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Review

A systematic review and meta-analysis of treatment outcomes following antibiotic therapy among patients with carbapenem-resistant *Klebsiella pneumoniae* infections

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ABSTRACT

Introduction: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections are a major global public health challenge. This study aimed to systematically review the evidence on treatment outcomes (mortality, clinical and microbiological response) following antibiotic therapy administered for CRKP infections.

Methods: Medline, EMBASE, the Cochrane Central Register of Controlled Trials, and the International Pharmaceutical Abstracts databases were searched from inception to 26 December 2018. Data were analysed via meta-analysis techniques using random-effects (DerSimonian and Laird) modelling.

Results: Fifty-four observational studies involving 3195 CRKP-infected patients who received antibiotic treatment were included. The pooled mortality, clinical and microbiological response rates were 37.2% (95% confidence interval [CI] 33.1–41.4%), 69.0% (95% CI 60.1–78.2%) and 63.7% (95% CI 53.7–74.1%), respectively. Compared with combination therapy, monotherapy was associated with a higher likelihood of mortality (odds ratio [OR] 1.45, 95% CI 1.18–1.78%), but there were no statistically significant differences in the likelihood of achieving clinical and microbiological responses. There were no statistically significant differences in the pooled likelihood of mortality, clinical or microbiological responses between two-drug and three-or-more-drug combination therapies or combination-containing and combination-sparing regimens of polymyxins, tigecycline, aminoglycosides and carbapenems. Moreover, clinical outcomes did not significantly differ among the various monotherapies.

Conclusions: These data highlight the need for systematic studies and well-designed randomised clinical trials to identify and evaluate the most appropriate antibiotic therapies for CRKP infections towards informing clinical decision-making. Furthermore, continuous surveillance of antimicrobial susceptibility patterns at local, regional, and national/international levels are important to support empirically-based therapy until susceptibility results for the isolate from the patient are available.

1. Introduction

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections are a major global public health issue and are associated with significant morbidity and mortality [1,2]. The World Health Organization (WHO) has classified CRKP as one of the critical priority pathogens requiring urgent research and development of new and effective antibiotic therapies [2]. Yet, a limited number of antibiotics are in development against CRKP [3]. This, along with increasing resistance to available therapies, has reinforced discussions about rational and optimised use.

Nonetheless, the lack of randomised controlled trials (RCTs) has hampered the development of robust guidelines informing appropriate antibiotic selection for CRKP. Thus, a systematic analysis of published data is necessary. Previous reviews have examined treatment outcomes following antibiotic therapy for carbapenem-resistant Enterobacteriaceae (CRE) infections; however, analyses have largely been descriptive [4,5]. Others have also provided pooled estimates of treatment outcomes

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following antibiotic therapy for CRE infections, but the emphasis has been on polymyxins and tigecycline [6,7]. To optimise patient care, there is a compelling need to examine the entirety of evidence on treatment outcomes following all available antibiotic options specifically for infections caused by CRKP - the CRE with the most rapidly increasing prevalence [5]. Moreover, an estimated 2.1 million serious infections worldwide were attributable to CRKP in 2014 alone [8].

This study conducted a systematic review and meta-analysis to characterise treatment outcomes amongst CRKP-infected patients following antibiotic therapy in clinical settings.

2. Methods

2.1. Search strategy

The following were searched from inception to 26 December 2018 for studies reporting treatment outcomes (mortality, clinical or microbiological response) among antibiotic-treated patients with CRKP infections: Medline, EMBASE, Cochrane Central Register of Controlled Trials, and the International Pharmaceutical Abstracts databases. The references of eligible studies and related reviews were manually searched.

2.2. Selection criteria

Studies reporting outcomes among antibiotic-treated CRKP-infected patients were eligible for inclusion. Studies involving both infected and colonised patients were included if the treatment outcomes of the infected patients could be separately extracted. Case reports or series of < 10 patients, studies in children, *in vitro* or animal studies, conference abstracts and reports were excluded.

2.3. Study quality assessment

Study quality was assessed via the Newcastle-Ottawa scale (NOS) for nonrandomised trials included in meta-analyses [9]; to be included, a score of ≥ 5 was required.

2.4. Data extraction and definitions

The following study information was collected: first author, publication year, sample size, study period, design, country, population characteristics (gender distribution, mean age, site of infection, etc.), antibiotic susceptibility testing (AST), antibiotic regimen, treatment outcomes, and reported adverse events. All-cause mortality evaluated at end of follow-up was the primary outcome and, where specified, data on 14-day and 30-day mortality were collected. The secondary outcomes were clinical and microbiological responses and adverse events. Due to the lack of standard criteria for the assessment and reporting of clinical and microbiological responses, the definitions were adopted as employed in individual studies.

2.5. Statistical analysis

Freeman-Tukey double arcsine transformed proportions [10] were pooled to estimate the overall all-cause mortality, and clinical and microbiological response rates via random-effects (DerSimonian-Laird) model [10]. For the comparison of treatment outcomes following specific antibiotic therapies, the effect measure was expressed as an odds ratio [OR]. Statistical heterogeneity was quantified with Cochran's Q test and the I^2 statistic. I^2 values of 25%, 50%, and 75% were considered to be low, moderate, and high degrees of heterogeneity, respectively [10]. Potential sources of heterogeneity were investigated via subgroup analyses as per the following: study region (North America vs. other), publication years ($\leq$ 2012 vs. 2013–2018), and study design (prospective vs. retrospective). Publication bias was assessed by funnel plot visualisation and quantified with Egger's test [10]. The robustness of pooled estimates was tested via leave-1-out sensitivity analyses and a study was deemed influential if the pooled estimate without it was outside the 95% confidence interval [CI] of the overall pooled estimate. Analyses were performed using Stata 15/IC (StataCorp LP, Texas, USA) and P-value < 0.05 was considered statistically significant.

3. Results

3.1. Study characteristics

Fifty-five articles (54 unique studies) of 1863 screened articles were included. The included studies were conducted in seven countries (USA, Greece, Italy, Brazil, China, Spain and Israel) and published during 2007–2018 (Table 1). All were observational studies and involved 3352 CRKP-infected patients, 95.3% (n = 3195) of whom received antibiotic treatment. About 64.4% (1712 of 2658) of patients in 36 studies were admitted into intensive care units.

3.2. Infection characteristics

Across 51 studies, 68.6% (2147 of 3128) of patients had bacteraemia, whereas 35.1% (532 of 1514) of patients in 28 studies had pneumonia. In 42 studies, 25.7% (698 of 2717) of patients had urinary tract infections (UTI) and 36.9% (209 of 567) of patients had polymicrobial infections in 13 studies. Of the 54 included studies, infections were associated with CRKP isolates producing KPC-type carbapenemase in 21 studies, whereas the isolates were found to harbour VIM in five studies. One study identified OXA-48-type carbapenemase in CRKP isolates, while the mechanism of resistance associated with the CRKP isolates was not specified in 19 studies. In eight studies, mixed population isolates that produced either of the enzymes (KPC, OXA-48, VIM or NDM) or no specific enzyme were reported. Of isolates tested against colistin, polymyxin B, gentamicin, tigecycline and fosfomycin, resistance occurred in 31.1% (684 of 2198), 9.8% (19 of 193), 35.7% (813 of 2279), 20.2% (429 of 2123) and 47.3% (150 of 317), respectively. Higher resistance rates were reported for amikacin (84.2%, 1405 of 1669), aztreonam (98.7%, 154 of 156), tobramycin (94.4%, 337 of 357) and piperacillin/tazobactam (99.6%, 496 of 498). Fig. 1 presents the *in vitro* resistance to specific antimicrobial agents as per mechanism of resistance of the CRKP isolates.

3.3. Mortality

Across 51 studies involving 3019 antibiotic-treated patients, the pooled mortality rate was 37.2% (95% CI 33.1–41.4%; $I^2 = 76.8\%$). The pooled mortality rate in 21 studies (n = 1414) with KPC-producing CRKP isolates was 32.8% (95% CI 27.7–38.1%; $I^2 = 61.3\%$), and in five studies (n = 81) with VIM-producing isolates it was 48.8% (95% CI 31.9–65.8%; $I^2 = 55.5\%$). Further sub-group analyses based on study region, publication year and study design did not significantly reduce heterogeneity levels.

Across 29 studies, monotherapy was associated with a higher mortality (OR 1.45, 95% CI 1.18–1.78%; $I^2 = 0.0\%$) than combination therapy. However, no significant differences in mortality were observed between two-drug and three-or-more-drug combination therapies (Table 2). Similarly, no significant differences in mortality were noted between: patients treated with carbapenem-containing and carbapenem-sparing combination regimens; polymyxin (i.e. polymyxin B or colistin)-containing and polymyxin-sparing combination therapies; tigecycline-containing and tigecycline-sparing

Table 1
Descriptive characteristics of included studies.

First author, publication year	Study type, country	Study period	Overall sample size	Age (years)	Female (%)	Population characteristics	Site of infection	Resistance mechanism	Susceptibility breakpoints used by authors
Alexander, 2012	SC retrospective, USA	2006–2008	20	62.5 (mean) 20–90 (range)	70	Inpatients, transplant received (15%), polymicrobial (30%)ICU (15%)	UTI (100%), BSI (15%)	KPC-producing	CLSI (2009), US FDA (for tigecycline)
Bergamasco, 2012	SC retrospective, Brazil	2009–2010	12	55.3 (mean) 54.5 (median) 37–74 (range)	16.7	SOT (100%), CVD (50%), diabetes (8.3%), liver disease (33.3%), renal insufficiency (8.3%)	BSI (75%), UTI (33.3%), SSSI (16.7%), pneumonia (16.7%)	KPC-producing	CLSI (2009), US FDA (for tigecycline)
Brizendine, 2015	SC retrospective, USA	2006–2012	22	56 ± 10.3 (mean ± SD)	27	SOT (100%), ICU (64%)	UTI (100%), BSI (32%)	CRKP	NA
Capone, 2013	MC prospective, Italy	2010–2011	91	NA	39.6	Inpatients, diabetes (34%), immunosuppression (46%), COPD (34%), CKD (30%), cancer (21%), chronic liver disease (7%), septic shock (16.5%), ICU (48.4%)	UTI (31.9%), BSI (37.4%), LRTI (15.4%), SSTI (12.1%), IAI (3.3%)	KPC-producing VIM-producing Extended spectrum beta-lactamases + OmpKs	EUCAST
Cprek, 2016	SC retrospective, USA	2013–2014	18	62.5 (median) 51–67 (IQR)	44	CVD (56%), diabetes (44%), pulmonary disease (56%), immunocompromised state (39%), ICU (83%), polymicrobial (33.3%)	BSI (38.9%), pneumonia (33.3%), UTI (22.7%), SSSI (5.6%), IAI (22.2%)	CRKP	CLSI (2009)
Daikos, 2009	MC prospective, Greece	2004–2006	14	NA	NA	NA	All BSI	VIM-1-producing	CLSI (2004)
Daikos, 2014	MC retrospective, Greece	2009–2010	37	NA	NA	NA	All BSI	KPC-producing and VIM-producing	EUCAST (2013), US FDA (for tigecycline)
Dubrovskaya, 2013	SC retrospective, USA	2007–2011	40	76 (median) 21–92 (range)	47.5	Diabetes (45%), CAD (57.5%), baseline renal insufficiency (35%), septic shock (25%), polymicrobial infection (32.5%), ICU (52.5%)	Bacteraemia (35%), UTI (30%), pneumonia (17.5%), SSTI (10%), IAI (5%), osteomyelitis (2.5%)	CRKP	US FDA (for polymyxin B and tigecycline)
Gomez-Simmonds, 2016	MC retrospective, USA	2006–2013	134	62 (median) 50–74 (IQR)	39	Diabetes (33%), advanced kidney (23%) or liver disease (20%), transplant recipients (23%), immunosuppressant medication (23%), neutropenic (4%), malignancies (20%), septic shock (31%), ICU (62%)	All BSI	CRKP	CLSI (2015), US FDA (for polymyxin B and tigecycline)
Ji, 2015	SC prospective, China	2011–2012	51	65.4 (mean)	39.2	Diabetes mellitus (9.8%), congestive heart disease (41.2%), COPD (11.8%), haematological malignancy (2%), chronic liver disease (7.8%), ICU (72.5%), polymicrobial (21.6%)	BSI (11.8%), UTI (2%)	KPC-producing	CLSI (2013), EUCAST (2011) (for colistin), US FDA (for tigecycline)
Machuca, 2017	SC prospective, Spain	2012–2016	104	NA	45.2	All inpatients, chronic renal disease (26%), baseline renal failure (42.3%), diabetes (34.6%), COPD (14.4%), transplant (10.6%), active solid tumour (28.8%), septic shock (46.2%), critical care (53.8%)	BSI (100%), UTI (26%), pneumonia (37.5%)	KPC-producing	EUCAST (2000), US FDA (for tigecycline)

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Table 1 (*continued*)

First author, publication year	Study type, country	Study period	Overall sample size	Age (years)	Female (%)	Population characteristics	Site of infection	Resistance mechanism	Susceptibility breakpoints used by authors
Michalopoulos, 2010	SC prospective, Greece	2008	11	67.5 ± 14.5 (mean ± SD)	54.5	Diabetes (27.2%), COPD (27.2%), ICU (100%)	BSI (54.5%), VAP (45.5%), UTI (36.4%)	CRKP	For fosfomycin, inhibition zone ≥ 16 mm was interpreted as susceptible using the disc diffusion test
Mouloudi, 2010	SC retrospective, Greece	2007–2008	37	17–81 (range)	24.32	SOT (21.6%), renal disease (18.9%), liver disease (13.5%), respiratory disease (8.1%), heart disease (18.9%), immune suppression (32.4%), diabetes (10.8%), ICU (100%)	All BSI	KPC-producing and metallo-β-lactamase producing	CLSI (2007), US FDA (for tigecycline), EUCAST (2010)(for colistin)
Nguyen, 2010	SC retrospective, USA	2004–2008	48	60 (median) 37–86 (range)	33.3	CVD (79%), SOT (42%), diabetes (35%), malignancy (33%), cirrhosis (29%), HIV (8%), continuous renal replacement/haemodialysis (44%), septic shock (42%), ICU (52%)	All bacteraemia	CRKP	CLSI
Qureshi, 2012	SC retrospective, USA	2005–2009	41	62 (median) 25–90 (range)	58.5	Diabetes (24.4%), COPD (4.9%), chronic renal failure (22%), CVD (12.2%), cerebrovascular disease (4.9%), chronic liver disease (7.3%), malignancy (36.6%), transplant (22%), HIV (7.3%), immunocompromised state (63.4%), renal dialysis (26.8%), ICU (53.7%)	Bacteraemia (100%), pneumonia (24.4%), UTI (17.1%)	KPC-producing	CLSI (2009 and 2011)
Qureshi, 2014	SC retrospective, USA	2009–2012	21	51 (median) 24–67 (range)	28.6	MI (14%), CHF (9%), PVD (14%), cerebrovascular accident (14%), COPD (9%), diabetes (85.7%), immunosuppression (52%), transplant recipient (52%), polymicrobial infection (24%)	All UTI	CRKP	NA
Sanchez-Romero, 2012	SC retrospective, Spain	2009	28	55 (mean)	32.1	ICU (100%)	UTI (17.9%), CAB (25%), LRTI (17.9%), meningitis (10.7%), IAI (7.1%), soft tissue (3.6%), pneumonia (25%)	VIM-1-producing	CLSI (2011), EUCAST (2011) (for tigecycline)
Satlin, 2011	MC retrospective, USA	2005–2010	143 (representing 156 cases)	69 (median)	61	Outpatients (11%), inpatients (89%), ICU (12.2%)	All UTI	CRKP	CLSI, US FDA (for tigecycline)
Souli, 2008	SC retrospective, Greece	2003–2006	13 (representing 14 cases)	68 (mean) 23–84 (range)	23.1	All inpatients, ICU (77%), diabetes (15.4%), COPD (7.7%), acute renal failure (53.8%), chronic renal failure (15.4%), congestive heart failure (23.1%), PVD (7.7%), cancer (23.1%), ischaemic stroke (15.4%), polymicrobial (7.7%)	BSI (84.6%), pneumonia (23.1%)	VIM-1 metallo-β-lactamase	CLSI (2006), BSAC (for colistin), US FDA (for tigecycline)
Souli, 2010	SC retrospective, Greece	2007–2008	18	67 (mean) 42–82 (range)	44.4	All inpatients, ICU (61.1%), CVD (38.9%), cancer (44.4%), diabetes (27.8%), COPD (22.2%), acute pulmonary oedema (5.6%), chronic renal failure (27.8%), acute renal failure (5.6%), end-stage renal failure (5.6%), neutropenia (5.6%), septic shock (5.6%)	BSI (77.8%), UTI (5.6%), pneumonia (11.1%)	KPC-2-producing	CLSI (2009), EUCAST (2009) (for tigecycline and colistin)

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Table 1 (*continued*)

First author, publication year	Study type, country	Study period	Overall sample size	Age (years)	Female (%)	Population characteristics	Site of infection	Resistance mechanism	Susceptibility breakpoints used by authors
Souli, 2017	MC prospective, Greece	2012–2015	27	59 (median) 15–83 (range)	44.4	Inpatients (100%) ICU (55.6%), cancer (7.4%), rheumatoid arthritis (7.4%), septic shock (22.2%)	UTI (59.3%), BSI (48.1%), pneumonia (7.4%), external ventricular drainage (3.7%)	KPC-2-producing	CLSI (2012), EUCAST (2012) (for fosfomycin, colistin, tigecycline)
Shields, 2016a	SC retrospective, USA	2010–2014	33	59.4 (mean) 28–85 (range)	30.3	SOT (39.4%) cancer (21.2%), diabetes (9.1%), neutropenia (3%), CVD (12.12), end-stage renal disease (15.15%), end-stage liver disease (6.1%), chronic respiratory failure (6.1%), HIV (3%), rheumatoid arthritis (3%)	BSI (100%), UTI (3%) respiratory tract infection (9.1%), abdominal infection (42.4%)	KPC-producing	CLSI (2009)
Trecarichi, 2016	MC prospective, Italy	2010–2014	161	NA	47.2	Haematological malignancy (100%), diabetes (15.5%), chronic hepatic failure (1.8%), chronic renal failure (4.3%)	BSI (100%), UTI (10.6%), respiratory tract infection (11.8%)	CRKP	NA
Tumbarello, 2012	MC retrospective, Italy	2010–2011	125	62.3 (mean)	41.6	All inpatients, ICU (42.4%), diabetes (23.2%), heart failure (19.2%), chronic renal failure (9.6%), solid tumour (20%), haematological malignancy (10.4%), septic shock (13.6%)	BSI (100%), UTI (13.6%), LRTI (22.4%)	KPC-producing	CLSI (2011), EUCAST (2011) (for colistin), US FDA (for tigecycline)
Tumbarello, 2015	MC retrospective, Italy	2010–2013	661	68 (median) 55–76 (IQR)	36.9	COPD (16%), CVD (41.6%), diabetes (25.4%), cerebrovascular disease or dementia (12.2%), haematological malignancy (13.5%), solid tumour (22.2%), liver disease (10.9%), chronic renal failure (18.4%), HIV (3%), neutropenia (10.6%), SOT (7.9%), shock (15.1%), ICU (34.8%)	BSI (67.6%), LRTI (12.9%), IAI (6.4%), UTI (12.4%), other (0.8%).	KPC-producing	EUCAST (2015)
Vardakas, 2015	SC retrospective, Greece	2006–2009	32	65.8 ± 13.5 (mean ± SD)	50	ICU (100%), CVD (81.3%), diabetes (43.8%), urologic disease (34.4%), cancer (28.1%), respiratory disease (25.8%), neurological disease (22.6%), septic shock (64.5%), polymicrobial (37.5%)	BSI (68.8%), LRTI (12.5%), UTI (25%), IAI (9.4%), SSTI (9.4%)	CRKP	CLSI (2010), US FDA (for tigecycline)
Venugopalan, 2017	SC retrospective, USA	2010–2016	36	NA	63.9	CVD (86.1%), pulmonary disease (22.2%), diabetes (50%), malignancy (19.4%), CKD (27.8%), seizure disorder (8.3%)	BSI (100%), UTI (41.7%), lung infection (22.2%), IAI (2.8%)	CRKP	CLSI (2010)
Weisenberg, 2009	SC retrospective, USA	2006	21	60.9 (mean)	47.6	All inpatients, cancer (23.8%), solid organ transplant (4.8%), end-stage renal disease (4.8%), cerebral haemorrhage (4.8%), CVD (9.5%)	BSI (42.9%), pneumonia (23.8%), tracheobronchitis (19%), UTI (23.8%)	KPC-producing	NA
Daikos, 2007	MC retrospective, Greece	2003–2004	13	NA	NA	NA	All BSI	VIM-producing	NA
Maltezou, 2009	SC (partly retrospective, partly prospective), Greece	2007–2008	21	60.3 (mean) 16–94 (range)	52.4	ICU (76.2%), diabetes (28.6%), COPD (19%), CVD (33.3%), chronic renal disease (14.3%), neutropenia (4.8%), cancer (4.8%)	Pneumonia (62%), UTI (4.7%), bacteraemia (9.5%)	KPC-2 producing	CLSI (2007)

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Table 1 (*continued*)

First author, publication year	Study type, country	Study period	Overall sample size	Age (years)	Female (%)	Population characteristics	Site of infection	Resistance mechanism	Susceptibility breakpoints used by authors
Navarro-San, 2013	SC prospective, Spain	2010–2012	35	70.5 (mean) 38–92 (range)	42.9	Cancer (51.4%), CVD (14.3%), liver disease (2.9%), polymicrobial (8.6%), HIV (2.9%), renal disease (2.9%), septic shock (28.6%)	BSI (100%), pneumonia (2.9%), UTI (25.7%), SSTI (5.7%), IAI (22.9%)	OXA-48-producing	CLSI (2012), US FDA (for tigecycline)
Di Carlo, 2013	SC prospective, Italy	2011–2012	30	56.6 ± 15 (mean ± SD)	46.7	ICU (100%), cancer (63.3%), diabetes (6.7%), COPD (13.3%)	BSI (100%), IAI (30%)	KPC-3 producing	EUCAST (2013)
Balandin, 2014	SC retrospective, Spain	2009–2011	15	54.5 ±13.9 (mean ± SD)	33.3	All ICU, septic shock (13.3%), cancer (26.7%), SOT (20%)	BSI (20%), pneumonia (33.3%), UTI (33.3%), meningitis (6.7%)	VIM-producing	CLSI (2011), EUCAST (2011) (for tigecycline)
Kontopidou, 2014	MC (partly retrospective, partly prospective), Greece	2009–2010	127	61.3 (mean) 17–86 (range)	32.3	ICU (100%), diabetes (24.4%), COPD (22.8%), chronic renal failure (13.4%), chronic heart failure (18.9%), chronic hepatic failure (3.1%), immunosuppression (11.0%), polymicrobial (89.8%)	Bacteraemia (54.3%), pneumonia (27.6%), UTI (10.2%), IAI (4.7%)	KPC-producing VIM-producing	CLSI (2010), EUCAST (2012) (for colistin and tigecycline)
McLaughlin, 2014	SC retrospective, USA	2010–2011	15	59.5 ± 11.3 (mean ± SD)	53.3	Diabetes (20%), renal dysfunction (20%), liver dysfunction (13.3%), neutropenic (6.7%)	BSI (100%), UTI (60%), lung infection (13.3%), IAI (6.7%)	KPC -producing	CLSI (2010)
Pontikis, 2014	MC prospective, Greece	2010–2012	15	54.9 (mean) 18–82 (range)	20	ICU (100%), septic shock (33.3%), polymicrobial (26.7%)	BSI (60%), pneumonia (26.7%), UTI (6.7%), meningitis (6.7%), IAI (13.3%)	KPC-2-producing	CLSI (2012), US FDA (for tigecycline)
Mammina, 2010	SC retrospective, Italy	2009	10	56.7 (mean) 17–81 (range)	60	ICU (100%), septic shock (20%), respiratory failure (40%), heart failure (20%)	BSI (50%), UTI (30%), lung infection (40%)	KPC-3 producing	NA
Oliva, 2017	MC prospective, Italy	2012–2015	32	55.1 ± 15.2 (mean ± SD)	28.1	Septic shock (25%)	BSI (56.3%), pneumonia (28.1%), UTI (28.1%)	CRKP	NA
Gonzalez-Padilla, 2015	SC retrospective, Spain	2012–2013	50	60.5 (median) 19–86 (range)	36	Renal failure (32%), ICU (44%), septic shock (60%)	Pneumonia (48%), bacteraemia (36%), UTI (20%), IAI (2%), SSTI (2%), CNS infection (2%)	KPC-producing	EUCAST
Neuner, 2011	SC retrospective, USA	2007–2009	60	60.4 ± 1.8 (mean ± SD)	37	Diabetes (35%), coronary artery disease (26%), COPD (12%), CKD (26%), end-stage liver disease (16%), SOT (16%), haematological disorders (18%), ICU (51%)	BSI (100%), UTI (13.7%), pulmonary infection (11.7%), IAI (11.7%)	CRKP	CLSI (2009), US FDA (for tigecycline)
Falagas, 2007	MC retrospective, Greece	2000–2006	53	61.5±18.8 (mean ± SD)	28	Diabetes (24.5%), renal failure (22.6%), liver disorders (7.5%), haematological disorders (5.6%), ICU (71.6%)	Bacteraemia (26.4%), pneumonia (22.6%), UTI (22.6%)	CRKP	NA
Sbrana, 2013	SC retrospective, Italy	2011–2012	22	51 ± 16 (mean ± SD)	10	ICU (100%), septic shock (13.6%)	BSI (46.2%), pneumonia (61.5%), UTI (7.7%)	KPC-producing	EUCAST (2012)
Papadimitriou-Olivgeris, 2017	SC retrospective, Greece	2012–2015	139	56.7 ± 18 (mean ± SD)	23.7	ICU (100%), diabetes (18%), COPD (6.5%), chronic heart failure (12.2%), chronic renal failure (2.9%), malignancy (12.9%), septic shock (53.2%)	BSI (100%), pneumonia (0.7%), abdominal infection (2.9%)	KPC-producing VIM-producing NDM-producing	EUCAST (2016)

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Table 1 (*continued*)

First author, publication year	Study type, country	Study period	Overall sample size	Age (years)	Female (%)	Population characteristics	Site of infection	Resistance mechanism	Susceptibility breakpoints used by authors
Falcone, 2016	SC retrospective, Italy	2010–2014	111	59.3 ±15.2 (mean ± SD)	30	Chronic liver disease (1.8%), diabetes (18.9%), heart failure (10.8%), chronic renal failure (7.2%), COPD (18%), septic shock (100%), ICU (100%)	BSI (100%), pneumonia (46.8%), UTI (22.5%), IAI (10.8%), SSTI (16.2%)	KPC-producing	EUCAST (2013), US FDA (for tigecycline)
Liao, 2017	SC retrospective, China	2012–2014	104	67.2 ± 15.7 (mean ± SD)	24	Diabetes (41.3%), COPD (27.9%), heart failure (23.1%), hepatic failure (1.9%), renal failure (23.1%), malignancy (13.5%), ICU (83.7%)	BSI (8.7%), pneumonia (81.7%), UTI (16.3%), IAI (3.8%)	CRKP	NA
De Pascale, 2017	MC retrospective, Italy	2012–2015	144	59.4 (mean)	35.4	Chronic heart failure (31.3%), chronic renal failure (10.4%), COPD (16%), diabetes (33.3%), chronic liver disease (12.5%), septic shock (54.9%), polymicrobial (16%), ICU (100%)	Pneumonia (51.4%), UTI (8.3%), BSI (57.6%), IAI (13.2%), SSTI (8.3%)	KCP-producing Class B metallo-beta-lactamases OXA-48 producing	EUCAST
Freire, 2015	SC retrospective, Brazil	2009–2013	31	54 (median) 21–72 (range)	38.7	All SOT, diabetes (29%), polymicrobial (32.3%), renal disease (54.8%)	UTI (32.3%), BSI (38.9%), pneumonia (9.7%)	KPC-producing	CLSI (2012), US FDA (for tigecycline), EUCAST (2014)
Hussein, 2013	SC retrospective, Israel	2006–2008	103	61.4 ±17 (mean ± SD)	29.1	All inpatients, cancer (35.9%), chronic liver disease (13.6), chronic renal disease (38.8%), ICU (30.1%)	All BSI	CRKP	CLSI (2006)
Simkins, 2014	SC retrospective, USA	2006–2010	13	53 ± 18 (mean ± SD)	46.2	All inpatients, SOT (100%), diabetes (62%), CAD or PVD (31%)	UTI (69%), SSTI (15%), BSI (38%)	CRKP	NA
Shields, 2016b	SC retrospective, USA	2015–2016	31	NA	NA	NA	NA	KPC-producing CRKP	CLSI
Russo, 2018	SC retrospective, Italy	2010–2015	128	60 ± 15.9 (mean ± SD)	30.5	Chronic liver disease (3.1%), diabetes (18%), heart failure (12.5%), CAD (35.9%), chronic renal disease (8.6%), COPD (17.2%), septic shock (100%), ICU (100%)	BSI (68.7%), pneumonia (43%), UTI (21.1%), SSTI (14.1%), IAI (10.9%)	KPC-producing	EUCAST (2013), US FDA (for tigecycline)
Su, 2018	MC retrospective, Taiwan	2013–2014	99	78 (median) 65–84 (IQR)	40.4	Diabetes (53.5%), COPD (16.2%), CHF (22.2%), cerebrovascular disease (30.3%), malignancy (29.3%), liver cirrhosis (9.1%), septic shock (16.2%), ICU (41.1%)	BSI (4%), pneumonia (49.5%), UTI (36.4%), IAI (9.1%)	CRKP	CLSI (2014), EUCAST (2015) (for colistin), US FDA (for tigecycline)
Varotti, 2017	SC retrospective, Italy	2010–2014	26	59 ± 13 (mean ± SD)	19	SOT (100%)	BSI (26.9%), UTI (65.4%), respiratory (3.8%)	KPC-3 producing	EUCAST (2017)
Pouch, 2015	MC retrospective, USA	2007–2010	20	57 (median) 51–67 (IQR)	45	SOT (100%), diabetes (45%), hypertension (25%), polymicrobial (5%)	UTI (100%), BSI (15%)	CRKP	CLSI (2009)
Duani, 2018	SC retrospective, Brazil	2011–2014	31	53.1 (mean)	41.9	ICU (51.6%)	BSI (100%)	KPC-producing	CLSI

Abbreviations: SC, single centre; MC, multicentre; UTI, urinary tract infection; BSI, bloodstream infection; CAB, catheter associated bacteraemia; CNS, central nervous system; SSTI, skin and soft tissue infection; IAI, intra-abdominal infection; LRTI, lower respiratory tract infection; VAP, ventilator-associated pneumonia; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; KPC, *Klebsiella pneumoniae* carbapenemase; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; SOT, solid organ transplant; CVD, cardiovascular disease; CKD, chronic kidney disease; CAD, coronary artery disease; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; BSAC, British Society for Antimicrobial Chemotherapy; FDA, Food and Drug Administration; IQR, interquartile range; SD, standard deviation; NA, not available

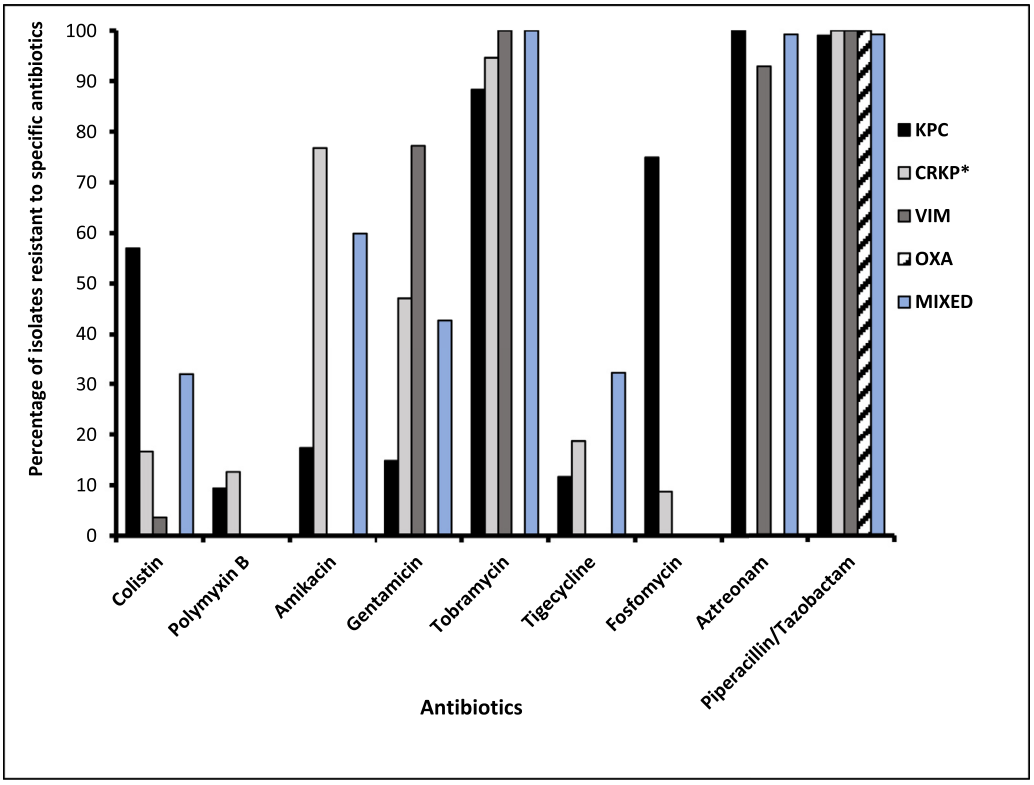

Fig. 1. Resistance rates of clinical isolates to specified antibiotics as per resistance mechanisms (number of isolates tested; **KPC**: colistin = 1243, polymyxin B = 53, amikacin = 1037, gentamicin = 1251, tobramycin = 94, tigecycline = 1128, fosfomycin = 179, aztreonam = 15, piperacillin/tazobactam = 101; **CRKP**: colistin = 350, polymyxin B = 140, amikacin = 435, gentamicin = 437, tobramycin = 168, tigecycline = 427, fosfomycin = 115, piperacillin/tazobactam = 193; **VIM**: colistin = 56, gentamicin = 57, tobramycin = 58, tigecycline = 30, aztreonam = 14, piperacillin/tazobactam = 42; **OXA-48**: piperacillin/tazobactam = 35; **Mixed**: colistin = 542, amikacin = 197, gentamicin = 534, tobramycin = 37, tigecycline = 538, fosfomycin = 23, aztreonam = 127, piperacillin/tazobactam = 127).
*CRKP resistance mechanism not specified

Table 2
Sub-group analyses comparing mortality and clinical and microbiological response rates following specific antibiotic therapies.

Outcome	No. of studies pooled	No. of patients	Odds ratio (OR) (95% CI)	Heterogeneity of included studies
Overall mortality				
Monotherapy vs. combination	29	1972	**1.45 (1.18–1.78); *P* < 0.001**	I^2 = 0.0%; Q = 27.9; *P* = 0.47
2-drug vs. ≥ 3-drug combination	20	1146	0.81 (0.55–1.19); *P* = 0.28	I^2 = 18.0%; Q = 25.6; *P* = 0.22
Carbapenem-containing vs. carbapenem-sparing	19	736	1.02 (0.65–1.61); *P* = 0.94	I^2 = 15.1%; Q = 21.2; *P* = 0.27
Polymyxin-containing vs. polymyxin-sparing	22	733	1.27 (0.77–2.09); *P* = 0.35	I^2 = 33.3%; Q = 31.5; *P* = 0.07
Aminoglycoside-containing vs. aminoglycoside-sparing	27	910	0.93 (0.62–1.37); *P* = 0.71	I^2 = 16.8%; Q = 31.3; *P* = 0.22
Tigecycline-containing vs. tigecycline-sparing	20	818	1.19 (0.74–1.90); *P* = 0.47	I^2 = 24.3%; Q = 25.1; *P* = 0.16
Clinical response				
Monotherapy vs. combination	11	291	1.07 (0.64–1.81); *P* = 0.79	I^2 = 0.0%; Q = 6.6; *P* = 0.76
2-drug vs. ≥ 3-drug combination	10	163	2.02 (0.90–4.51); *P* = 0.09	I^2 = 0.0%; Q = 3.9; *P* = 0.92
Carbapenem-containing vs. carbapenem-sparing	7	205	1.28 (0.69–2.39); *P* = 0.43	I^2 = 0.0%; Q = 4.8; *P* = 0.57
Polymyxin-containing vs. polymyxin-sparing	11	206	0.53 (0.27–1.05); *P* = 0.07	I^2 = 0.0%; Q = 7.1; *P* = 0.72
Aminoglycoside-containing vs. aminoglycoside-sparing	12	154	1.51 (0.67–3.43); *P* = 0.32	I^2 = 0.0%; Q = 7.5; *P* = 0.76
Tigecycline-containing vs. tigecycline-sparing	6	109	0.63 (0.26 –1.53); *P* = 0.30	I^2 = 0.0%; Q = 3.4; *P* = 0.63
Microbiological response				
Monotherapy vs. combination	7	120	0.97 (0.33–2.84); *P* = 0.95	I^2 = 0.0%; Q = 3.3; *P* = 0.78
2-drug vs. ≥ 3-drug combination	6	101	1.25 (0.41–3.81); *P* = 0.70	I^2 = 0.0%; Q = 2.1; *P* = 0.83
Carbapenem-containing vs. carbapenem-sparing	6	209	1.28 (0.66–2.47); *P* = 0.47	I^2 = 0.0%; Q = 2.8; *P* = 0.73
Polymyxin-containing vs. polymyxin-sparing	7	96	0.34 (0.11–1.01); *P* = 0.05	I^2 = 0.0%; Q = 2.3; *P* = 0.89
Aminoglycoside-containing vs. aminoglycoside-sparing	8	113	2.63 (0.83–8.40); *P* = 0.10	I^2 = 0.0%; Q = 1.4; *P* = 0.99
Tigecycline-containing vs. tigecycline-sparing	5	89	0.30 (0.05–1.83); *P* = 0.19	I^2 = 52.4%; Q = 8.4; *P* = 0.08

combinations; or patients on aminoglycoside-containing and aminoglycoside-sparing combinations. No significant differences were evident in mortality between individual monotherapies.

The pooled 14-day mortality rate across 13 studies (n = 1112) was 26.4% (95% CI 21.0–32.2%; I^2 = 59.4%), whereas (n = 1544) the pooled 30-day mortality rate was 34.1% (95% CI 30.1–38.3%; I^2 = 57.3%) across 28 studies. The comparative assessment of antibiotic regimen as per the 14-day and 30-day mortality showed similar patterns, as observed for the overall mortality.

3.4. Clinical response

Across 23 studies involving 759 patients, the pooled clinical response rate was 69.0% (95% CI 60.1–78.2%; I^2 = 82.8%). The

pooled clinical response rate was 80.9% (95% CI 68.4–91.1%; I^2 = 57.6%) across seven studies (n = 127) with KPC-producing CRKP isolates and 79.4% (95% CI 47.5–99.3%; I^2 = 77.0%) in three studies (n = 46) with VIM-producing isolates. Sub-group analyses based on study region, publication years, and study design did not significantly reduce heterogeneity levels. There were no statistically significant differences in the pooled likelihood of achieving a clinical response between monotherapy and combination therapies, or between two-drug combination and three-or-more-drug combination therapy, as well as between combination-containing and combination-sparing counterparts of tigecycline, polymyxins and aminoglycosides. Similarly, no significant differences in clinical response between the various monotherapies were observed.

3.5. Microbiological response

The pooled microbiological response rate across 18 studies with 581 patients was 63.7% (95% CI 53.7–74.1%; I^2 = 82.1%). The pooled microbiological response rate in seven studies (n = 147) with KPC-producing CRKP isolates was 55.6% (95% CI 33.3–76.9%; I^2 = 84.0%). Pooling was unable to be performed for other isolates. Heterogeneity levels did not significantly differ via sub-group analyses based on study region, publication years and study design. The pooled likelihood of microbiological response was not significantly different between monotherapy and combination therapy, two-drug and three-or-more-drug combinations or between combination-containing and combination-sparing regimens of carbapenem, tigecycline, polymyxins, and aminoglycosides. Similarly, no significant differences in microbiological response between the various monotherapies were noted.

3.6. Sensitivity analyses

The pooled mortality, clinical and microbiological response rates were unaffected by leave-1-out sensitivity analyses (plots not shown). Funnel plot visualisation revealed no evidence of publication bias and this was confirmed with Egger's tests (mortality P = 1.00; clinical response P = 0.26; microbiological response P = 0.90).

3.7. Adverse events

Twelve studies (n = 350) reported adverse events. Renal-related adverse effects were reported in 38 patients, 15 of whom were receiving gentamicin or amikacin, 20 receiving polymyxin-containing regimens, and three receiving aminoglycoside-sparing and polymyxin B-sparing regimens. In two studies (n = 54), seizures were reported in three patients, two of whom were on ertapenem plus meropenem, and the other on doripenem plus ertapenem combinations. However, in one of the patients it was noted upon review that, despite having reduced renal function, the doripenem and ertapenem doses were not sufficiently adjusted when therapy was initiated. Rash, eosinophilia, and aseptic meningitis were reported as reversible adverse events in one study among patients receiving double-carbapenem-containing regimens, while grey skin coloration occurred in three patients on polymyxin B monotherapy.

4. Discussion

This systematic review and meta-analysis found that about 1 in 3 CRKP-infected patients treated with antibiotics died, and < 70% achieved a clinical or microbiological response. Combination therapy was associated with lower mortality than monotherapy, but no significant differences in clinical and microbiological responses were observed. Clinical outcomes did not significantly differ between the various combination regimens or among the various monotherapies.

The lower mortality associated with combination therapy than monotherapy is consistent with previous findings [4,11] and likely attributable to the benefit of synergy in bacterial killing, as well as the capacity of combination regimens to exert broad-spectrum coverage, which is critical in cases of polymicrobial infections or during empirical treatment. Nonetheless, a recent RCT found no significant differences in clinical outcomes between colistin monotherapy and colistin-meropenem combination for severe *Acinetobacter baumannii* infections; however, the study was underpowered to specifically address this question for CRKP [12]. Those results along with the current ones – of no significant difference in clinical and microbiological responses – suggest that the use of combination therapy should be guided by broader clinical considerations (e.g. severity of illness, infection site, antimicrobial susceptibility pattern, and patient's comorbidities) to attain the desired outcomes.

The lack of significant differences in clinical outcomes between two-drug and three-or-more-drug combination therapies re-emphasises that other clinical factors, rather than just the number of antibiotics in the combination, may influence treatment results. Moreover, it is imperative that any potential gains from increasing the number of drugs are considered along with the possibility of increased adverse events [13].

While a previous review of 20 clinical studies reported lower mortality among carbapenemase-producing *Klebsiella pneumoniae* (CPKP)-infected patients treated with carbapenem-containing than carbapenem-sparing regimens, the current analysis found no such difference [4]. The inclusion of a carbapenem in treatment regimens for CRKP infections remains controversial, since KPC enzymes hydrolyse carbapenems [14] and most clinical cases of CRKP exhibit extremely high (> 32 mg/L) carbapenem MICs. Thus, the benefit of including a carbapenem in a combination regimen is dependent on the MIC of the infecting pathogen towards the carbapenem. Hence, high-dose carbapenem-combination regimens could be beneficial for isolates with relatively low or moderately elevated carbapenem MICs, but not for extremely high carbapenem MICs [15].

The current study found no significant differences in clinical outcomes between CRKP-infected patients treated with tigecycline-containing and tigecycline-sparing combination regimens, which is consistent with findings from a previous meta-analysis on CREs [6]. However, these findings are likely to be dependent on the infection site, as relatively low concentrations of tigecycline occur in serum, cerebrospinal fluid, urine and the epithelial lining fluid of the lung, for which tigecycline may not be recommended. Despite this, some studies have reported overcoming such pharmacokinetic limitations by administering higher than recommended daily doses [16], although patient populations that could benefit from such an approach need to be profiled bearing in mind the potential adverse effects.

Because polymyxins have demonstrated activity against Gram-negative bacteria, polymyxin-based combinations have been suggested for CRKP infections. Nonetheless, the current study found no significant differences in treatment outcomes between patients treated with polymyxin-containing and polymyxin-sparing regimens. Given the difficulties in determining an optimal dosage regimen, due to their narrow therapeutic window and high variability in pharmacokinetics (particularly with colistin), strategies to optimise dosing of polymyxins may contribute to improved outcomes.

In vitro studies have shown monotherapy or combination regimens of aminoglycosides to be effective against CRKP [17]. However, the current study found no significant differences in clinical outcomes between aminoglycoside-containing and aminoglycoside-sparing regimens. The high risk of adverse effects

such as nephrotoxicity and ototoxicity, and their relatively poor penetration into pulmonary and abdominal infection sites have limited the use of aminoglycosides. For CRKP infections with isolates susceptible to aminoglycosides and occurring at sites where high aminoglycoside concentrations can be achieved (e.g. bloodstream infections, UTI), treatment regimens that include an aminoglycoside may achieve therapeutic success [18]. Conversely, for infections occurring at sites with low aminoglycoside penetration, aminoglycoside-sparing regimens may be a reasonable alternative. However, outcomes are likely to be dictated by the antibiotics included in such aminoglycoside-sparing combinations, how active they are against the infecting pathogen, and their target site concentrations [19].

Some key strengths of the current meta-analysis include the inclusion of a large number of studies from multiple countries, the fact that the overall pooled mortality, clinical, and microbiological response rates were stable via leave-one-out sensitivity analyses, and the absence of publication bias.

There were also some limitations. There was significant heterogeneity, which was unexplained by sub-group analyses, and could be attributable to factors such as outcome definitions, pathogen genotypes, severities of illness, and infection sites, although their exact contributions could not be quantified. Most studies were of retrospective design and therefore amenable to selection bias. Furthermore, while the time to antibiotic initiation following AST results or the use of an active agent(s) could impact treatment outcomes, no detailed information was reported in most studies, and most studies provided insufficient information to allow an assessment of the likely adequacy of dosage regimens. Some sub-group analyses were based on a small number of studies involving few patients and may have been statistically underpowered to detect differences. Due to insufficient data, outcomes could not be examined as per different resistance mechanisms and this should be explored in future studies. Moreover, as the included studies spanned more than a decade, the AST breakpoints that were used might have evolved, which could have contributed to the variability across studies. Lastly, limiting the review to English articles may have limited its generalisability.

Overall, this comprehensive systematic review and meta-analysis provides insights into treatment outcomes among antibiotic-treated CRKP patients to facilitate the discussion around care optimisation. The results highlight the need for well-designed RCTs to evaluate the most appropriate antibiotic therapies for CRKP infections. Moreover, the results re-emphasise the importance of epidemiological surveillance of antimicrobial resistance at local, regional, national and international levels. This will provide data on antimicrobial susceptibility patterns (i.e. antibiogram) that could support an empirically-based therapy while awaiting the susceptibility results for the isolate from the patient.

In conclusion, mortality is high among antibiotic-treated CRKP-infected patients. Combination therapy has been associated with lower mortality than monotherapy, but no significant differences in clinical and microbiological responses were noted. Clinical outcomes did not significantly differ between different combination regimens or across different monotherapies. There is substantial scope for systematic studies, including consideration of the molecular characteristics of individual isolates, and well-designed RCTs to identify and evaluate effective treatment regimens for CRKP infections.

Declarations

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References

[1] Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. Lancet Infect. Dis. 2013;13:785–96.
[2] WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva: World Health Organization; 2017.
[3] WHO. Antibacterial Agents in Clinical Development: An analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017.
[4] Tzouvelekis LS, Markogiannakis A, Piperaki E, Souli M, Daikos GL. Treating infections caused by carbapenemase-producing Enterobacteriaceae. Clin. Microbiol. Infect. Dis. 2014;20:862–72.
[5] Falagas ME, Lourida P, Poulikakos P, Rafailidis PI, Tansarli GS. Antibiotic treatment of infections due to carbapenem-resistant Enterobacteriaceae: systematic evaluation of the available evidence. Antimicrob. Agents Chemother. 2014;58:654–63.
[6] Ni W, Han Y, Liu J, Wei C, Zhao J, Cui J, et al. Tigecycline Treatment for Carbapenem-Resistant Enterobacteriaceae Infections: A Systematic Review and Meta-Analysis. Medicine 2016;95:e3126.
[7] Ni W, Cai X, Wei C, Di X, Cui J, Wang R, et al. Efficacy of polymyxins in the treatment of carbapenem-resistant Enterobacteriaceae infections: a systematic review and meta-analysis. Braz. J. Infect. Dis. 2015;19:170–80.
[8] Temkin E, Fallach N, Almagor J, Gladstone BP, Tacconelli E, Carmeli Y. Estimating the number of infections caused by antibiotic-resistant Escherichia coli and Klebsiella pneumoniae in 2014: a modelling study. Lancet Glob. Health 2018;6:e969–79.
[9] G.A. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014.
[10] Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to meta-analysis. Wiley; 2009.
[11] Trecarichi EM, Pagano L, Martino B, Candoni A, Di Blasi R, Nadali G, et al. Bloodstream infections caused by Klebsiella pneumoniae in onco-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective survey. Am. J. Hematol. 2016;91:1076–81.
[12] Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect. Dis. 2018;18:391–400.
[13] Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with Gram-negative bacteria. Clin. Microbiol. Rev. 2012;25:450–70.
[14] Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin. Infect. Dis. 2011;53:60–7.
[15] Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psichogiou M, Argyropoulou A, et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections: Lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob. Agents. Chemother. 2014;58:2322–8.
[16] Sbrana F, Malacarne P, Viaggi B, Costanzo S, Leonetti P, Leonildi A, et al. Carbapenem-sparing antibiotic regimens for infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae in intensive care unit. Clin. Infect. Dis. 2013;56:697–700.
[17] Clancy CJ, Hao B, Shields RK, Chen L, Perlin DS, Kreiswirth BN, et al. Doripenem, gentamicin, and colistin, alone and in combinations, against gentamicin-susceptible, KPC-producing Klebsiella pneumoniae strains with various ompK36 genotypes. Antimicrob. Agents Chemother. 2014;58:3521–5.
[18] Shields RK, Clancy CJ, Press EG, Nguyen MH. Aminoglycosides for treatment of bacteremia due to carbapenem-resistant Klebsiella pneumoniae. Antimicrob. Agents Chemother. 2016;60:3187–92.
[19] Onufrak NJ, Forrest A, Gonzalez D. Pharmacokinetic and Pharmacodynamic Principles of Anti-infective Dosing. Clin. Ther. 2016;38:1930–47.