

Efficacy and safety of piperacillin/tazobactam versus imipenem/cilastatin therapy for pneumonia: a meta-analysis of randomized controlled trials

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Abstract: Piperacillin/tazobactam with its broad spectrum of antibacterial activity was used widely for the treatment of polymicrobial infections. The aim of this study was to compare the efficacy and safety of piperacillin/tazobactam with imipenem/cilastatin for pneumonia. We performed a literature search to identify studies that investigated the effects of randomized controlled trials on piperacillin/tazobactam versus imipenem/cilastatin. The primary study end-points were clinical and microbiological treatment success and treatment-related adverse events. Data analysis was performed by using Review Manager 5.2 software. Four randomized controlled trials met the inclusion criteria. Odds ratio (95% confidence interval (CI)) of clinical treatment success based on clinically evaluable population for patients treated with piperacillin/tazobactam compared with that of imipenem/cilastatin was 1.44 (0.96–2.16); odds ratio (95% CI) of microbiological treatment success based on microbiologically evaluable population for patients treated with piperacillin/tazobactam compared to that of imipenem/cilastatin was 1.58 (0.45–5.56); odds ratio (95% CI) of clinical and microbiological treatment success based on intention to treat population for patients treated with piperacillin/tazobactam compared with imipenem/cilastatin was respectively 1.03 (0.77–1.38) and 0.67 (0.42–1.09); odds ratio (95% CI) of treatment-related adverse events for pneumonia patients treated with piperacillin/tazobactam compared to that of imipenem/cilastatin was 1.10 (0.77–1.59). This meta-analysis provides that piperacillin/tazobactam can be used as safe and efficacious as imipenem/cilastatin in treating hospitalized patients with pneumonia. It is an appealing option for the treatment of severe pneumonia, especially nosocomially acquired pneumonia.

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1. Introduction

Pneumonia is a major cause of morbidity and mortality in low and middle income countries [1]. It represents a spectrum of diseases that range from community-acquired to hospital-acquired and ventilator-associated pneumonia [2]. Nosocomial pneumonia is the second most common cause of hospital acquired infection, and its mortality rate is more than any other nosocomial infection worldwide [3]. The increased mortality seems to be associated with a greater likelihood to receive an inappropriate empirical antibiotic therapy [2, 4]. From a clinical point of view, pneumonia, especially in the frail elderly patients, is often severe, difficult to treat, and accompanied by various complications.

For the initial empirical treatment of patients with pneumonia, the 2005 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines recommend the administration of broad-spectrum antibiotics [5]. Piperacillin/tazobactam (Pip-Tazo) is widely used for the treatment of this disease, because it is stable to beta-lactamase and effective against both gram-positive and gram-negative bacteria. Carbapenems hydrate such as imipenem/cilastatin are also used to empirically treat pneumonia patients and have been shown to be clinically effective and tolerable against pneumonia [6]. However, it has been reported that abuse of carbapenems leads to drug-resistant bacteria, such as *Acinetobacter baumannii* [7], *Pseudomonas aeruginosa* [8]. Carbapenems have a higher risk of developing resistant bacteria than penicillin antibiotics [9]. The range of current

antibiotics is limited, and developing new antibiotics is difficult. Therefore, it is necessary to use existing antibiotics properly to avoid development of resistance.

However, only a few prospective studies have evaluated the therapeutic effects of piperacillin/tazobactam versus imipenem/cilastatin in pneumonia [10-12]. Limited data are available for comparing the effects of these two antibiotics against pneumonia. In this study, we undertook a meta-analysis to compare the efficacy and safety of piperacillin/tazobactam with imipenem/cilastatin for the treatment of moderate-to-severe pneumonia.

2. Materials and Methods

2.1 Search strategy

Following the PRISMA statement guidelines for meta-analysis of randomized controlled trials (RCTs) [13], we performed a literature search for the purpose of identifying RCTs. We searched the electronic databases PubMed, Biomedical Central, Open Access Library, Google Scholar and The Cochrane Central Register of Controlled Trials (CENTRAL) up to 17 June 2014. A loose search strategy, using the terms “piperacillin”, “tazobactam”, “imipenem”, “cilastatin” as keywords, was performed in order to maximize the possibility of identifying all relevant records. The bibliographies of relevant studies were also manually examined to identify additional potentially eligible studies. Our searches were limited to human trials and the language was not restricted to English.

2.2 Eligibility criteria

Each study was screened and reviewed for eligibility independently by two authors. The preliminary search results were then screened on the basis of the following criteria.

Types of studies: Randomized controlled trials, comparing the efficacy and safety of piperacillin/tazobactam with imipenem/cilastatin for the treatment of pneumonia, were identified as part of this review, while review articles, observational studies, letters and commentaries were excluded.

Interventions: The intervention group was restricted to piperacillin in combination with tazobactam; the

control group was imipenem in combination with cilastatin.

Outcome: The study reported separately specific data in two groups regarding clinical treatment success, microbiological treatment success, or treatment-related adverse events. Trials focusing on pharmacokinetic and pharmacodynamic variables or economic evaluation were excluded.

Others: The article was written in English. If it was written in any other language, the article was excluded.

2.3 Data abstraction and qualitative assessment

Two investigators independently tabulated the data using a predefined data extraction form. A double-check procedure was performed to make sure the accuracy of the data extracted. In case of any disagreement between the two reviewers, a third reviewer extracted the data and results were attained by consensus. The following information was subtracted from the study: first author, publishing year, country, study design, type of infection, patient population, drug regimens, concomitant antibacterial agents, number of patients (intention to treat, clinically and microbiologically evaluable populations) and main results (clinical and microbiological outcomes, and treatment-related adverse events).

Quality assessment of included studies was conducted by two independent researchers through collecting data on sources of systematic bias using the Jadad scores [14]. Jadad scores ranged from 0 to 5, in which 0~2 indicated the poor quality and 3~5 were classified as high quality. Any differences between the two reviewers were resolved through discussion. There were no disagreements among the reviewers in quality scores.

2.4 Data analysis

We used Mantel-Haenszel method to calculate odds ratio (OR) and 95% confidence intervals (CI) for all primary outcomes (including clinical and microbiological treatment success, and drug related adverse events) throughout the meta-analysis. Meta-analysis of drug related adverse events was performed by comparing piperacillin/tazobactam with imipenem/cilastatin during the treatment and the post-treatment period, which was based on safety evaluable population. We assessed the statistical heterogeneity

among studies included in the meta-analysis with Cochrane's I^2 statistic, and quantified inconsistency with the I^2 statistic [$100\% \times (Q - df)/Q$]. I^2 ranges between 0% and 100%, and I^2 values of 25%, 50% and 75% are referred to as low, moderate and high estimates. When I^2 statistic was greater than 50%, suggesting substantial heterogeneity, a random effects model was used, whereas a fixed effects model was used when I^2 statistic was less than 50%, suggesting that heterogeneity could be neglected. Pooled summary statistics of the ORs for the individual studies are shown. Pooled ORs were calculated and a 2-sided p -value < 0.05 was considered to indicate statistical significance. All analyses were performed using Review Manager (Version 5.2. Copenhagen: The Nordic Cochrane

Centre, the Cochrane Collaboration, 2012).

3. Results

3.1. Search results

A total of 123 unique titles and abstracts were found from initial searches of the electronic database. With the eligibility criteria, 106 of which were excluded by scrutinizing the titles and abstracts. Moreover, an additional 13 articles were further excluded after a full-text review. A total of 4 RCTs that met inclusion criteria were included in the final analysis. The details of study selection flow are described in Fig. 1.

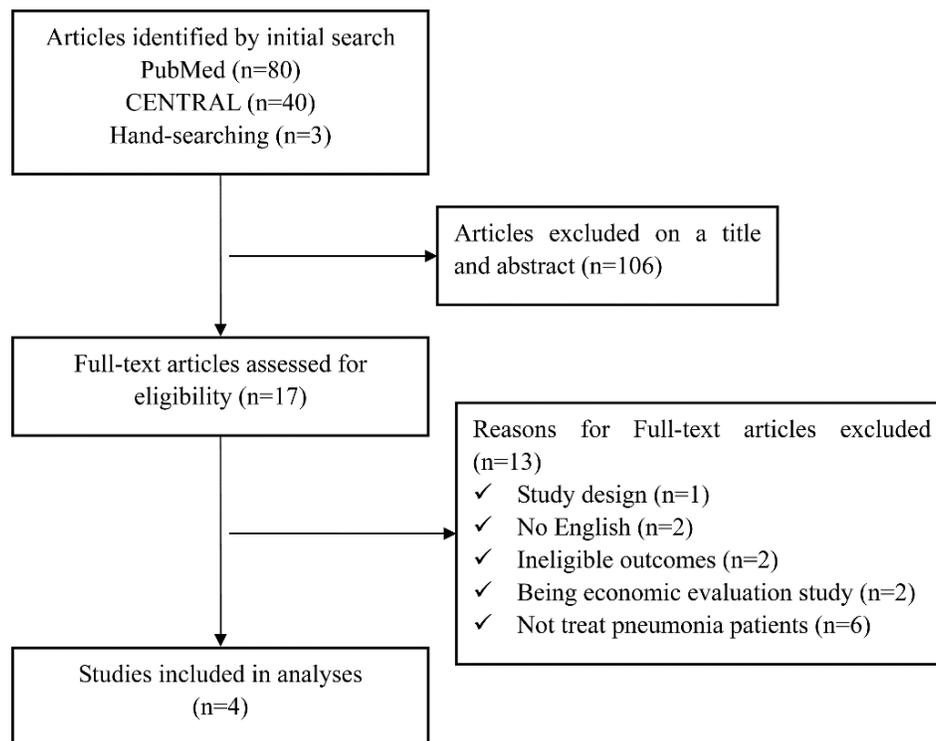


Fig. 1. Study flow diagram.

3.2 Study Characteristics

The main characteristics of the 4 included RCTs [10-12, 15] were summarized in Table 1. A total of 1,510 participants were included in this meta-analysis. Examination of individual trial design revealed that randomized treatment allocation sequences were generated in all included trials, but two studies lacked

appropriately described randomization procedures [10, 11]. All study had a description of withdrawal and dropouts, whereas two studies did not adopt double blind method [10, 15]. Only one study did not apply the intent to treat analysis [15]. The level of evidence for each article was graded from scores 2 to 4 according to the Jadad quality score (Table 2). Quality assessment suggested that the overall study quality was fair.

Table 1. Main characteristics of the included studies in the meta-analysis

Study	Country	RCT study design	Type of infection	Patient population	No. of participants	Drug regimens		Concomitant antibacterial agents	Intention to treat
						Pip-Tazo	IMP		
Schmitt, 2006	Germany	Multicentre, double blind, Phase IIIb	Nosocomial pneumonia	Hospitalised patients, at least 18 years-old	221	4 g/500 mg every 8 hours	1 g/1 g every 8 hours	Aminoglycoside If Pseudomonas aeruginosa was present	110 vs 111
Joshi, 2006	America	Multicenter, double blind	Acute nosocomial pneumonia	Hospitalized patients aged 18 years or older	449	4 g/500 mg IV every 6 hours	500 mg/500 mg IV every 6 hours	Tobramycin until identity, tobramycin or amikacin against Pseudomonas aeruginosa	222 vs 215
Ito, 2010	Japan	Single center, open-label	Moderate-to-severe pneumonia	Patients aged ≥ 15 years	469	5 g (1:4) given intravenously every 12 hours (adjusted for low creatinine clearance)	1 g (1:1) given intravenously every 12 hours (adjusted for low creatinine clearance)	Use of other add-on antibiotics was not permitted	81 vs 82
Jaccard, 1998	Switzerland	Multicenter, open-label	Nosocomial pneumonia and acute peritonitis	Patients were more than 16 years	371	4.5 g three times a day (adjusted to renal function)	500 mg four times a day (adjusted to renal function)	NR	151 vs 162

RCT, randomized controlled trials; MRSA, methicillin-resistant Staphylococcus aureus; Pip-Tazo, piperacillin/tazobactam; IMP, imipenem/cilastatin; IV, intravenously; NR, Not report.

Table 2. Jadad scores for assessment of trial quality of included trials.

First author	Randomized	Method of randomization clear and appropriate	Double blind	Methods of blinding appropriate	Description of withdrawal and dropouts	Sum (Jadad score)	ITT
Schmitt, 2006	1	0	1	1	1	4	Yes
Joshi, 2006	1	1	1	0	1	4	Yes
Ito, 2010	1	0	0	0	1	2	Yes
Jaccard, 1998	1	1	0	0	1	3	No

Points were awarded as follows: study described as randomized, one point; clear and appropriate randomization, one point; study described as double blind, one point; appropriate blind, one point; description of withdrawals and dropouts, one point. ITT, intent-to-treat.

3.3 Analysis of efficacy based on clinically evaluable population

Analysis was performed independently for two categories classified as clinical treatment success and microbiological treatment success, respectively. In the category of 3 trials with clinical treatment success, a total of 249 participants were randomized to the Pip-Tazo group and 257 participants were randomized to the control group. The odds ratio of clinical treatment success for patients treated with piperacillin/tazobactam compared with that of imipenem/cilastatin was 1.44 (95% CI: 0.96–2.16),

which was statistically insignificant ($p = 0.08$) (Fig. 2A). In the second category of 3 trials with microbiological treatment success, a total of 157 participants were randomized to the Pip-Tazo group and 160 participants were randomized to the control group. The odds ratio of microbiological treatment success for patients treated with piperacillin/tazobactam compared to that of imipenem/cilastatin was 1.58 (95% CI: 0.45–5.56), which was not statistically significant ($p = 0.48$). Heterogeneity was noted for this outcome ($I^2 = 74%$) (Fig. 2B), so the pooled OR was calculated using random effects model.

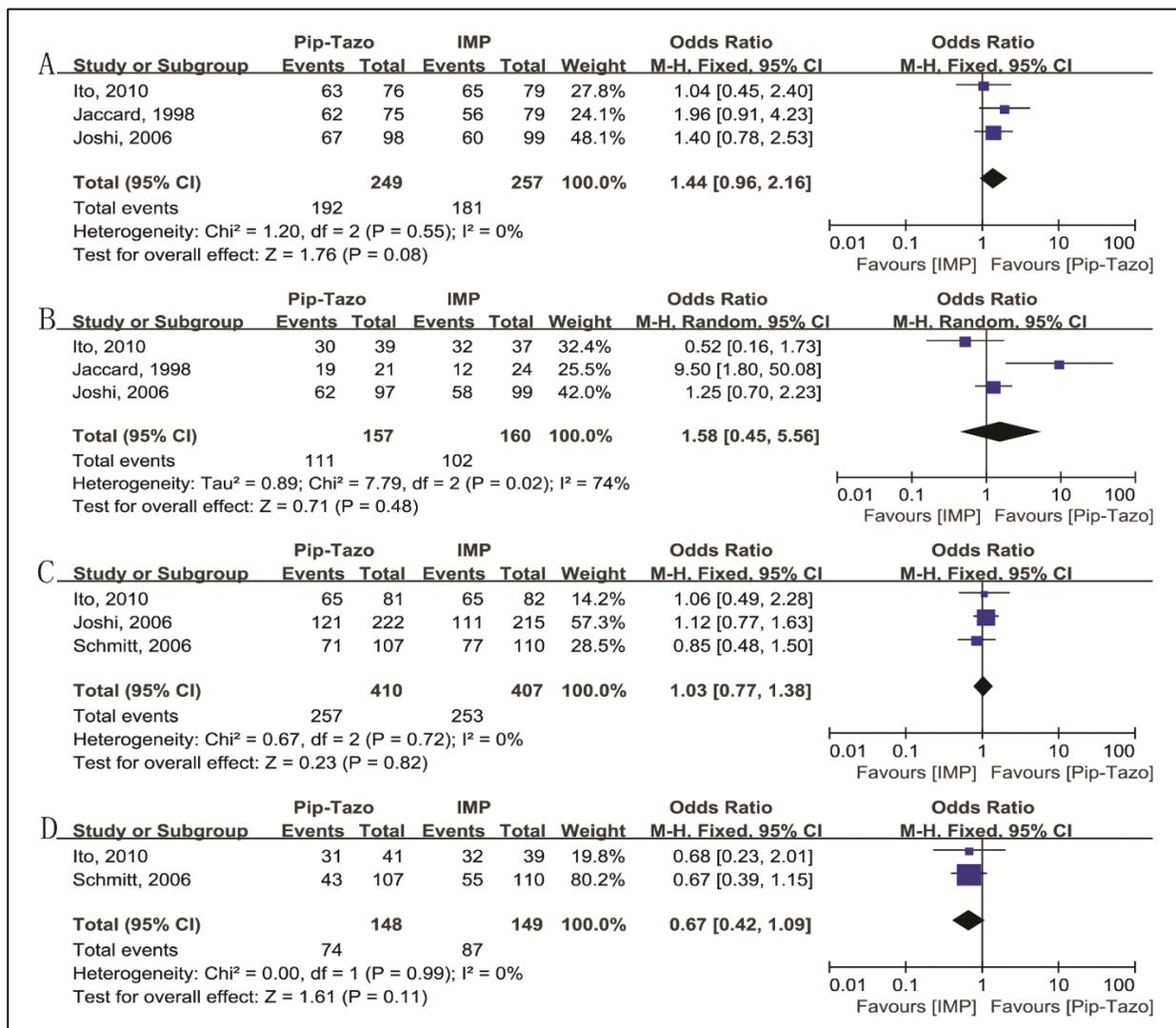


Fig. 2. Meta-analysis of efficacy comparing piperacillin/tazobactam with imipenem/cilastatin. A, clinical treatment success analysis based on clinically evaluable population; B, microbiological treatment success analysis based on clinically evaluable population; C, clinical treatment success analysis based on intention to treat population; D, microbiological treatment success analysis based on intention to treat population. Pip-Tazo, piperacillin/tazobactam; IMP, imipenem/cilastatin.

3.4 Analysis of efficacy based on intention to treat population

The following analyses are based on intention to treat population. For the three trials with clinical treatment success, a total of 410 participants were randomized to the Pip-Tazo group and 407 participants were randomized to the control group. The odds ratio (95% CI) of clinical treatment success for patients treated with piperacillin/tazobactam compared with imipenem/cilastatin was 1.03 (0.77–1.38), which was not statistically significant ($p = 0.82$) (Fig. 2C). For the two trials with microbiological treatment success, a total of 148 participants were randomized to the Pip-Tazo group and 149 participants were randomized to the control group. The odds ratio (95% CI) of microbiological treatment success for patients treated

with piperacillin/tazobactam compared with imipenem/cilastatin was 0.67 (0.42–1.09), which was not statistically significant ($p = 0.11$) (Fig. 2D).

3.5 Analysis of treatment-related adverse events

Three of the 4 relevant RCTs provided the drug related adverse events. Number (%) of patients with drug related adverse events was shown in Table 3. The odds ratio of treatment-related adverse events for pneumonia patients treated with piperacillin/tazobactam compared to that of imipenem/cilastatin was 1.10 (95% CI: 0.77–1.59). No statistically significant difference ($p = 0.60$) was observed between two drug regimens. Heterogeneity was insignificant for this outcome ($I^2 = 28\%$) (Fig. 3).

Table 3. Number (%) of patients with drug related adverse events.

Study	Piperacillin/tazobactam		Imipenem/cilastatin	
	No. of adverse events	Safety evaluable population	No. of adverse events	Safety evaluable population
Ito, 2010	24 (31.6)	76	30 (37.5)	80
Joshi, 2006	204 (91.9)	222	198 (92.1)	215
Schmitt, 2006	82 (74.5)	110	72 (64.9)	111

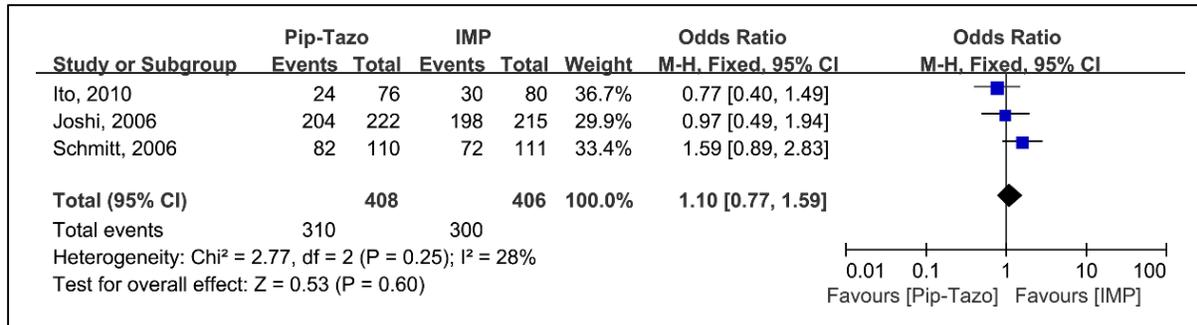


Fig. 3. Meta-analysis of treatment-related adverse events comparing piperacillin/tazobactam with imipenem/cilastatin during the treatment and the post-treatment period. Pip-Tazo, piperacillin/tazobactam; IMP, imipenem/cilastatin.

4. Discussion

This systematic review with a meta-analysis compared the efficacy and safety of piperacillin/tazobactam with imipenem/cilastatin in patients with pneumonia. Only a small number of studies, three trials of them about treating nosocomial pneumonia and one trial involving aspiration

pneumonia, met the eligibility criteria. The main result of this meta-analysis with regard to the primary efficacy outcome, clinical and microbiological treatment success, suggested that no difference existed between the two treatment arms. Likewise, the safety analysis regarding to the treatment-related adverse events proved no difference between the two compared treatment arms. Further, some prospective randomized comparison studies implied that there was no significant

difference between piperacillin/tazobactam and imipenem/cilastatin in the treatment of infectious diseases, such as diabetic foot infections [16], intra-abdominal infections [17-19], urinary tract infections [20], febrile neutropenia [21-23]. As a result, piperacillin/tazobactam and imipenem/cilastatin may be similarly effective in the treatment of polymicrobial infections.

An earlier meta-analysis performed by An et al [24] had provided evidence that piperacillin/tazobactam was as effectively and safely as ertapenem for the treatment of complicated intra-abdominal infections (cIAIs), acute pelvic infections (APIs) and complicated skin and skin-structure infections (cSSSIs). Another meta-analysis on the efficacy of piperacillin/tazobactam showed that extended or continuous infusion of carbapenems or piperacillin/tazobactam was associated with lower mortality [25]. However, the focus of our meta-analysis was to compare the efficacy and safety of piperacillin/tazobactam with imipenem/cilastatin, a well-established therapeutic agent, in patients with pneumonia.

Similar to other meta-analyses, our review has several limitations. Firstly, even though extensive searches were made, it cannot be entirely sure that all relevant articles were located and only four RCTs met our inclusion criteria, which is likely to produce inaccuracies in outcome reporting. Secondly, both double-blind and open-label studies were included in the present meta-analysis, a factor that might generate bias in the assessment of outcomes. Finally, although clear inclusion and exclusion criteria were made, significant differences still existed among drug regimens and concomitant antibacterial agents used.

In conclusion, our meta-analysis revealed that piperacillin/tazobactam is as effective and safe as imipenem/cilastatin in the treatment of moderate- to-severe pneumonia. However, further meta-analysis involving more known RCTs, accessing original trial data, should be performed.

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