Evaluation Outcomes Associated with Alternative Dosing Strategies for Piperacillin/Tazobactam: A Systematic Review and Meta-Analysis

Hui Yang, Xiangli Cui, Zhuo Ma, Lihong Liu

Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China.

Received, March 25, 2016; Revised, June 13, 2016; Accepted, July 4, 2016; Published, July 7, 2016.

Abstract - A better dosing strategy can improve clinical outcomes for patients. We systematically reviewed the literatures to determine whether any clinical benefits exist for piperacillin/tazobactam by extended or continuous infusion. **Methods -** A search of PubMed, Web of Science, ProQuest, ScienceDirect, Cochrane, Embase and related ICAAC and ACCP conferences were conducted up to September 5, 2015. Randomized controlled and observational studies that compared extended or continuous infusion with conventional intermittent infusion of piperacillin/tazobactam were identified from the databases above and analyzed. Two reviewers independently evaluated the methodology and extracted data from primary studies. A meta-analysis was performed using Revman 5.2 software. The quality of each study was assessed. Sensitivity analysis and publication bias were evaluated. **Results -** Three randomized controlled trials and twelve observational studies were included in this study. All included studies had high quality and no publication bias was found. Compared to the conventional intermittent infusion approach, the extended or continuous infusion group had a significant cost effectiveness (OR -0.89.02, CI (-114.69,-63.35), P<0.00001). No statistical difference was observed for clinical cure rate (OR 1.64, 95% CI (0.88, 3.30), P=0.12) between the two dosing regimens. The sensitivity analysis showed the results were stable. **Conclusions** - Our systematic review and meta-analysis found that the outcomes associated with alternative dosing strategies of piperacillin/tazobactam have changed compared with conclusions before for several literatures with large samples published. Further data on the outcomes should be generated for a better understanding of the extended or continuous infusion strategy. On the whole, our meta-analysis suggested that the extended or continuous infusion should be recommended for clinical use only considering its economic advantage, but there was no significantly higher clinical cure rate and lower mortality rate compared with the conventional intermittent infusion.

INTRODUCTION

As more is understood about antimicrobial agents through research, it is evidenced that proper use of antimicrobials can improve clinical outcomes and reduce resistance, while maintaining antimicrobial sensitivity in general population (1)-(4). Piperacillin/tazobactam is a broad class of antibiotics commonly used to successfully treat bacterial infections (5)-(6). Conventional dosing strategy of piperacillin/tazobactam is an intermittent 30-minute infusion, potentially resulting in serum concentrations below minimum inhibitory concentration (MIC) for a prolonged period of time (7). As a time-dependent antibiotic, the bactericidal activity of piperacillin/tazobactam is optimized when drug concentrations exceed the fractional time above the minimum inhibitory concentration (fT>MIC) for at least 30% to 50% (8)-(9). Several studies have consistently demonstrated that continuous infusion allows the maintenance of concentrations above the MIC for a longer period of time within the dosing interval (10)-(11).Two meta-analyses have been conducted to compare the clinical outcomes of patients who received prolonged or continuous infusions versus conventional intermittent infusions (12)-(13). According to the latest understanding, the extended or continuous infusion of piperacillin/tazobactam led to a higher clinical cure rate and a lower mortality rate than the conventional intermittent strategy (13). However, many new studies with large samples have been published recent years (14)-(16). Therefore, it is important and necessary to systematically investigate the clinical outcome differences between the two dosing strategies of piperacillin/tazobactam from those clinical trials in order to produce an evidence-based recommendation for which strategy is better for clinical practice.

Corresponding Author: Lihong Liu, Pharmacy Department of Beijing Chao-Yang Hospital, 8 Gongren Tiyuchang Nanlu, Chaoyang District, Beijing, China; Email: hongllh@126.com.

METHODS

Literature search

Relevant English language studies included in this review were identified from PubMed, Web of Science, ProQuest, ScienceDirect, Cochrane and related Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and American College of Clinical Pharmacology （ACCP） conferences databases. Databases were searched from inception up to September 5, 2015 using combinations of the following search terms: (piperacillin/tazobactam) AND (extended OR continuous OR prolonged OR intermittent OR discontinuous OR short OR traditional OR conventional OR intermittent) AND (duration OR infusion OR administration OR interval OR dosing).

Study selection

Articles reporting the comparative outcomes of patients treated with the two different dosing strategies of piperacillin/tazobactam were eligible for the meta-analysis, and the types of studies included were prospective study, retrospective study and randomized controlled trials (RCT). Two authors (H.Y and Z.M) independently screened titles and abstracts identified by the search process. Afterward, all full text articles from potentially eligible studies were retrieved and independently reviewed by the same authors using the aforementioned inclusion criteria. Any disagreement was resolved by discussion and in consensus with the principal author (X.L.C and L.H.L).

Quality assessment

Independent evaluation of methodological quality was performed by two reviewers (H.Y and Z.M). Discrepancies were resolved by involvement of a third review author (X.L.C) if required. RCTs were appraised for methodological quality using the criteria developed by the Cochrane risk of bias tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The Newcastle-Ottawa Scales (NOS) was used to assess the quality of observational studies (17).

Data extraction

Two reviewers (H.Y and Z.M) independently extracted relevant information for the meta-analysis. The following data were extracted from each study: the characteristics of each study (author, study design, years, country), patient population (numbers of patients, type and etiology of infection), drug regimens, and clinical outcomes (clinical cure, mortality, days in hospital, cost) of the two groups in each study. And clinical cure was defined as “cure” (the complete resolution of clinical signs and symptoms of infection, with no new signs or symptoms associated with the original infection) or “improvement” (the patient was not cured, but there was a resolution or a reduction of the majority of the clinical signs and symptoms of infection and no new or worsened signs associated with the original infection) in these studies. Days in hospital were directly described instead of statistical analysis considering different data expression.

STATISTICAL ANALYSIS

Analyses were performed using Review Manager for Windows (version 5.2). Odds ratio (OR) and 95% confidence interval (CI) were calculated for each outcome. The presence of heterogeneity between trials was assessed by $\chi 2$ test. A P-value of<0.10 was defined to note statistical significance in the analysis of heterogeneity. The extent of the inconsistencies was characterized using the I^2 statistic. Considerable heterogeneity was indicated by I^2> 50%. Mantel-Haenszel fixed effects model (FEM) was used when there was no significant heterogeneity between studies; otherwise, a random effects model was chosen. Adverse events were directly described instead of statistical analysis considering few sample sizes included. In order to evaluate the stability of results without estimation bias from individual study, sensitivity analysis was performed by exclusion of each study one by one. This process of excluding one study at a time allowed for identification of any single article that may have a large influence on the final results. Publication bias was assessed using the funnel plot method, of which funnel plot asymmetry was assessed by Egger’s linear regression test (18).

RESULTS

Literature search

A total of 15 studies with 4847 patients were identified that were eligible for inclusion in the meta-analysis. The whole literature search process is summarized in Figure 1.

Study description

The characteristics of the eligible studies are presented in Table 1. This meta-analysis included fifteen studies, among which were two prospective studies (19),(20),ten retrospective studies (14)-(16)，(21)-(27) and three RCTs (28)-(30). The patients of five of the included studies were persons who were admitted to the Intensive Care Unit (ICU) with severe infection, and the other nine studies included

only non-ICU patients with moderate or severe infection. Overall, 4847 patients were included in the analysis in the identified studies. In the included studies, conventional intermittent infusion regimens were 2.25-4.5g over 20 or 30min three or four times daily. The extended infusion regimens lasted greater than 3 hours and the continuous infusion regimens lasted 24 hours with the doses ranging from 6.75 to 13.5g daily.

Quality of included studies

Seven factors were used to evaluate the bias of the three RCT studies according to the Cochrane risk of bias tool. Most factors for all studies showed low bias. However, the method used to generate the allocation sequence in the RCT was not considered adequate, and allocation concealment was not described. On the whole, the included RCTs in our study were of relatively high quality (Supplementary Figure 1 and Supplementary Figure 2).

Included observational were of high quality. Eight factors were used to assess study quality according to NOS. The more factors the study met, the higher the quality of the study was. All studies were adequate in all criteria. The results showed that all observational studies were high quality (Supplementary Table 1).

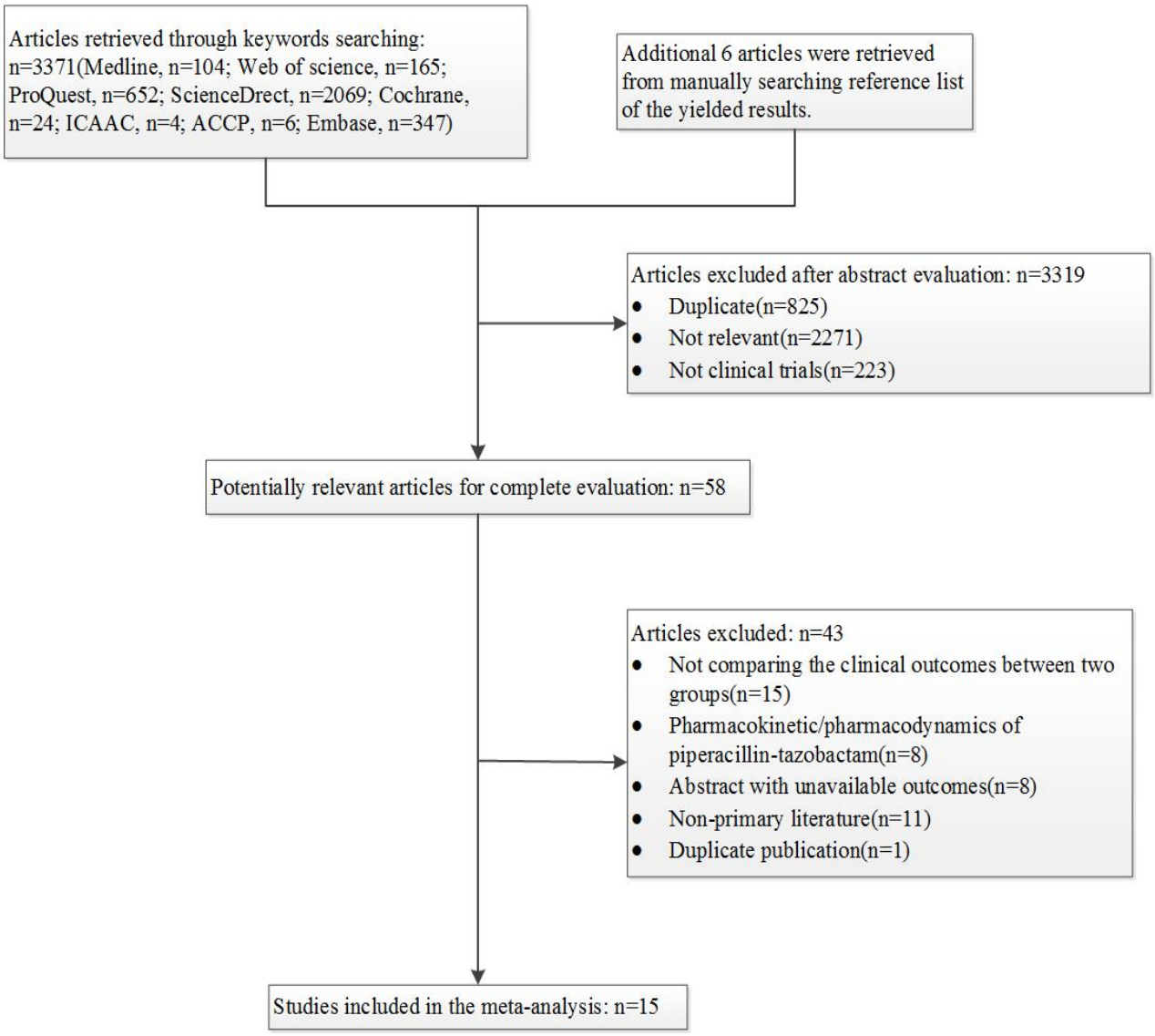

Figure 1. Flow chart depicting the selection process of studies included in the meta-analysis.

Clinical cure

Pooled outcomes of 7 studies reported clinical cure rate (19),(20),(23),(24),(14),(28),(30). Compared to the conventional intermittent infusion, the extended or continuous infusion had no significantly higher clinical cure rate (872 patients, OR 1.02, 95%CI 0.47-2.26, P=0.12; Figure 2). Significant heterogeneity was found among all the studies (I^2=51%, P=0.07). Subgroup analyses also indicated no statistical difference in clinical cure rate between the two infusion strategies. The funnel plot did not show obvious asymmetry, and there was no publication bias presented by Egger's test (P=0.440).

Mortality

Pooled outcomes of twelve studies, including two RCTs showed there was a statistically significant mortality advantage to extended or continuous infusion (OR 0.61, CI(0.67,0.99), P=0.04)(14),(16)(19),(21)-(27),(28)-(29). No significant heterogeneity was found among the studies (I^2=44%, P=0.06). Results of subgroup analyses are displayed in Figure 3. Stratification by study design showed that a mortality benefit was only associated with extended or continuous infusion in observational studies (OR 0.82，CI（0.67，1.00），P=0.05) but not in RCTs (OR 0.60，CI(0.19,1.93)，P=0.39). Obvious asymmetry was not found in the funnel plot. Egger's test showed no publication bias, and the p value was 0.420, which indicated no statistically significant difference. The results of sensitivity analysis showed substantial modification of the estimates after exclusion of individual study one by one which showed that the result was not reliable.

Cost

Pooled outcomes of three studies showed a statistically significant difference in healthcare costs between the two infusion strategies (2298 patients, OR -89.02, 95%CI (-114.69,-63.35), P＜0.00001, Figure 4)(16),(19),(30). Subgroup analyses showed that extended or continuous infusion group had a significantly cost benefit in cohort studies subgroup (OR= -83.24, 95%CI (-109.66, -63.35), P＜0.00001, Figure 4) and in RCT subgroup (OR =-187.23, 95%CI(-296.18,–78.28), P = 0.009; Figure 3). No significant heterogeneity was found among the studies (I^2=43%, P= 0.17). The results of sensitivity analysis showed no substantial modification of the estimates after exclusion of individual study one by one.

Length of hospital stay

Twelve of fifteen studies reported length of hospital stay (14)-(16),(19),(21)-(23),(25)-(27),(29)-(30). Seven studies reported length of stay by median, while the others used average. Grant et al reported that days of therapy were similar with both treatment groups (7.3±4.8 days for continuous infusion versus 8.7±7.1 days for conventional intermittent infusion, P = 0.26) (19). This finding was also found by other eight studies. However, Lodise et al (18), Lee et al (27) and Lu et al (30) reported that length of hospital stay was significantly shorter for patients who received extended or continuous infusion.

DISCUSSION

The purpose of this study was to conduct an updated review of these studies and to identify whether there is a clinical benefit of extended or continuous infusion on clinical cure rate, mortality, and economic benefit over cost. Our meta-analysis, including fifteen studies (two prospective studies, ten retrospective studies, and three RCTs), showed that the extended or continuous infusion strategy was associated with economic benefits compared with the conventional intermittent approach. The clinical cure rate and mortality were not significantly different between the two dosing approaches. The severity of infection was not included as part of the result analysis among these studies, but the average level of severity of infection between two dosing groups for each study was not significantly different.

Higher clinical cure rate for the extended or continuous infusion approach was not found in our study, which was in line with Falagas et al' research published in 2013 (12), but was contrary to the research of Yang et al in 2014 (13). Many new studies with better study design and larger samples have been published since April 2014 (14)-(16). A total of 1275 patents were included in the Cutro et al' analysis published in 2014 (14). Clinical cure rates were almost identical between extended infusion and conversional infusion, 18.4% versus 19.9% for all patients (P =0.756) in Cutro et al' study. This is the study with the largest sample size comparing different dosing protocols by the end of the 2014. This article made an impact on the final outcome of clinical cure rate. Subgroup analysis were made, which was not included in the study published by Yang, 2014 (13). The subgroup analyses showed that extended or continuous infusion had no significantly impact on clinical cure rate in the cohort studies subgroup or in the RCT subgroup. Sensitivity analysis is used to measure the stability of the results, and it did not modify the conclusion of the study when excluded during the sensitivity analyses.

Our meta-analysis only found that extended or continuous infusion was not worse to conventional

infusion. The result showed that mortality was lower among patients who received extended or continuous infusion of the piperacillin/tazobactam, but stratification by study design showed that a mortality benefit was only associated with extended or continuous infusion in observational studies but not in RCTs. In addition, sensitivity analysis showed substantial modification of the estimates after exclusion of individual study one by one, which indicates that the result was not reliable. All in all, we cannot reach the conclusion that extended or continuous infusion of piperacillin/tazobactam resulted in significantly lower mortality rate compared with the conventional intermittent infusion. Our result differs from the published articles in 2013 and 2014 (12)-(13). We conclude that the two studies included in our meta-analysis with large sample size led to different result. No significant differences between the extended infusion or continuous infusion and conversional infusion in inpatient mortality rates (10.9% versus 13.8%; P = 0.282) in Cutro et al' research in 2014 (14). Brunetti et al found that 14-day in-hospital mortality was similar between groups in 2150 patents in 2015 (OR=1.16; 95%CI = 0.85-1.58; P=0.37) (16). To our knowledge, the two studies were the largest sample size up till today comparing the two dosing strategies. This might explain the difference between the results.

This article is the first meta-analysis finding that the extended or continuous infusion of antibiotics is associated with economic benefits. Study suggested that extended or continuous infusion of piperacillin/tazobactam was more cost-effective than conversional infusion. The potential economic benefits might be attributed to lower cost of antibiotics acquisition as showed in studies that used lower doses in patients with extended infusion or fewer days of ICU or hospital stay (31)-(32). There were only three studies that included in economic analysis. More well-designed trials are needed to clarify this issue.

All studies that we analyzed were of high quality, including RCTs and observational studies. Therefore, our conclusions were relatively reliable, but the findings of this meta-analysis should be interpreted in view of certain limitation. First, only 3 of 15 of the included studies were RCTs, where small sample size might introduce bias. Additionally, information regarding concurrent medications was not released in the studies analyzed. Therefore, drug interactions were unknown and could not be evaluated in our analysis. Also, disease status and drug doses were not the same in all studies, which could influence the clinical outcomes.

In conclusion, evidence demonstrated that the extended or continuous infusion of piperacillin/tazobactamis associated with significant cost savings than the conventional intermittent strategy. Therefore, this alternative infusion strategy could be recommended in clinical practices. Further data should be generated for a better understanding of the extended or continuous infusion strategy.

ACKNOWLEDGEMENTS

We thank all the original authors of the included studies for their wonderful work.

AUTHOR CONTRIBUTION

The experiments were designed by LHL and performed by HY and XLC. The data were analyzed by HY and ZM. The manuscript was written by HY and revised by ZM, XLC and LHL.

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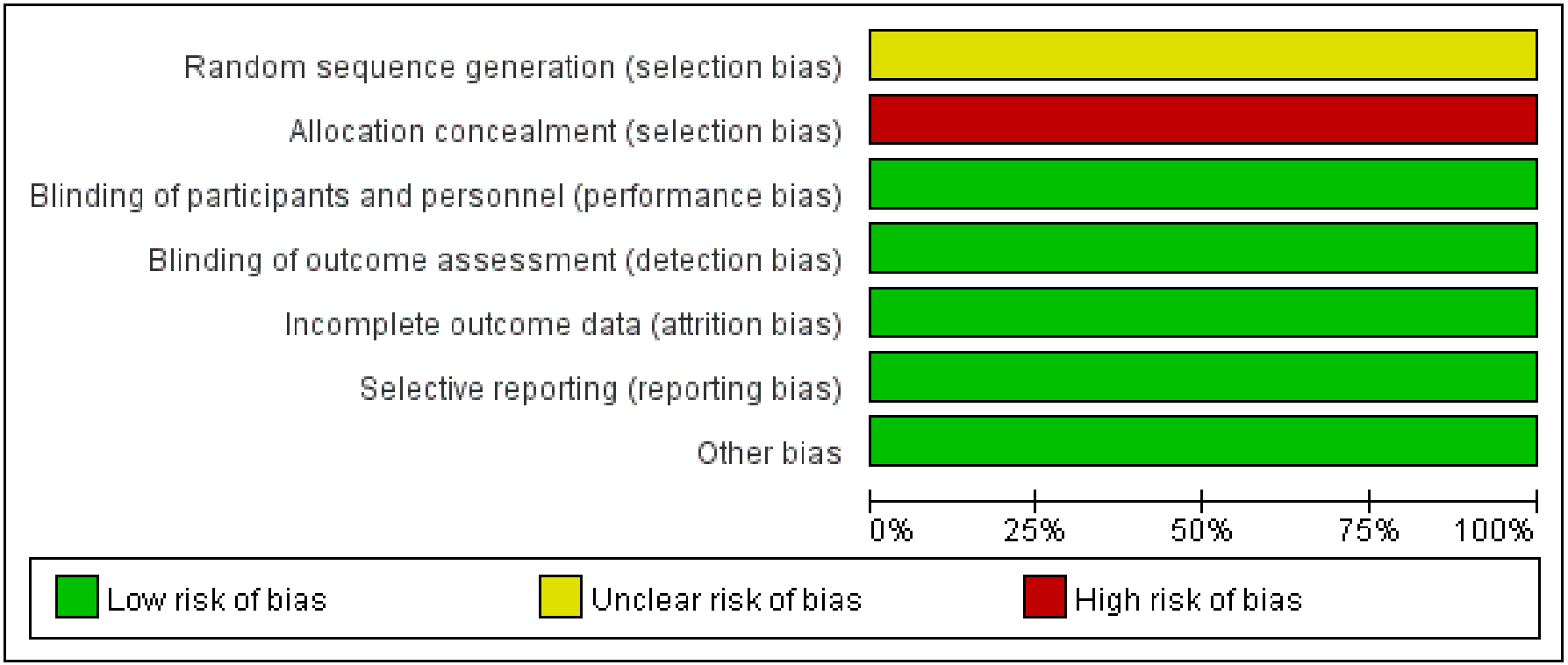
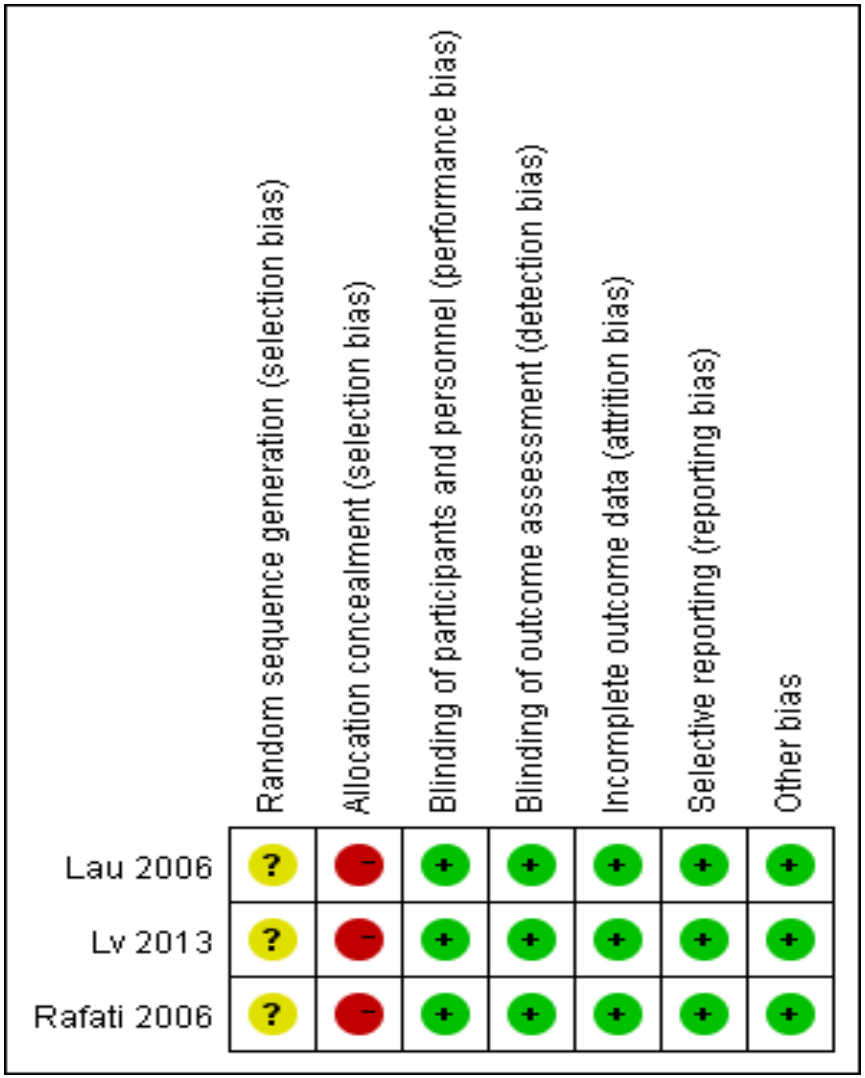


Supplementary Figure 1. Risk of bias summary



Supplementary Figure 2. Risk of bias graph

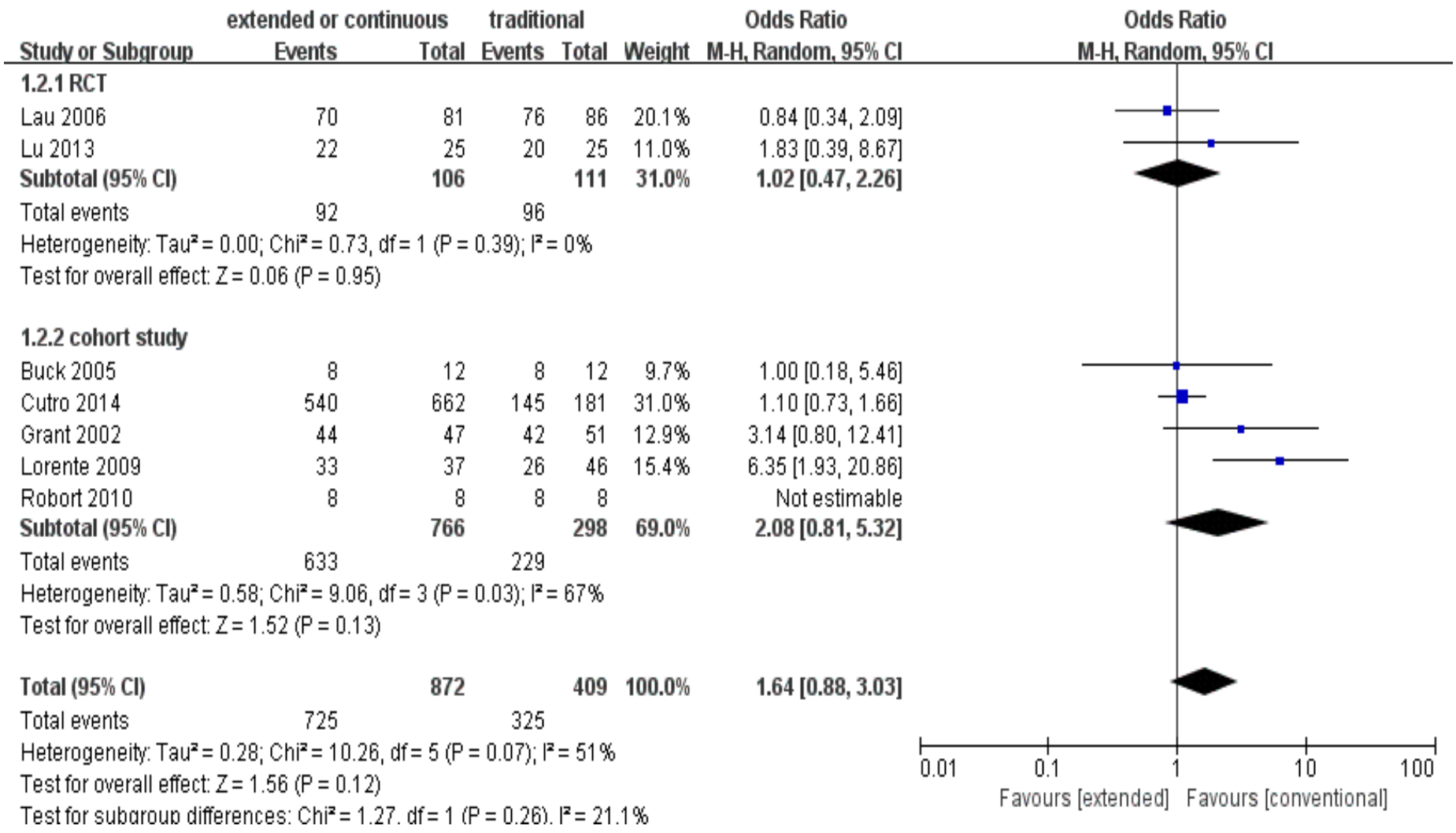


Figure 2. Forest plot depicting the odds ratios of clinical cure of patients receiving extended or continuous versus conventional intermittent infusion of piperacillin/tazobactam.

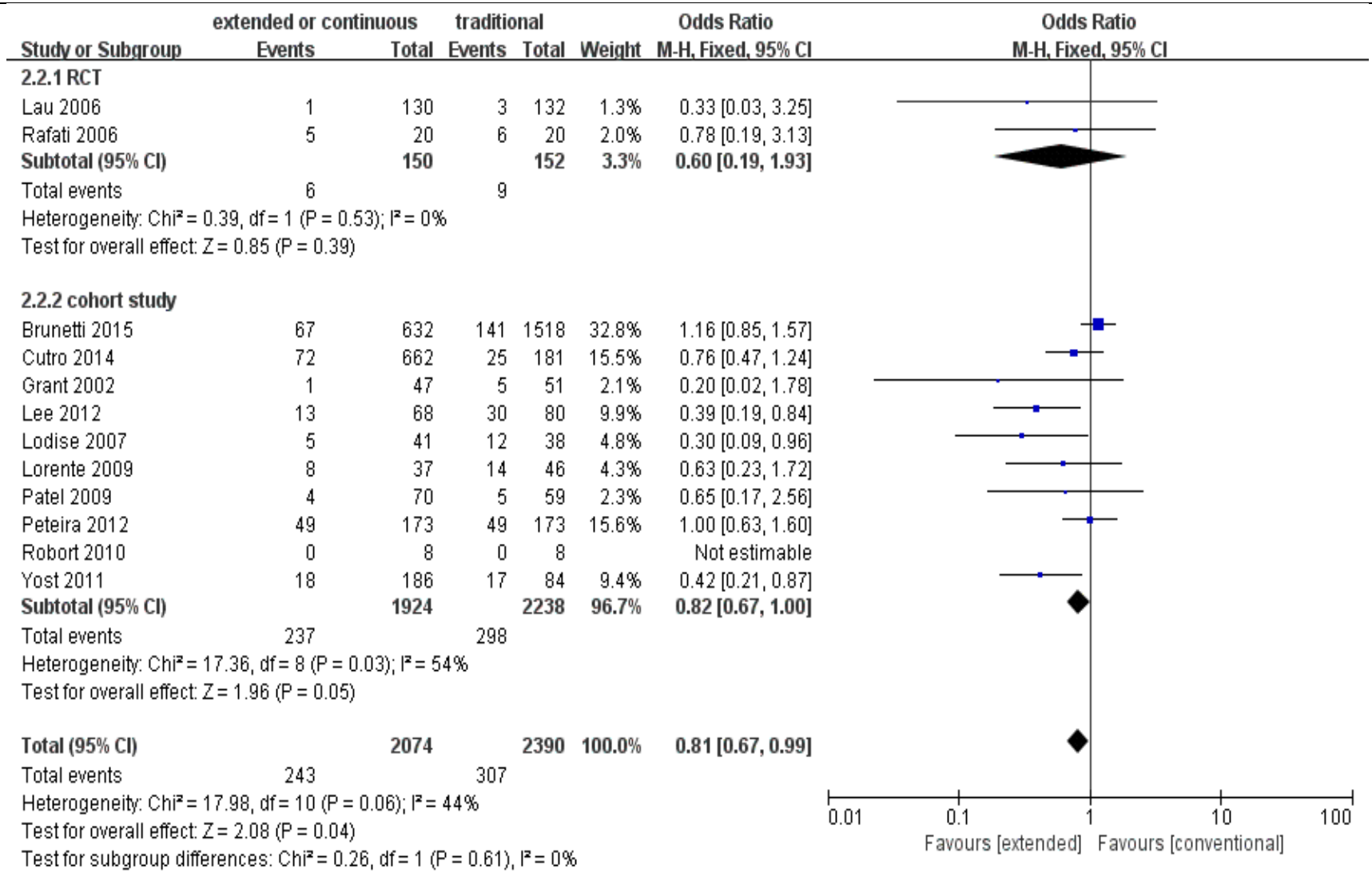


Figure 3. Forest plot depicting the odds ratios of mortality of patients receiving extended or continuous versus conventional intermittent infusion of piperacillin/tazobactam.

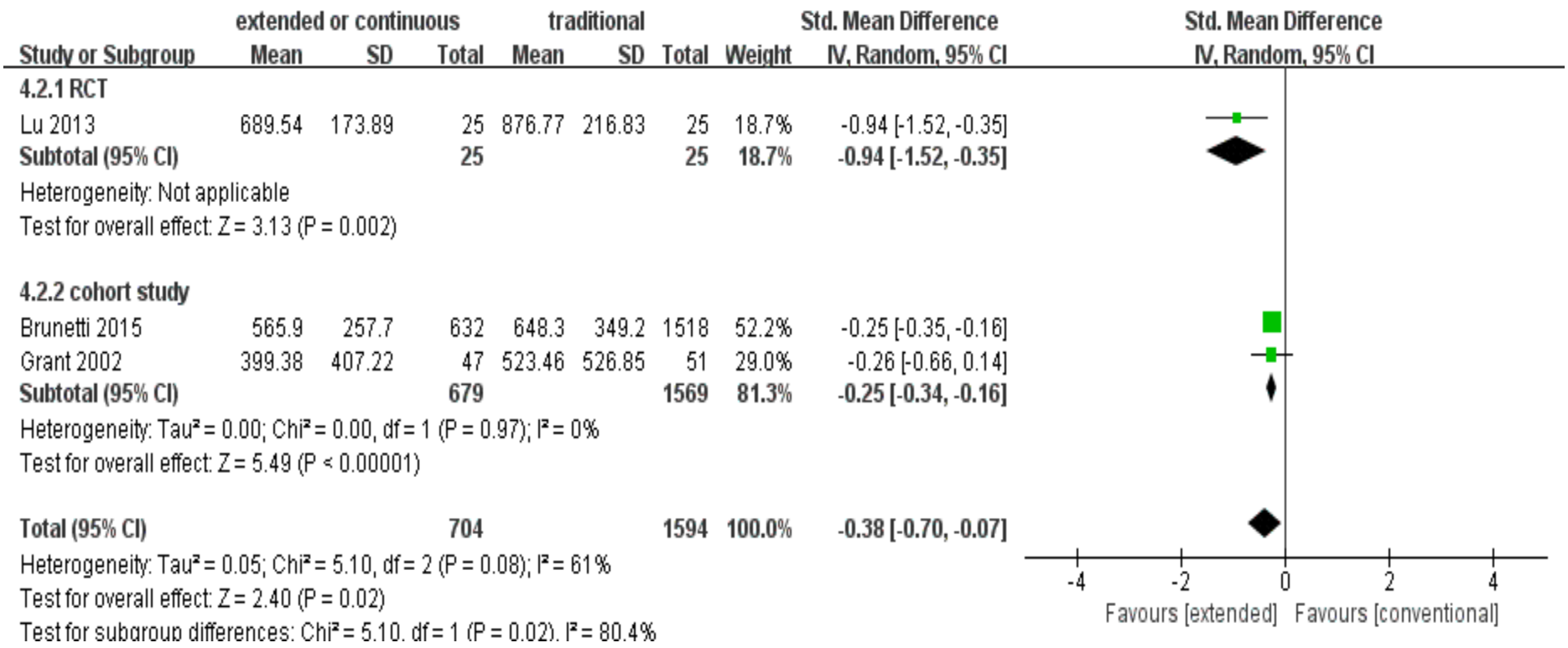


Figure 4. Forest plot depicting the odds ratios of cost of patients receiving extended or continuous versus conventional intermittent infusion of piperacillin/tazobactam.

Supplementary Table 1. Quality of observational studies (indicators from New-Castle-Ottawa scale)

Study	1a	2b	3c	4d	5Ae	5Bf	6g	7h	8i	Total quality scores
Grant 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Buck 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Lodise 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Patel 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Lorente 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Robort 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Yost 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Pereira 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Lee 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Cutro 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
McCormick 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Brunetti 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9

a. Indicates exposed cohort truly representative
b. Non-exposed cohort drawn from the same community
c. Ascertainment of exposure from the same community
d. Outcome of interest not present at start of study
e. Cohorts comparable on basis of site and etiology of infection
f. Cohorts comparable on others factors
g. Assessment of outcome of record linkage or independent blind assessment
h. Follow-up long enough for outcomes to occur.
i. Complete accounting for cohorts

Table 1. The characteristics of included studies

Author, year, reference	Study design; years, country	No. infections	CI or EI	II	Clinical cure			Mortality			Bacteriologic cure			Length of hospital stay			Cost		
					CI, n/N (%)	II, n/N (%)	P value	CI, n/N (%)	II, n/N (%)	Pvalue	CI, n/N (%)	II, n/N (%)	Pvalve	CI	II	Pvalue	CI	II	Pvalue
Grant,2002,[16]	Prospective, open-lable controlled trail;1999-2000, USA	98, all types of infection	9g q24h for HAP(n=24), 13.5g q24h for nosocomial infections(n=23)	3.375 q6h(n=2),4.5g q8h(n=49)	44/47 (94)	42/51 (82)	0.081	1/47(2.1)	5/51(9.8)	>0.5	25/28(89)	23/32(73)	0.092	7.3±4.8	8.7±7.1	0.26	$399.38±407.22	$523.49±526.85	0.028
Buck,2005,[17]	Prospective, randomized clinical observational trial;NR, Germany	24, CAP or HAP	9g q12h(n=12)[a]	4.5g q8h(n=12)	8/12(67)	8/12(67)	>0.05	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lau,2006,[28]	RCT, open-lable;2002-2004,USA	167, cIAIs	13.5g q24h(n=130)[b]	3.375 g over 30min q6h(n=132)	70/81 (86)	76/86 (88)	0.817	1/130(0.8)	3/132(2.3)	>0.05	47/56(83.9)	51/58(87.9)	0.597	NR	NR	NR	NR	NR	NR
Rafati,2006,[29]	RCT;2003-2004,Ira	40, ICU sept	8g daily over	3g over 0.5h	NR	NR	NR	5/20(25)	6/20(30)	0.72	NR	NR	NR	1.7±0.7	2.4±1.5	0.08	NR	NR	NR

	n	ic	24h g(n=20)[c]	q6h(n=20)															
Lodise,2007,[18]	Retrospective cohort;2000-2004,USA	194, aeruginosa Infection	3.375g over 4h,q8h (n=102)[d]	3.375 over 30min, q4h or q6h(n=92)	NR	NR	NR	5/41(12.2)	12/38(31.6)	0.04	NR	NR	NR	NR	NR	NR	NR	NR	NR
Patel,2009,[19]	Retrospective cohort;2006-2007,USA	129, Gram(-) infection	3.375g over 4h,q8h (n=70)	3.375 to 4.5g over 30min q6h or q8h(n=59)	NR	NR	NR	4/70(5.7)	5/59(8.5)	0.54	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lorente,2009,[20]	Retrospective cohort;2002-2007,Spain	83, ventilator-associated pneumonia	4.5g over 6h q6h(n=37)[e]	4.5g over 30min q6h(n=46)	33/37 (89.2)	26/46 (56.2)	0.0001	8/37(21.6)	14/46(30.4)	0.46	NR	NR	NR	21.81±12.34	25.61±19.84	0.62	NR	NR	NR
Robort,2010,[21]	Retrospective;2005,Australia	16, sepsis	13.5 continuous(n=8)	4.5g over 20min q6h or q8h(n=8)	8/8(100)	8/8(100)	NR	0/8(0)	0/8(0)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yost,2011,[22]	Retrospective Cohort;2	359, gram-	3.375g over 4h	NR(n=84)	NR	NR	NR	18/186(9.7)	17/84(20.2)	0.03	NR	NR	NR	NR	NR	NR	NR	NR	NR

	007-2010,USA	negative infections	q8h(n=186)																
Pereira,2012,[23]	Retrospective cohort;2006-2010,Portugal	346, ICU sepsis	NR(n=173)	t=30 min,dose NR(n=173)	NR	NR	NR	49/173(28.3)	49/173(28.3)	1.0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lee,2012,[24]	Retrospective;2009-2011,USA	148, ICU gram-negative infection	3.375g over4h q8h(n=68)	2.25-4.5g over 30min q6h or q8h(n=80)	NR	NR	NR	13/68(19)	30/80(38)	0.01	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lu,2013,[30]	RCT;2012,China	50, ICU HAP	4.5g over 3h q6h(n=25)	4.5g over 30min q6h(n=25)	22/25 (88)	20/25 (80)	＞0.05	NR	NR	NR	NR	NR	NR	6.00±1.05	8.20±1.03	<0.05	$689.54±173.89	$876.77±216.83	<0.05
Cutro，2014,[25]	Retrospective;2009-2011,USA	843, sepsis syndromes	2.25-3.375g over 4h q6h or q12h(n=662)	2.25-4.5 over 30min q8h or q12h(n=181)	540/662(81.6)	145/181(80.1)	0.756	72/662(10.9)	25/181(13.8)	0.282	NR	NR	NR	NR	NR	NR	NR	NR	NR
McCormick,2015[26]	Retrospective;2010,USA	200, all type	3.375g over 4h q8h	2.25-4.5g over	NR	NR	NR	NR	NR	NR	NR	NR	NR	18.5	15.6	0.083	NR	NR	NR

		s of infection	or q12h(n=100)	30 min q6h or q8h(n=100)															
Brunetti，2015,[27]	Retrospective;2009-2012,UAS	2150, all types of infection	3.375g over 4h q8-12h(n=632)	2.25g, 3.375g, or 4.5g over 30min q6-8h(1518)	NR	NR	NR	67/632(10.6)	141/1518(9.3)	0.37	NR	NR	NR	12.5±9.5	11.8±9.5	0.1	$565.90±257.70	$648.30±349.20	<0.0001

CI, Continuous infusion; EI, Extended infusion; II, Intermittent infusion; CAP, Community acquired pneumonia; HAP, Hospital acquired pneumonia; cIAIs, Complicated intra-abdominal infection; ICU, Intensive care unit; CCU, Critical care unit; VAP, Ventilator-associated pneumonia.

a. 2.5g single loading dose before starting continuous infusion.
b. A loading dose was administered before continuous infusion: 2.25g over 30min.
c. Loading dose was administered before continuous infusion: 2g.
d. Among patients with Acute Physiological and Chronic Health Evaluation-II score≥17.
e. A loading dose was administered before continuous infusion: 4.5g over 30min. A loading dose was administered before continuous infusion.