Combination versus monotherapy for the treatment of infections due to carbapenem-resistant Enterobacteriaceae

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Purpose of review
Combination therapy is a common strategy for treatment of multidrug resistant infections. Despite the strong twin rationales of improving efficacy and reducing resistance development, the evidence supporting this strategy remains controversial. The aims of this review are to assess the most recent studies supporting the use of combination therapy for treating infections because of carbapenem-resistant Enterobacteriaceae (CRE) and to highlight relevant areas for further research.

Recent findings
Evidence supporting the use of combination therapy for the treatment of CRE remains limited to in-vitro experiments and observational studies with considerable risk of bias. Very few antibiotic combinations have been tested in well designed randomized controlled trials, making it difficult to draw general conclusions for clinical practice.

Summary
Further studies are urgently needed to test the most promising synergistic combinations. New drugs potentially active against CRE should also to be tested in studies with adequate sample size and truly representative of the general patient population.

Keywords
antibiotic resistance, combination therapy, evidence-based medicine

INTRODUCTION

Since Ungar's discovery of the synergistic activity of penicillin and sulphonamides in 1943, the practice of combining antibiotics that are active *in vitro* to enhance their efficacy has attracted both clinicians and researchers. The first observations suggesting an improved clinical outcome after administration of antibiotic combinations were reported for the treatment of brucellosis and of enterococcal endocarditis, and an association between combination therapy and reduced resistance development was observed for tuberculosis treatment [1,2]. Combination treatment was established very early as the standard of practice – especially for these difficult-to-treat infections – and is still recommended in the current guidelines [3,4]. Over the intervening decades later more evidence has been acquired to recommend combination therapy in treatment of Gram-positive infections of prosthetic valves or orthopedic implants [5,6]. However, evidence supporting the use of definitive combination therapy against Gram-negative infections remains highly controversial. A systematic review of 17 studies comparing combination therapy and monotherapy in the treatment of bloodstream infections (BSIs) showed no significant difference for overall mortality, but a significant benefit of combination therapy was detected in the subgroup of *Pseudomonas aeruginosa* infections [7]. A more recent Cochrane review including 69 randomized clinical trials (RCTs) addressed the clinical implication of in-vitro synergy by comparing a β-lactam-aminoglycoside combination versus β-lactam alone in the treatment of sepsis. The authors did not find any significant

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Curr Opin Infect Dis 2018, 31:000–000
DOI:10.1097/QCO.0000000000000495

KEY POINTS

- Evidence from in-vitro studies of combination antibiotic treatment points to enhanced activity and a possible role in reducing resistance development.
- Clinical trials testing specific antibiotic combinations are limited, and little information can be generalized for current clinical practice.
- Further studies are needed to assess potential clinical benefits of combination antibiotic therapy.

difference in all-cause mortality for Gram-positive or Gram-negative infections. The subgroup of *P. aeruginosa* infections was underpowered to assess the effect [8]. Recently, interest in combination therapy has increased substantially because of the nearly empty antibiotic pipeline and the relentless global increase in the incidence of infections because of multidrug-resistant (MDR) bacteria [9]. However, despite the twin strong rationales for combination therapy use to improve efficacy and to reduce resistance development, the clinical benefits of antibiotic combinations are yet to be evaluated in adequately designed clinical trials. The evidence in favor of combination therapy for antibiotic-resistant Gram-negative infections is based largely on retrospective cohort studies that have a high risk of bias [10▪▪]. Major flaws of these studies include nonrandom allocation of patients, unclear definitions of combination treatment (i.e. referring both to the addition of two or more agents active *in vitro* or to the combination of inactive drugs with a supposed synergistic action), small sample size, lack of control for therapy modification, and inconsistency in inclusion of polymicrobial infections. Despite the limited evidence, a recent survey conducted among infectious diseases specialists practicing in 115 large teaching hospitals revealed that combination therapy for the treatment of carbapenem-resistant Enterobacteriaceae (CRE) is prescribed, at least occasionally, in 92.1% of the hospitals. More than half the respondents stated that the decision to prescribe combination treatment was based on strong scientific evidence [11▪]. The transition of this limited and flawed evidence into daily clinical practice is extremely dangerous from an antibiotic stewardship perspective because it reinforces the practice of using complex treatment schemes with unknown effect on either clinical outcomes and resistance development. The aims of this review are to summarize the state of the art of in-vitro and clinical studies of antibiotic combinations with potential coverage of CRE and to highlight relevant areas for further research.

A summary of our findings is detailed in Table 1.

POLYMYXIN–CARBAPENEM COMBINATIONS

Synergy between polymyxin and carbapenems against Gram-negative organisms has recently been assessed in a systematic review including 246 in-vitro experiments. Among the different methods evaluated, time-kill studies reported the highest synergy with a pooled rate of 44% (95% CI 30–59%) for *Klebsiella pneumoniae* and a reduction in resistance development when compared with polymyxin alone [12]. In clinical studies, superiority of polymyxin–carbapenem combinations for treating carbapenem-resistant Gram-negative infections has been shown in many observational studies, and this evidence has been summarized in two systematic

Table 1. Summary of the review findings

	In-vitro synergy	Reduction of resistance development	Enhanced clinical efficacy	References
Polymyxin–carbapenem	+	+	+/–	[10▪▪,14▪▪,15,18▪▪]
Polymyxin–fosfomycin	+	+	?	[19–24]
Tigecycline–polymyxin	+	?	+/–	[18▪▪,25–27]
Tigecycline–carbapenem	–	?	–	[25–28]
Aminoglycoside–tigecycline	+	+	?	[39–45]
Aminoglycoside–polymyxin	?	+/–	?	[39,40,44]
Aminoglycosides–fosfomycin	+	?	?	[39,40,45]
Ceftazidime/avibactam–polymyxin	–	–	?	[33▪▪]
Ceftazidime/avibactam–carbapenems	+	?	?	[34]
Ceftazidime/avibactam–azteonam	+	?	?	[35–38]

Table summarizes in-vitro and clinical studies assessing the efficacy of combination therapy for treatment of carbapenem-resistant Enterobacteriaceae. Evidence has been summarized as follows: (+) moderate/strong evidence favouring enhanced effect of combination; (–) evidence suggesting antagonistic effect of combination; (+/–) evidence is conflicting; (?) evidence absent or limited to noncontrolled studies.

reviews [10▪▪,13]. In the only systematic review displaying a meta-analysis the high risk of bias of the included studies led the authors to decide against recommending combination treatment, despite significantly lower mortality in patients treated with a polymyxin–carbapenem combination [odds ratio (OR) 1.58, 95% confidence interval (CI) 1.03–2.42] and the lack of heterogeneity detected among studies (I^2 0%). After the systematic review and meta-analysis, one RCT and two large retrospective cohort studies addressed this same question. Paul *et al.* randomized 406 patients with carbapenem-resistant Gram-negative infections to a definitive treatment with colistin or colistin–meropenem. No significant difference between the two study groups was observed in any the clinical outcomes. However, only 18% of the patients had an infection because of CRE, making results difficult to generalize to this population [14▪▪] Tumbarello *et al.* retrospectively analyzed 661 *K. pneumoniae* carbapenemase (KPC) infections treated with at least one agent active *in vitro* for a minimum of 48 h. Fourteen-day mortality in patients treated with two or more active agents was lower (OR 0.52, 95% CI 0.35–0.77), especially in patients with BSIs, pneumonia, or severe clinical presentation. Additionally, meropenem-containing combinations showed a significantly higher survival rate for isolates with a minimum inhibitory concentration (MIC) less than 8 mg/l [15]. Of note the included combination treatments showed high heterogeneity and treatment modification after the first 48 h of adequate treatment were not considered when allocating patients to the monotherapy or combination therapy group. On the basis of this study, expert reviews and the recent British Society for Antimicrobial Chemotherapy guidance recommended the use of meropenem-containing regimens in the presence of low MIC [16,17▪▪]. Gutierrez-Gutierrez *et al.* [18▪▪] investigated the association between 30-day mortality and the antibiotics administered for at least half of the total treatment duration in 437 patients from the INCREMENT cohort with KPC-BSI. The adjusted analysis showed that patients with severe infections had lower 30-day mortality when treated with more than one active drug than with active monotherapy. However, in a subgroup analysis of severely ill patients, no statistically significant survival advantage of a colistin–carbapenem combination compared with colistin monotherapy was seen (hazard ratio 0.56, 95% CI 0.26–1.23).

COLISTIN–FOSFOMYCIN COMBINATIONS

The rationale for the combination of colistin and fosfomycin is the potentially enhanced penetration of fosfomycin resulting from the permeabilizing effect on bacterial outer membrane caused by colistin. The real benefit of this combination is still uncertain; a small number of in-vitro experiments and observational clinical studies provide some evidence [19]. Wang *et al.* used an in-vitro pharmacodynamic model to assess the activity of three colistin–fosfomycin regimens against four strains of KPC with variable resistance patterns. An increased bactericidal effect against colistin-susceptible and fosfomycin-susceptible strains was observed for combination therapy compared with monotherapy. Combination therapy did not result in any additive effects for colistin-resistant isolates [20]. Zhao *et al.* found that combination treatment increased the bactericidal effect against double-susceptible strains. For colistin-resistant isolates, the enhancement of bactericidal effect was associated only with increase in fosfomycin concentration [21]. Souli *et al.* [22] performed a time-kill study in which increased bactericidal activity was observed with colistin–fosfomycin compared with monotherapy, but a synergistic effect was shown against only 11.8% of the isolates. An increased bactericidal effect against metallo-β-lactamase-producing (MBL) Enterobacteriaceae independent of fosfomycin susceptibility was reported in two studies [23,24]. In addition to enhancement of bactericidal activity, these in-vitro studies demonstrated that the combination of these two antibiotics plays an important role in the prevention of resistance emergence.

Clinical experience with fosfomycin for the treatment of MDR Gram-negative infections remains limited to small case series. The largest study was conducted by Pontikis *et al.* in 41 critically ill patients with CRE infections treated with fosfomycin in combination with colistin or tigecycline. Clinical outcome was successful in 54.2% of patients with a 28-day mortality of 37.5%. Development of resistance to fosfomycin was limited to three patients [19].

TIGECYCLINE-BASED COMBINATIONS

Two in-vitro studies have reported improved bactericidal activity of colistin–tigecycline when compared with monotherapy. The addition of meropenem to tigecycline or to tigecycline–colistin did not show any advantage [25,26]. This effect has also been observed in in-vivo models. In a simple animal model of CRE infections (*Galleria mellonella*), the combination of tigecycline and colistin was superior to monotherapy, even in isolates with high MICs for the two drugs [27]. In an in-vivo model of KPC-2 sepsis, colistin–tigecycline demonstrated a 100% survival in 80 rats, whereas meropenem–tigecycline resulted in significantly lower survival and was antagonistic *in vitro* [28].

The only clinical study even partially addressing the efficacy of this combination is the INCREMENT cohort study, which reported reduced mortality in high-risk patients with CRE-BSI treated with a tigecycline-containing combination or colistin monotherapy (hazard ratio 0.45, 95% CI 0.23–0.86). However, only 79 patients were included in this analysis, and it is very likely that patients receiving a tigecycline-containing combination were treated also with other antibiotics [18▪▪].

CEFTAZIDIME–AVIBACTAM-BASED COMBINATIONS

Ceftazidime–avibactam (CEF–AVI) is a fixed-dose combination of a broad-spectrum cephalosporin and a novel β-lactamase inhibitor. Avibactam is the key component of this new combination because of its activity against Ambler class A and class D serine carbapenemases, including KPC and OXA-48–like carbapenemases [29]. As the registration trials did not specifically take into account infections because of carbapenemase-producing isolates, limited data are available for use in this clinical context. Despite the evidence from case series suggesting a role of this drug in the treatment of severe infections because of CRE, no controlled studies explored this use [30–32]. Moreover, rapid development of resistance to this new drug has been documented [31]. Combination of CEF–AVI with another agent may represent a strategy for increasing bactericidal effect and reducing the emergence of resistance. Shields *et al.* have assessed the suitability of colistin as a partner in this combination in a time-kill analysis of 24 CRE isolates. Several concentrations of CEF–AVI were combined with a fixed concentration of colistin, but no enhanced bactericidal effect or suppression of resistance development was observed for CEF–AVI [33▪▪]. Gaibani *et al.* investigated the potential synergistic activity between CEF–AVI and other agents (ertapenem, imipenem, meropenem, gentamicin, tigecycline, and ciprofloxacin). The greatest reductions in MIC were obtained combining CEF–AVI with meropenem or imipenem with a possible role in the restoration of carbapenem activity in the presence of resistance to CEF–AVI explaining this phenomenon [34]. Despite avibactam's lack of activity against metallo-β-carbapenemases (Ambler class B), its combination with aztreonam has shown a synergistic effect in a small number of in-vitro and animal studies [35–38]. A combination of these two agents (even in a fixed-dose formulation), has been suggested as a possible target for future research, especially for infections sustained by MBL producers [17▪▪].

AMINOGLYCOSIDE-BASED COMBINATIONS

Aminoglycosides are an effective therapeutic option for CRE, even in the presence of colistin resistance [39,40]. The rate of aminoglycoside susceptibility among CRE is variable and based on local epidemiology. An improved bactericidal effect for aminoglycosides in combination compared with monotherapy has been suggested in a few time-kill studies even in the presence of isolates with high MIC for aminoglycosides [41,42]. In particular, improved bactericidal activity has been observed for amikacin or gentamicin combined with tigecycline or doxycycline compared with monotherapy [43]. Another study reported a reduced emergence of resistance at low concentrations for tigecycline–amikacin compared with other regimens (colistin–tigecycline and colistin–amikacin) [44]. In a time-kill experiment, an additive effect was observed with fosfomycin–amikacin [45].

Only a few studies provide clinical data on specific aminoglycoside-containing regimens for treatment of CRE infections. Gonzales-Padilla *et al.* and Shields *et al.* reported mortality rates of 38 and 30%, respectively, in patients with KPC–BSIs treated with aminoglycoside-containing regimens. Aminoglycosides as monotherapy in 8 (16%) patients and 10 (30%) patients showed no difference in mortality compared with combination. An overall reduced mortality seemed to be associated with low aminoglycoside MICs [39,40].

ONGOING STUDIES AND NEW DRUGS UNDER DEVELOPMENT

Some additional evidence of the clinical utility of a colistin–carbapenem combination may be provided by an ongoing RCT enrolling patients with extensively drug-resistant Gram-negative infections. Mortality and emergence of colistin resistance will be compared for colistin with placebo versus colistin–meropenem. Five of 13 centers have already completed recruitment, and final results are expected to be available by September 2021 (NCT01597973).

The efficacy of fosfomycin in the treatment of MDR *Escherichia coli* is currently under evaluation in an RCT comparing fosfomycin with carbapenem or ceftriaxone. The study will be of utmost relevance for clarifying the role of fosfomycin in the treatment of Gram-negative infections. However, patients with infections sustained by carbapenem-resistant bacteria are not included.

The recent development of new carbapenem-β-lactamase inhibitor combinations with in-vitro activity against KPC (e.g. imipenem–relebactam,

meropenem–vaborbactam) will also contribute to significantly modify the approach to treatment of CRE infections. The efficacy and safety of imipenem–relebactam versus imipenem–colistin have been compared in a phase 3 RCT in patients with imipenem-resistant bacterial infections. With the limitation of the small sample size (31 patients enrolled, randomized in a 2 : 1 fashion), 28-day all-cause mortality was 30% in the colistin–imipenem group and 9.5% in the imipenem–relebactam group with a 17.3% adjusted difference and a wide confidence interval (adjusted difference:17.3%, 95% CI −46.4 to 6.7) [46]. A phase 3 multicenter open-label RCT compared the efficacy of meropenem–vaborbactam to the best available treatment in 77 patients with selected serious infections because of CRE. The study is complete, and results are expected to be published soon (NCT02168946).

CONCLUSION

Combination therapy for the treatment of CRE infections is supported only by low-quality evidence, derived mainly from in-vitro and observational studies. Both aminoglycosides and tigecycline are important resources in the armamentarium against CRE infections. Within the strict limitations of the scant available evidence, tigecycline-containing combinations are associated with lower mortality than tigecycline alone, but no specific data are available on which drug should be included in the combination. Conversely, aminoglycoside-containing combinations do not provide better outcomes than aminoglycoside monotherapy. The combination of CEF–AVI and colistin is not supported by in-vitro studies, and no clinical studies evaluating this combination have been conducted. The combination of avibactam with aztreonam provides in-vitro coverage against MBL producers, but this combination requires further evaluation in the clinical practice. Further studies are also urgently needed to better understand the role of fosfomycin, alone or in combination with colistin, specifically to assess whether the enhanced bactericidal effect of combination therapy translates into improved clinical outcomes and reduced resistance development. Results from recently published RCTs pooled together with a similar ongoing RCT should finally shed some light on the longstanding debate about the added value of this combination. Newly developed drugs constitute a valuable resource in the fight against antimicrobial resistance; however, the potential in-vitro coverage against KPC should be supported by well designed trials with adequate sample size.

In conclusion, in an era of increasing antibiotic resistance, combination therapy should be considered only after its benefit for clinical outcomes has been adequately proven. Future trials should test specific combination schemes to assess whether the hypothetical benefit outweighs the risk of more side effects and the unclear impact on resistance development.

Acknowledgements

We thank Anne McDonough, a professional medical writer for editorial assistance. She was partly supported by WHO Priority pathogen list project, grant number 3021017.

Financial support and sponsorship

There are no financial support and sponsorship.

Conflicts of interest

There are no conflicts of interest.

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