VIRULENCE
2017, VOL. 8, NO. 4, 470–484
https://doi.org/10.1080/21505594.2017.1292196

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REVIEW

Therapeutic options for carbapenem-resistant Enterobacteriaceae infections

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ABSTRACT

In recent years, carbapenem resistance among Enterobacteriaceae has dramatically increased and represents an important threat to global health. The optimal therapeutic management of carbapenem-resistant Enterobacteriaceae (CRE) infections has not been established, because to date, no clinical trials have been performed with this objective. We aimed to summarize in the present review data provided by previous observational clinical studies that have investigated the impact of different treatment strategies on the outcome of CRE infections. Most of these studies reported that combination therapy with 2 or more drugs is superior to monotherapy in providing a survival benefit. The use of carbapenems in association with other active drugs is likely ineffective for CRE isolates with carbapenem Minimum Inhibitory Concentrations (MICs) >8 mg/l. The effectiveness of further therapeutic options for the treatment of extensively or pan-drug-resistant Enterobacteriaceae infections has been reported in vivo and in vitro, although few cases/case series have been reported. Novel antimicrobials that are effective against CRE are urgently needed.

ARTICLE HISTORY
Received 12 October 2016
Revised 25 January 2017
Accepted 1 February 2017

KEYWORDS
carbapenem-resistant Enterobacteriaceae; combination therapy; double-carbapenem combination; mortality; monotherapy

Introduction

During the last decade, carbapenem-resistant Enterobacteriaceae (CRE) have caused numerous outbreaks of severe nosocomial infections and have become endemic in several countries.[1-7] Severe infections caused by CRE have been associated with mortality rates exceeding 50% in some reports.[6-9] To date, the best clinical management of CRE infections has not been established, because clinical trials have been never performed to establish the optimal treatment strategies. CRE have historically been susceptible to polymyxins, tigecycline or aminoglycosides (mostly gentamicin), and these antibiotics are considered the drugs of choice for infections caused by such bacteria.[6-8] However, resistance to these antibiotics has recently been reported, with rates exceeding 35% in some circumstances.,[9,10] In addition, the use of carbapenems in combination with other active drugs has been reported as effective.[11-14] Finally, therapeutic options for treatment of extensively drug-resistant (XDR) or pan-drug-resistant (PDR) Enterobacteriaceae are scarce and poorly investigated.

The aim of this review is to focus on the current evidence regarding the antibiotic therapy of CRE infections, with particular emphasis on the association between different treatment approaches and mortality.

Methods

A literature search was performed using the PubMed database through July 2016 to identify studies investigating the relationship between antibiotic treatments and outcome. Searches were performed using the following search terms: (bacteremia OR bloodstream OR infection) AND (carbapenem resistant OR KPC) AND (Enterobacteriaceae OR *Klebsiella pneumoniae*).

For the review purpose, selected papers were included if the following conditions were met: 1. They were published in English; 2. patient cohorts included ≥ 40 cases; 3. the different antibiotic treatment approaches and their associated mortality rates were reported.

Characteristics of included studies

Overall, 11 studies were included in the present review (Table 1).[10,12-21] All of the included studies were conducted on infections caused by *Klebsiella pneumoniae*, except that of De Oliveira et al. which included a total of 118 cases of infections caused by CRE, the majority of which (108, 92%) were *K. pneumoniae*.[15] All 11 included studies were observational cohort studies; 3 were prospective,[10,20,21] one was conducted with a mixed retrospective/prospective design,[18] and the remaining

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Table 1. Summary of observational studies on carbapenem-resistant Enterobacteriaceae infections, with bacterial isolates' and patients' characteristics, antibiotic treatment and related outcome.

Reference	Study design	Country	Period	Setting	N. of patients	Source of bacterial isolates	BSI, n (%)	Enzyme type(s) (N.)	Resistance to colistin (%)	Resistance to gentamicin (%)	Resistance to tigecycline (%)	Antibiotic regimens (N.)	Died, %
Capone CMI 2013	Prospective observational cohort	Italy	2010–2011	Nine tertiary care hospitals	91	Clinical samples	34 (37.4)	KPC-3 (89) VIM-1 (3) CTX-M-15 plus porin defects (5)	36.1	79.6	20.4		25.8
												Monotherapy (NR)	NR
												Colistin (10)	40
												Gentamicin (16)	6.2
												Combination (54)	31.5
												Colistin plus tigecycline (16)	25
												Colistin plus fosfomycin (5)	0
												Colistin plus gentamicin (5)	40
												Tigecycline plus fosfomycin (6)	33.3
Daikos AAC 2014	Retrospective observational cohort	Greece	2009–2010	Two tertiary care hospitals	205	Blood	205 (100)	KPC-2 (127) KPC-2 plus VIM-1 (36) VIM-1 (42)	25.4	15.1	31.2		40
												Monotherapy (72)	44.4
												Tigecycline (27)	40.7
												Colistin (22)	54.5
												Aminoglycoside (9)	22.2
												Carbapenem (12)	58.3
												Other monotherapies (2)	0
												No active agent (12)	33.3
												Combination therapy (103)	27.2
												Carbapenem + tigecycline + aminoglycoside or colistin (11)	0
												Carbapenem + tigecycline (4)	50
												Carbapenem + aminoglycoside (9)	11.1
												Carbapenem + colistin (7)	42.8
												Tigecycline + aminoglycoside + colistin (11)	37.5
												Tigecycline + aminoglycoside (20)	45
												Tigecycline + colistin (21)	23.8
												Aminoglycoside + colistin (17)	29.4
												Other combination regimens (3)	0

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Table 1. (*Continued*)

Reference	Study design	Country	Period	Setting	N. of patients	Source of bacterial isolates	BSI, n (%)	Enzyme type(s) (N.)	Resistance to colistin (%)	Resistance to gentamicin (%)	Resistance to tigecycline (%)	Antibiotic regimens (N.)	Died, %
Falcone CMI 2016	Retrospective observational cohort	Italy	2010–2014	Single ICU Center	111	Clinical samples	53 (47.7)	KPC (types not reported)	51.3	78.9	0		39.6
												No use of *in vitro* active antibiotics (25)	64
												Definitive therapy with <2 antibiotics displaying *in vitro* activity (44)	77.2
												Definitive therapy with 2 or more antibiotics displaying *in vitro* activity (64)	10.9
												Colistin + Meropenem (5)	0
												Colistin + Tigecycline (6)	0
												Tigecycline + Gentamicin (12)	58.3
												Meropenem + Tigecycline (16)	41.1
												Colistin + Tigecycline + Meropenem (21)	19.1
												Tigecycline + Meropenem + Fosfomycin (12)	75
												Colistin + Tigecycline + Imipenem (5)	40
												Colistin + Tigecycline + Rifampicin (1)	0
												Meropenem + Ertapenem + Colistin (5)	20
												Colistin + Tigecycline + Meropenem + Gentamicin (19)	36.8
Gomez-Simmonds AAC 2016	Retrospective observational cohort	USA	2006–2013	Two tertiary care hospitals	141	Blood	141 (100)	NR	14	36	5		33.3
												Single active agent (68)	26
												Poymyxin B plus a BL (18)	28
												Poymyxin B without a BL (7)	29
												Tigecycline plus a BL (9)	11
												Tigecycline without a BL (17)	35
												Aminoglycoside plus a BL (9)	11
												Aminoglycoside without a BL (5)	20
												Other (3)	67
												Multiple active agents (73)	38
												Polymyxin B/Tigecycline plus a BL (22)	36
												Polymyxin B/Tigecycline without a BL (21)	52

												Polymyxin B/ Aminoglycoside plus a BL (5)	60
												Polymyxin B/ Aminoglycoside without a BL (8)	25
												Polymyxin B/Tigecycline/ Aminoglycoside plus a BL (2)	100
												Polymyxin B/Tigecycline/ Aminoglycoside plus a BL (3)	33
												Other combinations (8)	38
Kontopidou CMI 2014	Retrospective/ prospective observational cohort	Greece	2009–2010	19 ICU centers	127	Clinical samples	30 (23.6)	KPC (52; types not reported) VIM (22) KPC/VIM (6) NR (45)	20	21	33		25.2
												Monotherapy	
												Colistin (26)	23.1
												Aminoglycoside (22)	22.7
												Tigecycline (16)	31.3
												Combination Therapy	
												Tigecycline plus aminoglycoside (11)	18.1
												Colistin plus aminoglycoside (17)	11.7
												Colistin plus tigecycline (9)	44.4
												Colistin plus tigecycline plus aminoglycoside (4)	0
												Colistin plus tigecycline plus carbapenem (1)	NR
Tumbarello CID 2012	Retrospective observational cohort	Italy	2010–2011	Three tertiary care hospitals	125	Blood	125 (100)	KPC-3 (98) KPC-2 (27)	12	5.6	8.8		41.6
												Monotherapy (46)	54.3
												Tigecycline (19)	52.6
												Colistin (22)	50
												Gentamicin (5)	80
												Combination therapy (79)	34.1
												Tigecycline + colistin (23)	30.4
												Tigecycline + gentamicin (12)	50
												Other 2-drug combinations (21)	47.6
												Tigecycline + colistin + meropenem (16)	12.5
												Other 3-drug combinations (7)	28.5

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Table 1. (*Continued*)

Reference	Study design	Country	Period	Setting	N. of patients	Source of bacterial isolates	BSI, n (%)	Enzyme type(s) (N.)	Resistance to colistin (%)	Resistance to gentamicin (%)	Resistance to tigecycline (%)	Antibiotic regimens (N.)	Died, %
Tumbarello JAC 2015	Retrospective observational cohort	Italy	2010–2013	Five tertiary care hospitals	661	Clinical samples	447 (67.6)	KPC-3 (497) KPC-2 (164)	20	17.9	23		34.1
												Monotherapy (307)	38.4
												Tigecycline (116)	38.8
												Colistin (121)	37.2
												Gentamicin (70)	40
												Combination therapy (354)	30.2
												Two-drug combination (134)	28.3
												Three-drug combination (217)	30.8
												Combination including a carbapenem (205)	26.3
												Double-carbapenem combination (8)	37.5
												Combination plus rifampicin (12)	50
Qureshi AAC 2012	Retrospective observational cohort	USA	2005–2009	Two tertiary care hospitals	41	Blood	41 (100)	KPC (types not reported)	9.7	85.4	2.4		39
												Monotherapy (19)	57.8
												Colistin-polymyxin B (7)	57.1
												Tigecycline (5)	80
												Carbapenem (4)	50
												Gentamicin (1)	0
												Ampicillin-sulbactam (1)	0
												Piperacillin-tazobactam (1)	100
												Combination therapy (15)	13.3
												Colistin-polymyxin B + Carbapenem (5)	20
												Colistin-polymyxin B + Tigecyclin (1)	0
												Colistin-polymyxin B + Fluoroquinolone (1)	0
												Tigecycline + Carbapenem (3)	0
												Tigecycline +Aminoglycoside (2)	0
												Carbapenem-fluoroquinolone (1)	100
												Aztreonam-fluoroquinolone (1)	0
												Cefepime-gentamicin (1)	0

Trecarichi AJH 2016	Prospective observational cohort	Italy	2010–2014	Hematological wards of 13 tertiary care hospitals	149	Blood	149 (100)	NR	13.6	34.8	24.2		48.3
												Monotherapy (78)	35.9
												Tigecycline (13)	53.8
												Colistin (11)	54.5
												Gentamicin (5)	60
												Combination therapy (109)	36.7
												Tigecycline + Colistin (4)	25
												Tigecycline + Gentamicin (10)	10
												Colistin + Gentamicin (5)	20
												Colistin + Meropemem (10)	0
												Tigecycline + Colistin + Gentamicin (6)	33.3
												Tigecycline + Colistin + Meropenem (29)	34.5
												Tigecycline + Gentamicin + Meropenem (15)	40
												Colistin + Gentamicin + Meropenem (10)	60
												Other 3 drugs combinations[a] (7)	42.8
												Tigecycline + Colistin + Gentamicin + Meropenem (13)	76.9
Zarkotou CMI 2011	Prospective observational cohort	Greece	2008–2010	Single tertiary care hospital	53	Blood	53 (100)	KPC-2 (53)	24.5	60.4	3.8		33.9
												Monotherapy (15)	46.7
												Colistin (7)	66.7
												Tigecycline (5)	40
												Gentamicin (2)	0
												Carbapenem (1)	100
												Combination therapy (15)	0
												Tigecycline + Colistin (9)	0
												Tigecycline + Gentamicin (3)	0
												Tigecycline + Colistin + Carbapenem (2)	0
												Tigecycline + Colistin + Gentamicin (1)	0
												Tigecycline + Amikacin (1)	0
												Colistin + Gentamicin (2)	0
												Carbapenem + Gentamicin (1)	0

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Table 1. (*Continued*)

Reference	Study design	Country	Period	Setting	N. of patients	Source of bacterial isolates	BSI, n (%)	Enzyme type(s) (N.)	Resistance to colistin (%)	Resistance to gentamicin (%)	Resistance to tigecycline (%)	Antibiotic regimens (N.)	Died, %
De Oliveira CMI 2014	Retrospective observational cohort	Brazil	2009–2013	Three tertiary care hospitals	118	Clinical samples	78 (66.1)	KPC (types not reported)	NR	NR	NR		49.1
												Monotherapy (57)	36.8
												Carbapenem (25)	24
												Polymyxin (21)	61.9
												Aminoglycoside (9)	11.1
												Tigecycline (2)	50
												Combination therapy (61)	52.4
												Polymyxin + carbapenem (19)	57.8
												Aminoglycoside + carbapenem (8)	37.5
												Aminoglycoside + tigecycline (2)	0
												Tigecycline + carbapenem (2)	50
												Polymyxin + aminoglycoside (4)	25
												Polymyxin + aminoglycoside + carbapenem (12)	83.3
												Tigecycline + carbapenem + polymyxin (5)	60
												Aminoglycoside + polymyxin + tigecycline (1)	0
												Aminoglycoside + carbapenem + tigecycline (1)	0
												Aminoglycoside + polymyxin + carbapenem + tigecycline (6)	50

Notes. Abbreviations: NR, not reported; BL, β-lactam; ICU, intensive care unit.

7 studies were conducted retrospectively.[12-17,19] Eight studies were conducted in European countries (5 in Italy and 3 in Greece), 2 in the USA,[17,19] and one in Brazil.[15] All studies were conducted in tertiary care hospitals; however, 2 studies included only patients in intensive care units (ICUs),[16,18] and one included only patients having hematological malignancies.[20] Six studies were conducted exclusively on patients diagnosed with bloodstream infections (BSIs),[12,14,17,19-21] whereas the remaining 5 included cases of CRE infections in which CRE were isolated in clinical samples,[10,13,15,16,18] of which the percentage of blood infections ranged from 23.6% to 67.6%. With regard to the studies by Tumbarello et al., a proportion of the patients included in their 2015 study had been reported in previous articles from the same group; one of these publications, a report from 2012, is also included in this review.[12,13]

In addition, the 11 studies included in this review differed with regard to the breakpoint guidelines used for the MICs of different antibiotics and in their definitions of treatment regimens (i.e., monotherapy and combination therapy), which in some cases were not reported (Table 2). Table 2 shows the antibiotic regimens used in the different studies (when reported); in most studies, a loading dose and high-doses of both colistin and tigecycline were used, which have been reported to be associated with a better outcome without significant adverse effects.[22,23]

Microbiological characteristics of CRE isolates

Characterization of enzymes conferring carbapenem-resistance to Enterobacteriaceae isolates was reported in 9 studies, and *K. pneumoniae* carbapenemases (KPCs) were the most frequent.[10,12-16,18,19,21] In 5 of these studies, bla_{KPC} genes were specifically characterized and, overall, CRE isolates carried only bla_{KPC-3} and bla_{KPC-2} genes, with bla_{KPC-3} genes carried almost 3 times more frequently than bla_{KPC-2}.[10,12-14,21] Less frequently, CRE isolates harbored Verona integron-encoded metallo-β-lactamases (VIM), either alone or together with KPCs.[10,14,18] In an Italian study, the mechanism of carbapenem resistance of some CRE isolates was the production of CTX-M-15 in addition to porin defects.[10] Of note, no studies with the characteristics that we used as inclusion criteria for the present review included patients with CRE infections caused by isolates that displayed other types of carbapenem resistance mechanisms (e.g., production of New Delhi metallo-β-lactamase [NDM]- and/or OXA-48 enzymes).

Percentages of resistance of CRE isolates to the antimicrobials most used for the treatment of such infections (i.e., colistin, gentamicin and tigecycline) were reported in 10 of the 11 included studies; the rates of resistance ranged from 9.7% to 51.3% (mean 22.6%) for colistin, from 5.6% to 85.4% (mean 43.5%) for gentamicin, and from 0 to 33% (mean 15.2%) for tigecycline.[10,12-14,16-21]

Of note, despite the production of carbapenemases in the isolates described in the study by Daikos et al., almost 50% of the isolates were carbapenem-susceptible based on EUCAST breakpoints.[14]

Antimicrobial therapy and outcome

As defined by the inclusion criteria for the present review, all of the studies reported the different antibiotic treatment approaches and their associated mortality rates. The different treatment approaches were also included in the analysis of independent risk factors for mortality in 10 of the reviewed studies (Table 1),[12-21] whereas in that of Capone et al., multivariate analysis was adjusted for appropriate antibiotic treatment, combination therapy, and removal of the infectious source.[10]

The characteristics of the patient populations included in multivariate models of risk factors for mortality in the other 10 studies should by divided into 2 major categories: those whose cohort included all patients diagnosed with CRE infection, regardless of if they had received an active antimicrobial treatment of a minimum period,[15,16,18,19,21] and those that included only patients with CRE infections who were treated for at least 48 h with an effective antibiotic therapy (i.e., one or more active drugs displaying in vitro activity against the CRE isolate).[12-14,17,20] In fact, the inclusion of patients who did not receive a sufficient period of adequate definitive treatment of CRE infection could represent a bias in analyzing the impact of different treatment approaches on mortality and should be taken into account.

Given the above, in the study by Tumbarello et al. assessing risk factors for 30-day mortality in 125 patients with KPC-producing *K. pneumoniae* BSI, the mortality rate of patients who received monotherapy (54%) was significantly higher than that of patients treated with combination therapy (34%), and postantibiogram therapy with a combination of tigecycline plus colistin plus meropenem was independently associated with 30-day survival (Odds Ratio [OR] 0.11).[12] Similar findings were subsequently reported in the study by Daikos et al. analyzing the outcome of 205 patients with a BSI caused by KPC- or VIM-producing *K. pneumoniae* and in a more recent study by Tumbarello et al. conducted on a cohort of 661 adults including 447 with BSIs and 214 with non-bacteremic infections (lower respiratory tract, intra-abdominal structure, urinary tract or other sites) caused by KPC-*K. pneumoniae* isolates; both of these studies

Table 2. Summary of breakpoint guidelines used and reported definitions of therapeutic regimens in observational studies on carbapenemase-producing Enterobacteriaceae infections.

Reference	Breakpoint guidelines	Reported definitions of therapeutic regimens	Antibiotics' regimens used
Capone CMI 2013	EUCAST	NR	NR
Daikos AAC 2014	EUCAST; US. Food and Drug Administration interpretive criteria for tigecycline	Monotherapy: treatment with one *in vitro* active agent	Colistin: total daily dose 9 million IU given in 2 or 3 divided dosages; Tigecycline: total daily dose 100 to 200 mg administered in 2 divided dosages.
		Combination therapy: treatment with 2 or more *in vitro* active agents	Carbapenems: 1 g for imipenem and doripenem and 2 g for meropenem every 8 h. Aminoglycosides: once daily 5 mg/kg for gentamicin and 15 mg/kg for amikacin. Dosages adjusted to creatinine clearance when indicated
Falcone CMI 2016	EUCAST; US. Food and Drug Administration interpretive criteria for tigecycline	Monotherapy or combination therapy depending on the number of drugs used (1 or >1)	NR
Gomez-Simmonds AAC 2016	CLSI; US. Food and Drug Administration interpretive criteria for tigecycline	Single *in vitro* active agent	Colistin, tigecycline, aminoglycosides: NR
		Multiple active agents (MAA)	Meropenem: conventional (500 mg every 6 h or equivalent dosing for patients with renal insufficiency); high-dose (2 g every 8 h or equivalent); or high-dose, extended-infusion (2 g administered over 3 h every 8 h or equivalent) dosing categories.
Kontopidou CMI 2014	CLSI; EUCAST for colistin and tigecycline	Active monotherapy: therapy with one active agent according to the susceptibility test	Colistin: every 8–12 h for a total daily dose of 9 million IU. Tigecycline: loading dose, then administration every 12 h (100–200 mg/day).
		Active combined treatment: combination with >1 active agent according to the susceptibility test	Gentamicin: every 24 h (total daily dose 4–5 mg/kg) Meropenem: by extended infusion at a dose of 2 g every 8 h. Drug dosages adjusted on the basis of creatinine clearance.
Tumbarello CID 2012	CLSI; EUCAST for colistin; US. Food and Drug Administration interpretive criteria for tigecycline	Monotherapy or combination therapy depending on the number of in vistro-active drugs used (1 or >1)	Colistin: loading dose, then given every 8–12 hours for a total daily dose of 6 000 000–9 000 000 IU. Tigecycline: loading dose, then every 12 hours (100–200 mg/day). Gentamicin every 24 hours (total daily dose 4–5 mg/kg) Meropenem by extended infusion (lasting ≥ 3 hours) at a dose of 2 g every 8 hours. All dosages adjusted on the basis of creatinine clearance if necessary.
Tumbarello JAC 2015	EUCAST	Monotherapy or combination therapy depending on the number of in vistro-active drugs used (1 or >1)	Colistin: loading dose, then given every 8–12 hours for a total daily dose of 6 000 000–9 000 000 IU. Tigecycline: loading dose, then every 12 hours (100–200 mg/day). Gentamicin every 24 hours (total daily dose 4–5 mg/kg) Meropenem by extended infusion (lasting ≥ 3 hours) at a dose of 2 g every 8 hours. All dosages adjusted on the basis of creatinine clearance if necessary.

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Table 2. (*Continued*)

Reference	Breakpoint guidelines	Reported definitions of therapeutic regimens	Antibiotics' regimens used
Qureshi AAC 2012	CLSI	Combination therapy was defined as administration of 2 antimicrobials with Gram-negative activity for at least 48 h after the susceptibility results became available, regardless of the *in vitro* susceptibility to each agent	NR
Trecarichi AJH 2016	NR	Monotherapy included treatment with only one of the following drugs: gentamicin, colistin or tigecycline Combination therapy: all the other antibiotic regimens (including another active drug or a carbapenem)	NR
Zarkotou CMI 2011	CLSI; EUCAST for colistin; US. Food and Drug Administration interpretive criteria for tigecycline	NR	NR
De Oliveira CMI 2014	CLSI	Combination therapy: use of more than one antimicrobial drug for Gram-negative bacteria	NR

Notes. Abbreviations: NR, not reported; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

demonstrated an independent association of combination therapy with survival.[13,14] Of note, in both of these 2 studies, combination therapy was reported to have the greatest effect on survival in patients with more severe clinical characteristics, including patients with severe sepsis, septic shock, and rapidly fatal underlying disease in the study by Daikos et al. and those with high-risk BSIs, lung infections or high APACHE III scores and/or septic shock at infection onset in the study by Tumbarello et al.[13,14] Qureshi et al., who evaluated the clinical outcomes of 41 patients with BSI caused by KPC-producing *K. pneumoniae*, found that definitive therapy with a combination regimen was independently associated with survival (OR 0.07) and reported a 28-day mortality rate significantly lower among patients treated in with combination therapy (13.3%) compared with those who had received monotherapy (57.8%).[19] Zarkotou et al. reported a significant association of combinations of active antimicrobials with survival using univariate analysis in their cohort of 53 patients with BSI caused by KPC-producing *K. pneumoniae*; however, this association was not confirmed by multivariate analysis.[21]

In a more recent study, Gomez-Simmonds et al. assessed the outcomes of 141 patients with BSIs caused by carbapenem-resistant *K. pneumoniae* (CRKP) according to the number of in vitro active agents received and whether an extended-spectrum β-lactam antibiotic was administered. They did not find any association between the individual treatment characteristics, including use of single active agent versus multiple active agents or use of a β-lactam or not, and outcome; notably, the extended-spectrum β-lactam included meropenem (used in different doses: 500 mg every 6 h; 2 g every 8 h; 2 g administered over 3 h every 8 h), cefepime, and ceftazidime, and no stratifications for these different antibiotic approaches were performed.[17] Similar results have been reported by De Oliveira et al., who did not find any association of combination therapy with survival in their cohort of 118 patients with infections caused by KPC-producing Enterobacteriaceae, of whom 78 had BSIs; moreover they demonstrated that use of polymyxin was an independent predictor of mortality.[15] However, as noted by the authors, during the first 10 d of treatment of KPC-producing Enterobacteriaceae infections, 47 patients (40%) had 51 other infections whose etiologic agents had been identified as bacterial (77%), fungal (21%), or viral (2%); this could represent a bias in evaluating the role of different antibiotic approaches for CRE infections.[15]

Interestingly, combination therapy has also been found to influence survival in 2 studies that included patients with CRE infections in specific settings. Falcone et al. analyzed the outcomes of 141 ICU patients with KPC-producing *K. pneumoniae* infection and septic shock, reporting that a colistin-containing antibiotic regimen (Hazard ratio [HR] 0.21) and use of $\geq$ 2 *in vitro* active antibiotics as definite therapy (HR 0.08) were associated with favorable outcome. Trecarichi et al. evaluated risk factors for mortality in 149 patients having

hematological malignancies with BSIs caused by *K. pneumoniae* who had received ≥ 48 hr of adequate antibiotic therapy and found that combination therapy was independently associated with survival (HR 0.32).[16,20]

Role of carbapenems in the treatment of CRE infections

The issue of the role of carbapenems in the treatment regimen for CRE infections is widely debated at present. In their article published in 2011, Daikos and Markogiannakis reviewed clinical data about treatment and outcome of patients infected with CRKP and extracted data from 44 patients who had received carbapenem monotherapy. The analysis of outcome according to carbapenem MICs revealed that survival rates increased from 29% for MIC of > 8 mg/L to 60% for MIC of 8 mg/L and to 69% for MIC of 4 mg/L or less; these latter rates were similar to those observed in patients infected with non-carbapenemase-producing *K. pneumoniae* or who had received appropriate treatment other than carbapenem monotherapy. Thus, the authors concluded that carbapenems could represent a therapeutic option for treatment of CRE infections when the MIC is ≤ 4 mg/L if administered with a high-dose prolonged-infusion regimen and in combination with another active drug.[11]

Subsequently, some larger studies have investigated the correlation between carbapenem therapy, carbapenem MICs and outcome.[12-14] In a study by Tumbarello et al., the outcome of 36 cases of BSI caused by KPC-producing *K. pneumoniae* treated with combination therapy including meropenem were stratified according to the following meropenem MICs: for *K. pneumoniae* isolates with MICs ≤ 8 mg/l, the overall 30 day mortality was 15.8%, whereas it was 35.2% for isolates with MICs ≥ 16 mg/l.[12] Daikos et al. observed the lowest mortality rate (19.3%) in patients with CRKP BSIs who were treated with carbapenem-containing combinations if the carbapenem MIC was ≤ 8 mg/L and a significant increase in mortality (35.5%) in the subgroup of patients who had received a carbapenem-containing combination therapy but was infected by a CRKP isolate with a carbapenem MIC >8.[14] Tumbarello et al. have confirmed the data of Daikos et al. in their large cohort of patients (661) with infections caused by KPC-producing *K. pneumoniae* reporting that for patients whose combination regimens included meropenem, 14-day mortality rates were significantly lower than those associated with monotherapy only when the meropenem MICs for the KPC-*K. pneumoniae* isolates were ≤ 8 mg/L.[13] Of note, in these 3 latter studies carbapenems were administered at high doses,[12-14] and the 2 studies by Tumbarello et al. included extended infusions.[12,13]

More recently, Del Bono et al. assessed the achievement of pharmacokinetic/pharmacodynamic (PK/PD) targets of meropenem in 19 critically ill patients with BSIs caused by KPC-producing *K. pneumoniae* isolates with meropenem MICs ≥ 16 mg/l who were given 3-drug combinations including meropenem (at high doses-extended infusion)with tigecycline/gentamicin or tigecycline/colistin according tocolistin resistance or susceptibility of KPC- *K. pneumoniae* isolates, and demonstrated that meropenem failed to reach PK/PD targets (T > 40% 1xMIC and T > 40% 4xMIC) in all enrolled patients; furthermore, no synergy was observed between meropenem and the co-administered agents.[24]

In addition, Sbrana et al. reported a case series including a total of 26 episodes of infections caused by KPC-producing *K. pneumoniae* in 22 ICU patients who were treated with carbapenem-sparing regimens (tigecycline plus gentamicin or colistin) with low rate of crude mortality (14%); the authors supported the use of carbapenem-sparing regimens for the treatment of infections caused by CRE, referring to the limited data on the in vitro effectiveness of carbapenems against these bacteria and to an advantage in terms of decreasing selective pressure and consequent in-hospital epidemiology of antimicrobial resistance.[25]

Therapeutic options for treatment of XDR or PDR Enterobacteriaceae infections

The increasing frequency among CRE isolates of resistance to the drugs most commonly used for their treatment, i.e., polymyxins, aminoglycosides, and tigecycline, represents a particularly critical issue. The reported possible therapeutic options for treatment of XDR or PDR Enterobacteriaceae infections, defined according to a recent consensus document,[26] are mostly based on in vitro studies of synergism between different drugs or on the use of the few drugs (sometime "old," e.g., fosfomycin) to which CRE isolates display in vitro good susceptibility.

Using the checkerboard method, Tascini et al. evaluated the synergistic activity of 10 antibiotic combinations against 13 colistin-resistant KPC-producing *K. pneumoniae* isolates and demonstrated that combination of colistin plus rifampin was the only one that displayed consistent synergistic bacteriostatic activity against all the bacterial strains tested and bactericidal synergistic activity for 8/13 tested strains, thus suggesting that colistin plus rifampin could represent an option for treating colistin-resistant KPC-producing *K. pneumoniae* isolates.[27] However, no clinical data have been reported for this combination therapy.

Interestingly, Gonzalez-Padilla et al. conducted a retrospective cohort study examining 50 cases of sepsis caused by colistin-resistant KPC-3-producing *K. pneumoniae* and found that the use of targeted treatment with gentamicin was associated with a significantly lower mortality compared with the use of other targeted treatments not including gentamicin (20.7% vs. 61.9%). They also demonstrated a strong correlation between mortality and gentamicin MICs levels; in patients treated with gentamicin, mortality was lower if the strain displayed complete (MIC $\leq$ 2) rather than intermediate susceptibility (7.7% vs. 31.2%).[28]

Some reports have investigated the clinical efficacy of intravenous fosfomycin in patients with CRE infections. Michalopoulos et al. reported 11 cases of ICU patients having CRKP infections who were treated with intravenous fosfomycin in combination with other antibiotics; the clinical and microbiological outcome was good with an all-cause hospital mortality of 18.2%, and no adverse events were reported.[29] More recently, Pontikis et al. investigated clinical outcome of 48 fosfomycin-treated (mainly in combination with colistin or tigecycline) ICU patients having XDR fosfomycin-susceptible *P. aeruginosa* (n = 17) and *K. pneumoniae* (n = 41) carbapenemase-producing isolates; the authors reported a survival rate of 54.2%, evidence of bacterial eradication in 56.3% of cases, and development of fosfomycin-resistance in 3 cases. [30]

In addition, synergistic effects of fosfomycin against CRE have been reported with several antibiotics, including carbapenems, colistin, tigecycline, and netilmicin.[31]

Finally, some reports have highlighted the possible efficacy of double-carbapenem regimens for therapy of PDR CRE (in particular, KPC-producing *K. pneumoniae*) infections. In 2011 Bulik and Nicolau, based on a demonstrated increased affinity of KPC enzymes for ertapenem and the greatest potency of doripenem in regard to enzyme stability, evaluated the efficacy of a combination of ertapenem and doripenem in both an in vitro chemostat and an in vivo murine infection model and reported that the combination of these 2 carbapenems enhanced efficacy over either agent alone against KPC-producing *K. pneumoniae* isolates.[32] Subsequently, some cases of patients successfully treated with double carbapenem combinations have been reported.[33-36] Recently, the group of Oliva et al. reported a total of 15 patients with infections (8 of which were BSIs) caused by CRKP isolates who were treated with double-carbapenem combinations due to potential colistin nephrotoxicity and/or resistance; the clinical/microbiological response was 80%, and synergy was documented in vitro in 78.6% of isolates using checkerboard method and 85.7% in killing studies. Of note, the MIC 50/90 of the bacterial isolates were 256/512 μg/mL and 256/256 μg/mL for meropenem and ertapenem, respectively.[37] The largest case series (18 cases) on patients with infections with CRKP who received ertapenem-containing double-carbapenem therapy was recently published by Cprek and Gallagher, who reported an overall clinical success in 7/18 (39%) patients, a microbiologic success in 11/14 (79%) evaluable patients, and an overall mortality rate of 28% (5/18).[38]

Emerging and future therapeutic options

As reported above, novel antibiotic drugs that could be effective against CRE are urgently needed. However, to date, only the combination of avibactam, a novel β-lactamase inhibitor, and the third generation cephalosporin ceftazidime have been approved by the US. Food and Drug Administration for treating complicated urinary tract and complicated intra-abdominal infections. Ceftazidime-avibactam displays *in vitro* activity against CRE isolates that produce KPC and AmpC and partial activity against OXA enzymes; however, this drug is not active against metallo-β- lactamases such as NDM, VIM, or IMP.[39] However, clinical data on the efficacy of ceftazidime-avibactam in severe infections caused by CRE are scarce. Shields et al. reported a case series including 37 cases of patients with CRE infections who had received treatment with ceftazidime-avibactam; they observed a survival rate of 76% (28/37) and a clinical success rate of 59% (22/37); this latter rate did not differ for patients receiving monotherapy (58% [15/26]) or combination therapy (64% [7/11]). However, they also reported a rate of CRE infection recurrence of 23% among patients who had displayed clinical success and an overall microbiologic failure rate of 27%; of note, in 3/10 (30%) cases (on monotherapy) of microbiological failure, it was due to the development of ceftazidime-avibactam resistance (MIC >8 μg/mL) by the bacterial isolates.[40] In addition, very recently Temkim et al. reported a case series of 38 patients with infections (of which 68.4% had primary or secondary BSI) caused by CRE (36) or *Pseudomonas aeruginosa* (2) who were treated with ceftazidime-avibactam; 65.8% of patients concurrently received other antibiotics to which their pathogen was non-resistant *in vitro*, 73.7% experienced clinical and/or microbiological cure, and 20.8% with documented microbiological cure vs. 71.4% with no documented microbiological cure died. [41]

Other novel antimicrobials with in vitro activity against CRE (in different phases of clinical trials) include other combinations of avibactam with β-lactams (i.e., ceftaroline fosamil–avibactam and aztreonam–avibactam), the combinations of carbapenems with novel

β-lactamase inhibitors (i.e., meropenem-vaborbactam and imipenem/cilastatin–relebactam), a new aminoglycoside (plazomicin) and a new tetracycline (eravacycline). Notably, none of these antibiotics are effective against all carbapenemases, but they are targeted against specific enzymes.[42]

Conclusions

In recent years, carbapenem resistance among Enterobacteriaceae has dramatically increased and represents an important threat to global health. The optimal clinical management of CRE infections has not been established because no clinical trials have been performed with this objective. We aimed to summarize in the present review data provided by previous observational clinical studies that have investigated the impact of different treatment strategies on outcome. Most of these studies reported that combination therapy with 2 or more in vitro active agents is superior to monotherapy in providing a survival benefit. The role of carbapenems in treatment of CRE infections is widely debated; however, the use of carbapenems in association with other active drugs is probably more effective for CRE isolates with carbapenem MICs $\leq$ 8 mg/l. The possible effectiveness of double-carbapenem combinations, colistin plus rifampin, and fosfomycin-containing combinations have been reported in vivo and/or demonstrated in vitro, although in very few cases/case series; further large studies should confirm the real role of these therapeutic options that should be considered only for XDR or PDR CRE strains. Novel antimicrobials effective against CRE are urgently needed.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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