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REVIEW

Mortality-Related Risk Factors and Novel Antimicrobial Regimens for Carbapenem-Resistant Enterobacteriaceae Infections: A Systematic Review

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Objective: Carbapenem-resistant Enterobacteriaceae (CRE) has become a significant public health problem in the last decade. We aimed to explore the risk factors of mortality in patients with CRE infections and to focus on the current evidence on antimicrobial regimens for CRE infections, particularly from the perspective of mortality.

Methods: A systematic literature review was performed by searching the databases of EMBASE, PubMed, and the Cochrane Library to identify studies that evaluated mortality-related risk factors and antimicrobial regimens for CRE infections published from 2012 to 2022.

Results: In total, 33 and 28 studies were included to analyze risk factors and antibiotic treatment, respectively. The risk factors most frequently reported as significantly associated with CRE mortality were antibiotic use (92.9%; 26/28 studies), comorbidities (88.7%; 23/26 studies), and hospital-related factors (82.8%; 24/29 studies). In 10 studies that did not contain ceftazidime/avibactam (CAZ-AVI) therapy, seven demonstrated significantly lower mortality in combination therapy than in monotherapy. However, 5 of 6 studies identified no substantial difference between CAZ-AVI monotherapy and CAZ-AVI combination therapy. Six studies reported substantially lower mortality in CAZ-AVI regimens than in other regimens.

Conclusion: Several risk factors, particularly antibiotic use and patients' comorbidities, are strong risk factors for CRE mortality. The optimal regimen for CRE infections remains controversial. Combination therapy should be considered when carbapenems, colistin, tigecycline, or aminoglycosides are administered. CAZ-AVI appears to be a promising antibiotic for CRE infections. Most importantly, treatment should be individualized according to the source and severity of the disease or other highly related risk factors.

Keywords: carbapenem resistant Enterobacteriaceae, CRE, mortality, risk factors, antimicrobial, treatment

Introduction

The global emergence of antimicrobial resistance poses a threat to human health.[1] Carbapenem-resistant Enterobacteriaceae (CRE) or carbapenemase-producing Enterobacteriaceae (CPE) are Gram-negative bacteria that are resistant to the carbapenem drug class.[2] The major resistance mechanisms of CRE are: enzyme production, efflux pumps and porin mutations.[3] Of these, the production of carbapenemase including KPC, NDM, OXA-48, IMP, and VIM is the main resistance mechanism among CRE.[4] The KPC enzyme accounts for a high proportion and has the ability to hydrolyze not just carbapenems but also several other antibiotics, leading to high mortality rate.[5] CRE has become a major public health problem in the last decade due to the gradual increase in carbapenem resistance and the lack of effective antibiotics.[6,7]

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The infection types of CRE are mainly bloodstream, pneumonia, respiratory, and urinary tract infections (UTIs). CRE infection is associated with increased mortality.[2,6,8] In particular, CRE-caused bloodstream infections (CRE-BSIs) are associated with extremely high mortality, 30%-80%.[9,10] A recent meta-analysis that included 62 studies showed a mortality rate of 54.3% for BSIs and 13.5% for UTIs associated with carbapenem-resistant *K. pneumoniae* (*CRKP*).[10]

Several studies have evaluated risk factors for CRE mortality but results were inconsistent. These risk factors included Pitt bacteremia score, immunocompromised status, previous exposure to carbapenems, lack of infection source control, and inappropriate antibiotic treatment, etc.[11–14] Nevertheless, many studies have considered antibiotic use as significant risk factor for CRE infection and death.[15,16] The main treatment options for CRE infections are regimens utilizing carbapenem, tigecycline, colistin, aminoglycoside, or ceftazidime/avibactam (CAZ-AVI). The Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) have provided recommendations for treating CRE infections.[1,17] However, the optimal antimicrobial regimen for CRE infections is unknown as there are controversies regarding which is the safest and most effective antibiotic regimen among the available choices. More importantly, an increasing body of evidence suggests that therapy should be individualized according to the source and severity of the infection or other related factors.[18] Thus, it is difficult to establish the "gold standard" for treating *CRE* infections.

Our systematic review aimed to explore mortality risk factors in patients with CRE infections and to focus on current evidence on antimicrobial regimens for CRE infections. The results may provide clinical insight into reducing mortality in CRE patients and develop appropriate antibiotic regimens that offer a better prognosis for patients.

Methods

Mortality-Related Risk Factors

Search Strategy

Two authors independently searched the PubMed, Embase, and Cochrane Library databases to identify relevant studies from January 2012 to January 2022. The search strategy contained five core components, which were linked using the AND operator: (1) carbapenem (eg, carbapenem antibiotics), (2) resistance, (3) Enterobacteriaceae (eg, *Klebsiella pneumoniae, Escherichia coli*), (4) mortality (eg, death rate, case fatality rate), and (5) risk factors (eg, health correlates, the population at risk). Subject headings and free texts (ie, Medical Subject Headings [MeSH] terms) were identified for the five core components. In addition, relevant articles were selected by searching the references identified by this strategy. The complete search strategies are provided in the Supplementary Material (Part 1).

Selection Criteria

The CDC defines CRE as members of the Enterobacterales order resistant to at least 1 carbapenem antibiotic (meropenem, imipenem or ertapenem) or producing a carbapenemase enzyme.[1] Studies were eligible for inclusion if they 1) were hospitalized patients with CRE infections, 2) reported mortality-related risk factors, and 3) were prospective/retrospective observational cohort, case-control studies or randomized controlled trials (RCTs). Exclusion criteria were 1) studies not published in English, 2) reviews, case reports, or experimental studies, 3) studies conducted in patients ≤14 years, 4) studies that did not differentiate between infection and colonization, 5) studies that did not differentiate CRE and other bacteria, 6) studies that had unclear definition and ineligible analysis, and 7) studies that did not provide adequate information.

Quality Assessment

The quality of cohort or case-control studies was assessed based on the Newcastle-Ottawa Scale (NOS) score. Studies with a NOS score ≥ 5 were further analyzed. The scoring details are shown in the Supplementary Material (Part 1).

Data Extraction

Two authors independently extracted relevant data and information from included studies. The following information was collected: first author, publication year, country, study period, study design, pathogen, infection type, the definition of resistance, mortality day, sample size, the numbers of non-survivors, and characteristics of the study population. Data and information on mortality-related risk factors were also extracted.

Data Synthesis

The risk factors were divided into ten groups according to clinical characteristics: demographics, comorbidities, clinical severity assessment scores, hospital-related factors, invasive procedures, type of infection, antibiotic use, clinical index, CRE strain-related factors, and other factors (such as antibiotic resistance and dialysis).

The significance of the association between risk factors and CRE mortality was investigated by examining the statistical data reported in the study. All risk factors with a significant association in the univariate or multivariate analysis were included in the statistical analysis, and odds ratios (OR) for the associations were recorded. Subsequently, we calculated the proportions of studies that reported significance for each risk factor. We also calculated the sample size of each study.

Antimicrobial Regimens

A literature search was performed using the PubMed database from January 2012 to January 2022 to identify studies investigating the treatments of CRE infections. The search strategy contained four core components, which were linked using the AND operator: (1) carbapenem-resistant Enterobacteriaceae, (2) antibacterial agents, (3) treatments and (4) infections. Subject headings and free texts (MeSH terms) were identified for each core component. The search strategy is provided in the Supplementary Material (Part 2).

Studies were eligible for inclusion if they: 1) were hospitalized patients with CRE infections, 2) studied antimicrobial regimens of patients, 3) had reported clinical outcomes of patients treated for CRE infections, 4) were prospective/retrospective observational cohort, case-control studies or randomized controlled trials (RCTs). Exclusion criteria were 1) studies not published in English, 2) reviews, case reports, or experimental studies, 3) studies conducted in patients ≤ 14 years, 4) studies did not differentiate between infection and colonization, 5) studies did not differentiate CRE and other bacteria, 6) studies had unclear definition and ineligible analysis, 7) studies did not provide adequate information, and 8) studies did not included more than 30 cases. The primary outcome of the systematic review was 30-day mortality. When 30-day mortality was unavailable, 14-day mortality, 28-day mortality and in-hospital mortality were extracted.

Results

Mortality-Related Risk Factors

Results of Included Studies

In total, 448 articles were identified through database searching, and 12 additional articles were identified from reference lists. After removing duplicates and literature published before 2012, 391 articles were screened for eligibility, and 289 were excluded after reading the abstract and title. The remaining 102 full-text articles were assessed for eligibility, and 33 studies were included in the analysis.[11–14,19–47] The flow of the study selection is shown in Figure 1.

Study Characteristics

Table 1 shows the characteristics of the 33 studies from nine countries or regions. All were observational studies, 28 of which were retrospective and 5 of which were prospective, including 6 case-control, 27 cohort studies. Among the 33 studies, 9 were multicenter studies, and 24 were single-center studies. The sample size ranged from 39 to 661. The most frequently investigated pathogen was *CRKP*, followed by CRE (including *K. pneumonia, Escherichia coli* and other CRE pathogens), and CPE. The primary infections were BSIs (15 studies), followed by any infections (mainly pneumonia and UTIs, 14 studies).

CRE Mortality-Related Risk Factors

Binary logistic regression analysis model was used to analysis the mortality-related risk factors in all the included studies. The proportion of studies demonstrating an association between chosen risk factors and the mortality of CRE in univariate analysis is shown in Table 2. In particular, only those factors examined in at least two eligible studies were presented. Table 3 shows the significant risk factors ranked according to the proportion of reports. The most reported significant risk factors were antibiotic use (92.9% of studies; 26/28) followed by comorbidities (88.7%; 23/26),

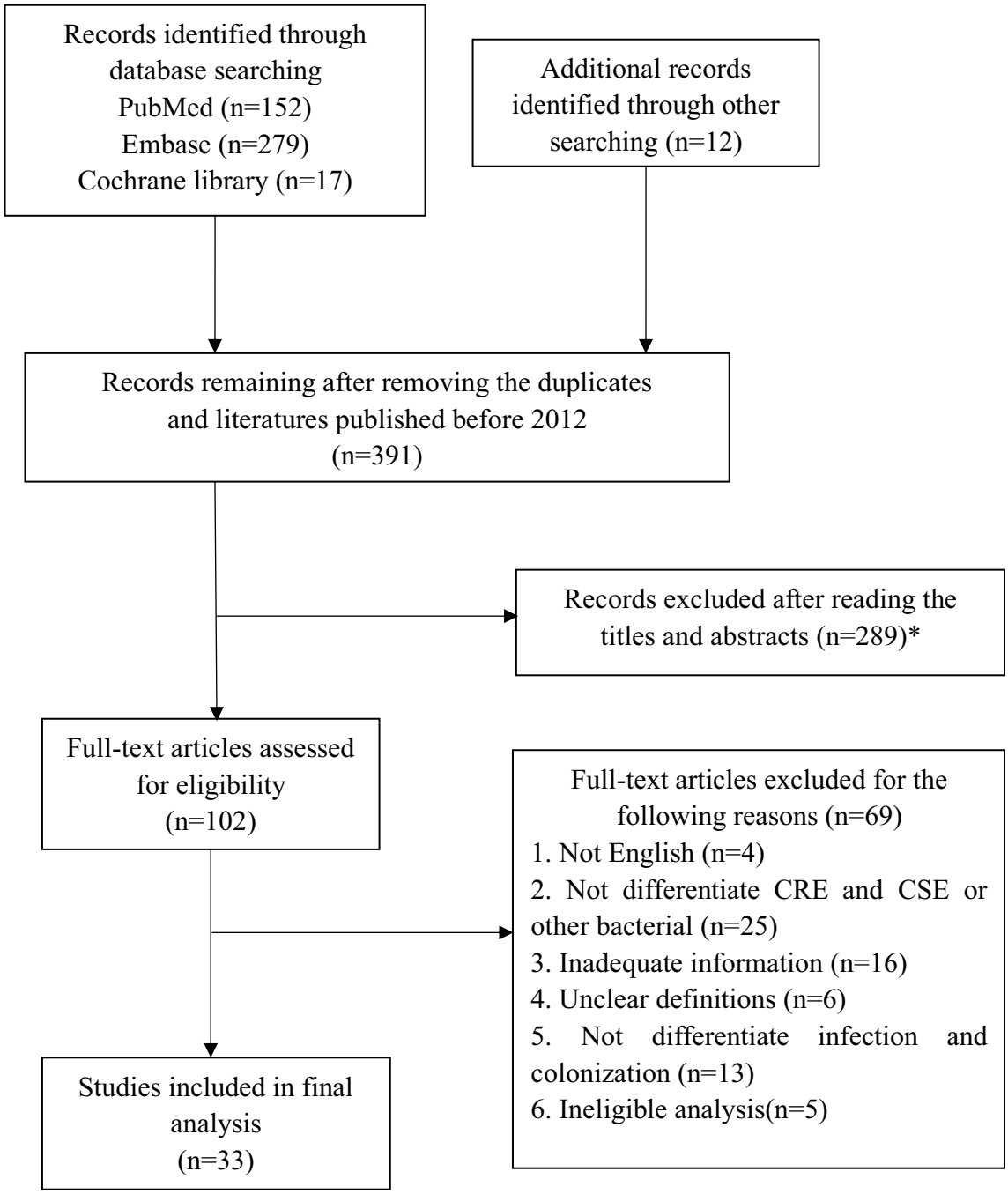

Figure 1 Flow diagram of included studies (Mortality-Related Risk Factors). *1. Children/not in adults; 2. Case report/review/experimental studies; 3. CRE colonization; 4. Risk factors about CRE infection; 5. The studies of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Pseudomonas aeruginosa, Acinetobacter baumannii and Gram-positive bacteria.

hospital-related factors (82.8%; 24/29), and clinical severity assessment scores (82.1%; 23/28) base on univariate analysis.

Furthermore, in univariate analysis, the individual significant risk factors associated with CRE mortality were the Sequential Organ Failure Assessment (SOFA) Score (100% of studies; 5/5), inappropriate definitive therapy (100%; 2/2), the Pitt bacteremia score (85.7%; 6/7), hematologic malignancy (72.7%; 8/11), septic shock (76.2%; 16/21), and bloodstream infections (75%; 6/8). Additionally, in Table 2, no risk factors with an OR value < 1 are shown. The

Table 1 Characteristics of the Eligible Studies (Mortality-Related Risk Factors)

Order	Study	NOS Score	Country/ Region	Study Period	Design	Population	Pathogen	Infection Type	Defnition of Resistance	Resistance	Mortality Day	Sample Size	Nonsurvivor Patients (%)
1	Tuon 2017[35]	6	Brazil	2010–2014	R, cohort/SC	VAP patients	CRE	Ventilator-associated pneumonia	CLSI 2013	Carbapenem	30 d	112	64/112(57.1)
2	Capone 2013[26]	6	Italy	2010–2011	P, cohort/SC	Colistin resistance patients	*CRKP*	Any infection	NA	Imipenem, meropenem, gentamicin	In-hospital	91	25/91(27.5)
3	Chang 2014[47]	6	China	2012–2012	R, cohort/MC	ICU patients	*CnsKP*	Any infection	CLSI M100-S22	Imipenem, meropenem	30 d	46	23/46(50)
4	Su 2018[40]	7	China	2013–2014	R, cohort/MC	In patients	*CRKP*	Any infection	CLSI 2014	Imipenem, meropenem	14 d	99	27/99(27.3)
5	Balkan 2014[43]	7	Turkey	2011–2013	R, nested/SC	In patients	CRE	BSI	EUCAST 2013	Carbapenem	28 d	36	18/36(50)
6	Shen 2020[13]	7	China	2018	R, cohort/SC	In patients	*CRKP*	BSI	CLSI 2017	Carbapenem	28 d	89	41/89(46.1)
7	Zuo 2020[12]	6	China	2015–2017	R, matched/SC	HAP patients	*CRKP*	Hospital-acquired pneumonia	CLSI 2017	Imipenem, meropenem	In-hospital	74	26/74(35.1)
8	Fang 2021[21]	6	China	2018–2020	R, cohort/SC	In patients	*CRKP*	Any infection	CLSI 2020	Carbapenem	28 d	115	26/115(22.6)
9	Lin 2019[41]	7	China	2012–2015	R, cohort/MC	In patients	CRE	BSI	CLSI; EUCAST	Carbapenem	14 d	64	20/64(31.3)
10	Zhou 2021[44]	8	China	2019	P, cohort/MC	In patients	CRE	BSI	CLSI 2020	Carbapenem	30 d	208	96/208(46.2)
11	Falcone 2016[31]	5	Italy	2010–2014	R, cohort/SC	ICU patients with septic shock	*KPC-Kp*	Septic shock	EUCAST 2013	Carbapenem	In-hospital	111	44/111(39.6)
12	Zhang 2021[33]	7	China	2016–2018	R, case-control/SC	In patients	*CRKP*	Any infection	CLSI 2018	Carbapenem	In-hospital	142	41/142(28.9)
13	Bar-Yoseph 2019[34]	6	Israel	2016–2017	P, cohort/SC	CRE patients focus on immunosuppression	CRE	Any infection	CLSI 2013	Carbapenem	All-cause	115	66/115(57.4)
14	Andrey 2020[22]	7	Brazil	2014–2016	R, cohort/SC	In patients	*KPC-Kp*	BSI	EUCAST 2018	Carbapenemase	30 d	165	100/165(60)
15	Di Domenico 2020[42]	5	Italy	2015–2019	R, cohort/SC	Oncological Patients	*CRKP*	Any infection	EUCAST	Carbapenem	30 d	53	19/53(35.8)
16	Tian 2020[45]	7	China	2014–2017	R, case-control/SC	In patients	*CR-ECL*	Any infection	CLSI 2017	Carbapenem	28 d	85	23/85(27.1)
17	Chotiprasitsakul 2018[23]	7	Thailand	2011–2016	R, cohort/SC	In patients	CRE	Any infection	CLSI 2013	Carbapenem	30 d	91	18/91(19.8)
18	Wang 2019[32]	7	China	2013–2017	R, cohort;/MC	In patients	CRE	BSI	CLSI 2015	Carbapenem	In-hospital	164	54/164(32.9)
19	Liu 2021[36]	7	China	2014–2017	R, cohort/SC	In patients	*CRKP*	BSI	EUCAST 2021	Carbapenem	30 d	89	46/89(56.7)
20	Palacios-Baena 2016[19]	8	Spain	2013	P, cohort;/MC	In patients	CPE	Any infection	CDC 2008	Carbapenem	In-hospital	164	14/164(8.5)

(*Continued*)

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Table 1 (Continued).

Order	Study	NOS Score	Country/ Region	Study Period	Design	Population	Pathogen	Infection Type	Defnition of Resistance	Resistance	Mortality Day	Sample Size	Nonsurvivor Patients (%)
21	Mora-Guzmán 2021[30]	6	Spain	2013–2018	P, matched/SC	In patients	CPE	(IAI) Intra-Abdominal Infections	CLSI 2015	Carbapenem	30 d	40	7/40(17.5)
22	Seo 2020[14]	7	Korea	2011–2018	R, cohort/SC	In patients	CRE	BSI	CDC 2008	Carbapenem	14 d	133	32/133(24.1)
23	Li 2019[38]	7	China	2011–2015	R, cohort/SC	In patients	CRE	BSI	CLSI 2016	Carbapenem	30 d	98	52/98(53.1)
24	Chen 2021[11]	7	China	2018–2020	R, cohort/SC	In patients	CRE	BSI	CLSI 2018	Carbapenem	30 d	187	78/187(41.7)
25	Lim 2020[37]	7	Singapore	2013	R, cohort/SC	In patients	CP-CRE	Any infection	NA	Carbapenem	30 d	155	55/155(35.5)
26	Rivera-Espinar 2020[28]	6	Spain	2012–2016	R, cohort/SC	Ventilator-Associated Pneumonia	*KPC-Kp*	Ventilator-Associated Pneumonia	CLSI 2017	Carbapenem	30 d	39	16/39(41.0)
27	Brescini 2019[46]	7	Italy	2011–2015	R, cohort/SC	In patients	*KPC-Kp*	BSI	EUCAST 2018	Carbapenem	30 d	112	39/112(34.8)
28	Lin 2015[20]	7	China	2013–2013	R, cohort/MC	In patients	*CnsKP*	Any infection	CLSI 2012	Carbapenem	14 d	154	49/154(31.8)
29	Cristina 2018[24]	7	Italy	2013–2014	R, cohort/MC	In patients	*CRKP*	BSI	EUCAST 2016	Carbapenem	14 d	213	56/213(26.3)
30	Li 2020[25]	7	China	2019	R, case-control/SC	In patients	*CRKP*	BSI	CLSIM100-S28	Carbapenem	In-hospital	164	72/164(43.9)
31	Geng 2018[27]	6	China	2014–2016	R, cohort/SC	ICU patients	*CRKP*	BSI	CLSI 2016	Carbapenem	In-hospital	40	25/40(62.5)
32	Tumbarello 2015[29]	7	Italy	2013	R, cohort/MC	In patients	*KPC-Kp*	Any infection	EUCAST 2015	Carbapenem	14 d	661	225/661(34.1)
33	Lee 2020[39]	6	China	2010–2015	R, cohort/SC	In patients	*CRKP*	Any infection	CLSI 2018	Carbapenem	30 d	171	66/171(38.6)

Abbreviations: NOS, Newcastle-Ottawa Scale; P, prospective; R, retrospective; MC, multicenter; SC, single center; NA, not available; VAP, ventilator-associated pneumonia; HAP, hospital-acquired pneumonia; ICU, intensive care unit; CRE, carbapenem resistant *Enterobacteriaceae; CRKP*, carbapenem-resistant *Klebsiella pneumoniae; KPC-Kp*, (*Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*); *CnsKP*, carbapenem non-susceptible *Klebsiella pneumoniae; CR-ECL*, carbapenem-resistant *Enterobacter cloacae*; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing guidelines.

Table 2 Proportion of Studies Demonstrating an Association Between Chosen Risk Factors and the Mortality of CRE in Univariate Analysis

Risk Factors Groups	Studies Examining Risk Factor Grouping, n (%)	Studies Showing Significant Association				
		Overall, n (%)	Odd Ratio (OR)	Sample Size of Study		
				N>200	50<N<200	N<50
Demographics						
Age	31 (93.9)	12/31 (38.7)	1.027, 1.03	1/3	10/23	1/5
Comorbidities	26 (78.8)	23/26 (88.7)	NA	2/2	18/20	3/4
Hematological malignancy	11 (33.3)	8/11 (72.7)	2.29,3.18	0/2	6/7	2/2
Chronic kidney disease	21 (63.6)	7/21 (33.3)	1.86	1/2	5/15	1/4
COPD	15 (45.5)	5/15 (33.3)	2.68	1/1	4/12	0/2
Cardiovascular disease	19 (57.6)	5/19 (26.3)	5.08, 1.91	1/1	3/14	1/3
Solid tumor	10 (30.3)	4/10 (40)	7.07, 0.61	2/2	2/5	0/3
Neutropenia	5 (15.2)	3/5 (60)	NA	0/1	2/2	1/2
Diabetes mellitus	22 (66.7)	2/22 (9.1)	3.56, 1.56	1/2	1/16	0/4
Immunocompromised status	21 (63.6)	2/21 (9.5)	NA	–	2/18	–
Chronic respiratory failure	4 (12.1)	2/4 (50)	2.14,	–	2/4	–
Other	16(48.5)	5/16 (31.3)	3.21, 4.9	0/1	5/13	0/2
Clinical severity assessment scores	28 (84.8)	23/28 (82.1)	NA	1/3	19/21	3/4
Charlson index	21 (63.6)	13/21 (61.9)	1.18, 1.119, 2.94	2/3	9/14	2/4
APACHE II Score	17 (51.5)	10/17 (58.8)	1.13, 1.07, 1.15, 7.3	0/2	9/13	1/2
Pitt Score	7 (21.2)	6/7 (85.7)	1.32, 10.2	1/1	5/5	0/1
SOFA Score	5 (15.2)	5/5 (100)	NA	-	4/4	1/1
Hospital-related factors	29 (87.9)	24/29 (82.8)	NA	1/3	20/23	3/3
ICU stay	21 (63.6)	7/21 (33.3)	3.237, 1.37	2/2	4/17	1/2
Length of Hospital stay	14 (42.4)	7/14 (50)	NA	1/2	6/9	0/3
ICU length of stay	5 (15.2)	2/5 (40)	NA	-	2/4	0/1
Hospital-acquired infection	7 (21.2)	2/7 (28.6)	6.04, 3.05	1/1	1/6	-
Other	4 (12.1)	2/4 (50)	NA	0/1	2/3	-
Invasive procedures	25 (75.8)	11/25 (44)	NA	2/2	9/19	0/4
Mechanical ventilation	18 (54.5)	7/18 (38.9)	2.703, 2.93, 10.18, 1.39	1/2	5/13	1/3
Central venous catheter	17 (51.5)	4/17 (23.5)	1.30	1/3	2/11	1/3
Urinary catheter	10 (30.3)	3/10 (30)	NA	1/2	2/8	0/1
Arterial cannula	5 (15.2)	2/5 (40)	2.435	1/2	1/3	-
Other	7 (21.2)	2/7 (28.6)	2.703, 2.73	1/1	1/6	-
Type of infection	33(93.9)	25/31(80.6)	NA	2/3	2025	3/5
Septic shock	21 (63.6)	16/21 (76.2)	4.592, 10.40, 6.03, 11.899, 14.67, 3.1	3/3	12/14	1/4
Bloodstream infection	8 (24.2)	6/8 (75)	1.97	1/1	4/6	1/1
Pneumonia	10 (30.3)	4/10 (40)	2.55, 3.9	-	4/10	-
Other	17 (51.5)	3/17 (17.6)	5.09	-	2/16	0/1
Antibiotic use	28 (84.8)	26/28 (92.9)	NA	2/3	21/21	3/4
Duration of antibiotic treatment	5 (15.2)	3/5 (50)	4.802	0/1	1/3	1/1
Exposure to Carbapenems	11 (33.3)	4/11 (36.4)	3.028	0/1	4/8	0/2
Inappropriate definitive therapy	2 (6.1)	2/2 (100)	11.52, 1.73	-	2/2	-
Gentamicin included	3 (9.1)	2/3 (66.7)	NA	–	2/2	-
Colistin monotherapy	3 (9.1)	2/3 (66.7)	4.05, 1.44	-	1/2	-
Other	10 (30.3)	4/10 (25)	2.383	1/1	3/9	-
Clinical index	5 (15.2)	3/5 (60)	NA	-	3/4	0/1
Creatinine	3 (9.1)	2/3 (66.7)	1.007	-	2/2	-
PCT	3 (9.1)	1/3 (33.3)	1.028	-	1/1	0/1
Other	4 (12.1)	2/4 (50)	NA	-	1/3	1/1
Type of CRE pathogens	7 (21.2)	5/7 (71.4)	NA	-	5/6	1/1
KPC-Kp colonization	3 (9.1)	2/3 (66.7)	NA	-	2/2	0/1
Klebsiella pneumoniae strain	3 (9.1)	2/3 (66.7)	NA	-	2/2	-
Other	1 (6.1)	1/2 (50)	NA	-	2/2	-
Other risk factors	26 (78.8)	18/26 (69.2)	NA	2/3	15/19	1/4
Antibiotic resistance	12 (36.4)	6/12 (50)	1.99, 2.167, 1.2, 3.062	2/3	4/9	-

(*Continued*)

Table 2 (Continued).

Risk Factors Groups	Studies Examining Risk Factor Grouping, n (%)	Studies Showing Significant Association				
		Overall, n (%)	Odd Ratio (OR)	Sample Size of Study		
				N>200	50<N<200	N<50
Co-infection with other resistant bacteria	3 (9.1)	2/3 (66.67)	3.486	-	2/3	-
Dialysis	3 (9.1)	2/3 (66.7)	2.4,	1/1	0/1	1/1
Solid organ transplantation	3 (9.1)	2/3 (66.7)	1.74	1/2	1/1	-
Steroid use ≥ 3 months	6 (18.2)	3/6 (50)	1.56, 4.75	1/1	2/4	-
Protective factors with OR< 1						
Appropriate antibiotic therapy	20 (60.6)	11/20 (55)	0.1, 0.09	0/2	8/14	2/4
Combination therapy	16 (48.5)	8/16 (50)	0.21, 0.69, 0.35	1/3	7/12	0/1
Colistin-based combination	5 (15.2)	4/5 (80)	0.52	0/1	3/3	1/1
Carbapenem included	8 (24.2)	2/8 (25)	0.59	1/2	1/5	0/1
Microbiological eradication	4 (12.1)	4/4 (100)	0.17	-	3/3	1/1

Abbreviations: CRE, carbapenem resistant *Enterobacteriaceae*; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; PCT, procalcitonin; NA, not available.

Table 3 The Proportion of Risk Factors Groups in Univariate Analysis and Multivariate

Risk Factor Groups	Univariate Analysis	Multivariate Analysis
Antibiotic use	26/28 (92.9)	17/21 (81)
Comorbidities	23/26 (88.7)	9/18 (50)
Hospital-related factors	24/29 (82.8)	4/11 (36.4)
Clinical severity assessment scores	23/28 (82.1)	14/19 (73.6)
Type of infection	25/31(80.6)	14/18 (77.8)
Type of CRE pathogens	6/7 (71.4)	2/4 (50)
Clinical index	3/5 (60)	0/2 (0)
Invasive procedures	11/25 (44)	3/5(60)
Age	12/31 (38.7)	1/9 (11.1)

Abbreviation: CRE, carbapenem resistant *Enterobacteriaceae*.

most reported risk factors were microbiological eradication (100% of studies; 4/4), colistin-based combination (80%; 4/5), appropriate antibiotic therapy (55%; 11/20), and combination therapy (50%; 8/16).

The summary of studies that reported a significant association with CRE mortality in multivariate analysis is shown in Table 3. Antibiotic use accounted for the highest proportion of studies (81.0%; 17/21), followed by type of infections (77.8%; 14/18), and clinical severity assessment scores (73.7%; 14/19).

Antimicrobial Regimens

Characteristics of Included Studies

In total, 28 eligible studies were included.[11,13,21,26,31,32,36,38–41,43,48–63] The characteristics of the studies are presented in Table 4. Only studies that reported mortality as a treatment outcome were presented. Of the 28 studies, 15 were multicenter, and 13 were single-center studies. All were observational studies (24 retrospective; 4 prospective, 5 case-control, and 23 cohort studies). The sample size of the included studies ranged from 36 to 595.

Ten studies focused on CPE, 12 *CRKP*, and 5 CRE. The primary infections were BSIs (17 studies), followed by pneumonia, respiratory, and urinary tract infections. In 22 studies, mortality at 28 or 30 days was provided. Three studies reported 14-day mortality, and 3 reported in-hospital mortality.

Table 4 Mortality of Infections Caused by CRE Among Different Antibiotic Treatment Regimens

Order	First Author and Year	Study Design; Period, Country	Population Characteristics; Most Common Underlying Diseases	No. of Patients	Site of Infection	Organisms	Susceptibility Breakpoints	Mortality	Combination Therapy (No. of Dead, % Mortality)	Monotherapy (No. of Dead, % Mortality)
1	Gutiérrez-Gutiérrez 2017[56]	M, cohort/SC, 2004–2013, ten countries	Inpatients (52.4% severe sepsis or septic shock)	437 (78% received appropriate therapy)	BSIs	CPE	CLSI 2012	30 d	Combination 41(35); Tige-included 29(35); Coli-included 28(38); AG-included 19(34); Carba-included 14(38); Fos-included 3(33)	Monotherapy 85(41); Coli 40(54); Mero or Imip 16(37); Cefepime 1(8); Azt 1(25); Tige 14(38); AG 11(41);
2	Navarro-San Francisco2013[48]	R, cohort/SC, 2010–2012, Spain	Inpatients (57.5% previous malignancy)	40 (78% received appropriate therapy)	40 Bacteremia (the sources: 12 UTI, 10 IAIs, 7 primary, 4 catheter related)	OXA-48-producing Enterobacteriaceae	CLSI 2012	30 d	Combination 13/21(48.7) carba-not included 11(52.4); carba-included 2(33.3);	Monotherapy 2 (28.8) Coli 0(0); Tige 0(0); Ami 1 (33.3); Carba 1(100);
3	Balkan2014[43]	R, nested /SC, 2011–2013, Turkey	Inpatients (41.6% solid tumor)	36 (100% received appropriate therapy)	36 BSIs (the sources: 22 primary, 8 IAIs, 2 pulmonary)	OXA-48-like producing Enterobacteriaceae	EUCAST 2013	28 d	Coli-dual 7(58.3); Coli-triple 3 (33.3); Non-coli-based 6(85.7);	Carba 2(40)
4	Villegas 2016[52]	P, cohort/MC, 2013–2014, Seven Latin American Countries	Inpatients (49% surgery and 49% immunosuppression)	53 (91% received definitive therapy)	53 BSIs (the sources: 16 catheter-related, 9 UTIs, 8 SSTIs, 7 RTIs, 5 GTIs, 5 primary)	CPE	CLSI 2014	28 d	Combination (mainly including Carba-containing regimens) 17(59)	Monotherapy (mainly including carba) 5(63)
5	Shen 2019[13]	R, cohort/SC, 2018, China	Inpatients (57.3% severe sepsis or septic shock)	89 (78.7% received appropriate therapy)	BSIs	*CRKP*	EUCAST 2019	28 d	Combination (35 tige-based, 20 poB-based, 9 CAZ-AVI-based) 15(50)	NA
6	Lee 2020[39]	R, cohort/SC, 2010–2015, Japan	Inpatients (63.4% diabetes mellitus)	171 (100% received appropriate therapy)	171 Bacteremia (the sources: 27 vascular catheter-related, 25 primary, 14 pneumonia, 15 urosepsis, 9 SSTIs, 6 IATs)	n*CP-CRKP*	CLSI 2018	30 d	Coli-based 17(28.8); Carba-sparing 5(25); Carba-containing 15(39.5)	Carba-sparing 22 (56.4); Carba-containing 24(50)

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Table 4 (Continued).

Order	First Author and Year	Study Design; Period, Country	Population Characteristics; Most Common Underlying Diseases	No. of Patients	Site of Infection	Organisms	Susceptibility Breakpoints	Mortality	Combination Therapy (No. of Dead, % Mortality)	Monotherapy (No. of Dead, % Mortality)
7	Li 2019[38]	R, cohort/SC, 2011–2015, China	Inpatients	98(83.7% received definitive therapy)	BSIs	CRE	CLSI 2016	30 d	Carba-containing 7(53.8); Carba-sparing 16(53.3); Tige-containing 20(69); Tige-sparing 3(21.4)	Colistin 2(66.7);
8	Liu 2021[36]	R, cohort/SC, 2014–2017, Taiwan	Inpatients (64% cardiovascular disease)	89(58.4% received appropriate therapy)	BSIs	CRKP	EUCAST 2021	30 d	Coli-included 18(64.3); Amk-included 4(30.8); Carba-included 20(54.1); Tige-included 3(100)	Monotherapy 1 (8.3)
9	Falcone 2016[31]	R, cohort/SC, 2010–2014, Italy	ICU patients with septic shock	111(77.5% received appropriate therapy)	BSIs (the sources: 53 Primary. 25 CVCs, 52 Pneumonia, 25 UTIs, 18 SSTI, 12 IAIs)	*KPC-Kp*	EUCAST 2013	30 d	Coli-included 14(22.6); Carba-included 29(34.9); Tige-included 35(39.3); No use of in vitro active antibiotics 16(64); Two or more in vitro active antibiotics used within 24 hours 8(22.2);	Only one in vitro active antibiotic used within 24 hours 20(40)
10	Tumbarello 2018[59]	R, matched/SC, 2016–2017, Italy	Inpatients (use CAZ-AVI as salvage therapy)	138(100% received CAZ-AVI therapy); 104(100% received other therapy)	BSIs	*KPC-Kp*	EUCAST 2017	30 d	Combination 66(41.5); CAZ-AVI-included 29(35.4); CAZ-AVI+Gen 8(32); CAZ-AVI+Coli 7(38.5); CAZ-AVI+Carba 7 (36.9); CAZ-AVI+Tige 6(37.5); CAZ-AVI+Fos 2(39.6); CAZ-AVI+Amk 1(50)	Monotherapy 30 (61.2); CAZ-AVI monotherapy 9 (40.9)
11	Chen 2021[11]	R, cohort/MC, 2018–2020, China	Inpatients	187(88.8% received definitive therapy)	BSIs (53 CVC, 45 LRTIs, 43 IAIs, 34 UTIs; 12 Primary)	CRE	CLSI 2018	30 d	CAZ-AVI + tige 2(15.4); CAZ-AVI + tige + poB 1(11.1); Tige + poB 19(41.3); Carba + tige 16 (36.4); Carba + AG 8(50); Carba + tige + poB 16(36.4); Carba + poB + AG 5(38.5);	CAZ-AVI 3 (23.1); Tige 13 (68.4)
12	Medeiros 2019[54]	R, cohort/SC, 2015–2016, Brazil	Inpatients	82(100% received definitive therapy)	BSIs (the source: 11 Catheter-associated BSI, 25 Pulmonary, 14 IAIs, 9 UTIs, 9 SSTIs)	*KPC-Kp*	CLSI 2015	30 d	Combination 18(37.5)	Monotherapy 22 (64.7)

13	De Oliveira 2015[60]	R, cohort/MC, 2009–2013, Brazil	Inpatients	78(100% received antibiotic therapy)	78 BSIs (51 primary, 4 pneumonia, 12 IAIs)	CPE	CLSI 2010	30 d	2-drug combination 16(44.4), PoB + carba 7(58.3), AG + carba 2(40), 3-drug combination 13(68.4)	Monotherapy 21 (36.8); Carba 6(24); poB 13 (61.9), AG 1 (11.1), tige 1(50)
14	Wang 2019[32]	R, cohort/MC, 2013–2017, China	Inpatients	164(60% received active therapy)	BSIs	CRE	CLSI 2018	In hospital	Combination 2(10); Tige-based 0(0); AG-based 1(33.3);	Monotherapy 27 (34.6); Tige 19 (61.3); Carba 5(20); AG 1(5.8)
15	Giannella 2017[57]	R, cohort/MC, 2010–2015, Italy	Inpatients	595(71.9% received high dose carbapenem based combination therapy)	BSIs	*CRKP*	EUCAST	14 d	Carba-containing 86(19.9); Carba-sparing 42(25.1)	NA
16	Lin 2019[41]	R, cohort/MC, 2012–2015, Taiwan	Inpatients	64(100% received appropriate therapy)	BSIs	*CRKP*	CLSI 2012	14 d	Combination 3(33.3);	Monotherapy 17 (30.9); Coli 12 (57.1); Tige 2 (18.2); Carba 1(20); FQ 1(25)
17	De Pascale 2017[55]	R, matched/MC, 2012–2015, Italy	ICU patients (critically ill patients)	48(100% received double carbapenem therapy); 96 (100% received standard therapy);	48 (25 pneumonia, 9 IAIs; 8 CVC; 6 primary 3 UTIs; 1 SSTIs)	*CRKP*	EUCAST	30 d	DC 14 (29.2); standard treatment (ie, Coli, Tige, or Gen), 46(47.9)	NA
18	Sousa 2018[58]	P, cohort/SC, 2015–2016, Spain	Inpatients	74(100% received CAZ-AVI therapy);	26 BSIs, 15 pulmonary, 14 UTIs,7 ventilator-associated	OXA-48-producing Enterobacteriaceae	EUCAST	30 d	CAZ-AVI-based 3(27);	CAZ-AVI 10(22);
19	Fang 2021[21]	R, cohort/MC, 2018–2020, China	Inpatients	105(67.8% received polymyxin B therapy, 32.2% received CAZ/AVI therapy);	105(66 Pneumonia, 58 BSIs, 32 IAIs, 12 UTIS)	*CRKP*	CLSI 2020	28 d	2 active antibiotic 13(25.5); 3 active antibiotic 10 (22.7)	1 active antibiotic 3(15)

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Order	First Author and Year	Study Design; Period, Country	Population Characteristics; Most Common Underlying Diseases	No. of Patients	Site of Infection	Organisms	Susceptibility Breakpoints	Mortality	Combination Therapy (No. of Dead, % Mortality)	Monotherapy (No. of Dead, % Mortality)
20	Capone 2013[26]	P, cohort/SC, 2010–2011, Italy	Inpatients (High rate of colistin resistance)	91(93.8% received appropriate therapy)	97(34 BSIs, 29 UTIs, 14 LRTIs, 11 SSTIs, 3 IAIs)	*CRKP*	CLSI	In-hospital	Coli-based 6(23.1), Coli + Tige 4(25); Coli + Fos 0(0); Coli +Gen 2(40); Tige+Fos 2(33.3)	Gen 1(6.25); Coli 4(40);
21	Su 2018[40]	R, cohort/MC, 2013–2014, Taiwan	Inpatients	99(67% received appropriate therapy)	49 Pneumonia, 36 UTIs, 9 IAIs, 3 Primary BSIs	*CRKP*	CLSI 2014	14 d	Appropriate combination therapy 2(33.3)	Appropriate monotherapy 13 (21.3), Tige 4 (26.6), Coli 6(40), Carba 3(25)
22	Van Duin 2018[53]	P, cohort/MC, 2011–2015, United States	Inpatients	38 treated first with CAZ-AVI and 99 with colistin	63 BSIs and 30 RTIs	CRE	CLSI 2014	30 d	CAZ-AVI-based 3(9); Coli-based 33(32)	
23	Tumbarello 2021[51]	R, cohort/MC, 2018–2020, Italy	Inpatients	577 (165 received CAZ-AVI monotherapy, 412 received CAZ-AVI combination therapy)	391 BSIs and 71 UTIs, 59 LRTIs, and 35 IAIs)	*KPC-Kp*	EUCAST 2020	30 d	CAZ-AVI-based 103 (25.0)	CAZ-AVI 43 (26.1)
24	Gu 2021[50]	R, cohort/SC, 2019–2020, China	Inpatients	42 patients were treated with CAZ-AVI and 48 with other active antibiotics	67 RTIs and 45 BSIs	*CRKP*	EUCAST 2020	30 d	CAZ-AVI-based therapy 8(19); other active antibiotics 15 (31.3)	
25	King 2017[61]	R, cohort/MC, 2015–2016, United States	Severely ill patients	60 (33 received CAZ-AVI monotherapy, 27 received CAZ-AVI combination therapy)	23 BSIs, 17 UTIs, 16 Pneumonia, 8 Wound, 4 IAIs	CRE	CLSI 2015	In-hospital	CAZ-AVI-based 9(33)	CAZ-AVI 10 (30)

26	Zheng 2021[49]	R, cohort/MC, 2019–2020, China	Critically ill Patients	62 (21 received CAZ-AVI monotherapy and 41 received CAZ-AVI combination therapy)	9 Primary BSIs, 25 RTIs, 12 IAIs, 11 UTIs	*CRKP*	CLSI 2019	30 d	CAZ-AVI-based 10(24.4)	CAZ-AVI 11 (47.6)
27	Satlin 2022[62]	R, cohort/MC, 2016–2018, United States	Inpatients	137 (68 received Single active agent, 23 received≥2 active agents)	BSIs (the source: 45 IAIs,18 Vascular catheter, 17 UTIs, 18 RTIs, 13 GTIs, 7 SSTIs)	CRE	CLSI 2020	30 d	≥2 active agents 10 (43.5)	Single active agent 12 (17.6); CAZ-AVI 32 (10.0); Poly 45 (30.0)
28	Chen 2022[63]	R, case-control /SC, 2019–2021, China	Inpatients	191 (47 received monotherapy,93 received 2 drug combination, 51 received 3 drug combination)	120 Pneumonia; 15 IAIs; 27 UTIs; 18 BSIs	*CRKP*	CLSI 2021	30 d	Two drug combination 26 (30.0); Three drug combination 8 (15.7)	Monotherapy 17 (36.2)

Abbreviations: P, prospective; R, retrospective; MC, multicenter; SC, single center; NA, not available; BSIs, bloodstream infections; UTIs, urinary tract infections; IAIs, intra-abdominal infections; RTIs, respiratory tract infections; LRTI, lower RTI; SSTIs, skin and soft tissue infections; GTIs, gastrointestinal tract infections; CVC, central venous catheter; ICU, intensive care unit; CPE, carbapenemase–producing *Enterobacteriaceae*; CRE, carbapenem resistant *Enterobacteriaceae; KPC-Kp, Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; Carba, carbapenem; Coli, colistin; PoB, polymyxin B; Tige, tigecycline; Fos, fosfomycin, AG, aminoglycoside, Mero, meropenem; Imi, imipenem; Azt, aztreonam; Amk, amikacin; CAZ-AVI, ceftazidime/avibactam; Gen, gentamicin; FQ, fluoroquinolone; DC, double carbapenem; PoB, polymyxin B.

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Antimicrobial Therapy and Outcome

All studies reported antibiotic treatment regimens and their associated mortalities. Mortalities ranged from 10% to 59% in 12 studies in patients who received combination therapies. However, mortalities ranged from 8.3% to 64.7% in 11 studies in patients who received monotherapies. Except for the 9 studies focused on CAZ-AVI therapy, 8 studies demonstrated significantly lower mortalities using combination therapies, 4 studies reported lower mortalities using monotherapies, and the remaining 7 studies reported no difference. However, in CAZ-AVI studies, 5 studies identified no substantial differences between CAZ-AVI monotherapy and CAZ-AVI combination therapies. Only one study reported significantly lower mortality in CAZ-AVI combination therapies.

Colistin, tigecycline, aminoglycosides, carbapenems, and CAZ-AVI were the most commonly used monotherapy antibiotics (Table 4). The mortality rates of monotherapies were attributed to use of: polymyxins, 40% to 66.7% in seven studies; tigecycline, 18.2% to 68.4% in six studies; aminoglycosides, 5.8–41% in four studies; carbapenems, 20% to 56.4% in eight studies; and CAZ-AVI, 22% to 47.6% in four studies (excluded 0% and 100%). In contrast, the corresponding mortalities of combination therapies were 22.6%-68.3%, 35%-69%, 32%-50%, 19.9%-53.8%, and 27%-41.5%, respectively. Carbapenem-containing therapies were associated with lower mortality than carbapenem-sparing therapies in three studies.[48,55,57] Two studies reported no significant differences between these two types of therapies.[38,39] In addition, CAZ-AVI- based therapies had substantially lower mortality than other regimens in six studies.

The "Old" Antibiotics

The older antibiotics for treating CRE infections are polymyxins, tigecycline, aminoglycosides, fosfomycin, and aztreonam. Polymyxins and tigecycline have been used as first-line agents to treat CRE infections. However, these monotherapies were often unsatisfactory, and the efficacy was uncertain even when combined with other antibiotics.[64] Aminoglycosides are limited by nephrotoxicity and are second-line agents due to the availability of newer β-lactams and β-lactamase inhibitor combinations.[65] The combination of polymyxin and tigecycline showed a good synergistic effect in vitro evaluation.[66] In vitro synergy was also observed when polymyxins were combined with aminoglycosides or carbapenems.[67,68] However, the clinical effect of synergy has not been identified.

In a single-center retrospective study, the outcome of 89 *CRKP*-caused BSI cases showed polymyxin-based therapy improved the survival rate compared to tigecycline-based treatment.[13] Conversely, another nationwide multicenter study (64 patients) analyzed BSIs caused by *CRKP* (n = 50) and *E. coli* (n = 14), showing that tigecycline monotherapy was a choice if the strains exhibited the minimum inhibitory concentration (MIC) ≤ 0.5 mg/L, and colistin monotherapy was not suitable.[41] Additionally, another study evaluated the treatment outcomes of a cohort of 36 patients with BSI due to OXA-48-like CPE, found that colistin-based dual combinations and preferably triple combinations were associated with significantly better outcomes when compared to non-colistin-based regimens ($P < 0.001$).[43] Similarly, combination therapy, mostly polymyxin B plus amikacin, showed a survival benefit compared with other regimens in patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (*KPC-KP*) BSIs.[54]

Despite renal toxicity and second-line status, aminoglycosides still have potential roles in treating CRE infections, especially when combined with newer agents. A small sample size study demonstrated that aminoglycosides had effectively treated *CRKP*-BSIs if the pathogen was susceptible to aminoglycoside, showing a 75% clinical cure rate.[65] Two observational studies revealed that aminoglycosides had better clinical outcomes compared to polymyxins or tigecycline in patients with CRE bacteriuria.[69,70] A prospective cohort study in patients with *CRKP*-UTIs observed that patients treated with aminoglycosides (adjusted hazard ratio HR 0.34, 95% confidence interval CI 0.15–0.73, P=0.0049) were less likely to fail compared to patients treated with tigecycline (adjusted HR 2.92, 95% CI 1.03–5.13, P=0.0425).[70] Similarly, the clinical success of aminoglycosides was 78.9% compared to other antibiotics (37.0%, P=0.007) in kidney transplant recipients with polymyxin-resistant CRE infections.[69] Data are limited regarding tigecycline, fosfomycin, and aztreonam treatments for CRE infections.

Carbapenems

Due to the increasing resistance to CRE, carbapenems are no longer reserved as a last-resort therapy for high-risk CRE infections. However, carbapenems in treating CRE infections are still widely debated.[6] Our analysis showed that

carbapenem-containing treatment had lower mortality than other regimens. Dosing strategies of carbapenems for CRE infections include using high doses with prolonged infusion, double carbapenems, or combination with other antibiotics.

Two comparative studies on the efficacy of double carbapenems versus other antibiotics for CRE treatment showed similar results.[55,71] A case-control (1:2) observational two-center study that involved critically ill adults demonstrated significantly lower mortality in patients treated with double carbapenems than standard treatment (ie, colistin, tigecycline, or gentamicin) (47.9% vs 29.2%, P = 0.04).[55] Likewise, a single-center retrospective study observed that the double carbapenem regimen was also effective compared with the best available regimens in patients infected with CRE, including those with severe clinical conditions, and even in extremely high meropenem MICs.[71]

A large sample study suggested that high-dose carbapenem-based combination therapy was a protective factor (HR 0.69, 95% CI 0.47–1.00, P=0.05) for *CRKP*-caused BSIs, even in high-level carbapenem resistance.[57] In a small sample study, 19 critically-ill patients with BSIs caused by *KPC-KP* (MICs ≥16 mg/L) were given combination therapy including meropenem, tigecycline, plus colistin or gentamicin. Meropenem was administered as an extended 3-hour infusion (2 g every 8 hours). High-dose meropenem failed to reach pharmacokinetics/pharmacodynamics targets.[72] However, another cohort study revealed that high-dose continuous-infusion meropenem optimized using real-time TDM (Therapeutic Drug Monitoring) improved clinical outcomes in the patients infected with *KPC-KP* (meropenem MIC ≤ 64 mg/L).[73] Real-time TDM-guided meropenem may represent a valuable adjunct for optimized care.[74] Tigecycline and colistin were the two antimicrobials most commonly combined with meropenem,[73] but their clinical effects of synergy are not entirely clear.

Ceftazidime-Avibactam

The CAZ-AVI was approved in 2015 to treat complicated intra-abdominal, urinary tract infections and hospital-acquired pneumonia.[75] Before introducing CAZ-AVI, combination therapy was associated with lower mortality than monotherapy for CRE infections. However, it seems inconsistent when CAZ-AVI was administered to CRE patients. A relatively large multicenter cohort of 138 patients with *KPC-KP* bacteremia infections revealed significantly lower mortality when treated with CAZ-AVI-containing regimens as salvage therapy after first-line treatment (36.5% vs 55.8%, P =0.005). The results indicated no significant difference in mortality between CAZ-AVI monotherapy and combination therapy.[59] Subsequently, the largest study published to date confirmed that combination therapies, including CAZ-AVI, were not associated with any significant change compared to CAZ-AVI monotherapy in mortality (26.1% vs 25.0%, P = 0.79),[51] which was also supported by three other observational studies.[11,58,61] On the contrary, lower mortality was observed in 41 critically ill patients treated with CAZ-AVI combined with antibiotics against *CRKP* infections (24.4% vs 47.6%, P = 0.028) suggesting that tigecycline, carbapenems, and fosfomycin could be optional concomitant antimicrobials.[49]

Several studies analyzed the efficacy of CAZ-AVI regimens compared to other antibacterial regimens on mortality in patients with CRE infections. Two multicenter observational studies compared the effectiveness of CAZ-AVI versus polymyxins for CRE, demonstrating the superiority of CAV-AVI over polymyxins in treating infections caused by *KPC-KP* or *CRKP*.[21,53] Interestingly, a potential survival benefit was found in a large cohort study comprising 577 adults with *KPC-KP* infections treated with prolonged CAZ-AVI infusions (over three hours).[51] Together, preliminary evidence suggests that CAZ-AVI appears to be a promising antibiotic for treating CRE infections. However, this option requires further evaluation.

Discussion

Most of the research on CRE infections was observational studies with a moderate to high risk of bias. It is challenging to perform RCTs on CRE infections due to the different susceptibility of CRE strains and many confounding factors.[56] The lack of RCTs has hindered the development of guidelines for managing CRE infections.[76]

Several systematic reviews and meta-analyses have been conducted on specific pathogens, such as *CRKP* and carbapenem-resistant *Acinetobacter baumannii* (*CRAB*), focusing on mortality and predictors.[10,16,77] Additionally, two meta-analyses analyzed the association between CRE and mortality.[8,10] Another systematic review analyzed mortality risk factors with carbapenem-resistant Gram-negative bacterial (CR-GNB) infections.[15] No systematic studies or meta-analyses have evaluated mortality-related risk factors for all CRE pathogens.

The duration of antibiotic treatment is controversial. Some studies reported that patients who received a short course of antimicrobial therapy had a poorer prognosis.[43,44] Other studies revealed that the short duration of antibiotic treatment was a protective factor.[78] The difference may be due to frequent changes in clinical conditions in critically ill patients with CRE infections, and antibiotic regimens are often modified during treatment. Therefore, it is difficult to evaluate the effect of the duration of antibiotic treatment on clinical outcomes.[43] The IDSA does not provide recommendations on the duration of therapy. Instead, IDSA advises clinicians that prolonged treatment is unnecessary against infections by resistant pathogens compared to infections caused by the same bacterial species with more susceptible phenotypes.[1]

The protective factors with an OR value less than 1 are mainly regarding antibiotic therapy, such as appropriate antibiotic treatment and combination therapies with a carbapenem, suggesting that the proper use of antibiotics may reduce the risk of CRE mortality. Proper antibiotic use has become an essential measure to prevent and treat CRE infections.[79]

Few monotherapy studies, except for CAZ-AVI, reported lower mortality outcomes, partly because patients who received monotherapies had less severe symptoms or a quickly controllable source of infection.[48] The ESCMID guidelines recommended that "old" antibiotics, including polymyxin, tigecycline, and aminoglycosides, be considered in patients with non-severe CRE infections. Newer antibiotics (meropenem-vaborbactam or ceftazidime-avibactam) are used in critically ill patients.[17] In clinical practice, combination therapies are commonly administered to patients with severe infections. However, studies have shown that the efficacy of combination therapies is uncertain. The in vitro synergy of specific antibiotics may not always translate into clinical effects. Dosages and duration of antibiotics and the susceptibility profiles of CRE pathogens may affect the treatment effectiveness.[17,80]

The effectiveness of colistin monotherapy was not satisfactory principally because the suboptimal dosing could not reach appropriate plasma concentrations. Still, it would increase the risk of death, particularly in severely ill patients with renal dysfunction.[81] In our analysis, colistin monotherapy was a mortality-related risk factor for CRE infections. Furthermore, a study supported a survival benefit in colistin-based dual combinations, preferably in triple combinations.[43] Therefore, combination with other in vitro active antibiotics might be the optimal option when treating CRE patients with colistin. In addition, aminoglycosides were more effective than polymyxins for treating CRE bacteriuria based on the ESCMID guidelines.

Carbapenem-containing regimens for CRE infections have been a long-standing topic of debate. The ESCMID guidelines suggested that clinicians should avoid carbapenem-containing combination therapies for CRE infections unless the MIC of meropenem is 8 mg/L.[17] However, IDSA guidelines recommend that meropenem should be avoided if isolates are carbapenemase producers, despite susceptibility to meropenem.[1] Our review obtained favorable outcomes when carbapenem-containing regimens were administered to CRE patients, and three studies supported a better outcome in patients treated with carbapenem-containing therapies than other treatments.[48,55,57] In contrast, two studies reported no differences.[38,39] Furthermore, high-dose continuous-infusion meropenem optimized by real-time TDM improved clinical outcomes even when there were extremely high meropenem MICs,[73,74] which can be an option for clinicians.

In addition to CAZ-AVI, other novel antibiotics against CRE infections have been approved or in advanced clinical development, including ceftolozane-tazobactam, meropenem-vaborbactam, and imipenem-relebactam.[82,83] We cannot accurately evaluate their effectiveness and safety due to the lack of data available for these new antibiotics against CRE. Preliminary evidence revealed a potential role of CAZ-AVI in patients with *CRKP* infections. Our review and two other meta-analyses demonstrate no substantial difference between CAZ-AVI monotherapy and CAZ-AVI combination therapy.[84,85] More post-marketing data from real-world studies and RCTs are needed to evaluate the effectiveness and safety of CAZ-AVI in treating CRE infections. However, the drug resistance of CAZ-AVI has gradually increased in recent years, and their effectiveness has been decreased due to β-lactamase production, efflux pumps and target modifications.[86]

Our systematic review has the following limitations: 1) No RCTs were included. 2) The size of included studies was small. 3) Owing to the high heterogeneity of the included studies in terms of study design, patient populations and CRE pathogens, and so comparative statistical analysis or meta-analysis of the results was not possible. and 4) In addition to antibiotic use, risk factors such as complications and septic shock also accounted for a high proportion of the dead patients. We could not control for these variables when analyzing the efficacy of antimicrobial regimens due to the limited data. It needs further investigation whether the patient's antibiotic regimen was different in the sepsis/non-sepsis group, organ dysfunctions/non- organ dysfunctions, or mild/critical patients' group.

Conclusions

Our systematic review has explored mortality-related risk factors and antimicrobial regimens of CRE infection. According to our review, antibiotics use, patients' comorbidities, and hospital-related factors are the most important mortality risk factors in patients with CRE infections. Combination therapies may offer a comparative advantage over monotherapy except for CAZ-AVI. When treating CRE infections, colistin monotherapy should be avoided. Aminoglycosides can be used for CRE bacteriuria. High-dose continuous-infusion meropenem and double carbapenems regimens could be considered. CAZ-AVI appears to be a promising drug for treating CRE infections, especially those involving bacteremia. Clinicians must consider mortality-related risk factors, and treatment should be individualized based on the source and severity of the disease.

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Disclosure

We declare that we have no conflicts of interest.

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