Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Review

Management of carbapenem-resistant *Enterobacteriaceae* infections

E. Durante-Mangoni*, R. Andini, R. Zampino

Internal Medicine, University of Campania 'L. Vanvitelli' & Unit of Infectious and Transplant Medicine, AORN Ospedali dei Colli-Monaldi Hospital, Naples, Italy

ARTICLE INFO

Article history:
Received 2 October 2018
Received in revised form
7 April 2019
Accepted 10 April 2019
Available online xxx

Editor: M. Paul

Keywords:
Ceftazidime-avibactam
Clinical failure
Colistin
Ertapenem
Extensively drug-resistant
Fosfomycin
Klebsiella pneumoniae
Meropenem
Mortality
Tigecycline

ABSTRACT

Background: Carbapenem resistance is defined as *in vitro* non-susceptibility to any carbapenem and/or documented production of a carbapenemase. This feature has rapidly spread worldwide among clinical isolates of *Enterobacteriaceae*, mostly *Klebsiella* spp., and is associated with diverse molecular mechanisms. Carbapenem resistance is often associated with resistance to all traditional β-lactams and other classes of antibiotics, denoting a typical example of an extensively drug-resistant phenotype.
Objectives: To summarize and interpret in a balanced manner the most clinically relevant data in terms of carbapenem-resistant *Enterobacteriaceae* (CRE) infection management.
Sources: Data were extracted by PubMed and clinicaltrials.gov search and manual scrutiny among references of analysed articles.
Content: Features of newer and older, rediscovered antimicrobial options for CRE are described. Observational studies and randomized clinical trials (RCT) of CRE treatment are summarized, with a specific focus on the effects of monotherapy compared with combination treatment.
Implications: The available evidence on the current management of CRE mostly comes from observational, non-comparative, retrospective, small studies, with a high risk of selection bias. Very little evidence comes from RCT. Conflicting results of RCT and observational studies call for caution before combination therapies are deemed superior to monotherapy. Data on newer agents have spurred enthusiasm but remain limited as concerns severe CRE infections. A balanced approach should guide the clinician in the choice of old or new drugs, and of monotherapies or combination regimens. Efforts should be made to perform adequately sized clinical trials answering well-defined research questions.
E. Durante-Mangoni, Clin Microbiol Infect 2019;■:1

Definition of carbapenem resistance in Enterobacteria

Carbapenem resistance (CR) refers to the ability of bacteria to survive and grow in the presence of clinically relevant concentrations of carbapenems. The US CDC defines carbapenem-resistant *Enterobacteriaceae* (CRE) as enterobacteria non-susceptible to any carbapenem (i.e. showing an MIC of ≥4 mg/L for doripenem, meropenem or imipenem or ≥2 mg/L for ertapenem) or documented to produce a carbapenemase [1]. There are at least three major mechanisms of CR in *Enterobacteriaceae* [2] (graphically summarized in Fig. 1): (a) production of carbapenemases, i.e. hydrolysing enzymes—usually located within the periplasmic space—that inactivate carbapenems by hydrolysis; (b) production of efflux pumps, actively extruding carbapenems from the bacterial cell; (c) porin mutation or loss, depriving the bacterial cell of the usual carriers that allow carbapenem entry through their outer membrane. Although carbapenemases specifically target carbapenems or other β-lactam antibiotics, efflux pump expression or porin changes may associate with resistance to multiple different antimicrobial classes [3] (Fig. 1).

Current breakpoints for *Enterobacteriaceae* usually detect all clinically important resistance mechanisms (including the majority of carbapenemases) [4]. However, an isolate possessing a carbapenemase gene can still be categorized as carbapenem-susceptible by phenotypic tests [5]. This is particularly relevant when rapid molecular tests are used, and phenotypic characterization should always be completed before definitive diagnosis of CR is established [4]. On the other hand, absence of a carbapenemase gene on

* Corresponding author. E. Durante Mangoni, Ospedale Monaldi, Piazzale Ettore Ruggieri, 80131 Napoli, Italy.
E-mail address: emanuele.durante@unicampania.it (E. Durante-Mangoni).

https://doi.org/10.1016/j.cmi.2019.04.013
1198-743X/

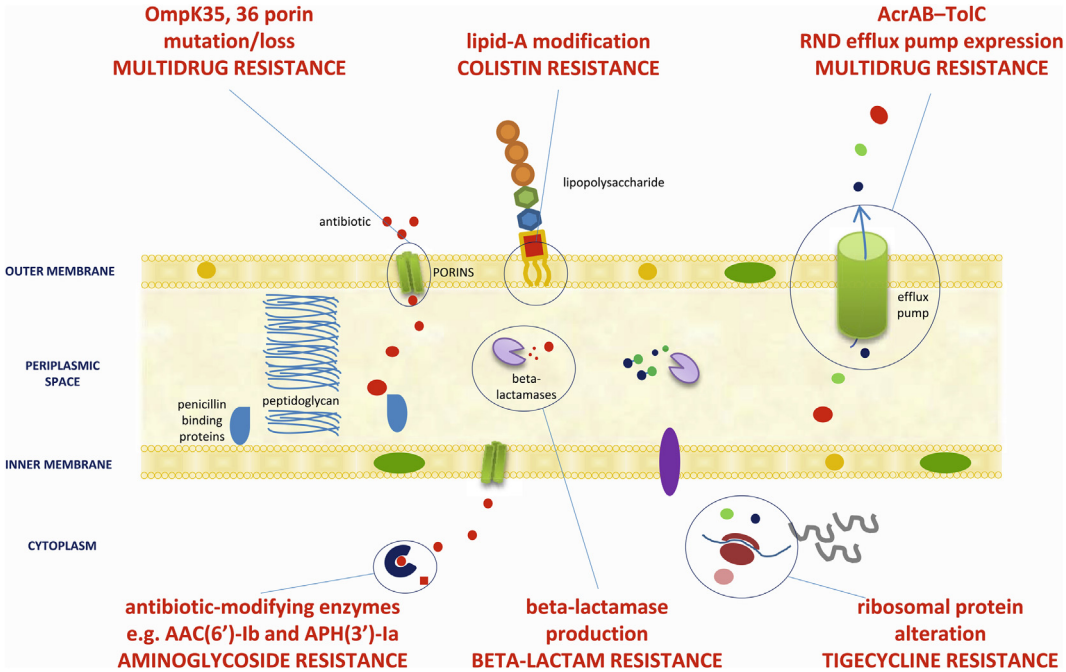

Fig. 1. Major mechanisms of antimicrobial resistance, including carbapenem resistance, in *Enterobacteriaceae*.

molecular typing should not imply susceptibility to carbapenems, as other CR mechanisms may be in place [1–3,5,6].

Table 1 summarizes the major and most clinically significant carbapenemases occurring worldwide in *Enterobacteriaceae* [7,8]. Although carbapenemase detection is essential for public health and infection control purposes, their precise characterization is also helpful in clinical practice because it impacts therapeutic decisions [9]. As shown in Table 1, different carbapenemases may or may not be targeted by individual β-lactams and β-lactamase inhibitors. Hence, the use of newer combinations of β-lactam with a carbapenemase inhibitor should hinge on a stepwise, precision-medicine approach, with CR infection diagnosis followed by carbapenemase molecular or phenotypic characterization [9]. Current microbiological methods allow us to obtain both of these data types in parallel.

Strategy for data search

Data presented in this themed review were extracted by a PubMed search and by manual scrutiny among the references of the analysed articles (see Supplementary material, Appendix S1 for details).

Antimicrobial options for CRE

Carbapenem resistance is often and variably associated with resistance to several other antimicrobial classes [10]. Table 2 reports a list of antimicrobials that are worth testing against CRE, with approximate rates of antimicrobial susceptibility using current EUCAST breakpoints. The most commonly *in vitro* active and potentially useful drugs remain ceftazidime-avibactam and newer inhibitor combinations, gentamicin, amikacin, colistin, tigecycline and fosfomycin [10]. Newer or emerging options include plazomicin, eravacycline and cefiderocol. A detailed review of the antimicrobial agents used for treatment of CRE infections has been recently published [5].

Avibactam is a non-β-lactam β-lactamase inhibitor that, combined with ceftazidime, is highly effective *in vitro* against KPC- and OXA-48-producing CRE [11]. Ceftazidime-avibactam has been used in several controlled studies not including CRE infections [12–15]. Observational studies have reported its efficacy and safety in CRE infections.

Vaborbactam is a boronic acid derivative, inhibiting group A KPC-type carbapenemases, that exerts bactericidal activity against KPC-producing CRE when combined with meropenem [16]. Meropenem-vaborbactam shows area-under-the-curve/MIC-dependent antimicrobial activity and retains the pharmacokinetic profile of carbapenems at exposures equivalent to 2+2 g dosed every 8 hours by 3-hour infusion [17,18]. It is non-inferior to piperacillin-tazobactam in complicated urinary tract infections (cUTI) [19], and its efficacy and safety data for CRE infections are emerging.

Relebactam is a non-β-lactam β-lactamase inhibitor, structurally related to avibactam. Its chemical differences with avibactam translate into a more stable acylation and, therefore, inhibition of the active site of KPC-2 carbapenemase, but also into a weak and inconsistent activity against OXA-48 [2,20]. Accordingly, when combined with imipenem, relebactam exerts bactericidal activity against KPC-producing CRE [20]. Relebactam shows area-under-the-curve/MIC-dependent antimicrobial activity and imipenem-relebactam retains the pharmacokinetic/pharmacodynamic (PK/PD) features of the other newer CRE-active combinations (time above MIC for the carbapenem and overall exposure for the β-lactamase inhibitor) at doses of 500 mg with 250 mg every 6 hours by intravenous infusion [21–23].

Gentamicin is still considered a mainstay of therapy for CR *Klebsiella*, whereas sometimes amikacin is the only *in vitro* active molecule [24–26]. Plazomicin is a recently marketed aminoglycoside showing improved stability to commonly encountered aminoglycoside-modifying enzymes compared with gentamicin and amikacin [27,28]. It has been cleared by the US Food and Drug Administration for cUTI including acute pyelonephritis based on the results of a non-inferiority trial where meropenem was the

Please cite this article as: Durante-Mangoni E et al., Management of carbapenem-resistant *Enterobacteriaceae* infections, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.04.013

Table 1
Clinically significant carbapenemases commonly expressed by *Enterobacteriaceae* with reduced susceptibility or resistance to carbapenems

Ambler Class	Acronym	Hydrolysing mechanism	Most common variants	Involved species	Carbapenem resistance extent	*In vitro* active molecules/therapeutic options
A	KPC	serine-based	KPC-2 KPC-3	*Klebsiella pneumoniae*, *Escherichia coli*, *Serratia marcescens*, *Enterobacter cloacae*	+++	ceftazidime-avibactam imipenem-relebactam meropenem-vaborbactam
B	NDM	zinc-based	NDM-1	*K. pneumoniae*, *E. coli*, *Enterobacter* spp.	+++	aztreonam aztreonam-avibactam
B	IMP	zinc-based	IMP-1	*K. pneumoniae*, *E. coli*, *Serratia* spp., *Enterobacter* spp., *Citrobacter* spp., *Proteus* spp., *Morganella* spp.	+	aztreonam aztreonam-avibactam
B	VIM	zinc-based	VIM-1 VIM-2	*K. pneumoniae*, *E. coli*, *Serratia* spp., *Enterobacter* spp., *Citrobacter* spp., *Morganella* spp., *Providencia* spp., *Proteus* spp.	+	aztreonam aztreonam-avibactam
D	OXA	serine-based	OXA-48	*K. pneumoniae*, *E. coli*, *Citrobacter* spp., *Proteus* spp.	++	ceftazidime-avibactam

comparator [29]. Plazomicin is active against most CREs, except strains producing New Delhi metallo-β-lactamases, that co-express specific 16S rRNA methylases (ArmA and RmtC) [27]. Because of its spectrum of activity, it is currently viewed as a potentially promising new option for extensively-drug-resistant Gram-negative microorganisms, especially CRE [30]. Interestingly, plazomicin did not show increased rates of nephrotoxicity compared with meropenem after a short 5-day course of therapy [29].

Colistin is still regarded as a key option for CRE infection [31–35]. Although resistance to colistin remains low in *Acinetobacter* and *Pseudomonas* species, it is emerging in CRE, especially *Klebsiella* [36,37]. In specific epidemiological settings, a dramatic and fast increase in colistin resistance has been observed and has been associated with increased mortality [38].

Tigecycline remains an option for CRE treatment in stable patients with skin or complicated intra-abdominal infections due to susceptible strains [39–42].

Higher than labelled doses of tigecycline (i.e. 200 mg/day in either one or two doses) have been proposed for the treatment of multidrug-resistant/ extensively-drug-resistant Gram-negative bacteria [43] based on PK considerations. High-dose tigecycline is mostly well tolerated, with vomiting and diarrhoea being common adverse events [44–46], although an association with a reversible coagulopathy has been recently described [47]. However, the evidence suggesting superiority of high-dose compared with standard-dose tigecycline remains elusive [44–46].

Fosfomycin activity has been documented against approximately 80% of CRE, especially KPC-producing *Klebsiella pneumoniae*, including colistin-resistant strains [48–50], although discordance between *in vitro* susceptibility and clinical effectiveness may occur [48].

A fosfomycin tromethamine oral regimen of 3 g every 48–72 h for a variable number of weeks has been shown to be effective in lower UTI caused by resistant Gram-negative agents, including CRE [51,52].

In small observational studies including, overall, approximately 60 cases of CRE infection, favourable clinical and microbiological outcomes have been described in a majority (55%) of patients, mostly in intensive care unit, treated with a combination of antibiotics including fosfomycin disodium [50,53,54]. Successful outcomes occurred in 9 of 15 (60%) infections caused by CRE resistant to colistin [50]. The true contribution of fosfomycin to the effectiveness of these combination regimens remains to be determined.

Eravacycline and cefiderocol are novel molecules that are active *in vitro* against CRE and still under clinical development [55–59]. Cefiderocol activity against CRE varies according to the expressed carbapenemase, with MIC_{90} of 1 mg/L for strains harbouring OXA-48-like, 2 mg/L for KPC-3, and 8 mg/L for TEM/SHV extended-spectrum β-lactamase, NDM and KPC-2 [60]. Little if any clinical data are available for eravacycline and cefiderocol in terms of effectiveness for CRE infections.

Observational studies of CRE treatment

The first uncontrolled studies assessing the results of treatment for CRE essentially focused on the effects of combinations of antibiotics compared with monotherapy [61–65]. These studies, and those published thereafter, uniformly showed superiority of combination therapy, although with a low quality of evidence [66]. Surprisingly, combinations including a carbapenem were those exerting the best results in terms of hospital mortality. A sizeable proportion of strains causing analysed cases—mostly KPC-3- and KPC-2-producing *K. pneumoniae*—were characterized by carbapenem MICs between 2 and 8 mg/L or 'low-level resistance' (MICs of 16–32 mg/L), and were receiving high doses of meropenem, i.e. 2 g every 8 h. Subsequent speculations suggested that at these doses meropenem could retain clinical effectiveness when combined with other molecules, especially colistin [67]. Clinical data apparently mirrored robust *in vitro* data showing synergism of different combinations against CREs (reviewed in ref. [68]). In the initial study by Tumbarello et al. [64], the combination associated with better outcomes was colistin-tigecycline-meropenem, although this was only used in 16 patients. Based on these early data, combination therapy became the standard of care [69], driving the continued massive use of carbapenems that had been one major selection factor for CRE emergence.

In a retrospective, multinational cohort study, among 343 patients receiving an *in vitro* active drug within 5 days of diagnosis of a carbapenemase-producing *Enterobacteriaceae* (mostly KPC) bloodstream infection (BSI), a superiority of combination therapy was shown only in the subgroup of patients at higher risk of death [70]. This study suggested that a generalized combination therapy approach in CRE infections may not be optimal. Again, multiple different combination regimens were considered in this study, mostly colistin plus tigecycline, aminoglycoside plus tigecycline and colistin plus carbapenem. At variance with previous studies, the recommendation emerging was to give at least two *in vitro* active molecules, but without inference on efficacy of specific combinations and no confirmation of benefit when including a carbapenem [70].

The scenario of KPC- and OXA-48-producing CRE is now changing dramatically after newer carbapenemase inhibitors have become clinically available [11]. An early report on ceftazidime-avibactam treatment of 37 CRE hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) and BSI cases, with

Please cite this article as: Durante-Mangoni E et al., Management of carbapenem-resistant *Enterobacteriaceae* infections, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.04.013

Table 2
Antimicrobials commonly tested against carbapenem resistant *Enterobacteriaceae*

Antimicrobial	EUCAST MIC breakpoint indicating resistance	Prevalence[a] of susceptible isolates	Remarks
Ceftazidime	>4	<3%	Resistance usually associated with concurrent expression of ESBL or AmpC β-lactamases
Cefepime	>4	<5%	
Aztreonam		<5%	Susceptibility or low-level resistance may be expected in case of metallo-β-lactamase carbapenemase expression. Resistance is the rule when other carbapenemases (KPC, OXA-48, etc.) or extended spectrum β-lactamases are co-expressed
Piperacillin-tazobactam	>16	<5%	Resistance usually associated with high-level expression of extended spectrum β-lactamases
Ceftazidime-avibactam	>8	>90%	Susceptibility expected in case of KPC or OXA-48 carbapenemase expression. Resistance is the rule when metallo-enzymes (NDM, IMP, VIM, etc.) are expressed
Imipenem	>8	<5%	Variable degrees of resistance may occur according to level of carbapenemase expression and concurrent presence of other mechanisms of carbapenem resistance
Meropenem	>8	<5%	
Doripenem	>2	<5%	
Amikacin	>16	50%	Cross resistance not the rule depending on actual subtype of modifying enzyme expressed
Gentamicin	>4	40%	
Ciprofloxacin	>0.5	<5%	Very low rates of susceptibility expected in endemic settings of carbapenem-resistant *Enterobacteriaceae* prevalence
Trimethoprim-sulphamethoxazole	>4	<5%	Sparse data available
Fosfomycin	>32	50%	Variable results according to the susceptibility method used
Tigecycline	>2	85%	Consistent susceptibility data across multiple studies and settings
Colistin	>2	80%	Broth microdilution recommended to avoid major errors

[a] Conservative estimates based on literature data (average rates) and the author's personal experience.

median Charlson co-morbidity index of 4 and median Sepsis-related Organ Failure Assessment (SOFA) score of 5, showed a 30-day mortality of 24% and a 90-day mortality of 38% [71]. Clinical success was achieved in 59% of patients (15/26 (58%) of those receiving monotherapy and 7/11 (64%) of those on combination therapy), and was lower for individuals with pneumonia and high baseline SOFA score. Microbiological failures occurred in 10 of 37 (27%) patients and ceftazidime-avibactam resistance (MIC >8 mg/L) developed in three of these ten cases after a median treatment of 15 days [71].

Another observational study describing ceftazidime-avibactam effectiveness in 60 CRE infections (59% in intensive care units) showed a 65% clinical success rate, a 53% microbiological cure rate and a 32% crude in-hospital mortality [72]. The participants were mostly co-morbid patients with BSI, cUTI and pneumonia due to *K. pneumoniae*. Ceftazidime-avibactam *in vitro* susceptibility was tested in 60% of cases and was active in 97% of them. Clinical outcomes were the same irrespective of whether ceftazidime-avibactam was used in monotherapy or combined with a carbapenem or polymyxin B. Interestingly, worse outcomes were observed in CRE pneumonia [72].

Similar outcomes have been observed for OXA-48-producing CRE treatment, with no mortality differences between ceftazidime-avibactam monotherapy and combinations [73], in the setting of haematological malignancies [74] and for non-*Klebsiella* CREs [75].

More recently, in a compassionate-use programme for 138 patients, ceftazidime-avibactam salvage therapy translated into a 34% mortality at 30 days [76]. In patients with BSI, ceftazidime-avibactam achieved a significantly greater survival rate when compared with an historical matched cohort of CRE BSI patients treated with other regimens. Ceftazidime-avibactam was an independent predictor of survival and appeared effective especially in BSIs [76]. Another study compared in an uncontrolled fashion ceftazidime-avibactam with other treatments (carbapenem-aminoglycoside, carbapenem-colistin, or monotherapy with aminoglycoside or colistin) for 109 BSI due to KPC-producing CRE (primary in 26% and secondary to an abdominal, respiratory or urinary tract infection in 72% of patients) [77]. Clinical success and 90-day survival were 85% and 92% with ceftazidime-avibactam compared with 40% and 55%, respectively, with any other regimen (both significant). Receipt of ceftazidime-avibactam was an independent predictor of clinical success (OR 8.64; 95% CI 1.61–43.39; p 0.01) and translated into lower rates of nephrotoxicity compared with aminoglycoside- and colistin-containing regimens. A comparable rate of clinical and/or microbiological cure was described in a further 36 cases of ceftazidime-avibactam salvage therapy, although a trend for a worse outcome in OXA-48 producers compared with KPC producers was observed in this study [78]. More recently, uniform superiority of ceftazidime-avibactam over colistin was described in a prospective, multicentre, observational study [79].

Taken together, available observational data suggest that ceftazidime-avibactam, given as three daily intravenous doses of 2.5 g every 8 h, infused over at least 2 h (or maybe more), is an important therapeutic option for the treatment of CRE infections. However, overall clinical efficacy remains unclear, with reported mortality rates between 24% and 34% [71–79]. Ceftazidime-avibactam appears to be less effective for OXA-48 producers [78], and there is no evidence of superiority for ceftazidime-avibactam-based combinations [71–73,76]. Failure appears to be more common in pneumonia [71,72] as well as in patients on renal replacement therapy [80], and efforts to prevent it should be exercised, also considering ceftazidime-avibactam PK/PD properties.

Despite some PK/PD limitations, tigecycline appears among all formulae of anti-CRE regimens, this molecule being still consistently active *in vitro* against CRE [40]. Observational data suggest that high doses (i.e. 200 mg loading followed by 100 mg every 12 h) might be more effective than standard doses, without additional toxicity, for CRE ventilator-associated pneumonia [43,44] and BSI [81], but conflicting data exist [45,46].

Randomized clinical trials of CRE treatment

Regrettably, very little evidence comes from randomized clinical trials including specifically patients with CRE infections. The recently completed multinational AIDA trial (NCT01732250) compared the effectiveness and safety of colistin alone with those of a colistin and high-dose meropenem combination against CR Gram-negative bacilli [82]. Among 406 randomized patients, only

Please cite this article as: Durante-Mangoni E et al., Management of carbapenem-resistant *Enterobacteriaceae* infections, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.04.013

Table 3
Clinical outcomes of the colistin versus colistin-meropenem randomized clinical trial in the subgroup of patients with carbapenem-resistant *Enterobacteriaceae* infections [82]

	Colistin arm	Colistin-meropenem arm	Risk ratio (95% CI)	p value
Clinical failure 14 days after randomization	23 (68%)	18 (46%)	0.78 (0.54–1.13)	0.185
14-day overall mortality	6 (18%)	6 (15%)	0.90 (0.32–2.51)	0.838
28-day overall mortality	12 (35%)	8 (21%)	0.62 (0.29–1.36)	0.235

73 had CRE infections, making the trial unpowered to specifically address the issue of superiority of combination therapy for these bacteria. Most CRE cases were BSI (56/73, 77%) and were due to *K. pneumoniae* (65/73, 89%). In the relevant post-hoc subgroup analysis (Table 3), colistin-meropenem combination translated into a numerically lower rate of clinical failures at 14 days and fewer deaths at 28 days after randomization. These differences, however, were not statistically significant, and most importantly no difference was observed in 14-day mortality, the most solid end-point related to treatment effects [82].

The issue of insufficient sample size could be at least partly overcome by the chance to combine AIDA results with those of the ongoing OVERCOME trial (NCT01597973), a phase III multi-centre, double-blind, randomized controlled clinical study comparing colistin plus placebo with the combination of colistin and meropenem. With an expected number of 65 CRE infections recruited in OVERCOME, a more definitive answer could be given to the still unsolved question as to whether a carbapenem should be given for colistin-based CRE treatment.

A handful of other trials have recently been completed or are currently ongoing, some with newer agents.

In a multicentre, randomized, open-label trial, 37 patients with CRE BSI or hospital-associated/ ventilator-associated pneumonia were treated with plazomicin (15 mg/kg/day) or colistin (5 mg colistin base/kg/day) in combination with meropenem or tigecycline, for 7–14 days [83]. Unfortunately, this trial was terminated prematurely due to slow enrolment. Death at 28 days or disease-related complications occurred in 24% of plazomicin-treated and in 50% of colistin-treated patients (−26% difference; 95% CI −55% to 6%). Numerically fewer deaths were observed at day 14 among patients who received plazomicin-based treatment over a 60-day follow up. A ≥0.5 mg/dL increase in serum creatinine concentration occurred in 16.7% of plazomicin-treated and 50% of colistin-treated patients [83].

The TANGO II, open label, randomized study assessed effect and safety of meropenem-vaborbactam versus best available therapy in 47 patients with various CRE infections, including BSI, cUTI, hospital-associated/ ventilator-associated pneumonia and complicated intra-abdominal infections [84]. Monotherapy with meropenem-vaborbactam was associated with improved clinical cure rates (65.6% versus 33.3%; 95% CI of difference, 3.3%–61.3%; p 0.03) compared with an assortment of regimens variably including ceftazidime-avibactam or mono- or combination therapies with polymyxins, high-dose carbapenems, aminoglycosides or tigecycline. Lower nephrotoxicity rates and a trend towards lower mortality were observed with meropenem-vaborbactam [84].

A double-blind, randomized trial including 31 evaluable patients compared imipenem-relebactam with colistin plus imipenem for CR infections [85]. Only seven CREs were included in this study. As a consequence, very little efficacy and safety data on imipenem-relebactam for CRE infections are currently available.

Summary of the evidence

The overall quality of data pertaining to current CRE infection treatment is low. Few randomized controlled trials have been performed, and most were underpowered to provide definitive answers for this specific setting [82–85]. Notwithstanding, randomized controlled trial data [82] have recently conflicted with observational study results [61–65] as well as apparently robust *in vitro* synergy data [66] regarding the improved clinical effectiveness or potency of antimicrobial combinations.

The advent of several newer drugs, especially new carbapenemase–inhibitor combinations, showing potent *in vitro* activity against CRE, has spurred great enthusiasm among clinicians. Indeed, these new molecules appear to have a favourable safety profile and PK/PD properties that theoretically overcome older drug defects [9,86]. Nonetheless, literature data are still elusive regarding these newer options and specifically their clinical effectiveness in CRE infections. The risk exists, therefore, that newer agents replace older ones, such as colistin, based on the weak evidence coming from observational studies, and with the added issue of greater health-care expenditure [86]. In addition, the development of resistance to newer CRE-active molecules is already a concern [71].

Conclusions

Despite the epidemiological importance and the considerable body of data produced, the scientific quality of the evidence supporting CRE infection management remains low. The best available therapy should be delivered based on clinical reasoning, considering the severity of the patient illness, the isolate susceptibility, the site of infection, the available drugs (including newer or experimental options) with their own PK/PD properties, and the optimal approach (monotherapy versus combination) [24]. Administration of multiple antibiotics has uncertain effects on patient outcomes and resistant species selection. Although some studies suggested a protective effect of antimicrobial combinations, others have clearly pointed to their role in fuelling antimicrobial resistance (reviewed in ref. [9]). The superiority of combinations that emerges from observational studies could well be the result of various biases. Healthier patients may be more likely to receive additional drugs, as well as patients who survive longer during the early phases of the treatment course. We should learn from these controversies that the observational design remains substantially weak in assessing antibiotic effects for complicated patients, and that caution needs to be exercised before definitive conclusions are drawn in the absence of robust randomized controlled trial support.

Physicians caring for persons with CRE infection are unquestionably left in a challenging situation: either they keep treating patients with older drugs, whose features are well characterized and whose drawbacks are well known; or they adopt the new antibiotics, despite the insufficient evidence of effect against CRE and their higher costs. A fine balance between these two tendencies is most likely the current best strategy. Nonetheless, greater efforts must be devoted to designing and performing randomized clinical trials for CRE treatment.

Transparency declaration

EDM received grant support from Merck Sharp & Dohme and Pfizer. The other authors have no conflicts of interest to disclose.

Please cite this article as: Durante-Mangoni E et al., Management of carbapenem-resistant *Enterobacteriaceae* infections, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.04.013

Funding

This study was funded in part by the EU AIDA grant Health-F3-2011-278348 and the US NIH Contract No. HHSN272201000039C.

Authors' contributions

EDM, RA and RZ conceived the structure of the review, performed the bibliographical search and selected the data to report. All authors contributed to the writing and critical revision of the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.04.013.

References

[1] Centers for Disease Control and Prevention. Facility guidance for control of carbapenem-resistant Enterobacteriaceae (CRE). November 2015 update – CRE toolkit. Available at: https://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html.
[2] Haidar G, Clancy CJ, Chen L, Samanta P, Shields RK, Kreiswirth BN, et al. Identifying spectra of activity and therapeutic niches for ceftazidime-avibactam and imipenem-relebactam against carbapenem-resistant *Enterobacteriaceae*. Antimicrob Agents Chemother 2017;61.
[3] Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella pneumoniae and other *Enterobacteriaceae*: an evolving crisis of global dimensions. Clin Microbiol Rev 2012;25:682–707.
[4] EUCAST. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed 20 September 2018.
[5] Doi Y, Paterson DL. Carbapenemase-producing *Enterobacteriaceae*. Semin Respir Crit Care Med 2015;36:74–84.
[6] Magiorakos AP, Burns K, Rodríguez Baño J, Borg M, Daikos G, Dumpis U, et al. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant *Enterobacteriaceae* into healthcare settings: guidance from the European Centre for Disease Prevention and Control. Antimicrob Resist Infect Control 2017;6:113.
[7] Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing *Enterobacteriaceae*. Emerg Infect Dis 2011;17:1791–8.
[8] Nordmann P, Poirel L. The difficult-to-control spread of carbapenemase producers among *Enterobacteriaceae* worldwide. Clin Microbiol Infect 2014;20:821–30.
[9] Perez F, El Chakhtoura NG, Papp-Wallace KM, Wilson BM, Bonomo RA. Treatment options for infections caused by carbapenem-resistant *Enterobacteriaceae*: can we apply "precision medicine" to antimicrobial chemotherapy? Expert Opin Pharmacother 2016;17:761–81.
[10] European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2016. Stockholm: ECDC; 2017. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net).
[11] Zasowski EJ, Rybak JM, Rybak MJ. The β-lactams strike back: ceftazidime-avibactam. Pharmacotherapy 2015;35:755–70.
[12] Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis 2016;16:661–73.
[13] Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone GG, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a Phase 3 randomized trial program. Clin Infect Dis 2016;63:754–62.
[14] Torres A, Zhong N, Pachl J, Timsit JF, Kollef M, Chen Z, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis 2018;18:285–95.
[15] Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. Clin Infect Dis 2016;62:1380–9.
[16] Hecker SJ, Reddy KR, Totrov M, Hirst GC, Lomovskaya O, Griffith DC, et al. Discovery of a cyclic boronic acid β-lactamase inhibitor (RPX7009) with utility vs. class A serine carbapenemases. J Med Chem 2015;58:3682–92.
[17] Griffith DC, Sabet M, Tarazi Z, Lomovskaya O, Dudley MN. Pharmacokinetics/pharmacodynamics of vaborbactam, a novel β-lactamase inhibitor, in combination with meropenem. Antimicrob Agents Chemother 2018;63. pii: e01659-18.
[18] Rubino CM, Bhavnani SM, Loutit JS, Morgan EE, White D, Dudley MN, et al. Phase 1 study of the safety, tolerability, and pharmacokinetics of vaborbactam and meropenem alone and in combination following single and multiple doses in healthy adult subjects. Antimicrob Agents Chemother 2018;62. pii: e02228-17.
[19] Kaye KS, Bhowmick T, Metallidis S, Bleasdale SC, Sagan OS, Stus V, et al. Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I Randomized Clinical Trial. JAMA 2018;319:788–99.
[20] Papp-Wallace KM, Barnes MD, Alsop J, Taracila MA, Bethel CR, Becka SA, et al. Relebactam is a potent inhibitor of the KPC-2 β-lactamase and restores imipenem susceptibility in KPC-producing *Enterobacteriaceae*. Antimicrob Agents Chemother 2018;62. pii: e00174-18.
[21] Lucasti C, Vasile L, Sandesc D, Venskutonis D, McLeroth P, Lala M, et al. Phase 2, Dose-ranging study of relebactam with imipenem-cilastatin in subjects with complicated intra-abdominal infection. Antimicrob Agents Chemother 2016;60:6234–43.
[22] Rizk ML, Rhee EG, Jumes PA, Gotfried MH, Zhao T, Mangin E, et al. Intrapulmonary pharmacokinetics of relebactam, a novel β-lactamase inhibitor, dosed in combination with imipenem-cilastatin in healthy subjects. Antimicrob Agents Chemother 2018;62. pii:e01411-e01417.
[23] Sims M, Mariyanovski V, McLeroth P, Akers W, Lee YC, Brown ML, et al. Prospective, randomized, double-blind, Phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections. J Antimicrob Chemother 2017;72:2616–26.
[24] Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of infections caused by extended-spectrum-β-lactamase-, AmpC-, and carbapenemase-producing *Enterobacteriaceae*. Clin Microbiol Rev 2018;31.
[25] Satlin MJ, Kubin CJ, Blumenthal JS, Cohen AB, Furuya EY, Wilson SJ, et al. Comparative effectiveness of aminoglycosides, polymyxin B, and tigecycline for clearance of carbapenem resistant *Klebsiella pneumoniae* from urine. Antimicrob Agents Chemother 2011;55:5893–9.
[26] Drusano GL, Louie A. Optimization of aminoglycoside therapy. Antimicrob Agents Chemother 2011;55:2528–31.
[27] Livermore DM, Mushtaq S, Warner M, Zhang JC, Maharjan S, Doumith M, et al. Activity of aminoglycosides, including ACHN-490, against carbapenem-resistant *Enterobacteriaceae* isolates. J Antimicrob Chemother 2011;66:48–53.
[28] Galani I, Souli M, Daikos GL, Chrysouli Z, Poulakou G, Psichogiou M, et al. Activity of plazomicin (ACHN-490) against MDR clinical isolates of *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter* spp. from Athens, Greece. J Chemother 2012;24:191–4.
[29] Wagenlehner FME, Cloutier DJ, Komirenko AS, Cebrik DS, Krause KM, Keepers TR, et al. Once-daily plazomicin for complicated urinary tract infections. N Engl J Med 2019;380:729–40.
[30] Theuretzbacher U, Paul M. Developing a new antibiotic for extensively drug-resistant pathogens: the case of plazomicin. Clin Microbiol Infect 2018;24:1231–3.
[31] Pogue JM, Ortwine JK, Kaye KS. Clinical considerations for optimal use of the polymyxins: a focus on agent selection and dosing. Clin Microbiol Infect 2017;23:229–33.
[32] Tran TB, Velkov T, Nation RL, Forrest A, Tsuji BT, Bergen PJ, et al. Pharmacokinetics/pharmacodynamics of colistin and polymyxin B: are we there yet? Int J Antimicrob Agents 2016;48:592–7.
[33] Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, et al. International consensus guidelines for the optimal use of the polymyxins. Pharmacotherapy 2019;39:10–39.
[34] Plachouras D, Karvanen M, Friberg LE, Papadomichelakis E, Antoniadou A, Tsangaris I, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. Antimicrob Agents Chemother 2009;53:3430–6.
[35] Durante-Mangoni E, Andini R, Signoriello S, Cavezza G, Murino P, Buono S, et al. Acute kidney injury during colistin therapy: a prospective study in patients with extensively-drug resistant *Acinetobacter baumannii* infections. Clin Microbiol Infect 2016;22:984–9.
[36] Sader HS, Castanheira M, Duncan LR, Flamm RK. Antimicrobial susceptibility of *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates from United States medical centers stratified by infection type: results from the international network for optimal resistance monitoring (INFORM) surveillance program, 2015–2016. Diagn Microbiol Infect Dis 2018;92:69–74.
[37] Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. Antimicrobial susceptibility of *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex and *Stenotrophomonas maltophilia* clinical isolates: results from the SENTRY Antimicrobial Surveillance Program (1997–2016). Open Forum Infect Dis 2019;6:S34–46.
[38] Capone A, Giannella M, Fortini D, Giordano A, Meledandri M, Ballardini M, et al. High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality. Clin Microbiol Infect 2013;19:E23–30.
[39] Ni W, Han Y, Liu J, Wei C, Zhao J, Cui J, et al. Tigecycline treatment for carbapenem-resistant *Enterobacteriaceae* infections: a systematic review and meta-analysis. Medicine (Balt) 2016;95:e3126.
[40] Sader HS, Castanheira M, Flamm RK, Mendes RE, Farrell DJ, Jones RN. Tigecycline activity tested against carbapenem-resistant *Enterobacteriaceae* from

18 European nations: results from the SENTRY surveillance program (2010–2013). Diagn Microbiol Infect Dis 2015;83:183–6.
[41] Zarkotou O, Pournaras S, Altouvas G, Pitiriga V, Tziraki M, Mamali V, et al. Comparative evaluation of tigecycline susceptibility testing methods for expanded-spectrum cephalosporin- and carbapenem-resistant gram-negative pathogens. J Clin Microbiol 2012;50:3747–50.
[42] US FDA. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm369580.htm Accessed 20 September 2018.
[43] Cunha BA, Baron J, Cunha CB. Monotherapy with high-dose once-daily tigecycline is highly effective against *Acinetobacter baumanii* and other multidrug-resistant (MDR) Gram-negative bacilli (GNB). Int J Antimicrob Agents 2018;52:119–20.
[44] De Pascale G, Montini L, Pennisi MA, Bernini V, Maviglia R, Bello G, et al. High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. Crit Care 2014;18:R90.
[45] Balandin Moreno B, Fernández Simón I, Pintado García V, Sánchez Romero I, Isidoro Fernández B, Romera Ortega MA, et al. Tigecycline therapy for infections due to carbapenemase-producing *Klebsiella pneumoniae* in critically ill patients. Scand J Infect Dis 2014;46:175–80.
[46] Vardakas KZ, Matthaiou DK, Falagas ME, Antypa E, Koteli A, Antoniadou E. Tigecycline for carbapenem-resistant *Klebsiella pneumoniae* infections in the intensive care unit. Infect Dis (Lond) 2015;47:751–3.
[47] Routsi C, Kokkoris S, Douka E, Ekonomidou F, Karaiskos I, Giamarellou H. High-dose tigecycline-associated alterations in coagulation parameters in critically ill patients with severe infections. Int J Antimicrob Agents 2015;45:90–3.
[48] Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. Fosfomycin Clin Microbiol Rev 2016;29:321–47.
[49] 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;47:269–85.
[50] Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, et al. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. Int J Antimicrob Agents 2014;43:52–9.
[51] Los-Arcos I, Pigrau C, Rodríguez-Pardo D, Fernández-Hidalgo N, Andreu A, Larrosa N, et al. Long-term fosfomycin-tromethamine oral therapy for difficult-to-treat chronic bacterial prostatitis. Antimicrob Agents Chemother 2015;60:1854–8.
[52] Seroy JT, Grim SA, Reid GE, Wellington T, Clark NM. Treatment of MDR urinary tract infections with oral fosfomycin: a retrospective analysis. J Antimicrob Chemother 2016;71:2563–8.
[53] Michalopoulos A, Virtzili S, Rafailidis P, Chalevelakis G, Damala M, Falagas ME. Intravenous fosfomycin for the treatment of nosocomial infections caused by carbapenem-resistant *Klebsiella pneumoniae* in critically ill patients: a prospective evaluation. Clin Microbiol Infect 2010;16:184–6.
[54] Navarro-San Francisco C, Mora-Rillo M, Romero-Gomez MP, Moreno-Ramos F, Rico-Nieto A, Ruiz-Carrascoso G, et al. Bacteraemia due to OXA-48-carbapenemase-producing *Enterobacteriaceae*: a major clinical challenge. Clin Microbiol Infect 2013;19:E72–9.
[55] Zhang Y, Lin X, Bush K. In vitro susceptibility of β-lactamase-producing carbapenem resistant *Enterobacteriaceae* (CRE) to eravacycline. J Antibiot (Tokyo) 2016;69:600–4.
[56] Kazmierczak KM, Tsuji M, Wise MG, Hackel M, Yamano Y, Echols R, et al. In vitro activity of cefiderocol, a siderophore cephalosporin, against a recent collection of clinically relevant carbapenem-non-susceptible Gram-negative bacilli, including serine carbapenemase- and metallo-β-lactamase-producing isolates (SIDERO-WT-2014 Study). Int J Antimicrob Agents 2019;53:177–84.
[57] Solomkin J, Evans D, Slepavicius A, Lee P, Marsh A, Tsai L, et al. Assessing the efficacy and safety of eravacycline vs ertapenem in complicated intra-abdominal infections in the Investigating Gram-Negative Infections Treated with Eravacycline (IGNITE 1) Trial: a randomized clinical trial. JAMA Surg 2017;152:224–32.
[58] Solomkin JS, Gardovskis J, Lawrence K, Montravers P, Sway A, Evans D, et al. IGNITE4: results of a phase 3, randomized, multicenter, prospective trial of eravacycline vs. meropenem in the treatment of complicated intra-abdominal infections. Clin Infect Dis 2018. https://doi.org/10.1093/cid/ciy1029.
[59] Portsmouth S, van Veenhuyzen D, Echols R, Machida M, Ferreira JCA, Ariyasu M, 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, non-inferiority trial. Lancet Infect Dis 2018;18:1319–28.
[60] Jacobs MR, Abdelhamed AM, Good CE, Rhoads DD, Hujer KM, Hujer AM, et al. ARGONAUT-I: activity of cefiderocol (S-649266), a siderophore cephalosporin, against Gram-negative bacteria, including carbapenem-resistant nonfermenters and *Enterobacteriaceae* with defined extended-spectrum β-lactamases and carbapenemases. Antimicrob Agents Chemother 2018;63:e01801–18.
[61] Qureshi ZA, Paterson DL, Potoski BA, Kilayko MC, Sandovsky G, Sordillo E, et al. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother 2012;56:2108–13.
[62] Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing K. pneumoniae: importance of combination therapy. Clin Infect Dis 2012;55:943–50.
[63] Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psichogiou M, Argyropoulou A, et al. Carbapenemase producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother 2014;58:2322–8.
[64] Tumbarello M, Trecarichi EM, De Rosa FG, Giannella M, Giacobbe DR, Bassetti M, et al. Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother 2015;70:2133–43.
[65] Papadimitriou-Olivgeris M, Fligou F, Bartzavali C, Zotou A, Spyropoulou A, Koutsileou K, et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infection in critically ill patients: risk factors and predictors of mortality. Eur J Clin Microbiol Infect Dis 2017;36:1125–31.
[66] Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. J Antimicrob Chemother 2017;72:29–39.
[67] Paul M, Carmeli Y, Durante-Mangoni E, Mouton JW, Tacconelli E, Theuretzbacher U, et al. Combination therapy for carbapenem-resistant Gram-negative bacteria. J Antimicrob Chemother 2014;69:2305–9.
[68] Zusman O, Avni T, Leibovici L, Adler A, Friberg L, Stergiopoulou T, et al. Systematic review and meta-analysis of *in vitro* synergy of polymyxins and carbapenems. Antimicrob Agents Chemother 2013;57:5104–11.
[69] Papst L, Beović B, Pulcini C, Durante-Mangoni E, Rodríguez-Baño J, Kaye KS, et al. Antibiotic treatment of infections caused by carbapenem-resistant Gram-negative bacilli: an international ESCMID cross-sectional survey among infectious diseases specialists practicing in large hospitals. Clin Microbiol Infect 2018;24:1070–6.
[70] Gutierrez-Gutierrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Pano-Pardo JR, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing *Enterobacteriaceae* (INCREMENT): a retrospective cohort study. Lancet Infect Dis 2017;17:726–34.
[71] Shields RK, Potoski BA, Haidar G, Hao B, Doi Y, Chen L, et al. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant *Enterobacteriaceae* infections. Clin Infect Dis 2016;63:1615–8.
[72] King M, Heil E, Kuriakose S, Bias T, Huang V, El-Beyrouty C, et al. Multicenter study of outcomes with ceftazidime-avibactam in patients with carbapenem-resistant *Enterobacteriaceae* infections. Antimicrob Agents Chemother 2017;61.
[73] Sousa A, Pérez-Rodríguez MT, Soto A, Rodríguez L, Pérez-Landeiro A, Martínez-Lamas L, et al. Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing *Enterobacteriaceae*. J Antimicrob Chemother 2018. https://doi.org/10.1093/jac/dky295.
[74] Castón JJ, Lacort-Peralta I, Martín-Dávila P, Loeches B, Tabares S, Temkin L, et al. Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing *Enterobacteriaceae* in hematologic patients. Int J Infect Dis 2017;59:118–23.
[75] Santevecchi BA, Smith TT, MacVane SH. Clinical experience with ceftazidime/avibactam for treatment of antibiotic-resistant organisms other than *Klebsiella pneumoniae*. Int J Antimicrob Agents 2018;51:629–35.
[76] Tumbarello M, Trecarichi EM, Corona A, De Rosa FG, Bassetti M, Mussini C, et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by KPC-producing *Klebsiella pneumoniae*. Clin Infect Dis 2019;68:355–64.
[77] Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. Antimicrob Agents Chemother 2017;61.
[78] Temkin E, Torre-Cisneros J, Beovic B, Benito N, Giannella M, Gilarranz R, et al. Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. Antimicrob Agents Chemother 2017;61.
[79] van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant *Enterobacteriaceae*. Clin Infect Dis 2018;66:163–71.
[80] Shields RK, Nguyen MH, Chen L, Press EG, Kreiswirth BN, Clancy CJ. Pneumonia and renal replacement therapy are risk factors for ceftazidime-avibactam treatment failures and resistance among patients with carbapenem-resistant *Enterobacteriaceae* infections. Antimicrob Agents Chemother 2018;62.
[81] Geng TT, Xu X, Huang M. High-dose tigecycline for the treatment of nosocomial carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections: a retrospective cohort study. Medicine (Balt) 2018;97:e9961.
[82] Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis 2018;18:391–400.
[83] McKinnell JA, Dwyer JP, Talbot GH, Connolly LE, Friedland I, Smith A, et al. Plazomicin for infections caused by carbapenem-resistant *Enterobacteriaceae*. N Engl J Med 2019;380:791–3.
[84] Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J, et al. Effect and safety of meropenem-vaborbactam versus best-

Please cite this article as: Durante-Mangoni E et al., Management of carbapenem-resistant *Enterobacteriaceae* infections, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.04.013

available therapy in patients with carbapenem-resistant *Enterobacteriaceae* infections: the TANGO II Randomized Clinical Trial. Infect Dis Ther 2018;7:439–55.

[85] Motsch J, de Oliveira C, Stus V, Koksal I, Lyulko O, Boucher HW, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind, comparator controlled trial comparing the efficacy and safety of imipenem/relebactam versus colistin plus imipenem in patients with imipenem-non-susceptible bacterial infections. In: Poster O0427 presented at the 28th ECCMID; 2018.

[86] Wright H, Bonomo RA, Paterson DL. New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn? Clin Microbiol Infect 2017;23:704–12.

Please cite this article as: Durante-Mangoni E et al., Management of carbapenem-resistant *Enterobacteriaceae* infections, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.04.013