



# Efficacy and Safety of Piperacillin-Tazobactam: Systematic Review and Metaanalysis

Rosanova Maria Teresa<sup>1\*</sup>, Bes David<sup>2</sup>, Sberna Norma<sup>3</sup>, Herrera Ramos Estefanía<sup>4</sup> and Lede Roberto<sup>5</sup>

<sup>1</sup>Infectious Diseases Chief of Clinical Practice Hospital Juan P. Garrahan, Buenos Aires-Argentina

<sup>2</sup>Internal Medicine Hospital Juan P. Garrahan, Buenos Aires-Argentina

<sup>3</sup>Pharmacy Chief Hospital Juan P. Garrahan, Buenos Aires Argentina

<sup>4</sup>Information Specialist Fundación Canaria de Investigación Sanitaria (FUNCANIS), Spain

<sup>5</sup>School of Medicine Universidad Abierta Interamericana, Buenos Aires, Argentina

## Review Article

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**\*Corresponding author:** Dra Rosanova María Teresa MD PhD. Infectious Diseases Chief of Clinical Practice, Hospital Juan P. Garrahan Buenos Aires-Argentina, Email: margris2@yahoo.com.ar

## Abstract

**Introduction:** Piperacillin-tazobactam (PTZ), although contested, is frequently utilized for empirical treatment of Gram-negative bacteria treatment.

**Objective:** Systematic review to evaluate if PTZ is associated with lower rates of treatment failure and less adverse effects than other comparators.

**Material and Methods:** Literature search in Embase, and MEDLINE databases using “piperacillin tazobactam” as leading term. A study qualified, when a properly randomized control trial (RCT) compared the efficacy and safety of PTZ with other antibacterial agents in an “intention to treat analysis” of clinically evaluable patients.

**Results:** Eleven studies fulfilled inclusion criteria. Pooled RR of failure risk rate was 25% less using PTZ than other comparators (0.75; CI 95% 0.59-0.95). Adverse effects were similar.

**Conclusions:** PTZ can be adequately considered for empirical treatment of patients with Gram-negative bacteria infections

**Keywords:** Piperacillin-Tazobactam; Efficacy; Bacterial Infections; Safety; Gram Negative; Empiric Therapy; Systematic Review; Failure

## Introduction

Piperacillin-tazobactam (PTZ) is one of the most frequently utilized antibiotic agents for empirical Gram-negative bacteria coverage and remains active against a large proportion of extended-spectrum-beta-lactamase-producing Gram-negative bacteria [1] (ESBL-GN.) The efficacy of PTZ, its similar safety profile and the possibility of its use as monotherapy decreasing the need for combined antibiotic treatments, make the drug an attractive option in clinical practice [1,2].

Carbapenems have been considered the most effective therapy for serious infections caused by resistant Gram negative bacteria; however, increased use has selection pressure for carbapenem resistance, an emerging threat which has contributed to increased selective pressure of multi-resistant Enterobacteriaceae [2-5]. To counterbalance this, PTZ is proposed as a carbapenem-sparing agent to reduce the incidence of multidrug-resistant bacteria and super infections [2].

With all these previous considerations, physicians have to prescribe the most appropriate empirical antibiotic therapy for Gram-negative infections.

To clarify this, we carried out a systematic review (SR) to evaluate if PTZ is associated with a lower rate of treatment failure compared with other antibiotics.

## Material and Methods

### Search Strategies

A literature search was carried out in Embase and

MEDLINE databases using the search terms “piperacillin tazobactam” with the following filters: Clinical Trial, Review, Comparative Study, Systematic Reviews, Randomized Controlled Trial (RCT), Controlled Clinical Trial, Practice Guideline, Meta-Analysis and Guidelines, and Use in Human Studies. The International Clinical Trials Registry Platform (WHO) and The Cochrane Library were also searched. Articles published in English, Spanish, or French till September 2019 was reviewed and articles reference lists were manually searched for additional relevant studies. See Table 1 Search strategy results.

Database	Access platform	Initial date	Access date	Results
				Total
MEDLINE	Ovid SP	1946	30/09/2019	957
EMBASE	Elsevier	1974	30/09/2019	1133
COCHRANE LIBRARY	Clarivate Analytics	1995	30/09/2019	142
TOTAL				2232
DUPLICATED				607
TOTAL				1625
International Clinical Trials Registry Platform (WHO)				32

**Table 1:** Search strategy results.

The efficacy endpoint that was analyzed was treatment failure, which was defined as the inverse of trials' endpoints “success” according clinical evolution (CE). Safety end-point was the presence of any adverse effects (AE).

### Study Selection

Data extraction and qualitative assessment were performed independently by two reviewers (MTR and DB). In case of disagreement, a third reviewer (RL) analyzed the data and managed the scientific discussion until consensus was reached.

Studies qualified if RCT assigned testing interventions by randomization procedures (non violable) with proper allocation concealment (non predictable); assessed the efficacy and safety of PTZ versus other antibacterial agent in an “intention to treat analyses” of clinically evaluable patients and had a loss-to-follow-up rate  $\leq 15\%$ . Trials were included regardless their blinded or open-label design. Only trials in which the research unit were patients were considered.

### Data Analysis and Statistical Methods

Efficacy end points were based on clinical evaluable (CE)

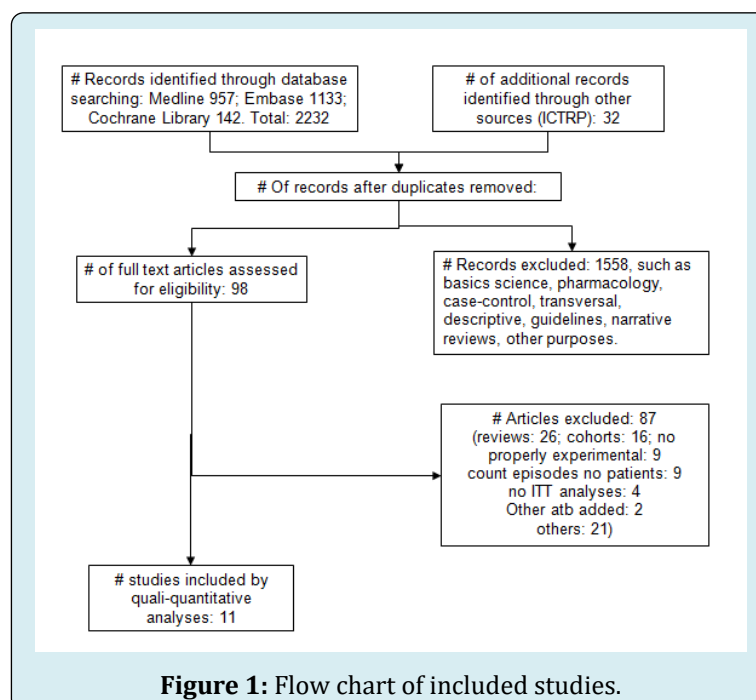
populations of each study. Pooled risk ratio (RR) and 95% confidence intervals (CIs) were calculated for treatment failure and safety outcomes using the random-effects model (Der-Simmonian-Laird) for more conservative analysis irrespective heterogeneity results. Calculations were carried out using the Metaanalysis calculator by EPIDATA software (WHO) ver. 3.1. Heterogeneity bias was estimated according to the Q-test and  $I^2$  index. Publication bias was estimated by the Egger's test. A subgroup analysis was performed to assess bias associated to double blind or open label RCT related bias using J Primo, Sagunto Hospital, Spain software, applying the Mantel-Haenszel procedure. In any stage, the null hypothesis was rejected if  $p < 0.05$ . This study complies with the suggestions of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6].

## Results

Literature search identified a total of 2264 related papers of which only 11 fulfilled inclusion criteria; and thus, were included in the SR. Figure 1 shows the results of the articles' selection process and Table 2 summarizes the main characteristics of the included articles.

Author year	Indication	Intervention		Failure / Total	AE / Total
		exper	control		
Eklund, 1993	Intra-abdominal infections	pip-taz	impipinem / cilastin	Exper.: 4 / 55 Control: 18 / 58	Exper.: 13 / 55 Control: 14 / 58
Marra, 1997	Serious bacterial infections	pip-taz	imipinem	Exper: 24 / 75 Control: 23 / 75	Exper: 4 / 75 Control: 12 / 75
Jaccard, 1998	Nosocomial neumonía or peritonitis	pip-taz	imipinem / cilastatin	Exper: 17 / 151 Control: 29 / 162	Exper.: 22 / 151 Control: 24 / 162
Ohlin, 1999	Intra-abdominal infections	pip-taz	cefuroxime / metronidazole	Exper: 37 / 140 Control: 39 / 1298	Exper: 13 / 105 Control: 9 / 100
Alvarez, 2000	Nosocomial Pneumonia	pip-taz / amikacin	ceftazidime / amikacin	Exper: 10 / 88 Control: 10 / 36	Exper: 21 / 88 Control: 5 / 36
Naber, 2002	Complicated urinary tract infections	pip-taz	Imipenem / cilastatin	Exper: 25 / 147 Control: 31 / 152	Exper: 20 / 147 Control: 16 / 152
Roy, 2003	Acute pelvic infection	pip-taz	etarpenem	Exper: 12 / 153 Control: 8 / 163	Exper: 43 / 192 Control: 48 / 214
Erasmus, 2004	Intra-abdominal infections	pip-taz	impipinem / cilastin	Exper: 3 / 111 Control: 3 / 103	Exper: 16 / 111 Control: 19 / 103
Saltoglu, 2010	Diabetic foot infections	pip-taz	imipenem / cilastatin	Exper: 16 / 30 Control: 23 / 32	Exper: 9 / 30 Control: 3 / 32
Aamir, 2015	Febrile neutropenia	pip-taz	cefepime	Exper: 5 / 20 Control: 4 / 20	Exper: 5 / 20 Control: 6 / 20
Zhang, 2016	Diabetic foot infections	pip-taz	etarnepem	Exper: 6 / 224 Control: 14 / 219	Exper: 1 / 275 Control: 3 / 275

**Table 2:** Treatment failures and Safety of PTZ vs comparator in included studies.  
Exper: Pip-taz; Control: comparator.



Only 4 trials out of 11 were double-blind [7-10]. The rest were open-label, single blind or no blindness. Two RCT included patients treated for diabetic foot infections [8,11] four comprised patients with intra-abdominal infections [10,12-14] one focused on oncology patients with treated for febrile neutropenia [15] and four compared patients treated for other types of infections [9,7,16,17].

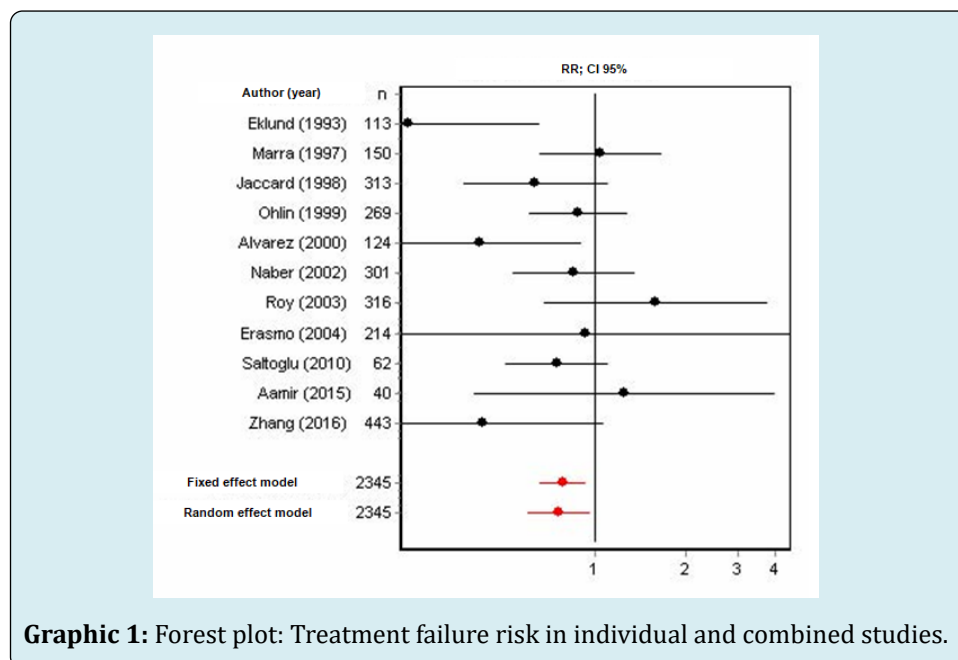
The pooled incidence of treatment failure of the PTZ group was 13.32% and of the comparator group, 17.55%. Table 3 shows the pooled RR (CI95%) for the risk of failure, the effect size of each study and the results of the sensitivity analysis.

Author	Year	N patients	RR	CI 95%	Sensitivity analysis
Eklund	1993	113	0.23	0.08-0.64	5.56
Marra	1997	150	1.04	0.64-1.67	-5.02
Jaccard	1998	313	0.62	0.36-1.09	1.88
Ohlin	1999	269	0.87	0.59-1.27	-3.53
Alvarez	2000	124	0.4	0.18-0.89	5.14
Naber	2002	301	0.84	0.52-1.35	-2.46
Roy	2003	316	1.59	0.67-3.80	-3.79
Erasmus	2004	214	0.92	0.19-4.49	-0.85
Saltoglu	2010	62	0.74	0.49-1.10	-0.89
Aamir	2015	40	1.25	0.39-3.98	-2.18
Zhang	2016	443	0.41	0.16-1.07	3.51
Fixed effect model			0.77	0.65-0.92	
Random effect model			0.75	0.59-0.95	

**Table 3:** Risk of treatment failure in individual studies and pooled results.

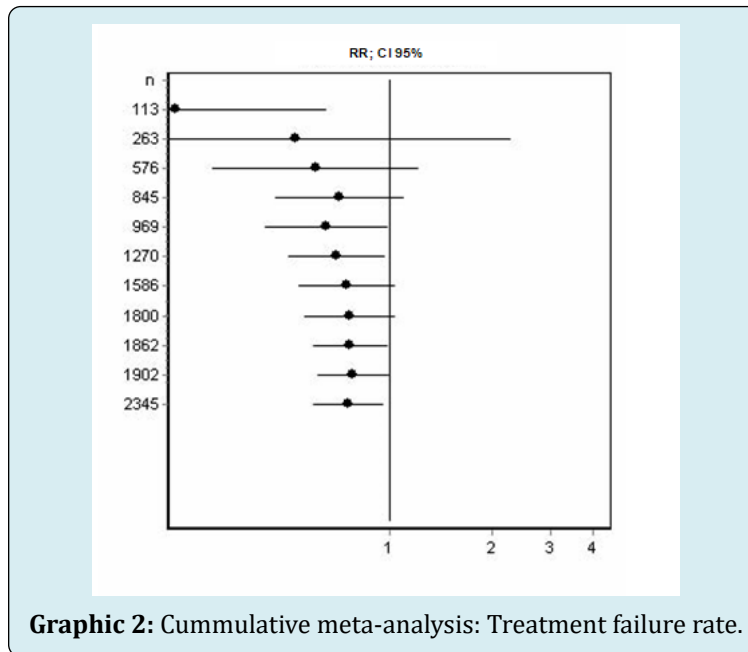
No relevant heterogeneity was detected (Q-test 14.93; DF 9; p 0.09.  $I^2$  35%). Pooled RR failure risk rate was 25%

less using PTZ than other comparators (0.75; CI 95% 0.59-0.95) (Graphic 1).



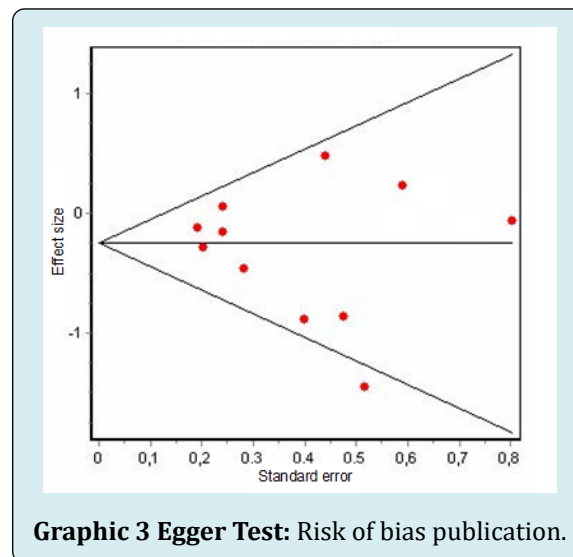
Cumulative metaanalysis (Graphic 2) illustrates that as the sample size increases, the effect size achieves more

relevance and accuracy, showing a consistent trend toward less risk of treatment failure using PTZ.



The sensitivity analysis shows that [12] (5.56%) is the most influential study and the least, [14] (-0.85%). Both used the same comparator (imipinem-cilastin) and for the same indication (intraabdominal infections). The planned subgroup analyses according blindness, reveals that the pooled RR in double blind studies (n 1210 patients), is 0.91;

CI 95% 0.61 to 1.35, while that of the open label studies (n 1135), 0.67; CI 95% 0.49 to 0.90. The difference between them was not statistically significant, yielding a p value of 0.23 (Z statistic 1.20). No risk of bias of publication was detected (Graphic 3).



Adverse events: Nor heterogeneity nor publication bias was detected in this comparison.

Treatment groups had similar rates of adverse events (15.75% vs. 14.28%) (Pooled RR 1.02; CI95% 0.81-1.29).

## Discussion

We conducted this SR to assess in children and adults, with all sorts of bacterial infections, the comparative

effectiveness and safety of PTZ against available comparators.

Some authors state that PTZ is another treatment option to carbapenems, but limited to mild infections or urinary tract infections [6,18,19].

This SR analyzed PTZ vs another antibiotic comparator in a wide type of infections, including intraabdominal infections, febrile neutropenia, infections in diabetic patients, nosocomial pneumonia, all of which cannot be considered minor clinical threats.

Our results suggest that PTZ leads to a lower rates of treatment failure and is well tolerated, consistent with the good safety profile of the beta-lactam class [1-5]. The cumulative metaanalysis showed a clear trend that the risk of treatment failure is lower for PTZ than for comparators, and that the incidence of adverse events was not different.

A strength of our study is that, to the best of our knowledge, this is the first systematic review and metaanalysis on the efficacy and safety of PTZ that includes only properly randomized controlled trials minimizing selection bias. This means that given the precautions taken to minimize selection bias by including only properly RCT, the clinician, who must often prescribe antibiotic treatments before having the microbiological results, can be confident that the risk of failure with empirical PTZ is lower than if another antibiotic is indicated.

Concerns arose, when it was found that all RCT studies were conducted in a diversity of underlying diseases, with some antibiotic comparators that are not typically indicated in clinical practice for treatment of these pathologies, using different doses and follow-up periods, with some infections not being microbiologically documented or in absence of ESBL-GN, some studies with few participants and mostly having treated adults. However, no significant heterogeneity was identified in the study.

On the other hand, it is not possible to totally rule out that the obtained results are not linked to the bias protection grade of the adopted design.

Further studies are needed to better understand the role of PTZ in empiric treatment of patients in intensive care settings, with ESBL-GN microbiologically documented infections and particularly, in children.

## Conclusions

PTZ can be considered an adequate antibiotic option for empirical treatment of serious infections due to gram negative bacterias.

## Summary points

Piperacillin tazobactan (PTZ) is an antibiotic frequently used in medical practice for the treatment of Gram negative infections. The present SR suggests that PTZ has a lower risk of therapeutic failure than other antibiotics, while the safety profiles are the same.

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