these microorganisms, 85% of which were in fact AmpC producers. Eighty-eight patients received targeted therapy with piperacillin-tazobactam and 77 with meropenem or cefepime (60). Mortality rates were 10% and 12%, respectively, while in 41 propensity-matched pairs, mortality rates were 15% and 7%, respectively (odds ratio [OR] = 0.50; 95% CI = 0.13 to 2.0). We found no comparative studies of plasmid-mediated AmpC producers. Despite the major limitations of the studies included, the results suggest that an *in vitro*-active BLBLI would be effective against these organisms.

Newer BLBLIs (Ceftolozane-Tazobactam and Ceftazidime-Avibactam)

Ceftolozane-tazobactam combines a new cephalosporin (ceftolozane) with enhanced antipseudomonal activity with a classic β-lactamase inhibitor (tazobactam). The drug was approved by the FDA and the European Medicines Agency (EMA) for treatment of cIAI (in combination with metronidazole) and cUTI, including pyelonephritis. This compound has been shown to be active *in vitro* against >90% and 42 to 98% of ESBL-producing *E. coli* and *K. pneumoniae* isolates, respectively (61). One study analyzed the outcomes for 150 patients with infection due to ESBL-E in pivotal trials of ceftolozane-tazobactam against cUTI (the comparator was levofloxacin) and cIAI (the comparator was meropenem) (62). Rates of clinical cure and microbiological eradication were higher with ceftolozane-tazobactam (98.1% and 72.2%, respectively) than with levofloxacin (82.6% and 47.8%, respectively) against cUTI; 82% of isolates were susceptible to ceftolozane-tazobactam, whereas only 25% were susceptible to levofloxacin. Against cIAI, ceftolozane-tazobactam and meropenem outcomes were similar (clinical cure rates were 95.8% and 88.5%, respectively; the same percentages were found for microbiological eradication).

Ceftazidime-avibactam combines a well-known third-generation cephalosporin with a new (non-β-lactam) β-lactamase inhibitor. It was recently approved by the FDA and the EMA for treating cUTI and cIAI (the latter in combination with metronidazole); the EMA also includes an indication for HAP and other infections due to Gram-negative bacteria with limited treatment options. Avibactam inhibits class A enzymes, including ESBLs and *Klebsiella pneumoniae* carbapenemases (KPC), as well as class C and some OXA β-lactamases, but is not active against metallo-β-lactamases (MBLs) (61). In the pivotal trial against cUTI, ceftazidime-avibactam and doripenem were compared. Clinical cure among patients with ceftazidime-resistant isolates (mostly due to ESBL production) was 89.3% (67/75 patients) with ceftazidime-avibactam and 89.3% (75/84 patients) with doripenem (63). In the pivotal trial for treatment of cIAI, ceftazidime-avibactam plus metronidazole showed a rate of clinical response against ceftazidime-nonsusceptible *Enterobacteriaceae* (around 80% were ESBL producers) similar to that with meropenem (81.8% [36/44 patients] versus 85.5% [53/62 patients]) (64), and it showed an efficacy similar to that of the best available therapy (mostly carbapenems) in a pathogen-directed trial of patients with cUTI and cIAI caused by ceftazidime-resistant *Enterobacteriaceae* (65).

The available data therefore support the efficacy of both new BLBLIs against susceptible ESBL producers in patients with cUTI, and also of ceftazidime-avibactam against cIAI, although it should be noted that the resistance rate among ESBL producers is higher for ceftolozane-tazobactam than for ceftazidime-avibactam (61). However, because of their potential added value against XDR organisms (XDR *P. aeruginosa* in the case of ceftolozane-tazobactam and KPC- or OXA-48-producing *Enterobacteriaceae* in the case of ceftazidime-avibactam), it seems prudent to reserve these drugs for these particular organisms. We found no studies providing clinical data on infections caused by AmpC producers.

Oxyiminocephalosporins (Cefotaxime, Ceftriaxone, Ceftazidime, and Cefepime)

According to present breakpoints recommended by EUCAST (66) and CLSI (67), some ESBL-E are susceptible to cephalosporins (68, 69). Producers of TEM and SHV types of ESBLs are susceptible to cefotaxime more frequently than CTX-M producers are, and the opposite is the case for ceftazidime and cefepime. This is because different ESBL types vary in the ability to hydrolyze specific cephalosporins (3, 4). The proportion of AmpC producers (by either plasmid-borne genes or derepressed or hyperexpressed chromosomal genes) that are susceptible to cephalosporins (except cefepime) is lower (70).

Before 2010, *Enterobacteriaceae* with cephalosporin MICs of ≤8 mg/liter were considered susceptible. Patients with BSI due to ESBL-E treated with cephalosporins had worse outcomes than expected, even when isolates showed MICs within the range of susceptibility (71), which prompted the recommendation to report all ESBL-E as resistant. However, PK-PD stochastic models suggested that the breakpoints for cephalosporins were too high and that outcome was dependent only on the probability of attaining the PK-PD target, regardless of ESBL production (72, 73). As a result, EUCAST and CLSI lowered the susceptibility breakpoints of cephalosporins for *Enterobacteriaceae* (as of 2017, isolates with MICs of ≤1 mg/liter are susceptible according to EUCAST breakpoints [66]; breakpoints according to CLSI are ≤1 mg/liter for cefotaxime, ≤2 mg/liter for cefepime, and ≤4 mg/liter for ceftazidime [67]), and it is recommended to report the susceptibility as found, irrespective of ESBL production.

Clinical data on outcomes for patients with infections caused by ESBL-E who were treated with active cephalosporins versus other options are limited and sometimes contradictory (68, 74–79). Goethaert et al. found similar mortality rates for 21 and 23 patients with BSI due to TEM-23-producing *Enterobacter aerogenes* who were treated empirically with cefepime (2 g every 8 h) and carbapenems, respectively (74). Most patients received combination therapy, and there was no adjustment for confounders. Chopra et al. found an adjusted OR for mortality of 1.66 (95% CI = 0.71 to 3.87) for patients treated with cefepime (dose not specified) compared to that for carbapenems in patients with ESBL-E BSI (76). Lee et al. found higher mortality with cefepime (1 to 2 g every 8 h) than with carbapenems, using multivariate analysis and propensity score matching (77). The outcomes were somewhat worse for isolates with cefepime MICs of 2 to 8 mg/liter than for those with MICs of ≤1 mg/liter. Finally, Wang et al. found a trend toward higher mortality with cefepime (2 g every 8 h) than that with carbapenems in a propensity score-matched analysis (hazard ratio [HR] = 2.87; 95% CI = 0.88 to 9.41) (78). In a study of *Enterobacter cloacae* bacteremia, ESBL production was independently associated with increased mortality in patients treated with cefepime, even after controlling for the MIC (79). Another study evaluated the impact of the cefotaxime or ceftriaxone MIC on the outcomes for 409 patients with community-onset bacteremia due to community-onset BSI due to *Enterobacteriaceae* (mostly *E. coli*) who were treated empirically with these drugs (80); 94% of isolates were susceptible (MICs of ≤1 mg/liter). Patients with susceptible isolates had a lower risk of mortality in adjusted analysis, but no comparisons with different drugs were given. The arguments against the use of cephalosporins include the inoculum effect shown in *in vitro* and *in vivo* models (44, 81–83) and the possibility of hyperexpression of bla_{ESBL} genes (84).

In view of the data available so far, we would not recommend using a cephalosporin with *in vitro* susceptibility as targeted therapy for patients with invasive infections due to ESBL producers. For patients who received an active cephalosporin empirically, we recommend switching to an alternative drug as targeted therapy, except for stable patients with nonobstructive UTI or if the source of infection has been removed. If a cephalosporin is to be used, a high dose is recommended.

AmpC producers are usually susceptible to cefepime unless other mechanisms of resistance also exist. An observational study of BSI due to *Enterobacter cloacae* found a higher mortality for patients treated with cefepime than for those treated with carbapenems when the isolates had MICs of 4 to 8 mg/liter (79). The meta-analysis mentioned found no significant differences in outcomes for patients with BSI caused by *Enterobacteriaceae* harboring chromosomally encoded AmpC who were treated with cefepime or carbapenems, although only a minority of patients included had isolates with derepressed AmpC (8). Tamma et al. compared mortality rates for hospitalized patients with blood, bronchoalveolar lavage, or intra-abdominal fluid cultures growing AmpC-producing *Enterobacter* spp., *Serratia* spp., or *Citrobacter* spp. with derepressed AmpC and treated with cefepime (1 to 2 g every 8 h) or meropenem; after comparing 32 propensity score-matched pairs, no effect on mortality was demonstrated (31% and 34%, respectively) (85). This contrasts with the fact that cefepime is also less active *in vitro* and *in vivo* with high inocula of AmpC producers (86–88). More clinical comparative studies of cefepime against derepressed AmpC mutants and plasmid-mediated AmpC producers are needed.

In summary, at high doses, cefepime seems to be a reasonable alternative to carbapenems for the treatment of invasive infections caused by susceptible *Enterobacteriaceae* with chromosomally encoded AmpC. There is very little experience regarding the efficacy of cefepime against plasmid-mediated AmpC producers.

Cephamycins

The inability of ESBLs to efficiently hydrolyze cephamycins, which include cefoxitin, cefotetan, cefmetazole, moxalactam, and flomoxef, means that cephamycins are active against ESBL producers in the absence of other resistance mechanisms (2). Cephamycins are not active against AmpC producers. The use of these drugs was discouraged after early anecdotal reports of development of resistance in ESBL producers during treatment due to porin loss (89, 90). Later, several observational studies comparing the efficacies of cephamycins (mainly flomoxef and cefmetazole) and carbapenems in infections due to ESBL producers were published (91–97). The studies included patients with BSI, predominantly UTI, and one included only patients with pyelonephritis (93). In all but two studies (95, 96), there were small numbers of patients treated with cephamycins, ranging from 7 to 29. Only one study showed worse outcomes with these drugs (92), but most had limited or inadequate control for confounders and low statistical power. In most of the studies, the patients who received carbapenems seemed to be more seriously ill. Matsumura et al. found similar mortality rates among patients receiving targeted therapy for 59 patients treated with flomoxef or cefmetazole and 54 treated with carbapenems, after propensity score adjustment (95). Lee et al. found similar mortality rates with flomoxef and carbapenems when the MIC of flomoxef was $\leq$1 mg/liter but not when it was 4 to 8 mg/liter (96).

The available data suggest that cephamycins may be an alternative to carbapenems for some nonsevere infections, particularly UTI, where they can serve as carbapenem-sparing options. More data are needed for other types of infection and more seriously ill patients. In any case, high doses and close follow-up are recommended.

Temocillin

Temocillin is active against *Enterobacteriaceae* and is stable against hydrolysis by ESBLs and AmpC β-lactamases; it has little useful activity against *Pseudomonas* spp. (98, 99). Unfortunately, it is currently available for intravenous use in only a few countries (such as the United Kingdom and Belgium), and there is very little published experience

regarding its use against these pathogens. In a murine model of UTI, the efficacy of temocillin was similar to that of imipenem against CTX-M-15-producing *E. coli* (100). Balakrishan et al. (101) reported 92 patients with infections due to *Enterobacteriaceae* (41 had UTI and 42 BSI from diverse sources) who were treated with temocillin; 53 of the isolates were ESBL or derepressed AmpC producers. Clinical and microbiologial cure rates were 86% and 84%, respectively. In a crude analysis, ESBL or AmpC production had no impact on outcome. No clinical studies have been found comparing temocillin with carbapenems or other antibiotics in infections caused by ESBL- or AmpC-producing *Enterobacteriaceae*. Its efficacy seems to correlate with higher doses (2 g every 12 h), although recent pharmacokinetic-pharmacodynamic data suggest 2 g every 8 h (or in continuous infusion) as the optimal dose for a susceptibility breakpoint of $\leq$16 mg/liter (102). More clinical studies, and particularly RCT, are needed to establish the role of temocillin in the treatment of ESBL and AmpC producers.

Aminoglycosides

Data on the effectiveness and limitations of aminoglycosides in treating *Enterobacteriaceae* infections can be extrapolated to infections caused by ESBL or AmpC producers. A systematic review and meta-analysis showed that aminoglycosides had efficacies similar to those of comparators against urinary infections but lower efficacies against other types of infection (103). From a general perspective, the aminoglycoside–β-lactam combination for the treatment of sepsis is disappointing, as it does not seem to provide any extra benefit but increases the risk of toxicity (104). The results of a recent observational study also showed that even short-course (median, 2 days) adjunctive empirical gentamicin increased the risk of renal toxicity but did not protect against mortality in patients with severe sepsis or shock in an area with low resistance rates (and, in fact, the addition of gentamicin did not increase the probability of appropriate coverage) (105). Importantly, the proportions of patients treated with vancomycin among those receiving and not receiving gentamicin in that study were 41% and 18%, respectively, although its effect was controlled for in multivariate analysis. It is not known whether the results would be different in areas with high rates of ESBL-E or for patients without shock or not receiving vancomycin. Using INCREMENT cohort data, Palacios-Baena et al. compared the empirical use of drugs other than carbapenems or BLBLIs (86 patients; 43 received an aminoglycoside) and carbapenems (249 patients) for BSI due to ESBL producers for mortality, clinical cure, and length of hospital stay. No significant differences (or trends) in any outcome were shown (106). Toxicity was not formally evaluated, but significant toxicity would be expected to have some effect on length of stay. Smaller studies of cancer patients with BSI (107) and children with UTI (108) also showed a reasonable effectiveness of aminoglycosides against ESBL-producing organisms in these populations. Finally, the variability in serum concentrations achieved may be important for isolates presenting MICs near the breakpoint in critically ill patients, since therapeutic failure against susceptible strains may be expected in these patients if the pharmacodynamic target is not reached (109).

In view of the above-mentioned findings, it seems that using aminoglycosides adds toxicity rather than benefits, and therefore they cannot be recommended as empirical drugs in areas with low rates of resistance to β-lactams or other first-line drugs. Nonetheless, they may still be considered an empirical option in carbapenem-sparing regimens (as monotherapy or combined with a narrower-spectrum β-lactam) in areas where ESBLs and/or AmpC are prevalent, particularly in UTI and sepsis. In any case, the aminoglycoside should immediately be changed to a better-tolerated drug once the susceptibility results are available.

Among the aminoglycosides, amikacin usually provides better coverage against ESBL and AmpC producers (110). Plazomicin is a new aminoglycoside with good activity against ESBL and AmpC producers (111, 112) and is reviewed in the section on carbapenemase producers.

Tigecycline

Tigecycline is a glycylcycline and, as such, is not affected by ESBLs or AmpC β-lactamases. Tigecycline exhibits predominantly bacteriostatic activity. Its spectrum of activity includes Gram-positive bacteria, *Enterobacteriaceae* (except for members of the *Proteae* family), *A. baumannii*, and anaerobes. It is not active against *P. aeruginosa* (113). The drug is approved in Europe and the United States for the treatment of complicated skin and skin structure infections and cIAI; in the United States, it is also approved for community-acquired bacterial pneumonia. Importantly, both the FDA and the EMA issued warnings because the drug was associated with an increased risk of mortality and clinical failure in meta-analyses of randomized trials (114–117). Hence, tigecycline was recommended only when other options were not available or were unsuitable. Although there is scant clinical experience with infections caused by ESBL producers (118–120), the results would be expected to be similar to those with non-ESBL producers. Because tigecycline is more frequently needed for the treatment of carbapenem-resistant *Enterobacteriaceae* (CRE), more information is provided in the relevant section.

Fosfomycin

Fosfomycin is an old antibiotic which remains active against most ESBL- and AmpC-producing *E. coli* and *K. pneumoniae* (and other MDR *Enterobacteriaceae*) isolates (121, 122). An oral formulation of fosfomycin trometamol is available in some countries and has been used extensively for the treatment of uncomplicated UTI; it also shows good efficacy against cystitis caused by ESBL-producing strains (123–126). An observational study compared fosfomycin trometamol (89 patients) administered at 3 g every 48 or 72 h with ertapenem (89 patients) as a step-down regimen in patients with invasive infections due to ESBL producers (28); readmission rates were similar (14.6% and 13.5%, respectively).

The intravenous formulation is available in Spain, France, Germany, and Austria, among other countries. In a recent meta-analysis, the efficacy of fosfomycin in randomized trials (most of which were performed more than 15 years ago) was similar to those of comparators for treatment of diverse infectious syndromes, and the drug was well tolerated (127). One of the main problems with this drug is the potential emergence of resistance during therapy, which seems to be less frequent in *E. coli* than in other bacteria (128). Recent studies suggest that what actually happens is selection of resistant mutants already present when therapy is started (129). Because of this, for severe infections, fosfomycin has traditionally been recommended for use in combination with other drugs (126, 128). The most appropriate dosing schedules range from 4 g every 6 to 8 h to up to 8 g every 8 h (129, 130). For monotherapy, the drug has been tested as empirical therapy (6 g every 8 h) in an RCT of cUTI, including pyelonephritis; a preliminary report of the trial showed that fosfomycin met the noninferiority criteria against piperacillin-tazobactam for overall success (131). It is also being tested compared to ceftriaxone or meropenem as targeted therapy in an RCT of bacteremic UTI due to multidrug-resistant *E. coli* (132). Until the results of these studies are fully available, no recommendation can be made about the use of this drug for monotherapy against ESBL or AmpC producers.

Fluoroquinolones and Trimethoprim-Sulfamethoxazole

Fluoroquinolone resistance is very frequent among ESBL producers (3, 4) but is not universal. In most cases, resistance is due to chromosomal mutations. Some isolates may also show low-level resistance due to the presence of plasmid-mediated quinolone resistance (PMQR) mechanisms (133).

Tumbarello et al. found that 8 of 16 patients with BSI due to ESBL-E who were treated with ciprofloxacin died. The MICs of ciprofloxacin for all these patients were 0.5 to 1 mg/liter (134). Endimiani et al. described worse results with ciprofloxacin than with imipenem for a small cohort of patients with BSI due to TEM-52-producing *K. pneumoniae*, which was associated with the fact that the MICs of ciprofloxacin were

frequently higher than 0.25 mg/liter (135). According to these data, the current EUCAST susceptibility breakpoint (≤0.25 mg/liter) seems to be more appropriate than the breakpoint of ≤1 mg/liter recommended by CLSI, at least for ESBL-E. The study by Palacios-Baena et al. mentioned above, which examined the outcomes for patients with BSI due to ESBL-E who were treated empirically with active drugs other than BLBLIs or carbapenems, included 19 patients treated with a fluoroquinolone as the only active drug according to CLSI breakpoints, and the mortality rate was 10.5%, similar to that for patients treated with carbapenems (106).

With respect to the impact of PMQR mechanisms, data from an animal model suggest a reduced efficacy of ciprofloxacin or levofloxacin. The presence of *qnr* genes also increased the mutant prevention concentration (MPC) (136–141). The clinical impact of PMQR mechanisms has been studied in only a few observational studies, with discrepant results. The available data are difficult to interpret, as many isolates also had other mechanisms of resistance and a small number of patients were treated with quinolones (142–144). However, because PMQR (particularly *qnr* genes) is common in ESBL-E (133), caution is needed in treating patients with quinolones, particularly using CLSI breakpoints.

A small proportion of ESBL-E isolates are susceptible to trimethoprim-sulfamethoxazole. Although no clinical studies specifically investigating the efficacy of this drug were found, the results are expected to be similar to those for non-ESBL producers, and it may therefore be an option mainly for cUTI.

THERAPY AGAINST CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE*

CRE may arise due to carbapenemase production (currently the most frequent mechanism) or to the combination of permeability problems with production of other β-lactamases, such as ESBLs or AmpC (145–152). Carbapenemases are rapidly spreading worldwide and fall into 3 main groups: KPC enzymes, belonging to Ambler class A; MBLs, belonging to molecular class B and including NDM, VIM, and IMP enzymes, among many others; and OXA enzymes, belonging to class D (in *Enterobacteriaceae*, OXA-48 is the most prevalent one). Their epidemiology is heterogeneous, and their capacity to hydrolyze carbapenems and other β-lactams is similarly variable (145–147). The most frequent carbapenemase-producing *Enterobacteriaceae* (CPE) organism so far has been *K. pneumoniae*, which causes infections predominantly identified as health care-associated infections. The treatment options against these infections are very limited. The most frequently used active antimicrobials so far have been "second-line" agents, including polymyxins, tigecycline, fosfomycin, and (occasionally) aminoglycosides (145–152). Some isolates are susceptible to minocycline, doxycycline, chloramphenicol, trimethoprim-sulfamethoxazole, and temocillin (152–156). The new β-lactamase inhibitors, avibactam and vaborbactam, inhibit KPC (avibactam also inhibits OXA-48) but not MBLs (61, 152).

Because the options are so limited, all potentially active drugs should be tested *in vitro*. For many patients, it is necessary to create individualized antibiotic therapy regimens in line with the source and severity of infection, susceptibility testing data, and information available from *in vitro*, *in vivo*, and clinical studies (see below) (149, 157). Dose modification may also be necessary (Table 2). As with all pathogens, careful evaluation of the clinical significance of a CRE isolate is assumed in order to prevent unnecessary treatment (154). A summary of recommendations for regimens to be considered in the treatment of CRE according to the data presented in the following subsections is found in Table 3. It should be noted that many carbapenemase producers also coproduce ESBLs, and the impact of the production of both enzymes on treatment is not well established.

Monotherapy versus Combination Therapy

As the efficacy of some frequently *in vitro*-active drugs against CPE in monotherapy, such as the polymyxins, tigecycline, or fosfomycin, is doubtful (see below), the use of combination therapy for the management of infections caused by these organisms has been explored with the objective of investigating the potential synergistic or additive

TABLE 2 Recommended dosing for the most frequently used drugs against carbapenem-resistant *Enterobacteriaceae* (CRE) for patients with normal renal function[a]

Drug	Usual/standard dose(s)	Dosing for CRE and comments
Meropenem	1 g/8 h	2 g/8 h by EI (isolates with MICs of 2–8 mg/liter; for isolates with higher MICs, it is probably not efficacious)
Ertapenem	1 g/24 h	Consider 2 g/day for double-carbapenem regimens
Colistin[b]	From the EMA, loading dose, 6–9 MU, and then 9 MU/day in 2–3 doses; from the FDA, 2.5–5 mg of colistin base activity/kg/day	EMA dose is recommended for severe CRE infections; the need for a loading dose and high continuation dose in patients without severe infection/shock is controversial
Polymyxin B[c]	From the FDA, 1.5–2.5 mg/kg/day in 2 doses	For mild infections and isolates with MICs of ≤1 mg/liter, the FDA dose is probably appropriate; for severe infections and isolates with MICs of up to 4 mg/liter, a loading dose of 2–2.5 mg/kg followed by 3 mg/kg/day in 2 doses is recommended (controversially)
Tigecycline	100-mg loading dose and then 50 mg/12 h	For HAP, cUTI, BSI, or shock, consider a 200-mg loading dose and then 100 mg/12 h
Gentamicin, tobramycin	5–7 mg/kg/day	For HAP or shock without other options, higher doses (10–15 mg/kg) might be considered, but the risk of toxicity is high; TDM is recommended
Amikacin	15–20 mg/kg/day	For HAP or shock without other options, higher doses (25–30 mg/kg) might be considered, but the risk of toxicity is high; TDM is recommended
Fosfomycin	4 g/6 h to 8 g/8 h	Use in combination; high sodium concn
Temocillin	2 g/8–12 h	KPC producers are occasionally susceptible; continuous infusion improves PK-PD target attainment
Aztreonam	1–2 g/8 h	MBL producers are susceptible if they are not ESBL or AmpC producers
Ceftazidime	1–2 g/8 h	OXA-48 producers are susceptible if they are not ESBL or AmpC producers
Ceftazidime-avibactam	2.5 g/8 h	KPC and OXA-48 producers are frequently susceptible
Meropenem-vaborbactam	2/2 g/8 h	KPC producers are frequently susceptible

[a]Please refer to the text for explanations and references. EI, extended infusion; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; HAP, hospital-acquired pneumonia; cUTI, complicated urinary tract infection; BSI, bloodstream infection; MU, million units; TDM, therapeutic drug monitoring; MBL, metallo-β-lactamase.
[b]One million units of colistimethate sodium = 80 mg colistimethate sodium = 34 mg of colistin base activity.
[c]One million units of polymyxin B = 100 mg of colistin base activity.

effects of certain combinations of antimicrobials. Many *in vitro* studies and some *in vivo* studies have investigated the effects of double and triple combinations of drugs with different mechanisms of action (158–210). A systematic review of studies of *in vitro* synergy of polymyxins and carbapenems showed synergy against 50% of carbapenem-resistant isolates (95% CI = 30 to 69%) in time-kill studies (less when the checkerboard or Etest method was used). Combinations were also associated with less development of resistance to colistin *in vitro*, but data about carbapenems were not provided (211). Antagonism was infrequent. Overall, KPC-producing *K. pneumoniae* was studied most often. Some conclusions that can be drawn from the data in these studies are as follows: (i) it is difficult to extrapolate findings due to heterogeneity in methodologies, overrepresentation of KPC producers, concurrent mechanisms of resistance, bacterial species, clones, susceptibilities of isolates, and concentrations of antimicrobial agents tested; (ii) the effects of the most frequently tested combinations varied widely; (iii) triple combinations (colistin with carbapenem and rifampin or tigecycline, colistin with double carbapenems) seemed to provide synergistic effects more frequently, although these were less frequently studied, with diverse effects in different strains; (iv) the synergistic effects of combinations including meropenem were more frequent when the MIC was ≤16 mg/liter; and (v) combinations including colistin and rifampin (with or without carbapenems) were frequently synergistic against colistin-resistant isolates. Individual testing to guide therapy in cases with very limited options is desirable, but delays in providing results, the intrinsic difficulties of such studies, and a lack of evidence of clinical correlation should be taken into account.

No RCT were found that compared combination therapy with monotherapy for patients with CPE infections. Designing such a trial would be complex because of the

TABLE 3 Summary of recommended regimens for treatment of infections caused by carbapenem-resistant *Enterobacteriaceae*[a]

Risk level, therapy type, and isolate susceptibility	Drugs
High risk,[b] combination therapy	
Susceptible to a β-lactam (use according to susceptibility)	Backbone: ceftazidime-avibactam (preferred) or meropenem-vaborbactam; alternatively, meropenem (if MIC is ≤8 mg/liter) or ceftazidime or aztreonam
	Accompanying drug (no data available about the need for combination therapy if ceftazidime-avibactam or meropenem-vaborbactam is used as the backbone): colistin, tigecycline, aminoglycoside, or fosfomycin (if isolate is intermediate to the backbone drug, consider using 2 of these)
Resistant to all β-lactams (including isolates with meropenem MICs of >8 mg/liter), susceptible to at least 2 drugs, including colistin	Backbone: colistin
	Accompanying drug: tigecycline, aminoglycoside (high risk of nephrotoxicity), or fosfomycin
Resistant to all β-lactams and colistin, susceptible to at least 2 drugs	Backbone: tigecycline or aminoglycoside
	Accompanying drug: tigecycline or aminoglycoside, fosfomycin
Pandrug-resistant or susceptible to only one drug	Meropenem plus ertapenem or ceftazidime-avibactam plus aztreonam; add any active drug; consider active investigational drugs if available; consider *in vitro* testing of combinations for synergy
Low risk,[c] monotherapy	
According to susceptibility	Ceftazidime-avibactam, meropenem-vaborbactam, meropenem, ceftazidime, aztreonam, colistin, tigecycline, aminoglycoside (if intermediate susceptibility, choose another option or use combination)

[a]Close clinical and microbiological follow-up is needed. If any of the following is needed, consider the source: colistin, preferred over other accompanying drugs in cases of HAP/VAP; tigecycline, to be considered mostly for cIAI (if used for HAP, BSI, or cUTI, consider double dosing); aminoglycoside, to be considered mostly for cUTI (if needed for HAP, consider a high dose), and TDM is recommended; fosfomycin, to be considered mostly for cUTI but, if needed, also as a third drug for any source. For cIAI, consider adding metronidazole except for with meropenem and tigecycline. It may be wise to reserve the newer drugs (ceftazidime-avibactam and meropenem-vaborbactam) for high-risk patients whenever possible. HAP, hospital-acquired pneumonia; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; TDM, therapeutic drug monitoring.

[b]High risk is defined as having septic shock or, for bloodstream infections, an INCREMENT mortality score of ≥8 points (severe sepsis or shock at presentation, 5 points; Pitt score of ≥6, 4 points; Charlson index of ≥2, 3 points; and source of infection other than urinary or biliary tract, 3 points).

[c]Low risk is defined as having an INCREMENT mortality score of <8 points.

heterogeneous susceptibilities. Observational studies comparing the outcomes for patients treated with monotherapy or combination therapy were reviewed, and control for confounders was taken into account. Most studies focused on or supplied data for BSI (212–229) (Table 4), while others included other types of infection (213, 215, 227, 230–236) (Table 5). Systematic reviews published in 2014 found major limitations in the studies analyzed and therefore could not draw strong conclusions (47, 237). Another systematic review and meta-analysis of infections due to carbapenem-resistant bacteria (not just *Enterobacteriaceae*) found lower mortality with colistin combinations than with colistin monotherapy, although again, the authors drew attention to the limitations of the studies (238).

Some important methodological issues should be taken into account in analyzing these data. First, the impact of combination therapy is evaluated mostly as targeted therapy and therefore has a risk of survivor bias and confounding by indication. Second, the definitions of exposure to different therapy regimens are heterogeneous, including diverse criteria for number of days from onset of infection to initiation of treatment, duration of treatment, and inclusion of inactive drugs in combination regimens in some studies, as well as different criteria for considering antibiotics to be active (for example, EUCAST versus CLSI breakpoints and susceptible versus nonresistant status). Third, the drugs used are diverse, and therefore it is frequently impossible to evaluate whether specific combinations or drugs in monotherapy are better than others. Fourth, in many studies, the sample size is very limited. Finally, control for confounders is also frequently insufficient.

The most frequent type of bacteria included were KPC-producing *K. pneumoniae*, although some studies included mainly OXA-48 producers (212, 220, 235), NDM producers (219), or noncarbapenemase producers (230). Some studies focused on specific populations, such as intensive care unit (ICU) patients (221, 230), hematological or cancer patients (224, 225, 233), or children (219, 232). As Tables 4 and 5 show, some studies found combination therapy to be associated with lower mortality rates, while

TABLE 4 Observational studies providing comparative data on monotherapy and combination therapy for bloodstream infections due to carbapenem-resistant *Enterobacteriaceae*[a]

Reference	Design, no. of sites	Included infections	Carbapenemase(s)	Mortality definition	No. of deaths/no. of patients treated with MT (%)	No. of deaths/no. of patients treated with CT (%)	CT protective or not; adjusted OR (95% CI) for mortality with CT[b]
212	Retrospective, 1 site (Turkey)	BSI due to CRE	Mostly *K. pneumoniae* OXA-48	28-day	2/5 (40)	16/31 (51.5)	MV analysis not performed
213	Prospective, 9 sites (Italy)	BSI due to ERT^r *K. pneumoniae* (BSI subanalysis)	Mostly KPC	In-hospital	4/9 (44.4)	11/25 (44)	CT not protective (OR not provided)
214	Retrospective, 2 sites (Greece)	BSI due to CR *K. pneumoniae*	Mostly KPC, some VIM	28-day	32/72 (44.4)	28/103 (27.2)	CT protective; 0.48 (0.28–0.81)
215	Retrospective, 3 sites (Brazil)	Infections due to KPC-producing *K. pneumoniae* (BSI subanalysis)	KPC	30-day	15/34 (44.1)	24/44 (54.4)	CT not protective (OR not provided)
216	Retrospective, 2 sites (USA)	BSI due to CR *K. pneumoniae*	Most (probably) KPC	30-day	18/68 (26.4)	28/73 (38.3)	CT not protective; with BL, 1.8 (0.6–5.6); without BL, 1.1 (0.3–3.6)
217	Retrospective, 16 sites (worldwide)	BSI due to CPE	74% KPC	30-day	85/208 (40.9)	47/135 (34.8)	CT protective only in high-risk patients; 0.54 (0.32–0.89)
218	Prospective, 1 site (Spain)	BSI due to KPC-producing *K. pneumoniae*, COL^r	KPC	30-day	14/32 (43.8)	18/72 (25)	CT protective in septic shock
219	Retrospective, 1 site (India)	Children, BSI due to CRE; includes inactive drugs	66% *K. pneumoniae*, 72% NDM	30-day	Not specified	Not specified	Crude OR = 0.23 (0.05–1.0); MV analysis not performed
220	Retrospective, 1 site (Spain)	BSI due to OXA-48 producers	OXA-48	30-day	2/7 (28.5)	13/27 (48.1)	MV analysis not performed
221	Retrospective, 1 site (Greece)[c]	BSI due to CS and CR *K. pneumoniae* in ICU	Mostly KPC	30-day	18/57 (31.5)	7/38 (18.4)	CT protective; 0.23 (0.07–0.75); also with shock
222	Retrospective, 2 sites (USA)	BSI due to KPC-producing *K. pneumoniae*; includes inactive drugs	KPC	28-day	11/19 (57.8)	2/15 (13.3)	CT protective; 0.07 (0.009–0.71)
223	Retrospective, 8 sites (USA)	BSI due to CRE	Mostly KPC	30-day	21/55 (38.1)	22/43 (51.1)	CT not protective (OR not provided)
224	Retrospective, 4 sites (Greece)	BSI due to CR *K. pneumoniae*, neutropenic patients	Mostly KPC	14-day	5/10 (50)	11/30 (36.6)	CT protective; 0.25 (0.07–0.81)
225	Prospective, 13 sites (Italy)	BSI due to CR *K. pneumoniae*, hematological patients	Not identified	21-day	69/77 (89.6)	40/72 (55.5)	CT protective; 0.52 (0.35–0.77)
226	Retrospective, 3 sites (Italy)	BSI due to KPC-producing *K. pneumoniae*	KPC	30-day	25/46 (54.3)	27/71 (34.1)	CT with COL plus TIG-MER protective; 0.11 (0.02–0.60)
227	Retrospective, 5 sites (Italy)[d]	Infections due to KPC-producing *K. pneumoniae* (BSI subanalysis)	KPC	30-day	80/156 (51.3)	93/291 (32)	MV analysis not performed for BSI
228	Retrospective, 11 sites (South America)	BSI due to CRE	Mostly KPC	28-day	5/8 (62.5)	17/29 (58.6)	MV analysis not performed
229	Retrospective, 1 site (Greece)	BSI due to KPC-producing *K. pneumoniae*	KPC	Infection related	7/15 (46)	0/20 (0)	CT not included in MV

[a]Superiority of specific combinations or drugs in monotherapy was not evaluated and cannot be discarded. MT, monotherapy; CT, combination therapy; OR, odds ratio; CI, confidence interval; BSI, bloodstream infection; CRE, carbapenem-resistant *Enterobacteriaceae*; MV, multivariable; ERT^r, ertapenem resistant; CR, carbapenem resistant; BL, β-lactam; CPE, carbapenemase-producing *Enterobacteriaceae*; COL^r, colistin resistant; CS, carbapenem susceptible; TIG-MER, tigecycline-meropenem.

[b]When the adjusted OR was provided for MT (with CT as a reference), the inverse was calculated.

[c]Patients with carbapenem-susceptible and -resistant *K. pneumoniae* isolates are compared in this study; here we extracted the data for carbapenem-resistant isolates only.

[d]Includes patients from reference 225.

TABLE 5 Observational studies providing comparative data for monotherapy and combination therapy for different types of infection due to carbapenem-resistant *Enterobacteriaceae*[a]

Reference	Design, no. of sites	Included infections	Carbapenemase(s)	Mortality definition	No. of deaths/no. of patients treated with MT (%)	No. of deaths/no. of patients treated with CT (%)	CT protective or not; adjusted OR (95% CI) for mortality with CT[b]
213	Prospective, 9 sites (Italy)	Infections due to ERT^r *K. pneumoniae*	Mostly KPC	In-hospital	8/37 (21.6)	17/54 (31.4)	CT not protective (OR not provided)
215	Retrospective, 3 sites (Brazil)	Infections due to KPC-producing *K. pneumoniae*	KPC	30-day	21/57 (36.8)	32/61 (52.4)	CT not protective (OR not provided)
227	Retrospective, 5 sites (Italy)[c]	Infections due to KPC-producing *K. pneumoniae*	KPC	30-day	118/307 (38.4)	107/354 (30.2)	CT protective; 0.52 (0.35–0.77)
230	Retrospective, 17 sites (Taiwan)	ICU infections due to CR *K. pneumoniae*/*E. coli*	Mostly AmpC/ESBL plus porin loss	30-day	7/23 (30.4)	5/10 (50)	CT not protective (OR not provided)
231	Prospective, 1 site (Brazil)	Infections due to CRE	Mostly KPC	Infection related	6/29 (20.6); for UTI, 6/28 (21.4)	38/78 (38.7); for UTI, 6/23 (26)	CT not protective (OR not provided)
232	Retrospective, 1 site (Colombia)	Children, CR *K. pneumoniae* infections	Not studied	Not specified	2/19 (10.5)	9/22 (40.9)	MV analysis not performed
233	Retrospective, 1 site (Brazil)	HAI due to KPC-producing *K. pneumoniae*, cancer patients	KPC	30-day	8/22 (36.6)	21/38 (55.2)	CT not protective (OR not provided)
234	Prospective, 1 site (Greece)	CR *K. pneumoniae* infections, ICU	KPC	Infection related	Not specified	Not specified	CT not protective (OR not provided)
235	Retrospective, 1 site (South Africa)	Infections due to OXA-48 producers	OXA-48	In-hospital	2/6 (33.3)	5/13 (38.4)	MV analysis not performed
236	2 sites (Brazil)	VAP due to CRE	Not specified	30-day	40/66 (60.6)	6/17 (35.2)	CT not protective (OR not provided)

[a]Superiority of specific combinations or drugs in monotherapy cannot be discarded. MT, monotherapy; CT, combination therapy; OR, odds ratio; CI, confidence interval; ERT^r, ertapenem resistant; CR, carbapenem resistant; ESBL, extended-spectrum β-lactamase; CRE, carbapenem-resistant *Enterobacteriaceae*; UTI, urinary tract infection; MV, multivariable; ICU, intensive care unit; VAP, ventilator-associated pneumonia; HAI, health care-associated infections.

[b]When the adjusted OR was provided for MT, the inverse was calculated.

[c]Includes patients from reference 225.

others did not. An analysis of the largest study of BSI, to date (217), showed that using more than one active drug had a protective effect on mortality only in the subset of patients with a high probability of dying (but not in the others) according to the validated INCREMENT CPE mortality score, which includes presentation with severe sepsis or shock, ≥6 points on the Pitt score, ≥2 points on the Charlson index, and a source of BSI other than the urinary or biliary tract (239). The results were corroborated by propensity score matching. Two previous studies found that combination therapy was protective, in a stratified analysis of patients with rapidly fatal underlying diseases or with septic shock (214) and in patients with BSI with a non-UTI source (227). Another study found that combination therapy was associated with lower mortality in patients with septic shock related to BSI due to colistin-resistant, highly carbapenem-resistant, KPC-producing *K. pneumoniae* (218).

These data suggest that combination therapy may be beneficial for high-risk patients, depending on the underlying situation, source of infection, and presence of septic shock, and also suggest that monotherapy may be enough for lower-risk patients. Note that ceftazidime-avibactam or meropenem-vaborbactam was not used in these studies, and therefore whether combination therapy is needed with these compounds is unknown. More studies are needed for isolates producing MBLs or OXA-48 enzymes and for CRE infections not caused by carbapenemases. The subsections below comment on the use of specific drugs. Curiously, rifampin was not included in the combinations studied despite the fact that several *in vitro* studies suggested a potential synergy with colistin, as mentioned above. In an RCT comparing colistin and rifampin with colistin monotherapy for serious infections caused by XDR *A. baumannii*, the combination was not found to provide any obvious benefit (240). The colistin dose in that study was lower than the one presently recommended, and the results cannot be extrapolated to *Enterobacteriaceae*.

Carbapenems for Treatment of CPE Infections

Carbapenemase activity against carbapenems varies according to the enzyme, and probably the expression levels of carbapenemase genes (145, 149, 241). Some CPE are in fact susceptible to carbapenems according to the susceptibility breakpoints currently recommended by CLSI (≤1 mg/liter for meropenem, imipenem, and doripenem and ≤0.5 mg/liter for ertapenem) (67) and EUCAST (≤2 mg/liter for imipenem and meropenem, ≤1 mg/liter for doripenem, and ≤0.5 mg/liter for ertapenem) (66). This is particularly frequent in OXA-48 producers, as noted in several outbreaks (220, 242). Stochastic modeling data suggest that the probability of reaching the target pharmacodynamic parameter is around 80% for isolates with a MIC of 8 mg/liter if meropenem is administered at 2 g every 8 h by extended infusion (243, 244).

This led to the consideration of carbapenems for treatment of infections with CPE isolates showing susceptibility or low-level resistance to these drugs. There are limited data available for carbapenems as monotherapy. Data from 22 articles analyzing the efficacy of imipenem or meropenem in relation to the MIC found that the clinical cure rate was 69% for isolates with a MIC of 4 mg/liter (32 patients) and 29% for isolates with MICs of >8 mg/liter (7 patients) (244). Efficacy for isolates with a MIC of 4 mg/liter was similar to that for patients with infections due to non-carbapenemase-producing strains. The available information is too limited to recommend carbapenems as monotherapy against carbapenem-susceptible CPE, but carbapenems may be an option for infections that are easy to treat (such as UTI). For isolates with higher MICs or other types of infections, we suggest an alternative drug or a combination therapy (see below).

The use of carbapenems in combination with other drugs has been evaluated in retrospective cohort studies. Some found that adding meropenem at high doses (2 g every 8 h by extended infusion) to another active drug was associated with lower mortality among patients with BSI (214, 226) or diverse types of infections (227) caused by CPE when the MIC was ≤8 mg/liter. Other studies found that the addition of a carbapenem conferred no advantage for patients with BSI (216, 217), and a recent study

found that treatment with meropenem at a high dose was independently associated with lower mortality in patients with carbapenem-resistant *K. pneumoniae* even in the case of isolates with MICs of ≥16 mg/liter (245). In all these studies, the predominant CPE was KPC-producing *K. pneumoniae*. The reasons for the discrepancies between studies are not clear. Inherent variability in determining MIC may have some influence. With the available information, if ceftazidime-avibactam or meropenem-vaborbactam cannot be used, it would be prudent to consider adding meropenem (using optimized dosing) to another active drug for patients with severe sepsis or shock if the MIC is ≤8 mg/liter, particularly if other *in vitro*-active drugs are not appropriate for the source of infection (for example, tigecycline for cUTI and tigecycline or aminoglycosides for ventilator-associated pneumonia) or if other combinations carry a high risk of toxicity (for example, colistin and aminoglycosides). It is not clear if carbapenems would also be beneficial in cases of CPE caused by MBLs, OXA-48, or other causes of carbapenem resistance. Some animal model studies did not find that carbapenems had the same efficacy against isolates with similar MICs but different mechanisms of resistance to carbapenems (246, 247), which argues against directly extrapolating the results obtained with KPC producers to other mechanisms of resistance. It should also be pointed out that use of carbapenems may theoretically facilitate the emergence of higher levels of carbapenem resistance due to permeability problems or increased expression of carbapenemases. Hence, it is worth studying carbapenem-sparing regimens.

Double Carbapenems

KPC exhibits a greater affinity for ertapenem than for other carbapenems (248), which led to the hypothesis that use of ertapenem might allow the other carbapenem to act. This seems to work *in vitro* only if the meropenem MIC is ≤128 mg/liter (249–253), and not for all strains (203). Some small, noncomparative case series have shown promising results (250–253). Ertapenem and meropenem have been found to be synergistic *in vitro* against other types of carbapenemase-producing *Enterobacteriaceae* (209). A comparison of 28-day mortality was carried out recently between ICU patients with carbapenem-resistant *K. pneumoniae* infections (90% were KPC producers) who received double carbapenems, with ertapenem as targeted therapy (48 patients; 35 of these received a third drug), and 96 patients who received other treatment regimens (52 received a combination of drugs) (254). Patients in both treatment arms were matched by SAPS-II score at admission and SOFA score at diagnosis of infection. Half the patients had pneumonia. In a multivariate analysis, double-carbapenem therapy was associated with lower mortality (adjusted OR = 0.33; 95% CI = 0.13 to 0.87), and among the patients treated with double carbapenems, 66% had XDR isolates. Because of significant potential negative ecological effects, and until more data are available, this combination should be considered only when there are no other reasonable options.

Polymyxins

Polymyxins are cationic polypeptide antibiotics, and only polymyxin B and polymyxin E (colistin) are used in clinical practice (255–257). Polymyxins are active against *Enterobacteriaceae*, except for *Proteus* spp., *Serratia* spp., *Morganella* spp., and *Providencia* spp. They have been a cornerstone in the management of infections due to CRE in the past, mostly because of being the last resort against these bacteria on many occasions. There is more clinical information available on colistin.

Whether colistin as monotherapy is as efficacious as the so-called first-line drugs against susceptible *Enterobacteriaceae* (β-lactams and fluoroquinolones) is a matter of controversy. Direct comparisons in observational studies are challenged because patients treated with colistin usually have carbapenem-resistant *Enterobacteriaceae* and are frequently more seriously ill. A systematic review including mostly patients with MDR *P. aeruginosa* and *A. baumannii* found higher mortality and toxicity for patients treated with colistin than for those treated with other drugs, mostly β-lactams (258), although similar data for *Enterobacteriaceae* are scarce. A randomized trial comparing

colistin with meropenem (both combined with levofloxacin) in patients with ventilator-associated pneumonia is under way (259).

With regard to the question of whether colistin is more effective in combination with other drugs, apart from the general information provided above, Hirsch and Tam reviewed 15 articles including 55 patients with KPC-producing *K. pneumoniae* infections treated with colistin and found that colistin was less effective as monotherapy than in combination (260). In a meta-analysis of infections due to carbapenem-resistant bacteria, Zusman et al. found that polymyxin monotherapy was associated with higher mortality than that with colistin combinations, although the authors drew attention to significant limitations of the studies (238). In the INCREMENT cohort, colistin monotherapy was associated with increased mortality compared to that with combinations including tigecycline, colistin, and carbapenems (217). Overall, the drugs most frequently combined with colistin have been carbapenems, tigecycline, aminoglycosides, and fosfomycin. The potential additive nephrotoxicity of colistin and aminoglycosides is a concern. Two randomized controlled trials comparing colistin versus colistin plus meropenem are being performed; one of them includes patients with severe infections due to carbapenem-resistant Gram-negative bacteria (261), and the other includes patients with BSI or pneumonia due to XDR Gram-negative bacilli (https://clinicaltrials.gov/ct2/show/NCT01597973).

The most appropriate dose of colistin is also controversial. Colistin is administered as a prodrug (colistimethate sodium) that needs to be converted to the active drug. The previous standard dosage regimen recommended for colistin is now considered insufficient by most authors (Table 2) (262–265), and administration of a loading dose followed by a high maintenance dose has been suggested based on pharmacokinetic-pharmacodynamic models (263–266). The European Medicines Agency recommends a 9-million-unit (MU) loading dose for critically ill patients, followed by 9 MU/day in 2 or 3 doses (267). The FDA, however, makes no recommendation about loading dose and recommends 2.5 to 5 mg/kg of body weight/day of colistin base activity for patients with normal renal function (34 mg of colistin base activity = 1 MU) (268). Whether use of a loading dose and higher daily doses is associated with improved efficacy is again controversial. No comparative randomized trials have been found, although several observational or quasi-experimental studies with discrepant results have been published (269–276). In most studies, renal toxicity was more frequent with higher doses. It should also be pointed out that most studies included not only CRE but also *P. aeruginosa* and *A. baumannii*. A small randomized trial compared the rates of nephrotoxicity of colistin administered as a 9-MU loading dose followed by 4.5 MU every 12 h or as 2 MU every 8 h (20 patients in each arm); the rates of acute kidney injury based on RIFLE criteria were 60% and 15%, respectively ($P = 0.003$) (277).

Dosing regimens are not well established for polymyxin B either. Polymyxin B is administered as an active drug and therefore does not need *in vivo* conversion to be active. In a retrospective cohort study of 151 patients with BSI due to carbapenem-resistant Gram-negative bacteria (102 isolates were *Enterobacteriaceae*), a dosing regimen of $<$1.3 mg/kg/day was independently associated with higher mortality (278), thus supporting the standard recommendation of administering 1.5 to 2.5 mg/kg/day in 2 doses. In a multivariate analysis in that study, a daily dose of $\geq$250 mg was associated with acute kidney injury. However, a population pharmacokinetic study of critically ill patients suggested the use of 3 mg/kg/day in patients with severe infections and isolates with MICs of $\leq$2 mg/liter (279). Stochastic modeling also suggests the importance of administering a loading dose of polymyxin B (278, 279).

Regarding comparative data on colistin and polymyxin B, the available data suggest that colistin is associated with a higher risk of nephrotoxicity than polymyxin B (280, 281). However, no clear differences in clinical benefits (including cure rates or mortality) have been demonstrated for one over the other so far (281, 282). Dose adjustment is recommended for both drugs in patients with renal insufficiency, according to the FDA label; however, since exposures to polymyxin B are similar in patients with and without renal insufficiency and clearance of the drug is not affected by renal function, the

dosing of this drug should probably not be adjusted according to renal function (278, 283, 284).

Resistance to polymyxins is increasing, with outbreaks of colistin-resistant CRE reported in different parts of the world (285–289). Colistin resistance has been associated with an increased risk of mortality (213, 290, 291), and exposure to colistin has been identified as a risk factor for infections due to colistin-resistant CPE (288). More recently, plasmid-mediated resistance (mediated by *mcr* genes) was discovered (292). While the association between *mcr* genes and carbapenemase production is anecdotal so far (293–298), the association of these genes with successful mobile genetic elements or clones, together with the use of colistin in veterinary and human medicine leading to increased selection pressure, is a cause for concern. Furthermore, susceptibility testing with colistin is problematic: broth microdilution methods are recommended because diffusion tests are not reliable (66), and semiautomated methods may cause very major errors (as explained at http://www.eucast.org/ast_of_bacteria/warnings/ [accessed 22 October 2017]). The EUCAST breakpoint for colistin susceptibility (which is also the epidemiological cutoff value) is ≤2 mg/liter (66); CLSI does not provide breakpoints for polymyxins and *Enterobacteriaceae* (67).

In summary, polymyxins are still frequently key drugs for the treatment of CRE, but their actual efficacy and optimal dosing are not well defined; combination therapy is probably beneficial for high-risk patients.

Tigecycline

Tigecycline frequently remains active against CRE *in vitro* (113, 119, 145, 148–150). As mentioned in the section on treatments for infections with ESBL- and AmpC-producing *Enterobacteriaceae*, tigecycline is recommended only when other options are unavailable or unsuitable, which is often the case for infections due to CRE. A recent meta-analysis reviewed 21 studies comparing outcomes associated with tigecycline versus other antimicrobial agents used for treatment of CRE infections (299). No significant differences in patient mortality were found between patients treated with tigecycline and those treated with other antibiotics. In subgroup analyses, tigecycline in combination was associated with lower mortality. The analysis was limited by the heterogeneity of the studies, types of infection, and comparators.

The problem of the lower efficacy of tigecycline has been linked to dosage (396). The concentrations reached at sites of infection may be lower than desired with the standard dose (100-mg loading dose and then 50 mg/12 h) (202), particularly in cases of HAP (300) and despite the fact that the drug is concentrated in the tissues. Tigecycline concentrations in blood are also low (113), which raised doubts early on about its efficacy in bacteremic infections. A meta-analysis including mostly observational studies found no significant differences in mortality and higher rates of clinical cure for patients with BSI treated with tigecycline than those treated with other regimens, although the studies were heterogenenous with respect to design, type of infection, microorganism, comparators, and dosing (301). In subgroup analysis, monotherapy wth tigecycline was associated with higher mortality than that with combination therapy.

In a phase 2 randomized trial for treatment of HAP, patients were randomized to receive 150 mg of tigecycline followed by 75 mg/12 h (36 patients), 200 mg of tigecycline followed by 100 mg/12 h (35 patients), or imipenem-cilastatin at 1 g/8 h (34 patients) (302). The clinical cure rate was higher for patients receiving the highest dose of tigecycline than those receiving the lower dose, but the study was underpowered to detect superiority. The rates of serious adverse events were similar across groups, but diarrhea, nausea, and vomiting were more frequent at the highest tigecycline dose. A systematic review carried out in 2014 found three other observational studies that compared the outcomes for patients with infections caused by Gram-negative pathogens (mostly MDR) who received the standard dose of 50 mg/12 h and those receiving 100 mg/12 h (303). Two of these studies, performed on ICU patients, found better results with the high-dose regimen, and for the subset of patients with VAP in one of

them (304, 305), and one did not (306). A recent case series of ICU patients showed a decrease in plasma fibrinogen levels and a prolongation of international normalized ratio (INR) and activated partial thromboplastin time (aPTT) values during high-dose tigecycline treatment in ICU patients (307).

Tigecycline concentrations in urine are also low, and the drug has not been evaluated in an RCT for UTI. Since UTI is a frequent type of infection among patients with CRE (308), tigecycline has been used anecdotally, sometimes with apparently good results (309). However, it is associated with a lower rate of clearance of carbapenem-resistant *K. pneumoniae* in patients with bacteriuria or UTI than that with aminoglycosides (310, 311) and therefore does not seem to be the best option for this type of infection.

Since tigecycline remains active against a significant proportion of CRE isolates, it might be useful as part of the treatment regimens against many infections caused by these pathogens. Higher doses may be considered for severe infections with very limited options, particularly pneumonia and BSI.

Aminoglycosides

General aspects of aminoglycoside use were discussed previously, in the section on ESBL- and AmpC-producing *Enterobacteriaceae*. A variable, occasionally large proportion of CRE isolates are susceptible to some members of the aminoglycoside family, except for isolates producing 16S rRNA methyltransferases, which confer resistance to all aminoglycosides (312). These acquired enzymes are particularly frequent among NDM producers and are increasingly being described for KPC producers (312–314).

Aminoglycosides have been used both alone and in combination (more frequently) in the management of infections caused by CRE; indeed, aminoglycosides are often part of the combination therapies listed in the studies in Tables 4 and 5. The aminoglycosides have been found to be independently associated with higher rates of clearance of carbapenem-resistant *K. pneumoniae* from urine than those for tigecycline and polymyxin B (310); it should be noted that concentrations of polymyxin B in urine are low (279), while colistimethate is eliminated in part in the urine, where it is converted to colistin. Studies comparing outcomes for patients treated with and without aminoglycosides are scarce. One study investigated the outcomes for 157 patients with physician-diagnosed UTI due to carbapenem-resistant *K. pnuemoniae* (mostly KPC producers); treatment with aminoglycosides was associated with a lower probability of failure (other drugs were colistin, tigecycline, trimethoprim-sulfamethoxazole, and fosfomycin) in an adjusted analysis (311). In that study, amikacin was active against 83% of the isolates. A study carried out in Spain included 50 patients with sepsis due to colistin-resistant, clonally related KPC-producing *K. pneumoniae* isolates and compared 30-day mortality for patients treated with gentamicin (29 patients) and without gentamicin (21 patients) (315). Overall, 48% of patients had HAP and 20% had UTI. In a multivariate analysis, treatment with gentamicin (particularly for isolates with MICs of $\leq$2 mg/liter) was associated with lower mortality. It should be noted, reflecting the extensive resistance of the isolates, that most patients not receiving gentamicin were considered to have received suboptimal treatment (meaning that the treatment regimen included only drugs with intermediate susceptibility). Crude mortality rates were 7.7% (1/13 patients) and 31.2% (5/16 patients) for isolates with gentamicin MICs of $\leq$2 mg/liter (susceptible, according to EUCAST) and 4 mg/liter (intermediate), respectively. The gentamicin dose was 4 to 5 mg/kg, with dose adjustment based on therapeutic drug monitoring. It is important that resistance to gentamicin among KPC producers is high in many areas (311).

As with other drugs used in the treatment of CRE infections, the adequacy of the generally recommended dosage for aminoglycosides (5 to 7 mg/kg/day for gentamicin and tobramycin; 15 to 20 mg/kg/day for amikacin) has also been questioned. A study of patients with severe sepsis or septic shock who were treated with amikacin at 25 mg/kg/day showed that only 70% reached peak concentrations of $>$64 mg/liter, which would be $\geq$8 times the susceptibility breakpoint against *Enterobacteriaceae* according

to EUCAST (8 mg/liter) (316); the same dose, however, should be enough for isolates with a MIC of 4 mg/liter to reach the same target (317). An initial dose of 2,500 mg followed by therapeutic drug monitoring has been suggested for patients with body weights of >40 kg (318, 319). Importantly, the peak concentration/MIC ratio has been challenged as the only pharmacokinetic-pharmacodynamic target to be considered for aminoglycosides (320). Use of even higher doses in patients with high-flow hemofiltration has been explored for MDR Gram-negative infections with very limited options (321). To investigate the impact of the maximum concentration of drug in serum (C_{max}) on mortality, a retrospective observational study including 110 patients with septic shock who received amikacin at 30 mg/kg/day was carried out in two ICUs; around half the patients had infections caused by *Enterobacteriaceae* (322). Mortality rates were 28.3% for 46 patients reaching C_{max} values of 60 to 80 mg/liter, 40% for 20 patients reaching <60 mg/liter, and 58.8% for 44 patients reaching >80 mg/liter. In a multivariate analysis, C_{max} values of >80 mg/liter were independently associated with increased mortality (OR = 3.96; 95% CI = 1.54 to 10.2). A randomized trial would be needed to compare the efficacies and safeties of higher doses of aminoglycosides. At this time, we are cautious about recommending them except for patients with septic shock due to CRE infection with very few other available alternatives.

Fosfomycin

Fosfomycin was also reviewed in the section on ESBL- and AmpC-producing *Enterobacteriaceae*, so only specific information about CRE infections is added here. Fosfomycin is active against a significant proportion of CRE isolates (121, 122, 153, 323) and was therefore frequently included as part of combination therapy in the studies listed in Tables 4 and 5. Since we found no studies with sufficient numbers of patients to compare the outcomes for patients treated with and without fosfomycin, its role as an individual drug is difficult to ascertain. Development of resistance has been described even for its use in combination for infections caused by KPC producers (324). A multicenter case series analyzing 48 patients admitted to the ICU and treated with fosfomycin for XDR, fosfomycin-susceptible pathogens has been reported (325). The predominant infections were VAP and BSI, the median dose was 24 g per day, and the most frequent accompanying drugs were colistin and tigecycline. The 28-day mortality rate was 37.5%, and clinical outcomes were considered successful at day 14 for 54.2% of patients, with failure in 33.3% of patients. Resistance development occurred in 3 cases.

Because of the scarcity of information, fosfomycin is not a first option against serious CRE infections when other active drugs are available, but it may be needed in some patients with scarce options. In such cases, a fosfomycin dose of 16 to 24 g per day in combination is recommended.

β-Lactams Other than Carbapenems: Temocillin for KPC Producers, Aztreonam for MBL Producers, and Cephalosporins for OXA-48 Producers

Temocillin is active against a small proportion of KPC producers, using British Society for Antimicrobial Chemotherapy breakpoints (≤8 mg/liter; ≤32 mg/liter for UTI) (153, 326), and against CRE isolates with combinations of impermeability and ESBL or AmpC production (153). Promising results with temocillin were found in a murine model of intra-abdominal infection against KPC-producing *E. coli* isolates with temocillin MICs of ≤16 mg/liter (327). Unfortunately, we found no published clinical experiences. OXA-48 producers show high resistance to temocillin, which has been proposed as a diagnostic marker for these enzymes (328, 329).

Aztreonam is not efficiently hydrolyzed by MBLs (145, 149, 150). In an *in vitro* model, it showed slow bactericidal activity against VIM-1-producing *K. pneumoniae* (330). Animal model studies showed efficacy against susceptible isolates producing NDM and VIM MBLs (331, 332). The problem here is that a large proportion of MBL producers coproduce ESBLs, thus making them aztreonam resistant (333). Clinical experience is lacking in any case.

The case of OXA-48 is somewhat similar. This enzyme has low hydrolytic activity against cephalosporins and does not confer cephalosporin resistance (334), but most OXA-48 producers are resistant because they are also ESBL producers (242, 335). However, since some OXA-48 producers also show low carbapenem MICs, they may not be detected, particularly if they do not also coproduce an ESBL. Ceftazidime showed significant antibacterial activity in animal models against OXA-48 producers lacking ESBLs or AmpC (336, 337). Again, no clinical experience has been published.

Ceftazidime-Avibactam

As previously reviewed in the section on ESBL- and AmpC-producing *Enterobacteriaceae*, ceftazidime-avibactam is active *in vitro* against most KPC- and OXA-48-producing *Enterobacteriaceae* and some carbapenem-resistant strains due to a loss of impermeability or ESBL or AmpC production at the EUCAST and FDA susceptibility breakpoint (≤8/4 mg/liter) (61, 338–342). Activity against KPC and OXA-48 producers has been confirmed in animal studies (343, 344). Curiously, in a murine thigh infection model, ceftazidime-avibactam (but not ceftazidime alone) also showed efficacy against ESBL- and NDM-producing *E. coli* and *K. pneumoniae* isolates highly resistant to ceftazidime-avibactam, suggesting that ceftazidime resistance was due mostly to the ESBL (345). These results were replicated in a murine lung infection model with NDM-, OXA-48-, and CTX-M-producing *K. pneumoniae* isolates (346). However, data for patients are lacking, and therefore we would not recommend ceftazidime-avibactam for patients infected with MBL-producing *Enterobacteriaceae*.

There are some published experiences of the treatment of CRE because this combination has been tested in compassionate use programs for the treatment of infections caused by XDR *Enterobacteriaceae* and recently received approval. We found 7 case series or cohort studies that included 6 to 60 patients with CRE infections who were treated with ceftazidime-avibactam (Table 6) (347–353). Some patients may have been included in more than one of these series. Ceftazidime-avibactam was used as targeted therapy, sometimes as salvage therapy after failure with other drugs. It was administered in combination with other active drugs in 30 to 100% of cases. Mortality rates ranged from 7.6% to 39% for patients with BSI and from 8% to 50% when total infections were considered in each study. Overall, there were no obvious differences in mortality or clinical response between patients treated with monotherapy or a drug combination. In three studies, there was a comparison with patients not treated with ceftazidime-avibactam. The first study included hematological patients with BSI due to CRE and compared 8 patients treated with this combination with 23 treated with other regimens (347). In the crude analysis, clinical cure (but not mortality) was more frequent with ceftazidime-avibactam, although the small patient numbers precluded multivariate analysis. In another study of patients with BSI due to CRE, 13 patients treated with ceftazidime-avibactam were compared to those receiving other regimens (348). Clinical response was more frequent with ceftazidime-avibactam in the adjusted analysis, which was clearly limited because of small numbers. Finally, van Duin et al. used the CRAKCLE prospective cohort data to compared the outcomes for patients with diverse types of infections due to CRE (>95% KPC-producing *K. pneumoniae* isolates) and treated with ceftazidime-avibactam (38 patients; 39% had BSI and 24% had HAP) or colistin (99 patients; 48% had BSI and 21% had HAP); combination therapy was used in 63% and 94% of patients treated with ceftazidime-avibactam and colistin, respectively (353). Inverse probabilities of treatment weighting-adjusted mortality were 9% and 32%, respectively (absolute difference, 23%; 95% CI, 9 to 35%). At day 30, patients treated with ceftazidime-avibactam had a 64% (95% CI, 57 to 71%) adjusted probability of a better outcome.

In one study, ceftazidime-avibactam resistance developed in 3 of 10 isolates recovered from recurrent infections (349) due to mutations in the $bla_{\text{KPC-3}}$ gene (354). This was also described in another case (355). Curiously, the same mutation restored carbapenem susceptibility in some isolates (354, 355). Acquisition of resistance due to mutations in the $bla_{\text{CTM-M-14}}$ gene conferring augmented ceftazidime hydrolysis has

TABLE 6 Case series and cohort studies providing outcome information for infections due to carbapenem-resistant *Enterobacteriaceae* treated with ceftazidime-avibactam[a]

Reference	Design, no. of sites; inclusion criteria	*n*	Types of infections and pathogens	No. of patients treated with CAZ-AVI	No. of patients treated with other regimens	Mortality definition (no. of deaths/no. of patients treated [%] [CAZ-AVI vs other regimens])	Clinical cure (no. of patients with cure/no. of patients treated [%] [CAZ-AVI vs other regimens])
346	Retrospective cohort, hematological patients, 4 sites; BSI due to CRE, ≥48 h of therapy	31	≈85% *K. pneumoniae*; ≈60% OXA-48 producers and 40% KPC producers; sources: 14 (45.1%) primary, 6 (19.3%) HAP	8 (all in combination); all isolates susceptible to CAZ-AVI	23 (17 [94.4%] in combination)	30-day; 2/8 (25) vs 12/23 (52.2); $P = 0.24$	Day 14; 6/8 (75) vs 8/23 (34.8); $P = 0.03$
347	Retrospective cohort, 1 site; BSI due to CR *K. pneumoniae*, ≥3 days of therapy	109	All *K. pneumoniae;* 97% KPC; 50% in ICU; Source: 50 (45.8%) IAI, 28 (25.6%) primary BSI	13 (5 [38.5%] in combination); all isolates susceptible to CAZ-AVI	96 (27 [28.2%] in combination)	30-day; 1/13 (7.6) vs 30/96 (31.2)	Day 30; 11/13 (85) vs 30/96 (40.6); $P = 0.006$; adjusted OR = 8.64 (95% CI = 1.61–43.39)
348	Retrospective, 1 site; CRE infections treated with CAZ-AVI	37	84% *K. pneumoniae*; 78.3% KPC	37 (11 [30%] in combination)	Not included	30-day; 9/37 (24.3)	23/37 (62); for monotherapy, 58%; for combination therapy, 64%; 10 (27%) recurrences, with 3 isolates developing resistance
349	Retrospective, 1 site; CRE infections treated with CAZ-AVI	6	All *K. pneumoniae*, KPC; all susceptible to CAZ-AVI	6 (4 [66.6%] in combination)	Not included	In-hospital; 3/6 (50)	4/6 (66.6); 2 relapses, no development of resistance
350	Retrospective cohort, 15 sites; CRE infections treated with CAZ-AVI, salvage therapy	38	34 *K. pneumoniae;* 23 KPC, 13 OXA-48; type of infection: 15 (39.4%) IAI, 7 (18.4%) HAP	38 (25 [65.8%] in combination)	Not included	In-hospital; overall, 15/38 (39.5); for IAI, 6/15 (40); for HAP, 5/7 (71.4)	28 (73.7); for monotherapy, 69.2%; for combination therapy, 76%; 2 relapses, no resistance detected
351	Retrospective cohort, 9 health care systems in USA; CRE infections treated with CAZ-AVI for ≥24 h	60	83% *K. pneumoniae*; type of infection: 38% BSI, 28% UTI, 27% HAP	60 (33 [55%] in combination); of 36 isolates tested, 23 susceptible to CAZ-AVI; treatment started a median of 8 (IQR, 5–22) days after infection	Not included	In-hospital; overall, 19/60 (32); for monotherapy, 30%; for combination therapy, 33%; for BSI, 39%; for UTI, 12%; for pneumonia, 56%	39/60 (65); for monotherapy, 67%; for combination therapy, 63%
352	Prospective cohort, 18 hospitals in USA; CRE infections	137	97% *K. pneumoniae*, 96% KPC-producers; type of infection: 46% BSI, 22% HAP, 14% UTI	38 (63% in combination)	99 (94% in combination)	30-day, adjusted; 8% vs 32% (difference, 23%; 95% CI, 9–35%)	30-day adjusted probability of better outcome (using desirable outcome ranking), 64% (95% CI, 57–71%) with ceftazidime-avibactam

[a]CAZ-AVI, ceftazidime-avibactam; BSI, bloodstream infection; CRE, carbapenem-resistant *Enterobacteriaceae*; HAP, hospital-acquired pneumonia; CR, carbapenem resistant; IAI, intra-abdominal infection; UTI, urinary tract infection; IQR, interquartile range.

also been described for a *K. pneumoniae* isolate coproducing OXA-48 (356). The development of resistance to ceftazidime-avibactam should therefore be checked in all cases by performing follow-up cultures. Studies are needed to evaluate the overall rate of this phenomenon and whether it is associated with monotherapy, dosing, or high-inoculum infections.

The lack of *in vitro* activity of ceftazidime-avibactam against MBL producers and the fact that many MBL producers also coproduce other β-lactamases (such as ESBLs, AmpC, OXA-48, etc.) have attracted some attention to the potential effect of combining ceftazidime-avibactam with aztreonam. Synergistic effects have been seen in *in vitro* and *in vivo* studies (346, 357), and indeed, some patients were successfully treated with this combination (208, 397). This raises the possibility of using atypical combinations of BLBLIs and other β-lactams, such as piperacillin-tazobactam plus aztreonam, against MBL and ESBL producers, although many of these should be tested *in vitro*, *in vivo*, and on patients before any recommendations can be provided. As stated below, aztreonam-avibactam is undergoing clinical development.

Although more data are needed, ceftazidime-avibactam may already be considered the new keystone in the treatment of severe infections due to KPC- and OXA-48-producing *Enterobacteriaceae*.

Meropenem-Vaborbactam

Vaborbactam is another new β-lactamase inhibitor which has been shown to restore the ativity of meropenem against KPC producers; however, it does not enhance the activity of meropenem against MBL producers (NDM or VIM) or OXA-48 producers (358, 359). It was recently approved by the FDA for the treatment of cUTI due to susceptible enterobacteria, based on the data from a phase 3 trial in which meropenem-vaborbactam showed noninferiority to piperacillin-tazobactam (398). The preliminary results of a small phase 3 trial including diverse types of infections caused by CRE showed higher rates of clinical cure with meropenem-vaborbactam than with the best available therapy (57.1% of 28 patients versus 26.7% of 15 patients; absolute difference, 30.5%; 95% CI, 1.5 to 59.4%), as well as lower rates of nephrotoxicity (360); recruitment was stopped because of the superiority of meropenem-vaborbactam. Despite the limited information available, limitations of the study include heterogeneous infections (with a majority of cUTI) and very diverse treatment regimens in the control arm, some of which might have been substandard.

Pipeline of Drugs against CRE

Plazomicin is a new aminoglycoside undergoing clinical development. It escapes the activity of aminoglycoside-modifying enzymes and is therefore active against a greater proportion of CRE than those with gentamicin, tobramycin, and amikacin. Nonetheless, like all other aminoglycosides, it is affected by 16S rRNA methyltransferases (111, 361–363). The results of a phase 3 randomized trial comparing plazomicin (15 mg/kg/day) and meropenem (1 g/8 h) for treatment of cUTI, including pyelonephritis, have been reported; 388 patients were included in the microbiological modified intention-to-treat (mMITT) population, and plazomicin showed a higher rate of microbiological response (87.4% versus 72.1%) (364). The rates and severities of adverse events were similar. The results of an open-label phase 3 trial of patients with BSI or HAP/VAP caused by CRE, comparing plazomicin (17 patients) and colistin (20 patients) in combination with tigecycline or meropenem, have also been reported. Mortality rates were 11.8% and 40%, respectively (difference, 28%; 95% CI, 0.7 to 52.5%). Renal toxicity was less frequent with plazomicin (365).

Eravacycline is a novel fluorocycline antibiotic with *in vitro* activity against MDR Gram-positive and Gram-negative pathogens, including carbapenemase-producing *Enterobacteriaceae* (366–368). The drug has demonstrated noninferiority to ertapenem in

the treatment of cIAI in a phase 3 trial (369). Another RCT involving comparison with meropenem in cIAI is being developed, and trials against cUTI are planned.

Cefiderocol is a new siderophore cephalosporin that is active against MDR Gram-negative organisms, including carbapenemase-producing *Enterobacteriaceae* (370–375). At a dose of 2 g every 8 h, it reaches >50% time above the MIC for MICs of up to 8 mg/liter (376). It has also been shown to be effective against KPC- and NDM-producing *K. pneumoniae* in a rat respiratory tract infection model, particularly when administered over 3 h (377). Preliminary results of a phase 3 trial against cUTI have reported noninferiority to imipenem, and the results are consistent with superiority (378).

Aztreonam-avibactam is an interesting combination because of the ability of avibactam to inhibit ESBLs, AmpC, KPC, and OXA-48 enzymes and the stability of aztreonam against MBLs. Therefore, this compound is active against many CPE isolates, regardless of the carbapenemase produced (242, 332, 379–388), and is undergoing phase II trials against intra-abdominal infections, in association with metronidazole.

Relebactam is another β-lactamase inhibitor with activity against KPC and ESBL producers (KPC producers with major OmpK36 mutations affecting permeability have higher MICs). It is less active against OXA-48 and not active against MBLs (389–395). It is being studied in combination with imipenem in phase 3 studies of cIAI and cUTI.

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