Eur Respir J 2007; 29: 548–560
DOI: 10.1183/09031936.00080206

Carbapenems for the treatment of immunocompetent adult patients with nosocomial pneumonia

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ABSTRACT: The comparative effectiveness and safety of carbapenems with other β-lactams and fluoroquinolones for the empirical treatment of patients with hospital-acquired pneumonia remains controversial.

In the present study, a meta-analysis of 12 relevant randomised controlled trials was performed.

Overall, carbapenems were associated with lower mortality than fluoroquinolones or β-lactams, alone or in combination with aminoglycosides (odds ratio 0.72, 95% confidence interval 0.55–0.95). There was no difference between the compared antibiotics regarding treatment success (1.08, 0.91–1.29), microbiological success (1.04, 0.72–1.50) or development of adverse effects (0.81, 0.46–1.43). In the subset of patients with *Pseudomonas aeruginosa* pneumonia, carbapenems were associated with lower treatment success (0.42, 0.22–0.82) and lower eradication of *P.* strains (0.50, 0.24–0.89).

Carbapenems are equivalent to fluoroquinolones or β-lactams, alone or in combination with aminoglycosides, for the empirical treatment of immunocompetent adult patients with hospital-acquired pneumonia. However, there is limited evidence, based predominantly on unblinded randomised controlled trials, that carbapenems are associated with lower mortality than the comparators; this association was not observed in a subset analysis of randomised controlled trials with a high methodological quality score. In patients with *Pseudomonas aeruginosa* pneumonia, carbapenems are associated with worse outcomes than the comparators.

KEYWORDS: *Acinetobacter baumannii*, β-lactams, intensive care unit, meropenem, *Pseudomonas aeruginosa*, ventilator-acquired pneumonia

Although pneumonia is a frequently self-limited infection, it is currently the sixth leading cause of death in the developed world. Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection and the leading cause of death due to nosocomial infections, even if appropriate treatment is administered [1, 2]. The mortality of patients with HAP is high, even among patients who receive appropriate antibiotic treatment, and in patients with ventilator-associated pneumonia (VAP) it can be as high as 30–80%. However, early administration of appropriate antibiotics has been associated with shortening of the course of infection and lower mortality [3–6]. Therefore, early appropriate treatment is recommended.

The severity of pneumonia and the development of resistant bacteria to several of the traditionally implicated antibiotics have lead to the widespread use of broad-spectrum antibiotics for the treatment of patients with HAP. The choice of antimicrobial treatment for patients with HAP and VAP depends on several risk factors, including duration of hospitalisation before the diagnosis of pneumonia, prior use of antibiotics and duration of mechanical ventilation. Intravenous administration of antibiotics is commonly recommended and used. According to the guidelines of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA), the most appropriate antibiotic choices for patients with HAP and no known risk factors for multidrug pathogens or early onset of pneumonia are ceftriaxone, ampicillin/sulbactam or fluoroquinolones as monotherapy [7]. In patients with known risk factors for multidrug pathogens or late-onset disease a combination therapy is recommended, including anti-pseudomonal β-lactam (cefepime, ceftazidime, imipenem/cilastatin, meropenem,

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Received:
June 19 2006
Accepted after revision:
September 08 2006

SUPPORT STATEMENT
All authors have no conflict of interest to disclose.

STATEMENT OF INTEREST
None declared.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

piperacillin/tazobactam) with an anti-pseudomonal quinolone (ciprofloxacin or levofloxacin) or an aminoglycoside (amikacin, gentamicin, tobramycin) plus linezolid or vancomycin (in case of suspected methicillin-resistant *Staphylococcus aureus* infection) [7].

Carbapenems have been shown to be effective for the empirical treatment of patients with HAP and are currently among the most widely prescribed antibiotics for such purposes. However, the Center for Disease Control has recently reported that ~15% of the *Pseudomonas aeruginosa* isolates are resistant to imipenem/cilastatin [8]. In addition, treatment with imipenem/cilastatin was an independent risk factor for development of resistance among Pseudomonas spp. [9].

The current meta-analysis of randomised controlled trials (RCTs) sought to clarify whether carbapenems are more effective and/or safer than other broad-spectrum antibiotics for the empirical treatment of patients with HAP.

METHODS

Data sources

Relevant RCTs for the present meta-analysis were identified from searches of PubMed (January 1950 to March 2006), Current Contents Connect and Cochrane Central Register of Controlled Trials. Search terms included ''carbapenem'', ''imipenem'', ''meropenem'', ''imipenem/cilastatin'', ''pneumonia'' and ''lower respiratory tract infection''. A recursive hand search of references was also performed for relevant articles, including review papers, to increase completeness. Abstracts presented at international conferences were not searched.

Study selection

Two reviewers (I.I. Siempos and K.G. Manta) independently searched the literature, and identified and examined relevant articles for further evaluation of data on effectiveness and toxicity. A study was considered eligible for inclusion in the meta-analysis if: 1) it was a randomised controlled clinical trial; 2) it studied the role of carbapenems in comparison with other broad-spectrum antibiotics or a combination of antibiotics for the empirical treatment of patients with HAP; 3) it assessed the effectiveness, toxicity and/or mortality of both therapeutic regimens. RCTs that included both patients with HAP and patients with community-acquired pneumonia were included in the analysis; however, only data regarding patients with HAP were extracted from those RCTs. Trials with both blind and unblind design were included, and only RCTs written in English, French and German were included in the analysis. Exclusion criteria included RCTs conducted primarily in neutropenic patients with solid organ tumours or haematological malignancies and trials that included <10 patients with pneumonia who received a carbapenem. Experimental trials and trials focusing on pharmacokinetic and/or pharmacodynamic parameters were also excluded. Finally, RCTs comparing the effectiveness and safety of two different carbapenems were not included in the analysis.

Data extraction

Using a standardised data collection form, two reviewers independently abstracted the following data from all eligible articles: year of publication; study design; patient population; number of patients (intention to treat (ITT), clinically evaluable (CE) and microbiologically evaluable), antimicrobial agents and doses used; mortality; clinical and microbiological outcomes and toxicity outcomes. All discrepancies between the two reviewers were resolved by the consensus of all authors. The two reviewers, blinded to author(s), journal and study institution, independently evaluated the methodological quality of each RCT. The following components were individually assessed: randomisation, generation of random numbers, details of double-blinding procedure, information on withdrawals and concealment of allocation. One point was awarded for the specification of each criterion; therefore, the maximum score for a study was 5. High-quality RCTs scored >2 points, while low-quality RCTs scored ⩽2 points, according to a modified Jadad score [10].

Definition of pneumonia

The diagnosis of HAP required a baseline chest radiograph demonstrating infiltrates or consolidation with or without effusion, and two of the following signs and symptoms: cough; new or worsened purulent sputum production; rales and/or signs of pulmonary consolidation; dyspnoea; tachypnoea; and/or hypoxaemia. In addition, at least two of the following findings were necessary: fever (⩾38°C or 100.4°F taken orally); respiratory rate of 30 breaths·min^{-1}; systolic hypotension (<90 mmHg); cardiac frequency of ⩾120 beats·min^{-1}; altered mental status; and total peripheral white blood cell (WBC) count of ⩾10,000 cells·mm^{-3}, with ⩾15% immature neutrophils (band forms), or WBC count of ⩽4,500 cells·mm^{-3}. The symptoms and the radiological findings should have started >48 h after admission to a hospital or a chronic care facility. Patients with HAP may be managed in a hospital ward or in the intensive care unit, when the illness is more severe. The diagnosis of VAP required the presence of fever or leukocytosis, production of purulent secretions and signs of a new consolidation in radiography in patients receiving mechanical ventilation support for >48 h [7].

Analysed outcomes

Primary outcome measures for the present meta-analyses were: all-cause mortality; treatment success (cure defined as resolution of all symptoms and signs of infection, or improvement defined as resolution of two or more of the baseline symptoms or signs of infection) in ITT and CE populations; treatment success in CE patients with early and late onset of HAP as well as in CE patients with infection due to *P. aeruginosa*; and adverse effects probably or possibly related to study regimens. The effectiveness of the empirical regimen was estimated at the test-of-cure visit, performed 1–28 days after the end of treatment. Patients considered CE in the individual RCTs who had an indeterminate clinical outcome at the test-of-cure visit were deemed unevaluable for the treatment success analysis. All-cause mortality was analysed based on the reported data for mortality during the study period (*e.g.* during treatment and follow-up period) in the ITT population. Treatment duration, number of patients that were withdrawn from the RCTs due to drug-related adverse effects, treatment success in microbiologically evaluable patients, pathogen eradication (documented or presumed) of Gram-negative and Gram-positive bacteria and the development of resistance to *P. aeruginosa* during treatment were all considered secondary outcomes measures.

Data analysis and statistical methods

The heterogeneity between RCTs was assessed by using a Chi-squared test; a p-value <0.10 defined statistical significance in the analysis of heterogeneity (in case of statistical significance for heterogeneity the p-value is provided in the manuscript). Publication bias was assessed by the funnel plot method using Egger's test (the p-values are provided in the manuscript when $p<0.05$ denoted publication bias) [11]. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for all primary and secondary outcomes were calculated using the DerSimonian–Laird random effects model [12].

RESULTS

Selected randomised controlled trials

Figure 1 presents a flow diagram describing the selection process applied to identify the pool of RCTs included in the meta-analysis. In total, 63 published reports of RCTs performed in patients with HAP who were treated with a carbapenem and a comparative regimen were identified. From these, 51 RCTs did not meet the inclusion criteria of the current meta-analysis for the reasons detailed in figure 1. Thus, 12 RCTs [64–75] were included in the current meta-analysis.

Table 1 lists the characteristics of the 12 RCTs [64–75] included in the meta-analysis. Overall, 2,731 patients with HAP were enrolled, while 2,612 patients comprised the ITT population. The mean (range) quality score of the included RCTs was 2.42 (1–5), which was considered good. The quality of five RCTs [64–67, 74] was high ($\geqslant 3$), while the quality of seven [68–73, 75] was low ($\leqslant 2$). The proportion of patients under mechanical ventilation was 100% in three trials [67, 68, 71], >70% in five trials [64–66, 72, 74] and 50% in two RCTs [69, 75], while the remaining RCTs [70, 73] did not provide relevant data. In one RCT, patients who developed pneumonia during their stay in a chronic care facility were also included in the study [64]. The demographic characteristics of patients also varied between different studies.

Administration of study drugs

The administration of study antibiotics to the included patients prior to enrolment was not allowed in all RCTs. The dosages of the administered drugs are shown in table 1. Imipenem/cilastatin or meropenem was administered in eight [64–66, 68, 69, 71, 74, 75] and four RCTs [67, 70, 72, 73], respectively. Imipenem/cilastatin was compared with fluoroquinolones in three RCTs (specifically, levofloxacin [65] and ciprofloxacin [68, 74]) and with other β-lactams in five trials (specifically, piperacillin/tazobactam [64, 69], aztreonam [71], cefepime [66] and ceftazidime [75]). Meropenem was compared with the combination of a cephalosporin (ceftazidime [67, 72, 73] and cefuroxime [70]) with an aminoglycoside (amikacin [67, 73], gentamicin [70] and tobramycin [72]). All drugs were administered *i.v.* and their dosages were adjusted according to the patient's renal function when appropriate. Carbapenem was infused *i.v.* over a period of 40–60 min in two trials [64, 74] and 20–30 min in four RCTs [70, 71, 73, 75], while the remaining studies did not provide data regarding the duration of *i.v.* infusion of carbapenems. No additional antibiotics were allowed in eight [66–70, 72, 73, 75] of the 12 RCTs included in the meta-analysis. In the remaining four trials [64, 65, 71, 74] other antibiotics could be added to the initial regimen. In fact, in two of them [64, 65] an aminoglycoside was part of the regimen at the beginning of treatment but was discontinued if *P. aeruginosa* was not the isolated microorganism. Vancomycin administration was also allowed in two RCTs [71, 74] if methicillin-resistant *S. aureus* or another resistant Gram-positive coccus was the isolated microorganism.

Duration of treatment

Of the RCTs included in the analysis, seven [64–69, 72] reported data on duration of treatment. As shown in table 1, treatment duration differed between the RCTs included in the meta-analysis but treatment duration was similar between treatment arms of the individual RCTs. In most of the RCTs in which this outcome was provided, the antibiotics were administered for ~9 days.

Mortality

Table 2 shows the primary outcome measures studied in the meta-analysis. All-cause mortality during the study period (based on the reported data) was available in seven [64–68, 71, 72] of the RCTs included in the meta-analysis. Specific data regarding the mortality of patients with HAP could not be extracted from the remaining five trials [69, 70, 73–75]. The administration of carbapenems for the treatment of patients with HAP was associated with fewer deaths than the administration of fluoroquinolones or β-lactams, alone or in combination with aminoglycosides (1,632 patients, OR 0.72, 95% CI 0.55–0.95). The ORs for mortality in the individual randomised controlled trials, as well as the pooled ORs, are presented in figure 2a. The observed mortality was 13.75% among patients treated with carbapenems and 18.01% for patients treated with fluoroquinolones and other β-lactams. However, if trials with a modified Jadad score of <3 were excluded from the analysis, there would be no difference in mortality between patients treated with carbapenems and those treated with fluoroquinolones or β-lactams, alone or in combination with aminoglycosides (1,224 patients, OR 0.76, 95% CI 0.55–1.04, [64–67]).

Treatment success in ITT and CE patients

The overall treatment success in the ITT population for the carbapenems and the comparator antibiotics were 61.7 and 60.2%, respectively. The treatment of patients with HAP with carbapenems was not associated with better success when compared to other antibiotics (2,082 patients, OR 1.08, 95% CI 0.91–1.29, data from eight RCTs [64–68, 72, 74, 75], fig. 2b). Furthermore, treatment with carbapenems was not associated with better success when compared with fluoroquinolones and other β-lactams, alone or in combination with aminoglycosides, in the CE population (1,592 patients, OR 1.07, 95% CI 0.77–1.49, data from 11 RCTs [64–70, 72–75], fig. 2c, Chi-squared test for heterogeneity $p=0.028$, Egger's test $p=0.021$, smaller studies favoured carbapenems). This was also the case after the exclusion of RCTs without mortality data (948 CE patients, OR 1.35, 95% CI 0.90–2.02, from six RCTs [64–68, 72], Egger's test $p=0.022$, smaller studies favoured carbapenems) as well as after the exclusion of RCTs with mortality data (644 CE patients, OR 0.73, 95% CI 0.49–1.10, from five RCTs [69, 70, 73–75]).

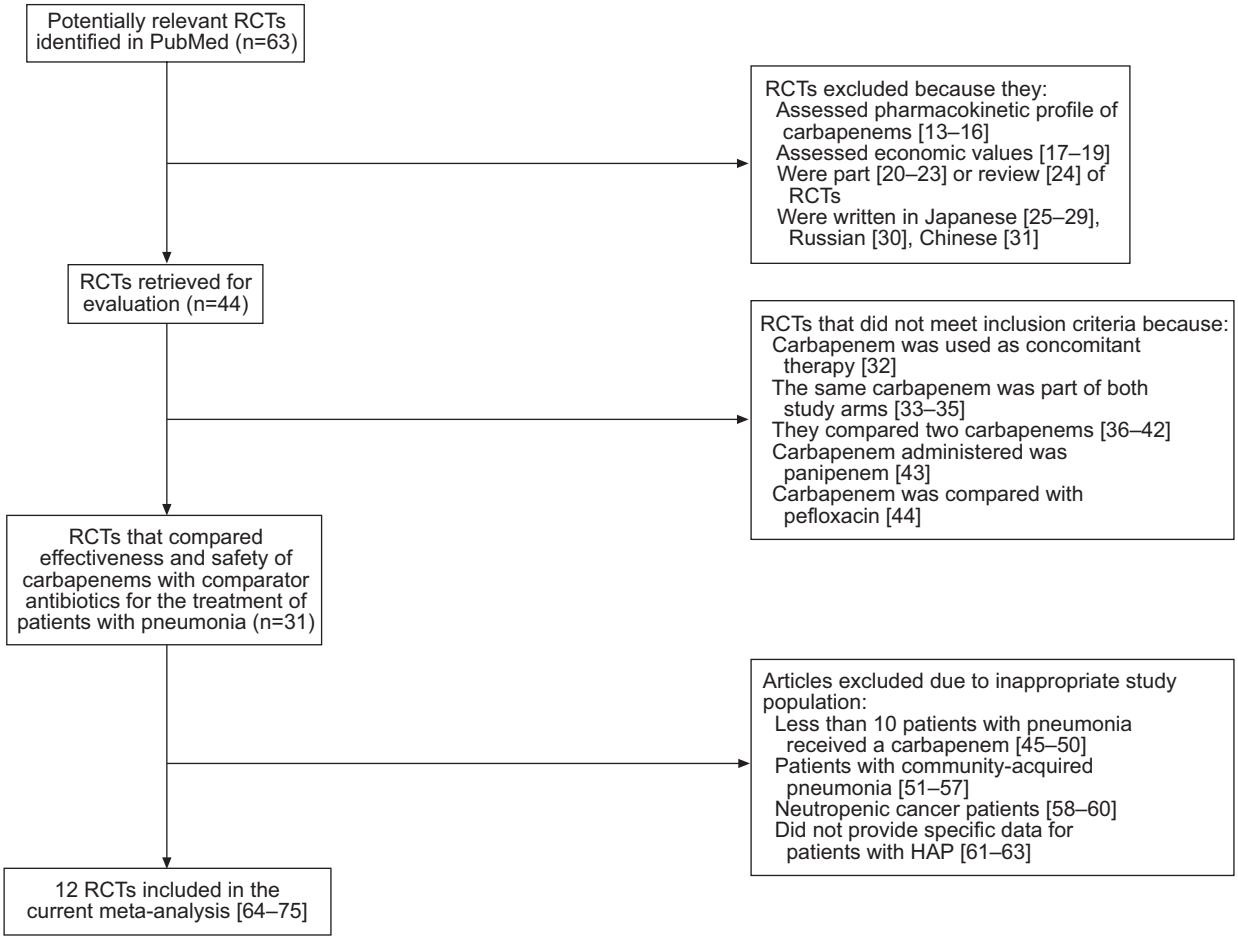

FIGURE 1. Flow diagram of the selection process for identification and inclusion of randomised controlled trials (RCTs) in the meta-analysis. HAP: hospital-acquired pneumonia.

Early and late-onset HAP

Only three [65–67] of the RCTs included in the meta-analysis provided information regarding the time of onset of HAP. All three RCTs reported data for late-onset pneumonia. The sensitivity analysis showed that there was no difference between carbapenems and the comparator antibiotics for the treatment of patients with late-onset HAP (555 patients, OR 1.34, 95% CI 0.91–1.97, fig. 2d).

Patients with *P. aeruginosa* HAP

The treatment of patients with HAP due to *P. aeruginosa* infections with carbapenems was associated with lower treatment success when compared with fluoroquinolones and other β-lactams, alone or in combination with aminoglycosides (202 CE patients, OR 0.42, 95% CI 0.22–0.82, data from six RCTs [65, 66, 68–70, 75], fig. 3a).

Comparator antibiotics: CE population

Several sensitivity analyses were performed to compare carbapenems with other classes of antibiotics. Carbapenems were not associated with better treatment success when compared with other β-lactams, alone or in combination with aminoglycosides (1,118 CE patients, OR 1.16, 95% CI 0.76–1.78, data from nine RCTs [64, 66, 67, 69–73, 75], Chi-squared test for heterogeneity p=0.032, Egger's test p=0.028, smaller studies favoured carbapenems). Treatment with imipenem was also not associated with better treatment success when compared with fluoroquinolones (474 CE patients, OR 0.93, 95% CI 0.51–1.69, data from three trials [65, 68, 74]) or β-lactams (771 CE patients, OR 0.80, 95% CI 0.57–1.11, data from five trials [64, 66, 69, 71, 75]). On the contrary, the administration of meropenem was associated with statistically significant better treatment success when compared to the combination β-lactam/aminoglycoside (347 CE patients, OR 2.30, 95% CI 1.36–3.91, data from four RCTs [67, 70, 72, 73]). This statistically significant outcome remained when one RCT [70] comparing meropenem with cefuroxime plus gentamicin was excluded (306 CE patients, OR 2.38, 95% CI 1.36–4.18).

Treatment success in microbiologically evaluable patients

Table 3 shows the microbiological outcomes of the 12 RCTs included in the meta-analysis. Ten RCTs [64–68, 70–74] reported data regarding treatment success in microbiologically evaluable patients. There was no difference between carbapenems and fluoroquinolones or other β-lactams, alone or in combination with aminoglycosides, regarding this outcome (1,125 patients, OR 1.04, 95% CI 0.72–1.50). In addition, no difference was observed between carbapenems and the comparator antibiotics for the eradication of *Acinetobacter baumannii* (52 isolates, OR 3.04, 95% CI 0.77–11.93, data from

TABLE 1 Main characteristics of the randomised controlled trials (RCTs) included in the meta-analysis

First author [Ref.]	Publication yr	Study design	Population	Regimen 1	Regimen 2	Additional antibiotics	Enrolled patients n#	ITT n#	Study quality score¶
JOSHI [64]	2006	MC DB RCT	Hospitalised (⩽18 yrs) with suspected or proven NP	*i.v.* imipenem/cilastatin 500 mg q6 h	*i.v.* piperacillin/tazobactam 4g/ 500 mg q6 h	Tombramycin or amikacin (in *P. aeruginosa* infection)	449	215 *versus* 222	5
WEST [65]	2003	MC RCT	Hospitalised with NP	*i.v.* imipenem/cilastatin 500 mg–1 g q6-8 h, followed by *p.o.* ciprofloxacin 750 mg q12 h	*i.v.* levofloxacin 750 mg *q24h*, followed by *p.o.* levofloxacin q24 h	Amikacin (or other aminoglycoside) for *P. aeruginosa* in IMI group. Ceftazidime (or other β-lactam) for *P. aeruginosa* in LEVO group. Vancomycin for *S. aureus* in both groups	438	218 *versus* 220	3
ZANETTI [66]	2003	MC RCT	ICU (⩾16 yrs) with NP with or without MV	*i.v.* imipenem/cilastatin 500 mg q6 h	*i.v.* cefepime 2 g q8 h	Not allowed	281	138 *versus* 132	3
ALVAREZ LERMA [67]	2001	MC RCT	ICU (⩾18 yrs) with VAP	*i.v.* meropenem 1 g q8 h	*i.v.* ceftazidime 2 g q8 h plus *i.v.* amicacin 15 mg·kg^{-1}·day^{-1} divided in two equal doses	Not allowed	140	69 *versus* 71	3
TORRES [68]	2000	MC RCT	Hospitalised (⩾18 yrs) with severe NP requiring MV	*i.v.* imipenem/cilastatin 2–4 g·day^{-1}	*i.v.* ciprofloxacin 800–1200 mg·day^{-1}	Not allowed (unless initiated >5 days before study)	152	77 *versus* 72	2
JACCARD [69]	1998	MC RCT	Hospitalised (>16 yrs) with NP	*i.v.* imipenem/cilastatin 500 mg q6 h	*i.v.* piperacillin/tazobactam 4 g/ 500 mg q8 h	Not allowed	NA	NA	1
JASPERS [70]	1998	MC RCT	Hospitalised elderly (⩽65 yrs) with serious NP	*i.v.* meropenem 1 g q8 h	*i.v.* cefuroxime 1.5 g q8 h plus *i.v.* gentamicin 4 mg·kg^{-1}·day^{-1} once daily or in two or three divided doses	Not allowed	NA	NA	1
POLK [71]	1997	MC RCT	Hospitalised trauma patients (18-80 yrs) with confirmed or presumed NP requiring MV	*i.v.* imipenem/cilastatin 500 mg q6 h	*i.v.* aztreonam 2 g q8 h plus *i.v.* vancomycin 1 g q12 h	Not allowed	122	59 *versus* 63	1
SIEGER [72]	1997	MC RCT	Hospitalised (>17 yrs) with nosocomial lower respiratory tract infections	*i.v.* meropenem 1 g q8 h	*i.v.* ceftazidime 2 g q8 h plus *i.v.* tobramycin 1 mg·kg^{-1} q8 h	Not allowed	211	104 *versus* 107	2
MOUTON [73]	1995	MC RCT	Hospitalised adult patients with serious lower respiratory tract infections	*i.v.* meropenem 1 g q8 h	*i.v.* ceftazidime 2 g q8 h plus *i.v.* amicacin 15 mg·kg^{-1}·day^{-1} divided in two or three equal doses	Not allowed	NA	44 *versus* 40	2
FINK [74]	1994	MC DB RCT	Hospitalised (usually in ICU) (⩽18 years) with severe pneumonia	*i.v.* imipenem/cilastatin 1 g q8 h	*i.v.* ciprofloxacin 400 mg q8 h	Antifungal, antiviral, topical antibiotics, metronidazole (for aspiration pneumonia in CIPRO group), vancomycin (for Gram-positive bacteraemia)	405	156 *versus* 156	5
NORRBY [75]	1993	MC RCT	Hospitalised (⩽16 yrs) with clinically suspected NP	*i.v.* imipenem/cilastatin 500 mg q6 h	*i.v.* ceftazidime 2 g q12 h	Not allowed	254	129 *versus* 125	1

ITT: intention to treat; MC: multicentre, DB: double-blind; NP: nosocomial pneumonia; *P. aeruginosa: Pseudomonas aeruginosa;* IMI: imipinem; LEVO: levoflavoxin; *S. aureus*: *Staphylococcus aureus*; ICU: intensive care unit; MV: mechanical ventilation; VAP: ventilator-acquired pneumonia; NA: not applicable; CIPRO: ciprofloxacin. #: only patients with hospital-acquired pneumonia are included (patients with community-acquired pneumonia are not included); ¶: according to a modified Jadad score.

TABLE 2 Outcome data from the selected randomised controlled trials for the meta-analysis (carbapenem *versus* comparators).

First author [Ref.]	Treatment duration days SD	Treatment success			Adverse effects				
		ITT at TOCV	CE at TOCV	CE/PS at TOCV	Mortality	Total	Patients withdrawn	Diarrhoea/ vomiting	Seizures
Joshi [64]	9.7 *versus* 9.4	111/215 (52) *versus* 121/222 (55)	60/99 (61) *versus* 67/98 (68)	NA	17/215 (8) *versus* 23/222 (10)	NA	NA	NA	NA
West [65]	9.1 *versus* 8.2	143/206 (70) *versus* 135/204 (66)	70/112 (63) *versus* 70/118 (59)	7/17 (41) *versus* 11/17 (64)	32/218 (15) *versus* 38/220 (17)	NA	NA	NA	NA
Zanetti [66]	9.4 (4.3) *versus* 9.1 (4.2)	78/138 (57) *versus* 78/132 (59)	75/101 (74) *versus* 76/108 (70)	23/32 (72) *versus* 23/27 (85)	19/101 (19) *versus* 28/108 (26)	20/141 (14) *versus* 33/138 (24)	0/141 (0) *versus* 1/138 (1)	9/141 (6) *versus* 7/138 (5)	0/141 (0) *versus* 0/138 (0)
Alvarez Lerma [67]	9.3 (4.2) *versus* 8.3 (4.0)	47/69 (68) *versus* 39/71 (55)	47/57 (83) *versus* 39/59 (66)	NA	16/69 (23) *versus* 20/71(28)	7/69 (10) *versus* 8/71 (11)	1/69 (1) *versus* 1/71 (1)	1/69 (1) *versus* 1/71 (1)	1/69 (1) *versus* 0/71 (0)
Torres [68]	9.3 (4.2) *versus* 8.4 (4.2)	40/57 (70) *versus* 34/52 (65)	27/34 (79) *versus* 29/41(71)	8/12 (67) *versus* 10/14 (71)	4/34 (12) *versus* 8/41 (20)[#]	NA	NA	0/77 (0) *versus* 0/72 (0)	0/77 (0) *versus* 0/72 (0)
Jaccard [69]	9.9 (4.6) *versus* 9.4 (4.3)	NA	56/79 (71) *versus* 62/75 (83)	12/24 (50) *versus* 19/21 (91)	NA	NA	NA	NA	NA
Jaspers [70]	NA	NA	17/20 (85) *versus* 16/21 (76)	0/0 (0) *versus* 0/2 (0)[¶]	NA	NA	NA	NA	NA
Polk [71]	NA	NA	NA	NA	9/59 (15) *versus* 10/63 (16)	NA	NA	NA	NA
Sieger [72]	7.8 *versus* 7.4	76/104 (73) *versus* 62/107 (58)	56/63 (89) *versus* 42/58 (72)	NA	13/104 (13) *versus* 23/107 (22)	23/104 (22) *versus* 20/107 (19)	2/104 (2) *versus* 1/107 (1)	2/104 (2) *versus* 2/107 (2)	0/104 (0) *versus* 0/107 (0)
Mouton [73]	NA	NA	30/37 (81) *versus* 23/32 (72)[+]	NA	NA	NA	NA	NA	0/44 (0) *versus* 0/40 (0)[+]
Fink [74]	NA	71/130 (55) *versus* 74/121 (61)	44/83 (53) *versus* 58/86 (67)	NA	NA	NA	NA	NA	NA
Norrby [75]	NA	81/129 (63) *versus* 79/125 (63)	81/110 (74) *versus* 79/101 (78)	13/19 (68) *versus* 13/17 (77)[¶]	NA	NA	NA	NA	NA

Data are presented as n/total number of subjects (%), unless otherwise stated. ITT: intention to treat; TOCV: test-of-cure visit, 1–28 days after the end of treatment; CE: clinically evaluable patients; CE/PS: patients with pneumonia due to *Pseudomonas aeruginosa;* NA: not available/applicable. [#]: these data refer to CE patients (not to ITT); [¶]: these data refer to *Pseudomonas* spp. (not only *P. aeruginosa*); [+]: patients with various lower respiratory tract infections (not only pneumonia) are included.

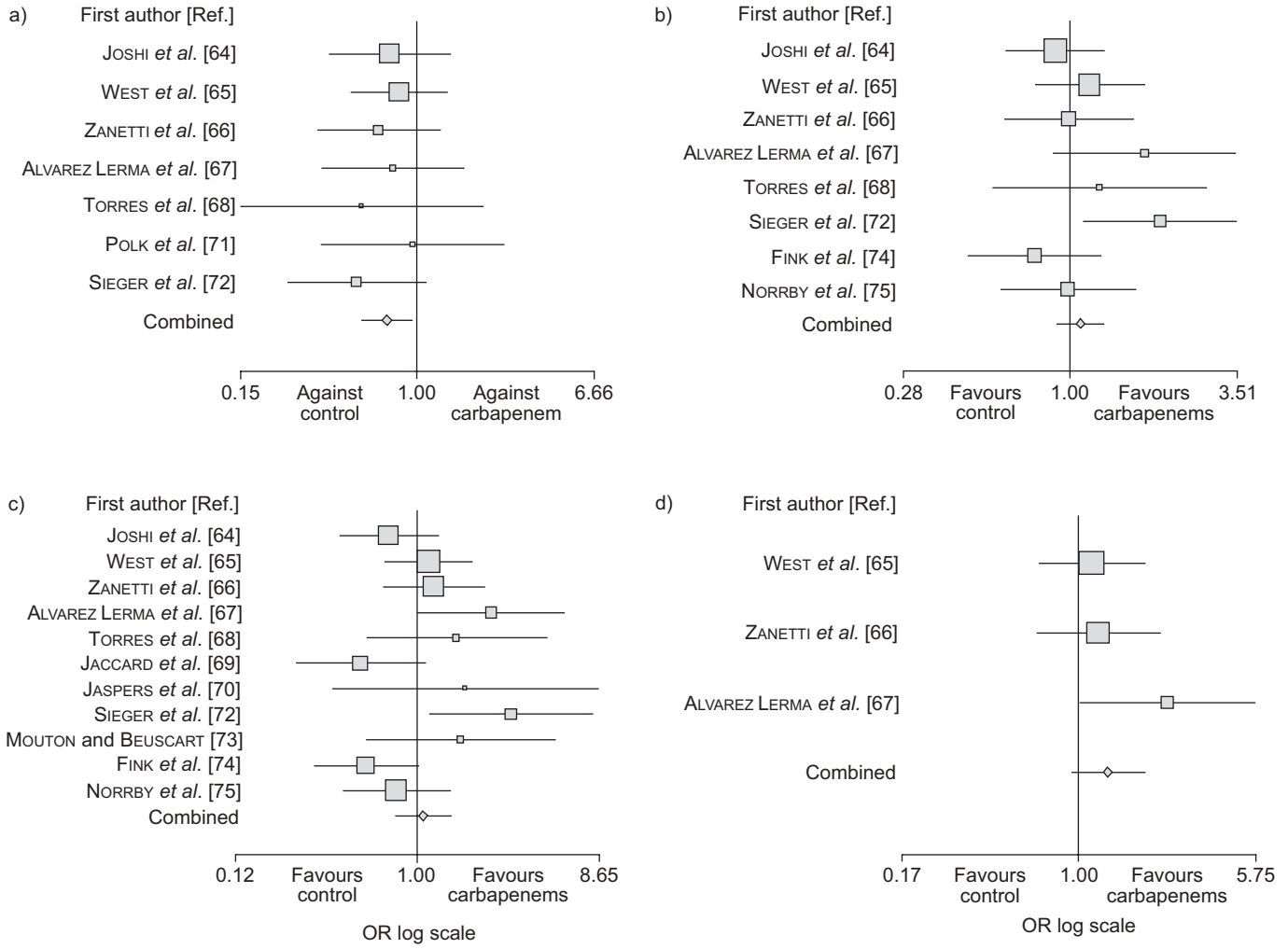

FIGURE 2. Odds ratio (OR) of mortality and treatment success of the empirical regimen for patients with nosocomial pneumonia. a) Mortality, Chi-squared test for heterogeneity: p=0.095; b) all intention-to-treat patients, Chi-squared test for heterogeneity: p=0.23; c) all clinically evaluable patients, Chi-squared test for heterogeneity: p=0.028; and d) patients with late-onset hospital-acquired pneumonia at risk for pneumonia due to multidrug-resistant bacteria, Chi-squared test for heterogeneity: p=0.33. Vertical line: no difference between the two regimens; ■: OR with size denoting the proportion of information given by each trial; ——: 95% confidence interval.

five RCTs [64, 65, 67, 72, 73]), *Klebisella pneumoniae* (72 isolates, OR 1.61, 95% CI 0.19–13.4, data from four RCTs [64, 65, 67, 72], Chi-squared test for heterogeneity p=0.061, Egger's test p=0.009, smaller studies favoured carbapenems) and *S. aureus* (205 isolates, OR 1.41, 95% CI 0.61–3.27, data from six RCTs [64, 65, 67, 72, 73, 75]). On the contrary, carbapenems were associated with fewer eradications of *P. aeruginosa* when compared with fluoroquinolones and β-lactams (200 isolates, OR 0.50, 95% CI 0.24–0.89, data from seven RCTs [64, 65, 67, 68, 72, 73, 75], fig. 3b), but it is not the case when the administered carbapenem was meropenem (69 isolates, OR 1.10, 95% CI 0.39–3.14, data from three RCTs [67, 72, 73], fig. 3c).

Development of resistance

Data regarding the development of resistance of *P. aeruginosa* during treatment were reported in only four [66, 68, 69, 75] of the RCTs included in the present study. Development of resistance during treatment was increased in patients treated with carbapenems compared with those treated with fluoroquinolones or β-lactams, alone or in combination with aminoglycosides (159 patients, OR 5.17, 95% CI 1.96-13.65, data from four trials [66, 68, 69, 75], fig. 3d). Specific data on superinfection or colonisation in patients with *P. aeruginosa* pneumonia were not available in the aforementioned RCTs [66, 68, 69, 75].

Adverse effects

Data regarding adverse effects possibly related to the study medications were reported in only three [66, 67, 72] of the RCTs included in the meta-analysis. An additional five [64, 65, 68, 71, 74] trials reported data on total adverse effects without specifying the number of drug-related adverse effects, while in four RCTs [69, 70, 73, 75] data regarding the number of patients with pneumonia who experienced adverse effects could not be extracted. Carbapenem administration was associated with fewer adverse effects; however, this difference was not statistically significant (630 ITT patients, OR 0.81, 95% CI 0.46–1.43). The majority of the reported adverse effects was mild-to-moderate in severity and involved the gastrointestinal tract (nausea, vomiting and diarrhoea). There was no

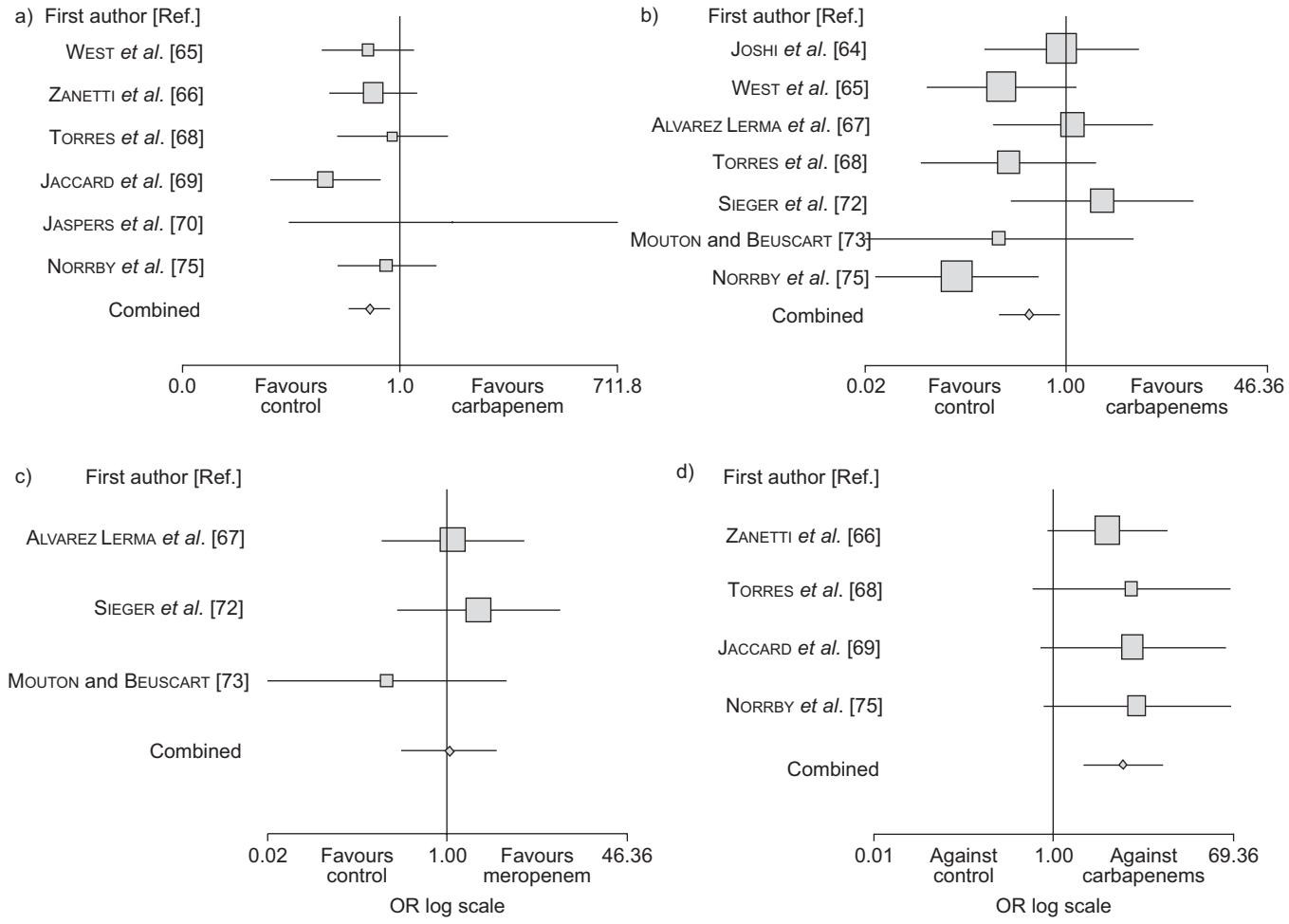

FIGURE 3. Odds ratio (OR) of treatment success for patients with nosocomial pneumonia due to *Pseudomonas aeruginosa*. a) Clinically evaluable patients, Chi-squared test for heterogeneity: p=0.467; b) eradication of *P. aeruginosa* strains, Chi-squared test for heterogeneity: p=0.219; c) eradication of *P. aeruginosa* strains (trials that compared meropenem with other antibiotics), Chi-squared test for heterogeneity: p=0.456; and d) development of resistance of *P. aeruginosa* during the trials, Chi-squared test for heterogeneity: p=0.940. Vertical line: no difference between the two regimens; ■: OR with size denoting the proportion of information given by each trial; ——: 95% confidence interval.

difference between the compared regimens in the number of patients that experienced an adverse effect from the gastrointestinal tract (779 ITT patients, OR 1.18, 95% CI 0.51–2.75, data from four RCTs [66–68, 72]) as well as in the number of patients that were withdrawn from the RCTs due to drug-related adverse effects (630 ITT patients, OR 1.05, 95% CI 0.21–5.14, data from three RCTs [66, 67, 72]). In addition, there was no difference between the compared regimens in the number of patients that developed seizures (863 ITT patients, OR 1.33, 95% CI 0.25–7.10, data from five RCTs [66–68, 72, 73]). It is also worth emphasising that the absolute number of seizures reported for carbapenems was very small (1 out of 434).

DISCUSSION

The results of the present meta-analysis suggest that there is no difference regarding treatment success, microbiological success or development of adverse effects between carbapenems and fluoroquinolones or β-lactams, alone or in combination with aminoglycosides, administered for the empirical treatment of immunocompetent adult patients with HAP. However, there is evidence, mainly from open-label trials, that administration of carbapenems is associated with lower mortality than the compared antibiotics. In addition, in the subset of patients with *P. aeruginosa* pneumonia, administration of carbapenems was associated with lower treatment success, higher development of resistance and lower eradication of *P. aeruginosa* strains.

It is interesting that although there was no difference between carbapenems and the comparator antibiotics regarding treatment success, administration of carbapenems was associated with lower mortality. This paradox could be explained by various possibilities. First, even with the inclusion of 12 trials, there may have been insufficient power to detect a difference in the outcome of treatment success. Secondly, misclassification that may have occurred on the assessment of the outcomes by the investigators performing the RCTs included in the present meta-analysis is another possibility. It should be noted that 10 out of the 12 RCTs included in the analysis were open-label trials; it is interesting that in a subset analysis performed by including only the trials with high methodological quality

TABLE 3 Microbiological outcomes from the selected randomised controlled trials for the meta-analysis (carbapenem *versus* comparators)

First author [Ref.]	Treatment success (microbiological evaluation)	Pathogen eradication				Development of resistance
		P. aeruginosa	*A. baumannii*	*K. pneumoniae*	*S. aureus*	*P. aeruginosa*
Joshi [64]	58/99 (59)	12/17 (71)	6/8 (75)	6/12 (50)	23/36 (59)	NA
	versus	*versus*	*versus*	*versus*	*versus*	
	62/98 (63)	13/18 (72)	7/9 (78)	12/14 (86)	24/31 (77)	
West [65]	57/94 (61)	5/17 (29)	7/9(78)	6/7 (85)	20/29 (69)	NA
	versus	*versus*	*versus*	*versus*	*versus*	
	62/93 (67)	10/17 (59)	1/2 (50)	9/11 (82)	19/31 (61)	
Zanetti [66]	38/71 (54)	NA	NA	NA	NA	9/27 (33)
	versus					*versus*
	47/77 (61)					3/25 (12)
Alvarez Lerma [67]	38/51 (75)	8/14 (57)	0/3 (0)	5/5 (100)	6/8 (75)	NA
	versus	*versus*	*versus*	*versus*	*versus*	
	24/45 (53)	7/13 (54)	0/2 (0)	1/2 (50)	4/7 (58)	
Torres [68]	17/34 (50)	3/12 (25)	NA	NA	NA	4/12 (33)
	versus	*versus*				*versus*
	20/41 (49)	7/14 (50)				1/14 (7)
Jaccard [69]	NA	NA	NA	NA	NA	6/24 (25)
						versus
						1/21 (5)
Jaspers [70]	10/12 (83)	NA	NA	NA	NA	NA
	versus					
	9/13 (69)					
Polk [71]	26/37 (70) *versus* 30/39 (77)	NA	NA	NA	NA	NA
Sieger [72]	56/63 (89)	12/15 (80)	6/7 (86)	9/9 (100)	8/10 (80)	NA
	versus	*versus*	*versus*	*versus*	*versus*	
	39/58 (67)	8/12 (67)	1/5 (20)¶	8/12 (67)	6/13 (46)	
Mouton [73]	17/24 (71)	5/11(46)	5/6 (83)	NA	2/3 (67)	NA
	versus	*versus*	*versus*		*versus*	
	13/17 (77)#	3/4 (75)#	0/1 (0)#,¶		3/3 (100)#	
Fink [74]	44/76 (58)	NA	NA	NA	NA	NA
	versus					
	57/83 (69)					
Norrby [75]	NA	7/19 (37)	NA	NA	15/16 (94)	6/19 (32)
		versus			*versus*	*versus*
		14/17 (82)+			13/18 (72)	1/17 (6)+

Data are presented as n/total number of subjects (%). *P. aeruginosa*: *Pseudomonas aeruginosa*; *A. baumanni*: *Acinetobacter baumannii*; *K. pneumoniae*: *Klebisella pneumoniae*; *S. aureus: Staphylococcus aureus;* NA: not available/applicable. #: patients with all lower respiratory tract infections (not only pneumonia) are included; ¶: these data refer to *Acinetobacter* spp. (not only *A. baumannii*); +: these data refer to *Pseudomonas* spp. (not only *P. aeruginosa*).

score (*i.e.* those with a modified Jadad score $\geqslant$3) no difference was found in mortality between carbapenems and comparators. The present authors also emphasise that subset analyses were performed to estimate treatment success in CE patients in RCTs [64–68, 72] that provided mortality data in the five RCTs [69, 70, 73–75] without such data. In both of these subanalyses there was no difference in treatment success in CE patients between the studied regimens; however, carbapenems were associated with worse treatment success, although without statistical significance, than comparators in the subanalysis of RCTs that did not provide mortality data [69, 70, 73–75]. Thirdly, early determination in the assessment of treatment success may also have contributed to misclassification of outcome. Specifically, the assessment for treatment success took place at the end of treatment in three RCTs [70, 72, 73], 3 days and 1–4 weeks after completion of therapy in four [66, 67, 71, 75] and five [64, 65, 68, 69, 74] RCTs, respectively. On the contrary, the mortality was assessed 2–4 weeks after completion of therapy. Finally, differences on development of adverse effects between the compared groups of patients, although without statistical significance, may also have contributed to the observed mortality difference.

Pathogen eradication has been shown to correlate with improved clinical outcomes and decreased recurrence of infection. It also contributes to the prevention of emergence

and dissemination of resistant pathogens [76]. The present meta-analysis showed no difference between carbapenems and the comparator antibiotics for the eradication of *A. baumannii*, *K. pneumoniae* and *S. aureus*. On the contrary, carbapenems were associated with fewer eradications of *P. aeruginosa* when compared with fluoroquinolones and β-lactams. This could explain the lower clinical success of this antibiotic in patients with *P. aeruginosa* HAP.

The propensity of *P. aeruginosa* to develop resistance during treatment with imipenem/cilastatin has been reported in four RCTs [66, 68, 69, 75] included in the present analysis as well as in other studies [77, 78]. This propensity, related to the decreased expression of an outer membrane porin channel [79], was not reduced by the simultaneous use of an aminoglycoside in one study [77], which was not included in the current meta-analysis. The development of resistance to imipenem/cilastatin in *P. aeruginosa* strains could explain the fewer pathogen eradications and, consequently, the lower clinical success of this antibiotic in patients with *P. aeruginosa* HAP. Unfortunately, the RCTs of the present analysis involving treatment with meropenem did not provide data regarding the development of resistance to meropenem in *P. aeruginosa*.

Overall, carbapenems appear to be as safe as fluoroquinolones and β-lactams, alone or in combination with aminoglycosides. The present meta-analysis did not demonstrate any increase in the incidence of seizures in the carbapenems-treated patients compared with patients treated with the comparators. The latter result could be explained by various possibilities. First, the well-known convulsion-inducing potential of carbapenems is more common among patients with central nervous system disease or renal impairment [80]. Such patients were excluded from the majority (three [67, 72, 73] out of five) of the studies included in the present meta-analysis that reported data on the number of patients who experienced seizures. Secondly, the dosages of the administered carbapenems were below the limit of 4,000 mg·day^{-1} and 6,000 mg·day^{-1}, for imipenem/cilastatin and meropenem respectively, that induce seizures [81]. Thirdly, the majority of patients included in the RCTs of the present meta-analysis that reported data on the incidence of seizures were under mechanical ventilation. The sedation during mechanical ventilation could prevent the carbapenems recipients from their convulsion-inducing effect.

The major limitation of the current meta-analysis is the small number (only three [65–67] out of 12) of the included RCTs that provided data regarding the time of onset of pneumonia and the risk factors for multidrug-resistant (MDR) pathogens. The lack of such data does not allow estimation as to whether the administration of meropenem and imipenem/cilastatin was according to the guidelines stated by the ATS and the IDSA, which eliminate their use in patients with late-onset pneumonia or risk factors for MDR pathogens [7]. Other limitations of the present study are that the clinical effectiveness was assessed at different days in the various RCTs included in the analysis and that most of the RCTS were not blinded. In addition, only trials published in English, French and German, which focused on non-neutropenic patients, were included. Finally, the findings should be interpreted in light of the fact that publication bias was detected (using the Egger's test) in some of the analyses performed.

In conclusion, despite the above limitations, the findings of the present meta-analysis, which is based predominantly upon open-label randomised controlled trials, suggest that carbapenems should be considered reliable options for the empirical treatment of immunocompetent adult patients with hospital-acquired pneumonia. However, the lack of effectiveness in the treatment of patients with *Pseudomonas aeruginosa* hospital-acquired pneumonia and the development of resistance of *Pseudomonas aeruginosa* during treatment with carbapenems in an era of increasing incidence of multidrug resistant Gram-negative bacteria are important facts that should limit their use to specific patient populations.

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