Optimizing therapy of bloodstream infection due to extended-spectrum β-lactamase-producing Enterobacteriaceae

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Purpose of review
Infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) are increasing worldwide. Carbapenems are usually regarded as the antibiotics of choice for the treatment of serious ESBL infections. However, because of the alarming emergence or carbapenem resistance, interest in effective alternatives has emerged. The present review summarizes the findings published on the antibiotics currently available for treatment of patients with an ESBL-E bloodstream infection (BSI).

Recent findings
Meropenem and imipenem are the drugs recommended for treatment of ESBL BSIs in critically ill patients, and in infections with high bacterial loads or elevated β-lactam minimum inhibitory concentrations. Ertapenem should be reserved for patients with less severe presentations, and should be used at high doses. In milder presentations or BSIs from low-risk sources, other carbapenem-sparing alternatives could be considered: cephamycins, fluoroquinolones, and particularly a β-lactam/β-lactam inhibitor combination (particularly piperacillin/tazobactam). Optimized dosing of piperacillin/tazobactam is recommended (high doses and extended infusion). There are few data on the use of the promising newly available drugs (e.g. ceftolozane/tazobactam, ceftazidime/avibactam, cefiderocol, and plazomicin), and it seems reasonable to reserve them as last-resort drugs.

Summary
Carbapenems should be used in patients with serious infections; alternatives could be used individually, particularly for definitive treatment of patients with milder presentations.

Keywords
bacteraemia, bacteremia, bloodstream infection, ESBL, extended-spectrum β-lactamase

INTRODUCTION

Infections because of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (ESBL-E) are increasing worldwide, and are associated with prolonged hospital stays, increased hospital costs, and high mortality [1].

Production of ESBLs limits therapeutic options, because they hydrolyze most β-lactams, including penicillins, third-generation cephalosporins, and aztreonam. In addition, resistance to other antibiotics is frequently observed (e.g. quinolones, trimethoprim-sulfamethoxazole, and aminoglycosides). Therefore, carbapenems constitute the recommended therapeutic regimens for the treatment of serious infections due to ESBL-E. Nevertheless, overuse of carbapenems has been associated with the alarming emergence of carbapenem-resistant organisms, which are spreading worldwide and impairing patient outcomes [2,3]. Therefore, interest in the use of carbapenem-sparing antibiotics for the treatment of infections because of ESBL-E has increased in recent years.

Herein, we review papers addressing currently available antibiotic options used as both empiric and definitive therapy for the treatment of

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KEY POINTS

- The emergence of carbapenem resistance among Gram-negative bacilli has sparked interest in the use of carbapenem-sparing alternatives for the treatment of infections due to ESBL-E.
- There are no well designed studies addressing the efficacy of most of the noncarbapenem regimens for the treatment of ESBL infections, and data are particularly scarce for patients with BSI.
- There is only one single RCT that shows less efficacy of PTZ compared to meropenem as definitive therapy for the treatment of BSI due to cephalosporin-resistant Enterobacteriaceae. Nevertheless, it has some limitations.
- Considering the available data, carbapenems should be used in patients with serious infections. Alternatives to carbapenems could be used individually, particularly for definitive treatment of patients with milder presentations.
- New available broad-spectrum antibiotics are active against ESBL-E, but it seems reasonable to reserve them for the treatment of infections due to other multidrug-resistant and extensively drug-resistant Gram-negative bacilli.

bloodstream infections (BSIs) because of ESBL-E published in the PubMed/MEDLINE database. Only studies published in English were included, with special attention paid to those published in the last 2 years. Also, priority was given to meta-analyses over individual studies. The following search terms were used: ESBL, extended-spectrum β-lactamase, bacteremia, bacteraemia, bloodstream infection, β-lactam/β-lactamase inhibitors (BLBLIs), carbapenem, piperacillin/tazobactam, ceftolozane/tazobactam, ceftazidime/avibactam, aminoglycoside, fosfomycin, temocillin, cephalosporin, cephamycin, cefepime, cefiderocol, tigecycline, fluoroquinolone, trimethoprim-sulfamethoxazole, and plazomicin.

CURRENT EVIDENCE CONCERNING THE TREATMENT OF EXTENDED-SPECTRUM β-LACTAMASE-PRODUCING ENTEROBACTERIACEAE BLOODSTREAM INFECTIONS

Carbapenems

Carbapenems, mainly meropenem and imipenem, have traditionally been considered the standard therapy for infections because of ESBL-E, because they remain stable to hydrolysis by these enzymes, and are less affected by the inoculum effect [4]. In a meta-analysis published in 2012, carbapenems showed lower mortality rates than other antibiotics (such as fluoroquionolones, aminoglycosides, and cephalosporins) when used in an empirical or definitive regimen [5]. In a recent meta-analysis that included 35 observational studies reporting on 3842 patients, this result was only confirmed in patients receiving cephalosporins, when compared to those treated with carbapenems. Nevertheless, the lack of results showing the inferiority of non-cephalosporin antibiotics should be interpreted with caution, because the pooled data were insufficient to draw firm conclusions [6▪▪]. Of note, meropenem showed very low mortality rates (3.7%) in the MERINO trial: a recently published randomized clinical trial (RCT) in which patients with BSIs because of cephalosporin-resistant Enterobacteriaceae were evaluated [7▪▪].

Clinical experience of doripenem is limited. The data extracted from a phase III RCT of doripenem showed efficacy equivalent to that of meropenem, imipenem, or piperacillin/tazobactam (PTZ) [8]. Also, a good clinical response (88%) was observed in patients treated with doripenem in the RCTs in which it was compared to ceftazidime/avibactam for complicated urinary tract infections (cUTIs) [9]. However, it has to be taken into account that the number of patients with BSIs included in these RCTs was small.

Ertapenem, a carbapenem with no activity against *Pseudomonas aeruginosa*, has been increasingly used as definitive therapy for ESBL-E infections. Despite the presence of methodological limitations in some studies comparing ertapenem with other carbapenems for the treatment of BSIs because of ESBL-E, they support its use in nonseverely ill patients [10–11,12▪]. However, in the series published by Collins *et al.* [11], higher mortality rates were observed in patients with severe sepsis treated with ertapenem than in those who received other carbapenems (60 vs. 36.1%). Furthermore, in the INCREMENT cohort, a trend towards higher mortality was found in patients with septic shock treated with ertapenem [12▪]. A plausible explanation for this worrisome finding is that the standard dose of 1 g/day may not be sufficient to achieve the PK/PD target, particularly in those patients with high-inoculum infections [13] and for strains with only intermediate susceptibility to this antibiotic [minimum inhibitory concentration (MIC) of 1 mg/L] [14]. In addition, albeit anecdotal evidence, ertapenem resistance during therapy has been reported [15].

Taking into account the current evidence, imipenem and meropenem would be the recommended treatment options for patients with more

severe presentations; whereas ertapenem should be reserved for patients with milder presentations. Ertapenem may be useful for outpatient management or in a de-escalation approach [16]. Moreover, when used, higher doses of this latter drug should be considered (1.5 or 2 g/24 h). The evidence regarding doripenem is too scarce to enable clear conclusions, although it has to be taken into consideration that it showed higher mortality and lower cure rates than the treatment it was compared to in ventilator-associated bacterial pneumonia (VABP) [17,18].

β-LACTAM/β-LACTAM INHIBITOR COMBINATIONS

Classic BLBLIs may be effective against ESBL producers if no other mechanisms of resistance are present; therefore, they represent a promising option as carbapenem-sparing alternatives for the treatment of infections because of ESBL-E. Notably, rates of resistance to BLBLIs in ESBL producers vary according to geographical area [19].

Concerns regarding the efficacy of BLBLIs against infections because of ESBL-E include the inoculum effect, and the worry that the efficacy of BLBLIs may vary according to the source of infection and the infecting species [20]. However, the inoculum effect also occurs with non-ESBL-producing organisms [21], and it has only been observed with PTZ: not with amoxicillin/clavulanate [21,22]. Moreover, in the INCREMENT cohort, the different sources of BSIs and the different infecting species did not affect the outcomes of patients treated with BLBLIs [12▪].

The role of BLBLIs in the treatment of BSIs because of ESBL-E is still controversial. A large body of data obtained from several well designed observational studies and their meta-analysis has shown that BLBLIs are not inferior to carbapenems in the treatment of BSIs because of ESBL producers [5,6▪▪,23▪,24▪]. However, some other studies have found opposing results [25–27]. Tamma *et al.* [25] reported lower mortality rates at day 14 in patients who received carbapenems as definitive therapy than in those receiving PTZ (8 vs. 17%). However, that study only included patients receiving a carbapenem as definitive therapy, the doses of PTZ used were frequently low, and the MIC for PTZ was 4 mg/l or less for only 40% of the isolates.

The MERINO trial is the only noninferiority RCT to compare meropenem with PTZ for the treatment of BSIs because of cephalosporin-resistant enterobacteria (including Amp-producing organisms) [7▪▪]. The study failed to demonstrate the noninferiority of PTZ compared to carbapenem, in terms of overall 30-day mortality (23/187 = 12.3 vs. 7/191 = 3.7%). However, the study did have some limitations that should be pointed out. First, a conservative 5% noninferiority margin was used that could be questioned. Moreover, the overall mortality rate in the meropenem group was unexpectedly low. In addition, the treatment arms had some imbalances regarding the sources of BSI and the severity of the disease. Then, empirical and step-down antibiotic treatment was not specified in some patients, whereas crossover of patients from one group to the other was allowed. Furthermore, none of the deaths recorded was associated with either the infection or the study drug, but were fundamentally due to noninfectious complications in patients with advanced cancer; and these are variables which, among other things, were not properly controlled for in the post-hoc tests carried out with multivariate analysis. Meanwhile, the rest of the secondary variables showed discrepant results, such as no significant differences being detected in the days before resolution of symptoms or in the microbiological cure rates, yet the 5% noninferiority margin for the 'clinical and microbiological' cure variable on day 4 of the treatment was not met. Moreover, patients with infections because of AmpC producers were also analyzed, which could have influenced the outcome. Finally, the susceptibility testing for PTZ was not the recommended/standard [28].

Of note, two observational studies focused on immunocompromised hematologic patients [29▪,30▪]. The BICAR study, a retrospective multicenter international study, did not find significant differences in early or overall 30-day mortality rates in neutropenic hematologic patients with BSIs because of ESBL producers who received BLBLIs (mostly PTZ) compared to carbapenems, as either empirical or definitive therapy [29▪]. However, the number of patients treated with BLBLIs in this study was small. In a more recently published single-center retrospective study, empirical treatment with cefepime or PTZ was not associated with increased 14-day mortality relative to empirical treatment with carbapenems in patients with hematologic diseases and ESBL-*Escherichia coli* BSI, although most patients were switched to carbapenems early in the treatment [30▪]. The great majority of patients in both studies were patients with nonhigh-risk BSIs from an endogenous source, which represent the great majority of patients with febrile neutropenia. These results would be reinforced by the results of the observational studies included in the aforementioned meta-analyses, which included a high proportion of 'low-risk' patients [5,6▪▪,23▪,24▪].

In summary, until better evidence is available, we recommend reserving carbapenems for neutropenic patients with sepsis and for high-inoculum infections caused by strains showing higher MICs

for BLBLIs, as detailed in the recommendations above, and as previously advocated [31].

Optimized dosing of PTZ is crucial in order to reach therapeutic drug targets, particularly in critically ill patients, and for isolates with high MICs [32▪]. Therefore, appropriate doses of PTZ (4.5 g every 6 or 8 h) administered via extended infusion should be used [33].

Amoxicillin/clavulanate is a good option for susceptible isolates in countries where this drug is available for intravenous (IV) use. Nevertheless, data regarding its use are more limited. As mentioned above, it does not suffer from the inoculum effect [20,21], and it may be used for oral switch treatment.

Cefoperazone/sulbactam may be resistant to hydrolysis by ESBLs, and is extensively used in many Asian countries [34]. Although data regarding its use are scarce, a recently published retrospective study suggested, through differences that were not statistically significant, that it may tend to have a lower success rate and a higher 14-day mortality rate than carbapenems, in patients with ESBL-E BSIs. Again, the number of patients included in the study, and particularly in the cefoperazone/sulbactam arm, was small, which may explain why the results did not reach statistical significance.

Taking into account the evidence currently available, BLBLIs (mainly PTZ) should be considered as a carbapenem-sparing alternative for the treatment of ESBL-E BSIs in low-risk patients who do not have a high-inoculum BSI and present without severe sepsis or septic shock. Optimized dosing and extended infusion are strongly recommended.

Table 1 summarizes the selected clinical studies comparing the efficacy of BLBLIs with carbapenems in patients with BSI due to ESBL-E published since 2012 [35–40].

NEWER β-LACTAM/β-LACTAM INHIBITOR COMBINATIONS

In recent years, two new combinations of a cephalosporin plus a β-lactam inhibitor have been introduced in the antibiotic armamentarium. Ceftolozane/tazobactam is the combination of a new cephalosporin (ceftolozane), with enhanced antipseudomonal activity, with a classic β-lactamase inhibitor (tazobactam). This combination exhibits good *in vitro* activity against ESBL-*E. coli* (>90%), and ESBL-*Klebsiella pneumoniae* (from 42 to 98%) [41]. It was approved by the US FDA and the European Medicines Agency (EMA) for the treatment of complicated intra-abdominal infections (cIAIs) in combination with metronidazole [42,43], and cUTI, including pyelonephritis [44]. A total of 150 patients with ESBL infections included in these pivotal trials were analyzed by Popejoy *et al.* [45]. In that post-hoc analysis, the rates of clinical cure (98.1 and 72.2%, respectively), and microbiological eradication (82.6 and 47.8%, respectively) of cUTI were higher with ceftolozane/tazobactam than with levofloxacin. Against cIAIs, no differences were found regarding clinical cure rates for ceftolozane/tazobactam and meropenem (95.8 and 88.5%, respectively). Similar results were obtained for microbiological eradication.

Ceftazidime/avibactam combines ceftazidime with a new (non-β-lactam) β-lactamase inhibitor. It is usually more active *in vitro* against ESBLs than ceftolozane/tazbactam [41]. It was approved by the US FDA and the EMA for treatment of cIAIs (in combination with metronidazole) [46,47] and cUTIs [48], with a recent additional indication by the EMA for VABP and other infections because of Gram-negative bacteria with reduced treatment options. Mendes *et al.* [9] performed a post-hoc analysis of the two pivotal trials in cUTIs comparing ceftazidime/avibactam and doripenem. The cure rates were 91.7% (76/83) and 88% (81/92), respectively. In the cIAI pivotal trial, this drug showed a rate of clinical response against ceftazidime-resistant Enterobacteriaceae similar to that of meropenem (about 80% were ESBL producers) [38]. In addition, in a pathogen-directed trial of patients with cIAIs and cUTIs because of ceftazidime-resistant Enterobacteriaceae, it showed similar efficacy to that of the best therapy available (mostly carbapenems) [49]. Finally, the noninferiority RCT comparing ceftazidime/avibactam and meropenem for the treatment of nosocomial pneumonia (including VABP) showed no differences in the rate of clinical cure [50].

Data regarding these new drugs should be interpreted with caution for bacteremic patients, because the studies include unknown [42,46] or a small number of patients with BSIs [43,44,46,47,50]. Moreover, because they are active against extensively drug-resistant *Pseudomonas aeruginosa* (ceftolozane/tazobactam) and KPC- or OXA-48-producing Enterobacteriaceae (ceftazidime/avibactam), it seems reasonable to reserve them for these particular organisms.

CEPHAMYCINS

Cephamycins (cefoxitin, cefmetazole, cefotetan, moxalactam, and flomoxef) remain active against ESBL-E isolates, but not against AmpC producers [51]. Concerns over these drugs for the treatment of ESBL-E include the potential development of resistance during treatment [52]. Clinical data on

Table 1. Selected clinical studies comparing the efficacy of β-lactam + β-lactam inhibitors with carbapenems in patients with bloodstream infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae published since 2012

Authors, year and reference	Study design	Antibiotics	Type of therapy	Source of infection	ESBL-producing organisms	Clinical outcomes	Comments
Kang *et al.* 2012 [35]	Multicenter retrospective cohort	PTZ vs. carbapenems	Empirical therapy	NA	*E. coli* (68%), *K. pneumoniae* (32%)	30-Day mortality was similar between those who received PTZ and carbapenem (22.2% vs. 26.9%, respectively, $P=0.59$). The multivariate analysis showed no difference (OR = 0.63; 95%CI 0.17–2.27, $P=0.34$)	PTZ was administered as definitive therapy in 23 patients
Rodríguez-Baño *et al.* 2012 [36]	Multicenter *post hoc* analysis of 6 prospective cohorts	BLBLIs vs. carbapenems	Empirical and definitive therapy	Urinary or biliary (70%)	*E. coli* (100%)	The 30-day mortality of patients who received BLBLIs vs. carbapenems were 9.7% vs. 19.4% ($P=0.1$) in the ETC, and 9.3% vs. 16.7% ($P>0.2$) in the DTC, respectively. The multivariate analysis showed no difference (OR = 0.63; 95%CI 0.17–2.27, $P=0.34$). The multivariate analysis showed no association between BLBLIs and increased mortality in both ETC (HH 1.14, 95%CI 0.29–4.40; $P=0.84$)and DTC (HH 0.76, 95%CI 0.28–2.07; $P=0.5$)	AMC and PTZ were found to be suitable carbapenem-sparing regimens in selected 'low-risk' patients
Tsai *et al.* 2014 [37]	Multicenter retrospective cohort	PTZ vs. carbapenems	Empirical and definitive therapy	UTI (51.1%) Pneumonia (15.1%) SSTI (14.9%) Catheter (10.6%) IAI (6.4%) Primary BSI (4.3%)	*P. mirabilis* (100%)	The rates of 30-day mortality (14.3% vs. 23.1%; $P=0.65$) and in-hospital mortality (19.1 vs. 30.8%, $P=0.68$) were nonsignificantly lower in the carbapenems group, compared to PTZ	
Ofer-Friedman *et al.* 2015 [38]	Bicenter retrospective cohort	PTZ vs. carbapenems	Definitive therapy	Nonurinary: Pneumonia (34%), SSTI (28%), Biliary (17%) IAI (9%), Primary BSI (8%) Unknown (5%)	*E. coli* (53%), *K. pneumoniae* (28%) and *P. mirabilis* (19%)	Treatment with PTZ was associated with increased 90-day mortality compared to carbapenems (OR 7.9 95%CI 1.2–53, $P=0.03$)	30-day mortality was higher in the PTZ group with borderline significance (60% vs. 34%, OR 3.0 $P=0.10$)
Tamma *et al.* 2015 [39]	Unicentric retrospective cohort	PTZ vs. carbapenems	Empirical therapy	Catheter (46%) UTI (21%) IAI (17%), Biliary (9%) Pneumonia (9%)	*E. coli* (31%), *K. pneumoniae* (68%) *and P. mirabilis* (1%)	The adjusted risk of 14-day mortality was higher in the PTZ group, compared to carbapenem group (OR 1.92; 95%CI 1.07–3.45)	PTZ was administered at 3.375g IV every 6h in 61% of the patients.
Ng *et al.* 2016 [40]	Bicenter retrospective cohort	PTZ vs. carbapenems	Empirical therapy	Catheter (46%) UTI (21%) IAI (19%) Pneumonia (9%) Biliary (9%)	*E. coli* (67%), *K. pneumoniae* (33%)	30-Day mortality was comparable between those who received PTZ and carbapenem (30.9 vs. 29.8%, respectively, $P=0.89$)	Empirical PTZ was not associated with increased mortality in the multivariate analysis (OR 1.00; 95% CI 0.45–2.17)

Table 1 (*Continued*)

Authors, year and reference	Study design	Antibiotics	Type of therapy	Source of infection	ESBL-producing organisms	Clinical outcomes	Comments
Gutiérrez-Gutiérrez *et al.* 2016 [12▪]	Multinational multicenter retrospective cohort	BLBLIs vs. carbapenems	Empirical and definitive therapy	Urinary (45%), Biliary (12%), Other (high-risk sources) (40%)	*E. coli* (73%), *K. pneumoniae* (19%), Other Enterobacteriaceae (8%)	The cure/improvement rates with BLBLIs and carbapenems were 80.0% and 78.9% in the ETC, and 90.2 and 85.5% in the DTC, respectively. The 30-day mortality rates were 17.6 and 20% in the ETC and 9.8% and 13.9% in the DTC, respectively. The adjusted OR (95%CI) for cure/improvement rate with BLBLIs was 1.37 (0.69 to 2.76) in the ETC, and 1.61 (0.58 to 4.86) in the DTC. Regarding 30-day mortality, the adjusted OR (95% CI) values were 0.55 (0.25 to 1.18) for ET and 0.59 (0.19 to 1.71) for DT.	The results were consistent in all subgroups studied, in a stratified analysis according to quartiles of propensity score (PS), and in PS-matched cases
Gudiol *et al.* 2017 [29▪]	Multinational multicenter retrospective cohort	BLBLIs vs. carbapenems	Empirical and definitive therapy	Primary (52.8%) Catheter (18.1%) IAI (15%) UTI (15%)	*E. coli* (73.7%), *K. pneumoniae* (23.1%), *K. oxytoca* (1.5%), *E. cloacae* (1.5%)	The 30-day mortality rates with BLBLIs and carbapenems were 20.8 and 13.4% ($P=0.33$) in the ETC, and 5.8% and 15.8% ($P=0.99$) in the DTC, respectively. Similar results were obtained regarding all the secondary endpoints. The results were consistent in the PS-matched cohorts	High-risk hematological patients with neutropenia.
Benanti *et al.* 2018 [30▪]	Unicentric retrospective cohort	PTZ (21) or cefepime (40) vs. meropenem (42)	Empirical therapy	IAI (52.4%), Catheter (15.5%) Unknown (17.4%), SSTI (8.7%), Pneumonia (7.7%) UTI (7.7%)	NA	The 14-day mortality rate was 0% in the PTZ group compared to 19% in the meropenem group. An adjusted risk could not be calculated because no patients empirically treated with PTZ died.	High-risk hematological patients. 92% and 77% were neutropenic in the meropenem and PTZ groups, respectively
Harris *et al.* 2018 [7▪▪]	Multinational multicenter randomized clinical trial	PTZ vs. meropenem	Definitive therapy	UTI (60.9%) IAI (16.3%) Unknown (7.3%), Mucositis/ neutropenia (5%) Pneumonia (3.1%) Surgical site infection (3.1%) Catheter (1.5%) SSTI (1.3%) Other (1.05%)	*E. coli* (86.5%), *K. pneumoniae* (13.4%)	The 30-day mortality rate was 12.3% in patients treated with PTZ, compared to 3.7% for those who received meropenem. Risk difference: 8.6% (1-sided 97.5% CI, $-\infty$ to 14.5%); $P=0.90$ for noninferiority.	In the subgroup of patients from any source with a Charlson score <2, mortality was 2.9% for patients treated with PTZ and 2.6% for patients treated with meropenem

AMC, amoxicillin-clavulanate; BLBLIs, β-lactam/β-lactam inhibitors; BSI, bloodstream infection; CI, confidence interval; DTC, definitive therapy cohort; ETC, empirical therapy cohort; IAI, intrabdominal infection; IV, intravenous; PTZ, piperacillin-tazobactam; SSTI, skin and soft tissue infection; UTI, urinary tract infections.

cephamycins for the treatment of ESBLs are scarce. In addition, the studies are limited by a remarkable risk of bias and small sample sizes [53–59]. The studies included patients with 'low-risk' BSIs, predominantly from the urinary tract. Only one study showed worse outcomes with these drugs than with carbapenems [53], whereas the others failed to identify any differences.

Until more data are available, cephamycins should only be used in patients with BSIs from urinary sources and due to isolates with low MICs. Moreover, they should be used at high doses.

OXYMINO-CEPHALOSPORINS

Cephalosporins show variable activity against ESBLs: cefotaxime is frequently more active against TEM and SHV producers than against CTX-M, whereas the opposite is the case for cefepime and ceftazidime. Previous data regarding the use of cephalosporins showed worse outcomes in patients treated with these drugs, even in the cases where they were considered as susceptible according to old MIC breakpoints [60].

More recently, the CLSI and EUCAST have significantly lowered the MICs of cephalosporins, and currently the recommendation is to report the MICs and the category (susceptible or resistant) regardless of ESBL production. The most frequent type of ESBL is CTX-M enzymes, which are frequently resistant to ceftazidime [61].

Interpretation of clinical data relating to patients treated with active cephalosporins (mostly ceftazidime and cefepime) is difficult because study results are sometimes contradictory and because of the risk of bias [62–65]. Some of the concerns regarding the diminished efficacy of cefepime for the treatment of ESBL infection are the inoculum effect [66], the failure to achieve PK/PD targets because of inadequate dosing or interval schedules [67], and the possibility of overexpression of bla_{ESBL} genes [68]. Some studies comparing cefepime and carbapenems for ESBL infections show no differences [62,63], whereas others suggest that cefepime is inferior [64,65]. In view of the data available, cephalosporins must be avoided for patients with BSIs because of ESBLs.

CEFIDEROCOL

Cefiderocol is an appealing new siderophore cephalosporin with a broad spectrum of activity against Gram-negative bacteria, including multidrug-resistant and extensively drug-resistant strains (e.g. ESBL-E, *Acinetobacter baumannii, P. aeruginosa,* and *Stenotrophomonas maltophilia*) [69].

A phase II noninferiority RCT to assess the efficacy and safety of cefiderocol compared with imipenem for the treatment of cUTIs was published recently, as part of a US FDA-guided streamlined antibacterial drug development program [70▪]. The great majority of infections were because of *E. coli* or *K. pneumoniae* in both groups (80 and 88%, respectively), and resistance to cephalosporins were observed in 53% of the *K. pneumoniae* isolates and 38% of the *E. coli* isolates in the cefiderocol group, compared to 57 and 16%, respectively, in the imipenem group. Among the 252 patients in the cefiderocol group, the primary efficacy endpoint was achieved in 183 patients (73%), compared to 65/199 patients (55%) in the imipenem group, with an adjusted treatment difference of 18.58% (95% confidence interval, 8.23–28.92; $P = 0.0004$), thereby establishing the noninferiority of cefiderocol compared to imipenem. More than 50% of the patients had pyelonephritis, but the number of patients with a BSI is not provided.

TEMOCILLIN

Temocillin, a 6-a-methoxy derivative of ticarcillin only available in the United Kingdom and Belgium, is a β-lactam antibiotic with potent bactericidal activity that is restricted to Enterobacteriaceae and *Burkholderia cepacia*, and with the capability to resist the hydrolysis of the Ambler class A and class C β-lactamases [71▪]. Thus, it retains *in vitro* activity against ESBL-E [72], and has demonstrated efficacy at eradicating infections in a murine model of ascending pyelonephritis caused by strains harboring these enzymes [73]. There are limited clinical data in the literature, particularly for ESBL BSIs, [74] and no RCTs have been conducted. The largest retrospective study of patients treated with this drug observed clinical and microbiological success in more than 82% of patients with ESBL-BSIs [75]. Notably, researchers identified failures in patients treated with insufficient doses, which should to be at least of 2 g/12 h in less severe, and 2 g/8 h in critically ill, patients [76].

FOSFOMYCIN

This drug exhibits a notably wide spectrum of activity, which encompasses multidrug-resistant Gram-negative bacilli, including ESBL producers [77]. There are oral formulations available (fosfomycin trometamol and fosfomycin calcium) that reach adequate urine levels and have been demonstrated to be effective in the treatment of lower UTIs caused by ESBLs [78]. The disodium formulation for IV administration in doses of 4 g/8 h has been shown

not to be inferior to PTZ for the treatment of cUTIs and acute pyelonephritis caused by susceptible Enterobacteriaceae isolates in a recent RCT [79]. IV fosfomycin was well tolerated, with hypokalemia and sodium overload being the most important adverse events to be aware on. The possible usefulness of this drug in the treatment of bacteremic UTIs caused by ESBL producing *E. coli* is the main research question of an ongoing RCT: the FOREST study, of as yet unpublished data [80▪].

TIGECYCLINE

Tigecycline covers a wide antimicrobial spectrum which includes ESBLs [81], and it has been proven to be efficacious both in animal models [82] and in clinical studies of severe infections caused by multidrug-resistant organisms (with a small number of patients with ESBL-BSI) [83,84]. Nevertheless, two meta-analyses reported lower efficacy and higher mortality rates in patients with severe infections treated with this drug than for the comparative drugs [85,86], with even worse outcomes particularly for Gram negative infections in one of them [86]. Thus, tigecycline is not recommended as an agent of choice in monotherapy for ESBL-BSI.

FLUOROQUINOLONES AND TRIMETHOPRIM-SULFAMETHOXAZOLE

ESBL-E frequently harbor determinants of quinolone resistance [87], either chromosomic or low-level plasmid-mediated (PMQR) [88]. The latter mechanism of resistance was associated with greater mortality in patients with ESBL-BSIs [89]. Of note, this low-level quinolone resistance can be overestimated when the CLSI clinical breakpoints are considered.

Some recent reports have described successful experiences of patients with ESBL-BSI caused by quinolone-susceptible isolates treated with these drugs [90]. Of special interest are the results of the multinational, retrospective cohort study of monomicrobial BSIs: the INCREMENT study. That showed similar outcomes for patients with ESBL-BSI treated with quinolones and with carbapenems after a propensity score-matched analysis [91▪▪].

Co-resistance to trimethoprim-sulfamethoxazole is also frequent in ESBL-producing strains [87]. In a recent retrospective study specifically comparing carbapenems with other alternative non-intravenous antibiotics for the definitive treatment of ESBL-BSI, patients treated with trimethoprim-sulfamethoxazole showed similar outcomes and a shorter hospital stay [90]. Finally, some isolated reports on its usefulness in the therapy of carbapenemase-producing Enterobacteriaceae may seem to suggest the same for isolates harboring ESBL [92].

Taking into account all the above findings, both quinolones and trimethoprim-sulfamethoxazole could be considered suitable non-IV carbapenem-sparing antibiotics for the definitive treatment of ESBL-BSIs.

AMINOGLYCOSIDES

Aminoglycosides exert a concentration-dependent, bactericidal effect by inhibiting the bacterial S30 ribosomal subunit. These drugs, and particularly amikacin, retain *in vitro* activity against ESBL-E [93]. As for the clinical aspects, these antibiotics have been proved not to be inferior to β-lactams in monotherapy for the treatment of UTIs caused by susceptible Enterobacteriaceae, [94] as well as in combination therapy in some small case series of ESBL-BSIs, both in oncological [95] and pediatric patients [96]. The larger series of ESBL-BSI patients treated with aminoglycosides comes again from the INCREMENT study, in which empirical therapy with aminoglycosides in 43 patients was not associated with higher 30-day mortality when compared with empirical carbapenem therapy [91▪▪]. Because of all this evidence, and taking into account the risk of nephrotoxicity as their major drawback, aminoglycosides seem to be a suitable option as a carbapenem-sparing empirical agent to combine with β-lactams in settings with a high ESBL prevalence.

Interestingly, plazomicin, a new aminoglycoside molecule specifically designed to evade the activity of aminoglycoside-modifying enzymes, improves and expands the spectrum towards ESBL and carbapenem-producing Enterobacteriaceae (except NDM-1) with the additional advantage of a presumably lower renal toxicity [97▪]. At a 15 mg/kg/day dose, it has been demonstrated not to be inferior to meropenem in an RCT of cUTIs, the EPIC study, where more than 26.5% of isolates causing infection were caused by ESBL strains, and up to 13% of the total UTI episodes were bacteremic, although it is not clear the exact number of ESBL-BSIs included in the plazomicin arm [98▪▪].

While waiting for more reports coming from 'real life' cases treated with this drug in the near future, all the foregoing makes it a promising alternative.

CONCLUSION

Taking into account the data currently available, carbapenems (meropenem and imipenem) are the recommended drugs for the treatment of ESBL BSIs in critically ill patients, infections with a high

bacterial load, or elevated β-lactam MICs. Ertapenem should be reserved for patients with less severe presentations, and should be used in high doses.

For patients with milder presentations and with BSIs from low-risk sources, such as UTIs, other carbapenem-sparing alternatives could be considered, particularly cephamicins, fluoroquinolones, and BLBLIs (mainly PTZ), with the most robust data available for BLBLIs. When used, optimized dosing of PTZ is recommended, with high doses and via extended infusion. The newly available drugs, namely ceftolozane/tazobactam, ceftazidime/avibactam, cefiderocol, and plazomicin, are promising alternatives to carbapenems. Nevertheless, there are currently relatively little data on their use, and because of their activity against other multidrug-resistant and extensively drug-resistant organisms, it seems reasonable to reserve them as last-resort drugs.

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Conflicts of interest

C. Gudiol has served as speaker at scientific meetings sponsored by Pfizer and MSD. G. Cuervo has participated as speaker at scientific meetings sponsored by Pfizer. J. Carratalà has participated as speaker at scientific meetings sponsored by Pfizer and MSD.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Schwaber MJ, Navon-Venezia S, Kaye KS, *et al.* Clinical and economic impact of bacteremia with extended-spectrum β-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2006; 50:1257–1262.
2. Albiger B, Glasner C, Struelens MJ, *et al.* European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSACPE) working group. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. Euro Surveill 2015; 20:.
3. Hauck C, Cober E, Richter SS, *et al.* Antibacterial Resistance Leadership Group. Spectrum of excess mortality due to carbapenem-resistant *Klebsiella pneumonia* infections. Clin Microbiol Infect 2016; 22:513–519.
4. Pitout JD, Laupland KB. Extended-spectrum β-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis 2008; 8:159–166.
5. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to enterobacteriaceae producing extended-spectrum (-lactamases: A systematic review and meta-analysis. J Antimicrob Chemother 2012; 67:2793–2803.
6. ■■ Son SK, LEE NR, Ko J-H, *et al.* Clinical effectiveness of carbapenem versus alternative antibiotics for treating ESBL-producing Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. J Antimicrob Chemother 2018; 73:2631–2642.

This recently published meta-analysis, which included data of 35 observational studies describing 3842 patients, reported lower mortality rates in patients treated with carbapenems only when compared with patients treated with cephalosporins.

7. ■■ Harris PNA, Tambyah PA, Lye DC, *et al.* Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E. coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance. JAMA 2018; 320:984–994.

This is the only randomized clinical trial comparing the efficacy of PTZ with meropenem as definitive therapy in patients with BSI due to cephalosporin-resistant Enterobacteriaceae that has been performed, showing a lower 14-day mortality rate in patients treated with meropenem. The results should be interpreted with caution because of several limitations.

8. Kaniga K, Flamm R, Tong SY, *et al.* Worldwide experience with the use of doripenem against extended-spectrum- (-lactamase-producing and ciprofloxacin-resistant Enterobacteriaceae: analysis of six phase 3 clinical studies. Antimicrob Agents Chemother 2010; 54:2119–2124.
9. Mendes RE, Castanheira M, Woosley LN, *et al.* Molecular β-lactamase characterization of Gram-negative pathogens recovered from patients enrolled in the ceftazidime-avibactam phase 3 trials (RECAPTURE 1 and 2) for complicated urinary tract infections: efficacies analysed against susceptible and resist. Int J Antimicrob Agents 2018; 52:287–292.
10. Lee NY, Lee CC, Huang WH, *et al.* Carbapenem therapy for bacteremia due to extended-spectrum-(-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*: implications of ertapenem susceptibility. Antimcrob Agents Chemother 2012; 56:2888–2893.
11. Collins VI, Marchaim D, Pogue JM, *et al.* Efficacy of ertapenem for treatment of bloodstream infections caused by extended spectrum-β-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2012; 56:2173–2177.
12. ■ Gutiérrez-Gutiérrez B, Bonomo RA, Carmeli Y, *et al.* Ertapenem for the treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae: a multinational preregistered cohort study. J Antimicrob Chemother 2016; 71:1672–1680.

Treatment with ertapenem was associated with higher mortality rates in patients with sepsis/septic shock compared with those who received other carbapenems, in a multinational retrospective cohort study (the INCREMENT project).

13. Burkhardt O, Kumar V, Katterwe D, *et al.* Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration. J Antimicrob Chemother 2007; 59:277–284.
14. Zhanel GG, Denisuik A, Vashisht S, *et al.* Pharmacodynamic activity of ertapenem versus genotypically characterized extended-spectrum (-lactamase (ESBL)-, KPC- or NDM-producing Escherichia coli with reduced susceptibility or resistance to ertapenem using an in vitro model. J Antimicrob Chemother 2014; 69:2448–2452.
15. Skurnik D, Lasocki S, Bremont S, *et al.* Development of ertapenem resistance in a patient with mediastinitis caused by *Klebsiella pneumoniae* producing an extended-spectrum β-lactamase. J Med Microbiol 2010; 59:115–119.
16. Veve MP, Wagner JL, Kenney RM, *et al.* Comparison of fosfomycin to ertapenem for outpatient or step-down therapy of extended-spectrum β-lactamase urinary tract infections. Int J Antimicrob Agents 2016; 48:56–60.
17. Kollef MH, Chastre J, Clavel M, *et al.* A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. Crit Care 2012; 16:R218.
18. FDA drug safety communication: FDA approves label changes for antibacterial Doribax (doripenem) describing increased risk of death for ventilator patients with pneumonia. https://www.fda.gov/Drugs/DrugSafety/ucm387971.htm; March 6, 2014.
19. Zalacain M, Biedenbach DJ, Badal RE, *et al.* Pathogen prevalence and antimicrobial susceptibility among Enterobacteriaceae causing hospital-associated intra-abdominal infections in adults in the United States (2012–2013). Clin Ther 2016; 38:1510–1521.
20. Delgado-Valverde M, Torres E, Valiente-Mendez A, *et al.* Impact of the MIC of piperacillin/tazobactam on the outcome for patients with bacteraemia due to Enterobacteriaceae: the Bacteraemia-MIC Project. J Antimicrob Chemother 2016; 71:521–530.
21. López-Cerero L, Picón E, Morillo C, *et al.* Comparative assessment of inoculum effects on the antimicrobial activity of amoxicillin-clavulanate and piperacillin-tazobactam with extended-spectrum β-lactamase-producing and extended-spectrum β-lactamase-nonproducing Escherichia coli isolates. Clin Microbiol Infect 2010; 16:132–136.
22. Docobo-Pérez F, López-Cerero L, López-Rojas R, *et al.* Inoculum effect on the efficacies of amoxicillin-clavulanate, piperacillin-tazobactam, and imipenem against extended-spectrum β-lactamase (ESBL)-producing and non-ESBL-producing *Escherichia coli* in an experimental murine sepsis model. Antimicrob Agents Chemother 2013; 57:2109–2113.

23. Sfei M, Askin G, Christos P. β-Lactam/β-lactamase inhibitors versus carbapenem for bloodstream infections due to extended spectrum β-lactamase producing Enterobacteriaceae: Systematic review and meta-analysis. Int J Antimicrob Agents 2018; 52:554–570.

In this systematic review and meta-analysis, a total of 25 observational studies describing 3842 participants were included and analyzed. Overall 30-day mortality of BL-BLI or PTZ for the treatment of ESBL-producing Enterobacteriaceae BSI was not statistically different from carbapenem.

24. Muhammed M, Flokas ME, Detsis M, *et al.* Comparison between carbapenems and β-lactam/β-lactamase inhibitors in the treatment for bloodstream caused by ESBL-producing Enterobacteriaceae: A systematic review and meta-analysis. Open Forum Infect Dis 2017; 4:ofx09.

This meta-analysis showed that mortality was not statistically different in patients with ESBL-BSI treated with BLBLIs compared to carbapenems, when used as empirical or definitive therapy.

25. Tamma PD, Han JH, Rock C, *et al.,* Antibacterial Resistance Leadership Group. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. Clin Infect Dis 2015; 60:1319–1325.
26. Tsai HY, Chen YH, Tang HJ, *et al.* Carbapenems and piperacillin/tazobactam for the treatment of bacteremia caused by extended-spectrum (-lactamase-producing Proteus mirabilis. Diagnostic Microbiol and Infect Dis 2014; 80:222–226.
27. Ofer-Friedman H, Shefler C, Sharma S, *et al.* 2015. Carbapenems versus Piperacillin-Tazobactam for bloodstream infections of nonurinary source caused by extended-spectrum β-lactamase-producing Enterobacteriaceae. Infect Cotrol Hosp Epidemiol 2015; 36:981–985.
28. Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Kahlmeter G. Antibiotics for ceftriaxone resistant gram-negative bacterial bloodstream infections. JAMA 2018; 321:612–613.
29. Gudiol C, Royo-Cebrecos C, Abdala E, *et al.* Efficacy of β-lactam/β-lactamase inhibitor combinations for the treatment of bloodstream infection due to extended-spectrum-β-lactamase-producing enterobacteriaceae in hematological patients with neutropenia. Antimicrob Agents Chemother 2017; 61:; pii: e00164-17.

This multinational retrospective study compared high-risk neutropenic hematologic patients with BSI because of ESBL-E treated with BLBLIs or carbapenems empirically or as definitive therapy. The 30-day case fatality rates and other secondary outcomes were similar in the two therapy groups of the two cohorts and also in the propensity-matched cohorts.

30. Benanti GE, Brown ART, Shigle TL, *et al.* Carbapenem versus cefepime or piperacillin-tazobactam for the empiric treatment of extended spectrum β-lactamase producing Escherichia coli bacteremia in patients with hematologic malignancy. Antimicrob Agents Chemother 2019; 63:; pii: e01813-18.

In this retrospective single center study, empiric treatment with cefepime or PTZ was not associated with increased 14-day mortality in a cohort of hematologic patients.

31. Tamma PD, Villegas MV. Use of β-lactam/β-lactamase inhibitors for extended-spectrum-β-lactamase infections: defining the right patient population. Antimicrob Agents Chemther 2017; 61:; pii: e01094-17.
32. Vardakas KZ, Voulgaris GL, Maliaros A, *et al.* Prolonged versus short-term intravenous infusion of antipseudomonal (-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis 2018; 18:108–120.

This systematic review and meta-analysis showed that prolonged infusion of antipseudomonal β-lactams for the treatment of patients with sepsis was associated with significantly lower mortality than short-term infusion.

33. Yang H, Zhang C, Zhou Q, *et al.* Clinical outcomes with alternative dosing strategies for piperacillin-tazobactam: a systematic review and meta-analysis. PLoS One 2015; 10:e0116769.
34. Su J, Guo Q, Li Y, *et al.* Comparison of empirical therapy with cefoperazone/sulbactam or a carbapenem for bloodstream infections due to ESBL-producing Enterobacteriaceae. J Antimicrob Chemother 2018; 73:3176–3180.
35. Kang CI, Park SY, Chung DR, *et al.* Piperacillin-tazobactam as an initial empirical therapy of bacteremia caused by extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. J Infect 2012; 64:533–534.
36. Rodriguez-Baño J, Navarro MD, Retamar P, *et al.* β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli*: a post-hoc analysis of prospective cohorts. Clin Infect Dis 2012; 54:167–174.
37. Tsai HY, Chen YH, Tang HJ, *et al.* Carbapenems and piperacillin/tazobactam for the treatment of bacteremia caused by extendedspectrum β-lactamase-producing Proteus mirabilis. Diagn Microbiol Infect Dis 2014; 80:222–226.
38. Ofer-Friedman H, Shefler C, Sharma S, *et al.* Carbapenems versus piperacillin-tazobactam for bloodstream infections of nonurinary source caused by extended-spectrum β-lactamase-producing Enterobacteriaceae. Infect Control Hosp Epidemiol 2015; 36:981–985.
39. Tamma PD, Han JH, Rock C, *et al.* Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. Clin Infect Dis 2015; 60:1319–1325.
40. Ng TM, Khong WX, Harris PN, *et al.* Empiric piperacillin-tazobactam versus carbapenems in the treatment of bacteraemia due to extended-spectrum β-lactamase-producing Enterobacteriaceae. PLoS One 2016; 11:e0153696.
41. van Duin D, Bonomo RA. Ceftazidime/avibactam and ceftolozane/tazobactam: second generation β-lactam/β-lactamase inhibitor combinations. Clin Infect Dis 2016; 63:234–241.
42. Lucasti C, Hershberger E, Miller B, *et al.* Multicenter, double-blind, randomized, phase II trial to assess the safety and efficacy of ceftolozane-tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. Antimicrob Agents Chemother 2014; 58:5350–5357.
43. Solomkin J, Hershberger E, Miller B, *et al.* Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance:results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clin Infect Dis 2015; 60:1462–1471.
44. Wagenleher FM, Umeh O, Steenberger J, *et al.* Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infection, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet 2015; 385:1949–1956.
45. Popejoy MW, Paterson DL, Cloutier D, *et al.* Efficacy of ceftolozane/tazobactam against urinary tract and intra-abdominal infections caused by ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*: a pooled analysis of phase 3 clinical trials. J Antimicrob Chemother 2017; 72:268–272.
46. Lucasti C, Popescu I, Ramesh MK, *et al.* Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, phase II trial. J Antimicrob Chemother 2013; 68:1183–1192.
47. Mazuski JE, Gasink LB, Armstrong J, *et al.* Efficacy and safety of ceftazidime/avibactam versus meropenem in the treatment of complicated intra-abdominal infections: results of a randomized, controlled, double-blind, phase 3 program. Clin Infect Dis 2016; 62:1380–1389.
48. Wagenlehner FM, Sobel JD, Newell P, *et al.* Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomize trial program. Clin Infect Dis 2016; 63:754–762.
49. Carmeli Y, Armstrong J, Laud PJ, *et al.* Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intraabdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis 2016; 16:661–673.
50. Torres A, Zhong N, Pachl J, *et al.* Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 noninferiority trial. Lancet Infect Dis 2018; 18:285–295.
51. Matsumura Y, Yamamoto M, Nagao M, *et al.* In vitro activities and detection performances of cefmetazole and flomoxef for extended-spectrum β-lactamase and plasmi-mediated AmpC β-lactamase-produginc Enterobacteriaceae. Diagn Microbiol Infect Dis 2016; 84:322–327.
52. Siu LK, Lu PL, Hsueh PR, *et al.* Bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in a pediatric oncology ward: clinical features and identification of different plasmids carrying both SHV-5 and TEM-1 genes. J Clin Microbiol 1999; 37:4020–4027.
53. Yang CC, Li SH, Chuang FR, *et al.* Discrepancy between effects of carbapenems and flomoxef in treating nosocomial hemodialysis access-related bacteremia secondary to extended spectrum β-lactamase producing *Klebsiella pneumoniae* in patients on maintenance hemodialysis. BMC Infect Dis 2012; 12:206.
54. Lee CH, Su LH, Chen FJ, *et al.* Comparative effectiveness of flomoxef versus carbapenems in the treatment of bacteraemia due to extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae* with emphasis on minimum inhibitory concentration of flomoxef: a retrospective. Int J Antimicrob Agents 2015; 46:610–615.
55. Matsumura Y, Yamamoto M, Nagao M, *et al.* Multicenter retrospective study of cefmetazole and flomoxef for treatment of extended-spectrum-β-lactamase-producing *Escherichia coli* bacteremia. Antimicrob Agents Chemother 2015; 59:5107–5113.
56. Lee CH, Su LH, Chen FJ, *et al.* Clinical and microbiologic characteristics of adult patients with recurrent bacteraemia caused by extended-spectrum β-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*. Clin Microbiol Infect 2015; 21:1105.e1–1105.e8.
57. Fukuchi T, Iwata K, Kobayashi S, *et al.* Cefmetazole for bacteremia caused by ESBL-producing enterobacteriaceae comparing with carbapenems. BMC Infect Dis 2016; 16:10–15.
58. Lee CH, Chen IL, Li CC, Chien CC. Clinical benefit of ertapenem compared to flomoxef for the treatment of cefotaximeresistant enterobacteriaceae bacteremia. Infect Drug Resist 2018; 11:257–266.
59. Demonchy E, Courjon J, Ughetto E, *et al.* Cefoxitin-based antibiotic therapy for extended-spectrum β-lactamase-producing Enterobacteriaceae prostatitis: a prospective pilot study. Int J Antimicrob Agents 2018; 51:836–841.

60. Paterson DL, Ko WC, Von Gottberg A, *et al.* Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum β-lactamases: implications for the clinical microbiology laboratory. J Clin Microbiol 2001; 39:2206–2212.

61. Oteo J, Navarro C, Cercenado E, *et al.* Spread of Escherichia coli strains with high-level cefotaxime and ceftazidime resistance between the community, long-term care facilities, and hospital institutions. J Clin Microbiol 2006; 44:2359–2366.

62. Goethaert K, Van Looveren M, Lammens C, *et al.* High-dose cefepime as an alternative treatment for infections caused by TEM-24 ESBL-producing Enterobacter aerogenes in severely-ill patients. Clin Microbiol Infect 2006; 12:56–62.

63. Kim SA, Altshuler J, Paris D, Fedorenko M. Cefepime versus carbapenems for the treatment of urinary tract infections caused by extended-spectrum β-lactamase-producing enterobacteriaceae. Int J Antimicrob Agents 2018; 51:155–158.

64. Lee NY, Lee CC, Huang WH, *et al.* Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum β-lactamase-producing enterobacteriaceae: MIC matters. Clin Infect Dis 2013; 56:488–495.

65. Wang R, Cosgrove SE, Tschudin-Sutter S, *et al.* Cefepime therapy for cefepime-susceptible extended-spectrum β-lactamase-producing enterobacteriaceae bacteremia. Open Forum Infect Dis 2016; 3:1–4.

66. Burgess DS, Hall RG 2nd. In vitro killing of parenteral β-lactams against standard and high inocula of extended-spectrum **β**-lactamase and non-ESBL producing *Klebsiella pneumoniae*. Diagn Microbiol Infect Dis 2004; 49:41–46.

67. Maglio D, Ong C, Banevicius MA, *et al.* Determination of the in vivo pharmacodynamic profile of cefepime against extended-spectrum-β-lactamase-producing *Escherichia coli* at various inocula. Antimicrob Agents Chemother 2004; 48:1941–1947.

68. Costa Ramos JM, Stein C, Pfeifer Y, *et al.* Mutagenesis of the CTX-M-type ESBL—is MIC-guided treatment according to the new EUCAST recommendations a safe approach? J Antimicrob Chemother 2015; 70:2528–2535.

69. Ito A, Kohira N, Bouchillon SK, *et al.* In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against nonfermenting Gram-negative bacteria. J Antimicrob Chemother 2016; 71:670–677.

70. ■ Portsmouth S, van Veenhuyzen D, Echols R, *et al.* Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, noninferiority trial. Lancet Infect Dis 2018; 18:1319–1328.

This phase 2, multicentre, double-blind, parallel-group noninferiority trial showed that cefiderocol (a new siderophore cephalosporin) was noninferior compared with imipenem for the treatment of cUTI in patients with MDRGN infections.

71. ■ Alexandre K, Fantin B. Pharmacokinetics and pharmacodynamics of temocillin. Clin Pharmacokinet 2018; 57:287–296.

Recent comprehensive review of this old drug.

72. Kresken M, Körber-Irrgang B, Pfeifer Y, Werner G. Activity of temocillin against CTX-M-producing *Escherichia coli* and *Klebsiella pneumoniae* from Germany. Int J Antimicrob Agents 2018; 51:159–160.

73. Alexandre K, Soares A, Chau F, *et al.* Temocillin breakpoints in pyelonephritis: evaluation in a murine model due to ESBL-producing Escherichia coli clinical isolates. J Antimicrob Chemother 2019; 74:1323–1326.

74. Gupta ND, Smith RE, Balakrishnan I. Clinical efficacy of temocillin. J Antimicrob Chemother 2009; 64:431–433.

75. Balakrishnan I, Awad-El-Kariem FM, Aali A, *et al.* Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother 2011; 66:2628–2631.

76. Laterre P-F, Wittebole X, Van de Velde S, *et al.* Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration. J Antimicrob Chemother 2015; 70:891–898.

77. Vardakas KZ, Legakis NJ, Triarides N, Falagas ME. Susceptibility of contemporary isolates to fosfomycin: a systematic review of the literature. Int J Antimicrob Agents 2016; 47:269–285.

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

79. Kaye KS, Rice LB, Dane A, *et al.* Fosfomycin for injection (ZTI-01) vs Piperacillin-Tazobactam (PIP-TAZ) for the treatment of complicated urinary tract infection (cUTI) including acute pyelonephritis (AP): ZEUS, a phase 2/3 randomized trial. Clin Infect Dis 2019; pii: ciz181.

80. ■ Rosso-Fernández C, Sojo-Dorado J, Barriga A, *et al.* Fosfomycin versus meropenem in bacteraemic urinary tract infections caused by extended-spectrum β-lactamase-producing Escherichia coli (FOREST): study protocol for an investigator-driven randomised controlled trial. BMJ Open 2015; 5:e007363.

Randomized clinical trial with still pending results that will define the usefulness of fosfomycin as a carbapenemic-sparing agent in bacteremic urinary infections caused by ESBLs.

81. Pournaras S, Koumaki V, Spanakis N, *et al.* Current perspectives on tigecycline resistance in Enterobacteriaceae: susceptibility testing issues and mechanisms of resistance. Int J Antimicrob Agents 2016; 48:11–18.

82. Goessens WHF, Mouton JW, ten Kate MT, *et al.* The therapeutic effect of tigecycline, unlike that of ceftazidime, is not influenced by whether the *Klebsiella pneumoniae* strain produces extended-spectrum β-lactamases in experimental pneumonia in rats. Antimicrob Agents Chemother 2013; 57:643–646.

83. Vasilev K, Reshedko G, Orasan R, *et al.* A phase 3, open-label, noncomparative study of tigecycline in the treatment of patients with selected serious infections due to resistant Gram-negative organisms including Enterobacter species, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. J Antimicrob Chemother 2008; 62(Suppl 1:i):29–40.

84. Heizmann WR, Löschmann P-A, Eckmann C, *et al.* Clinical efficacy of tigecycline used as monotherapy or in combination regimens for complicated infections with documented involvement of multiresistant bacteria. Infection 2015; 43:37–43.

85. Tasina E, Haidich A-B, Kokkali S, Arvanitidou M. Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. Lancet Infect Dis 2011; 11:834–844.

86. Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother 2011; 66:1963–1971.

87. Puerto AS, Fernández JG, del Castillo@@de DL, *et al.* In vitro activity of **β**-lactam and non-**β**-lactam antibiotics in extended-spectrum **β**-lactamase-producing clinical isolates of *Escherichia coli*. Diagn Microbiol Infect Dis 2006; 54:135–139.

88. Rodríguez-Martínez JM, Machuca J, Cano ME, *et al.* Plasmid-mediated quinolone resistance: two decades on. Drug Resist Updat 2016; 29:13–29.

89. Tumbarello M, Sanguinetti M, Montuori E, *et al.* Predictors of mortality in patients with bloodstream infections caused by extended-spectrum-β-lactamase-producing Enterobacteriaceae: importance of inadequate initial antimicrobial treatment.

90. Meije N, Pigrau C, Fernández-Hidalgo N, *et al.* Nonintravenous carbapenem-sparing antibiotics for the definitive treatment of bacteremia due to Enterobacteriaceae-producing ESBL or Amp-C β-lactamase. A propensity score study. Inter J Antimicrob Agents 2019. pii: S0924-8579(19)30111-6.

91. ■■ Palacios-Baena ZR, Gutiérrez-Gutiérrez B, Calbo E, *et al.* Empiric therapy with carbapenem-sparing regimens for bloodstream infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae: results from the INCREMENT cohort. Clin Infect Dis 2017; 65:1615–1623.

Retrospective analysis of a very large multinational cohort exploring the clinical outcomes of patients with ESBL BSI treated empirically with carbapenem-sparing regimens.

92. Murri R, Fiori B, Spanu T, *et al.* Trimethoprim-sulfamethoxazole therapy for patients with carbapenemase-producing *Klebsiella pneumoniae* infections: retrospective single-center case series. Infection 2017; 45:209–213.

93. Bouxom H, Fournier D, Bouiller K, *et al.* Which noncarbapenem antibiotics are active against extended-spectrum β-lactamase-producing Enterobacteriaceae? Int J Antimicrob Agents 2018; 52:100–103.

94. Vidal L, Gafter-Gvili A, Borok S, *et al.* Efficacy and safety of aminoglycoside monotherapy: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 2007; 60:247–257.

95. Gudiol C, Calatayud L, Garcia-Vidal C, *et al.* Bacteraemia due to extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. J Antimicrob Chemother 2010; 65:333–341.

96. Han SB, Jung SW, Bae EY, *et al.* Extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in febrile neutropenic children. Microb Drug Resist 2015; 21:244–251.

97. ■ Eljaaly K, Alharbi A, Alshehri S, *et al.* Plazomicin: A novel aminoglycoside for the treatment of resistant Gram-negative bacterial infections. Drugs 2019; 79:243–269.

A comprehensive review of this new aminoglycoside.

98. ■■ Wagenlehner FME, Cloutier DJ, Komirenko AS, *et al.* Once-daily plazomicin for complicated urinary tract infections. N Engl J Med 2019; 380:729–740.

A pivotal clinical trial that has demonstrated the noninferiority of plazomycin with respect to meropenem for the treatment of cUTIs and pyelonephritis.