Systematic Review and Meta-Analysis

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Continuous versus intermittent infusions of antibiotics for the treatment of infectious diseases

Meta-analysis and systematic review

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Abstract

Background: Severe sepsis and pneumonia are common problems in the intensive care units (ICUs) and cause high morbidity and mortality. Optimal doses and appropriate routes of antibiotics are critical to improve their efficacy, but their appropriate routes remain controversial.

Objective: The efficacy of antibiotic administration among critically ill patient populations remains controversial. Therefore, the present meta-analysis aimed to investigate the effectiveness of antibiotic administration in patients with infection and to assess whether the effect differs between the two antibiotic administration types.

Methods: A systematic search of studies on continuous infusions of intravenous antibiotics and traditional intermittent infusions of antibiotics for patients with infection was performed mainly in PubMed. The odds ratios (ORs) of the microbiological results as primary outcome and mortality rate, length of stay, and duration of antibiotic treatment as secondary outcomes were evaluated.

Results: The meta-analysis comprised 9 randomized controlled trials (RCTs) and 4 retrospective studies comprising 1957 participants. Current analysis showed that the overall OR of clinical success between the continuous and intermittent groups was 0.675 (95% confidence interval [CI]: 0.523–0.870). Comparing continuous and intermittent groups, the subgroup analysis showed a lower ICU stay (OR 0.834, 95% CI: 0.542–1.282), a higher mortality (OR 1.433, 95% CI: 1.139–1.801), and a longer antibiotic duration (OR 1.055, 95% CI: 0.659–1.689), but the results of present meta-analysis were not significant because of the limited number of enrolled trials.

Limitations: Heterogeneity of included trials and studies.

Conclusions: The results of present meta-analysis were insufficient to recommend continuous infusion of intravenous antibiotics better than traditional intermittent infusions of antibiotics at routine clinical care. Hope large-scale RCT to provide more rebuts evidence for making recommendations to warrant continuous infusions of intravenous antibiotics at clinical practice.

Abbreviations: CI = confidence interval, ICU = intensive care units, OR = odds ratio, RCT = randomized controlled trials.

Keywords: continuous infusions, intermittent infusions, intravenous antibiotics, meta-analysis

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1. Introduction

Severe sepsis and pneumonia are common problems in the intensive care units (ICUs) and cause high morbidity and mortality,[1–3] Early initiation of effective antimicrobial treatment is an important component of therapy against severe sepsis and pneumonia. [3–5] Using antibiotics at optimal doses and appropriate routes is critical to improve their efficacy,[6] but the appropriate routes of antibiotics are still controversial.[7]

Antibiotics are a common choice for treatment of severe sepsis and pneumonia. Among antibiotics, time-dependent antibiotics and their antibacterial activity are related to duration of the maintenance of their free concentration above the minimal inhibitory concentration (MIC) during each dosing interval. Extended infusions, especially continuous infusion of β-lactam antibiotics, can maintain the duration of antibiotic concentration above MIC and improve antibacterial activity. Furthermore, the pathophysiological changes associated with severe sepsis and pneumonia often affect distribution volume, drug clearance, and pharmacokinetic parameters.[8–10] The use of continuous administration of meropenem was studied in some trials and indicated greater pharmacokinetic efficacy,[8,9] bacteriological eradication,[11] and clinical cure rates.[12] These trials have not been conducted among patients with severe sepsis

and pneumonia, and meta-analysis studies are scarce. Shiu et al[7] reported no differences in mortality infection recurrence, clinical cure, super-infection post-therapy, and safety outcomes when continuous infusions of intravenous antibiotics were compared with traditional intermittent infusions of antibiotics. However, the efficacy of antibiotic administration among critically ill patient populations remains inconclusive. Therefore, the present meta-analysis aimed to explore the effectiveness of antibiotic administration in patients with infection and to examine whether the effect differs between 2 antibiotic administration types.

2. Methods

2.1. Search strategy and inclusion criteria

PubMed, Scopus, Cochrane Collaboration Central Register of controlled Clinical Trials, Cochrane Systematic Reviews, ClinicalTrials.gov EMBASE, CINAHL, and ISI Web of Science were searched for studies on the continuous infusions of intravenous antibiotics and traditional intermittent infusions of antibiotics for patients with infection, from the earliest record to July 2018. The bibliographies of included trials and related review articles were reviewed for relevant references. We included studies employing comparison among patients with infection receiving 2 antibiotic administration types. The search strategy comprised the following terms variably combined with 2 kinds of antibiotic administration types and target patients with infection: sepsis severe, pyemia, pyemias, pyohemia, pyohemias, pyaemia, pyaemias, septicemia, septicemias, poisoning blood, blood poisoning, blood poisonings, poisonings blood, antibacterial antibacterial agents antibacterial agents agents, antibacterial antibacterial compounds antibacterial compounds compounds, antibacterial bacteriocidal agents agents, bacteriocidal bacteriocides anti-mycobacterial agents agents, antimycobacterial anti mycobacterial agents antimycobacterial agents agents, antimycobacterial antibiotics. With regard to the types of included studies, we enrolled randomized controlled trials (RCTs) or comparative experimental trials, and retrospective studies, and excluded case series and case reports.

All patients who were diagnosed with severe sepsis or pneumonia or infection were admitted to ICU received antibiotic therapy. Antibiotic administration was indicated as empirical therapy for severe infection without a proven pathogen, or as a second-line antibiotic based on microbiological findings. Concomitant antimicrobial therapy was permitted. Diagnosis of severe sepsis was made according to the International Guidelines for Management of Severe Sepsis.[13] All retrieved studies were required to comprise at least 2 treatment arms, including continuous infusions of intravenous antibiotics and traditional intermittent infusions of antibiotics. Because the present meta-analysis aimed to compare 2 antibiotic administration types, some elements of outcome measures were not included in current quantitative analysis. The targeted population comprised patients with observed major outcome measures. The primary endpoints included clinical results. Secondary endpoints included mortality rate, length of stay, and duration of antibiotic treatment. Clinical success was defined as complete or partial resolution of temperature, clinical signs and symptoms of infection, and leukocytosis. Types of antibiotic administration were divided into continuous infusions of intravenous antibiotics (continuous group) and traditional intermittent infusions of antibiotics (intermittent group). Pulmonary infection only study was defined as a study in which target patients were diagnosed with pulmonary infection only, such as ventilator-associated pneumonia. Other studies were defined as nonpulmonary infection only study.

2.2. Data extraction and quality assessment

Two reviewers examined all retrieved articles and extracted data. We recorded the first author, publication year, study design, double-blind method, target diseases, intervention antibiotics, enrolled patients (continuous group/intermittent group), intention-to-treat, and quality assessment, and summary of the outcome measures. The methodological quality of enrolled studies was evaluated by using Jadad scoring[14] for the RCTs and the Newcastle–Ottawa quality assessment scale[15] for the comparative experimental trials.

2.3. Data synthesis and analysis

The odds ratios (ORs) of clinical results, microbiological results, mortality rate, length of stay, and duration of antibiotic treatment in continuous infusions of intravenous antibiotics compared with the traditional intermittent infusions of antibiotics comprised the outcome. A random effect model was employed to pool individual ORs; all analyses were performed using Comprehensive Meta-Analysis (v. 3) statistical software (Biostat, NJ). Between-trial heterogeneity was determined using I^2 tests; values $>50\%$ were regarded as considerable heterogeneity.[16] Funnel plots was used to examine potential publication bias.[16] Statistical significance was defined as P-values $< .05$.

3. Results

3.1. Study search and characteristics of included patients

We retrieved 400 nonduplicate references for our review of their titles and abstracts, and included 25 articles for meticulous evaluation after eliminating references violating the inclusion criteria (Fig. 1). We excluded 9 studies focusing on pharmacokinetics and pharmacodynamics, 2 studies focusing on pharmacological economics, and 1 study that contain poster abstract only. Therefore, the meta-analysis included 9 RCTs[11,17–24] and 4 retrospective studies.[12,25–27] The final quantitative analysis included 1957 participants. Patient age ranged from 24 to 72.6 years in the continuous group and from 26.6 to 79 years in the intermittent group. Diagnosis comprised sepsis, ventilator-associated pneumonia, *Staphylococcal aureus* infection, and *Pseudomonas aeruginosa* infection. Major antibiotics comprised meropenem, piperacillin-tazobactam, β-Lactam, ceftriaxone, and vancomycin. Patient characteristics, study methodology, and quality assessment of included trials are listed in Table 1.

3.2. Pooled odds for outcome between two antibiotic administration groups

The overall OR of clinical success comparing the continuous and intermittent groups was 0.675 (95% confidence interval [CI]: 0.523–0.870) (Fig. 2). The subgroup analysis showed a lower ICU stay in the continuous group than in the intermittent group (OR 0.834, 95% CI: 0.542–1.282) (Fig. 3), but the results were not significant because of the limited number of enrolled trials. However, the subgroup analysis showed a higher mortality rate in the intermittent group than in the continuous group (OR 1.433, 95% CI: 1.139–1.801), and a longer antibiotic duration in the intermittent group than in the continuous group (OR 1.055,

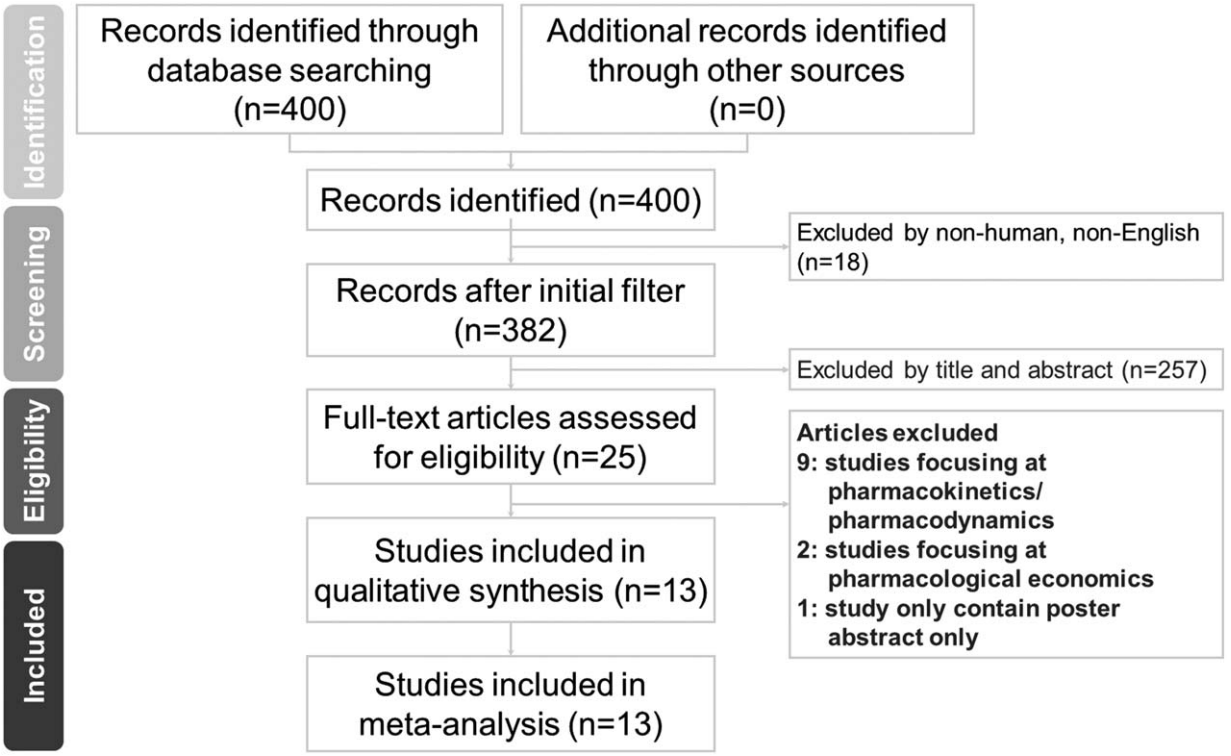

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for search and identification of included studies.

Table 1

Summary of the retrieved trials investigating 2 types of antibiotic administration on patients with infection.

Author, year	Study design	Double-blind	Target diseases	Intervention antibiotics	Enrolled patients (C/I)	ITT	Outcome measures	QA
Pulmonary infection only								
Lorente L (2006)[12]	RetS	No	VAP due to GNB	Meropenem	42/47	NM	Clin_R, Micro_R, MorR, LOS, D_>MIC	8*
Lorente L (2009)[17]	RCT	Yes	VAP	Piperacillin-Tazobactam	37/46	NM	Clin_R, Micro_R, MorR, LOS, D_Anti, D_fMIC	3#
Fahimi F (2012)[18]	RCT	No	VAP	Piperacillin-Tazobactam	31/30	NM	Clin_R, Micro_R, CPIS	3#
Nonpulmonary infection only								
Wysocki M (2001)[19]	RCT	No	Severe Staphylococcal infections	Vancomycin	61/58	NM	Clin_R, Micro_R, Safety, PK, Cost	3#
Lodise Jr TP (2007)[25]	RetS	No	PaInf	Piperacillin-Tazobactam	102/92	NM	Clin_R, MorR, LOS	8*
Roberts J (2007)[20]	RCT	No	Sepsis	Ceftriaxone	29/28	NM	Clin_R, Micro_R, MorR, LOS, D_Anti,	3#
Lee G (2012)[26]	RetS	No	Critically ill	Piperacillin-Tazobactam	68/80	NM	Clin_R, MorR, LOS	8*
Goncalves-Pereira J (2012)[27]	RetS	No	Critically ill	Piperacillin-Tazobactam	173/173	NM	Clin_R, MorR, LOS	8*
Chytra I (2012)[11]	RCT	No	Critically ill	Meropenem	120/120	NM	Clin_R, MorR, LOS, D_Anti, D_OrgFail, D-bacter	3#
Dulhunty JM (2013)[21]	RCT	Yes	Severe sepsis	β-Lactam	30/30	NM	D_>MIC, Clin_R, MorR, LOS, D_Anti, D_OrgFail, D-bacter	4#
Dulhunty JM (2015)[22]	RCT	Yes	Severe sepsis	β-Lactam	242/220	212/220	Clin_R, MorR, LOS, D_Anti, D_OrgFail, D-bacter	3#
Cotrina-Luque J (2016)[23]	RCT	No	PaInf	Piperacillin-Tazobactam	40/38	NM	Clin_R, Micro_R, MorR, LOS, D_Anti, Time_def, Time-micro	3#
Zhao HY (2017)[24]	RCT	No	Severe sepsis	Meropenem	25/25	NM	Clin_R, MorR, LOS, D_Anti	3#

C = continuous group, Clin_R = clinical results, CPIS = clinical pulmonary infection score, D_>MIC = duration of plasma antibiotic concentration above MIC, D_Anti = duration of antibiotics, D_fMIC = duration of fraction of MIC level, D_OrgFail = duration of organ failure-free days at day 14, D-bacter = duration of bacteremia, GNB = Gram-negative bacilli, I = intermittent group, ITT = intention-to-treat, LOS = length of stay, Micro_R = microbiological results, MorR = mortality rate, NM = not mentioned, PaInf = *Pseudomonas aeruginosa* infection, PK = pharmacokinetics, QA = quality assessment, RetS = retrospective, Time_def = time to defervescence, Time-micro = time to microbiological cure, VAP = ventilator-associated pneumonia.

#, the study was evaluated using Jadad scale. *, the study was assessed using the Newcastle-Ottawa scale.

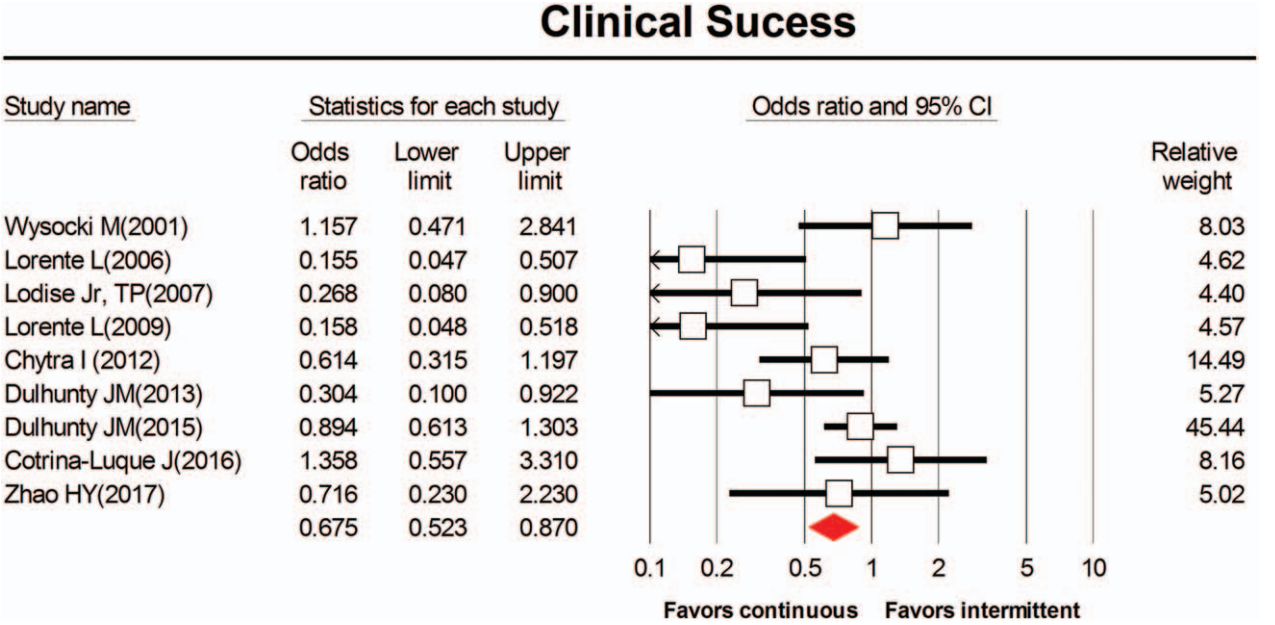

Figure 2. Forest plot of the overall odds ratios for clinical success in the continuous group versus the intermittent group.

95% CI: 0.659–1.689) (Fig. 4). The subgroup analysis showed more efficacy in pulmonary infection population in the continuous group compared with the intermittent group (OR 0.834, 95% CI: 0.542–1.282) (Fig. 5). With regard to OR heterogeneity, the I^2 was <0.01% in the continuous group and 93.5% in the intermittent group (Fig. 2). The subgroup analysis based on the different study designs and disease types for mortality, ICU stay, and pulmonary infection is listed in Tables 2–4. The pooled OR of mortality rate in the intermittent group compared with the continuous group was 1.433 (95% CI: 1.139–1.801), indicating a reduced mortality rate following the continuous group. Regarding the heterogeneity of OR, I^2 was less than 0.01% in both the overall included studies and subgroups. And the statistical significance reduced after the administration types were divided into both subgroups ($P=.168$ in the continuous group and $P=.793$ in the intermittent group). No significant publication bias was detected in the overall OR of outcome measures ($P=.255$). The funnel plots for OR of 2 antibiotic administration types for clinical success, ICU stay, and antibiotic duration are shown in Figs. 6–9, respectively.

4. Discussion

The present meta-analysis focused on the use of 2 antibiotic administration types for treating infected patients. It included 3 studies related to pulmonary infection only and 10 studies that recruited patients with nonpulmonary infection only. Compared with the intermittent group, infected patients in the continuous group had a higher clinical success and a shorter ICU stay, but the results were not significant because of the limited number of

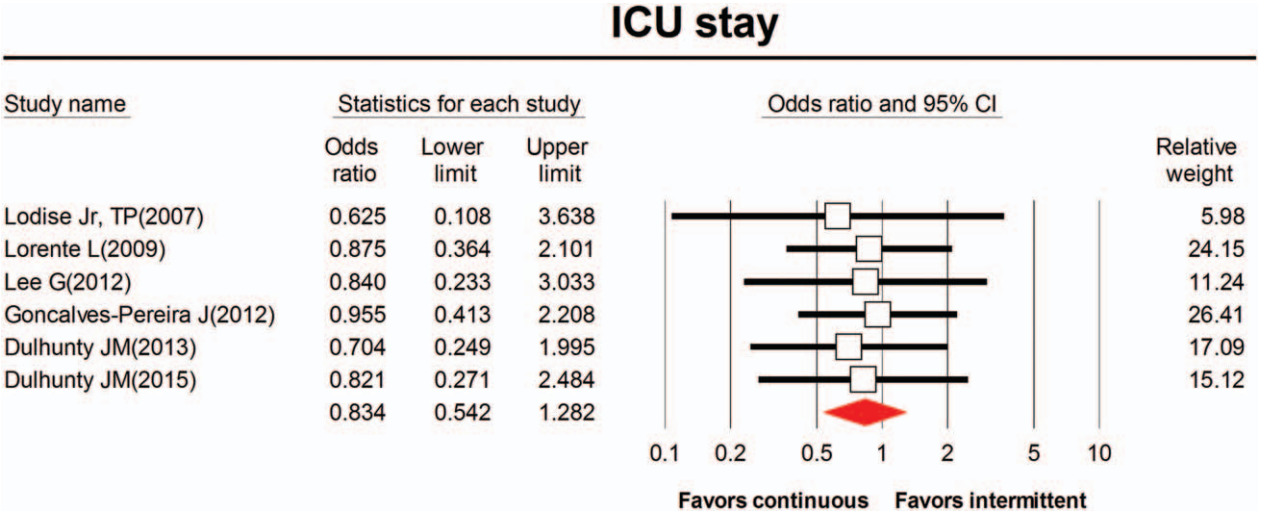

Figure 3. Forest plot of the overall odds ratios for intensive care unit stay in the continuous group versus the intermittent group.

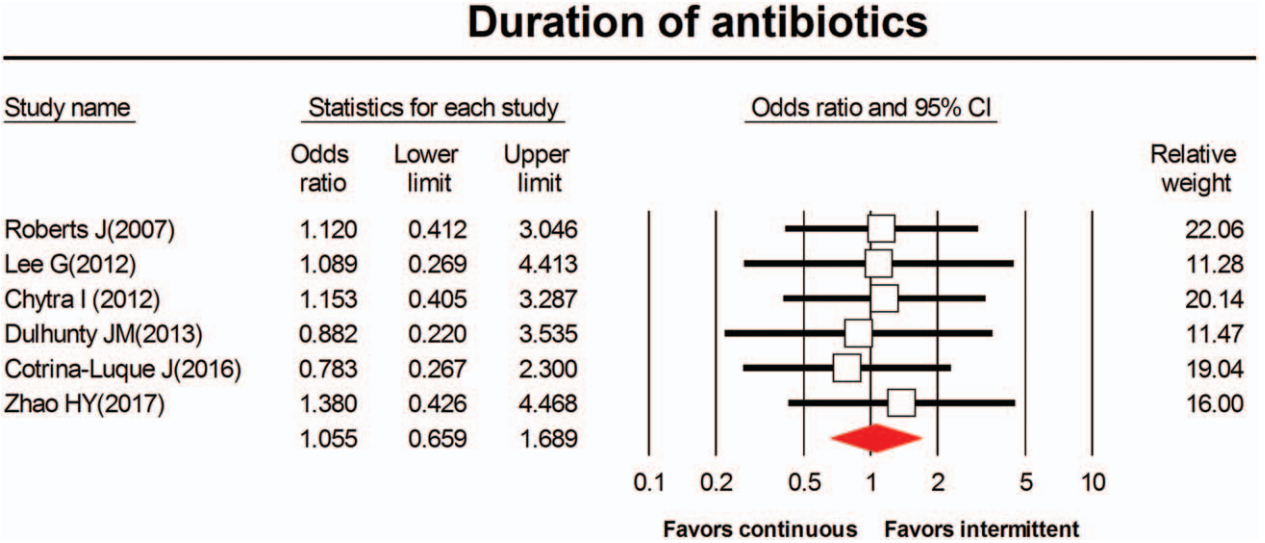

Figure 4. Forest plot of the overall odds ratios for antibiotic duration in the continuous group versus the intermittent group.

enrolled trials. Similarly, a lower incidence of mortality, a shorter total duration of antibiotic prescription, and more efficacy in pulmonary infection population were found in the continuous group, but the results were not significant due to the small sample sizes.

In the current study, the overall OR of clinical success comparing the continuous and intermittent groups was 0.675 (95% CI: 0.523–0.870). No significant differences were found in the primary clinical outcomes (cure rates) between the 2 groups. With regard to clinical success, the continuous group tended to show more favorable results. Zhao et al's results[24] are most comparable to those of Chytra et al[11] who found a nonsignificant difference in cure rates in a trial of 240 critically ill patients randomized to receive meropenem by continuous infusion versus intermittent administration (83% vs. 75%, respectively). Recently, Dulhunty et al[22] conducted an RCT in 25 ICUs to evaluate the efficacy of continuous versus intermittent infusion of β-lactam antibiotics in patients with severe sepsis and found no difference between the treatment groups in clinical cure rates (52.4% vs. 49.5%). By contrast, a retrospective study of meropenem[12] and that of other β-lactam agents found that continuous administration has better results than intermittent administration.[21,20,17]

The overall OR of mortality rate comparing continuous and intermittent groups was 0.834 (95% CI: 0.542–1.282). No significant difference was found in the mortality rate between participants in the continuous and intermittent groups. With regard to mortality rate, the continuous group tended to show

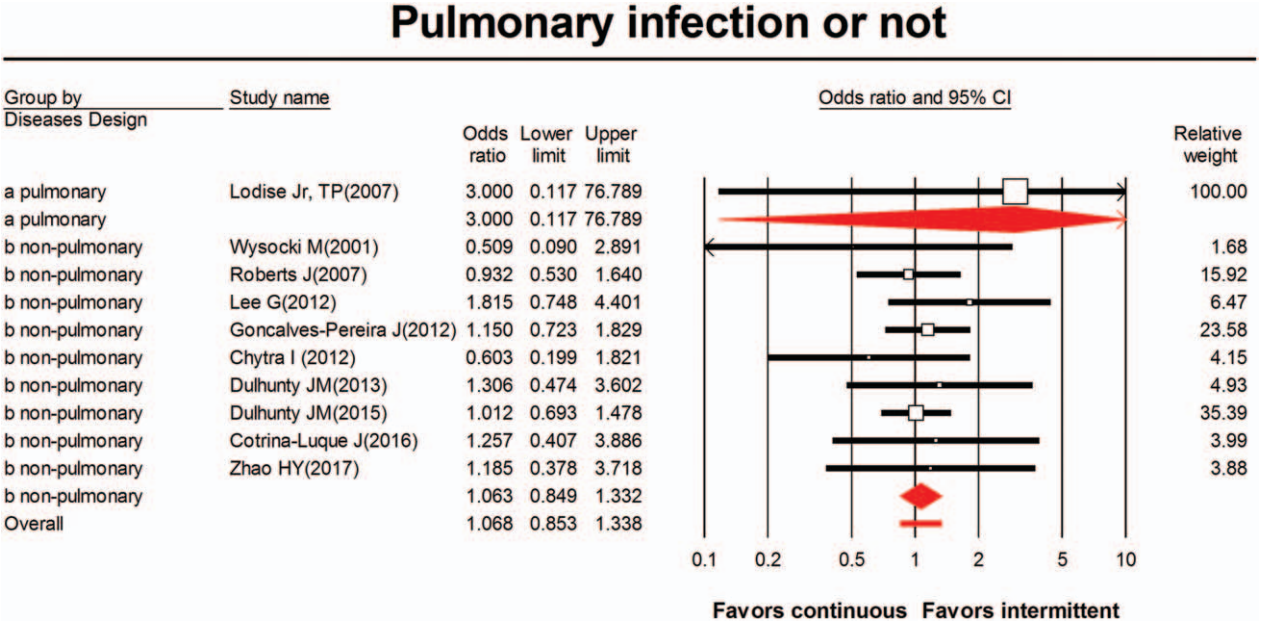

Figure 5. Forest plot of the overall odds ratios for pulmonary infection in the continuous group versus the intermittent group.

Table 2

Subgroup analysis of odds ratio based on study designs and antibiotic types and disease types for mortality rate.

Subgroup	Odds ratio	95% Confidence interval
Disease type		
Pneumonia only		
Randomized controlled trials	2.137	0.902–5.063
Nonpneumonia only		
Randomized controlled trials	1.357	0.981–1.879
Retrospective study	1.606	0.856–3.013
Antibiotic type		
Carbapenem only		
Randomized controlled trials	1.320	0.799–2.180
Retrospective study	11.081	1.353–90.773
Noncarbapenem only		
Randomized controlled trials	1.441	0.998–2.081
Retrospective study	1.606	0.856–3.013

Table 3

Subgroup analysis of odds ratio based on study designs and antibiotic types and disease types for intensive care unit stay.

Subgroup	Odds ratio	95% Confidence interval
Disease type		
Pneumonia only		
Randomized controlled trials	0.875	0.364–2.101
Nonpneumonia only		
Randomized controlled trials	0.832	0.519–1.332
Retrospective study	0.872	0.454–1.673
Antibiotic type		
Carbapenem only		
Randomized controlled trials	0.880	0.479–1.617
Noncarbapenem only		
Randomized controlled trials	0.805	0.454–1.429
Retrospective study	0.872	0.454–1.673

more favorable results and more efficacy in pulmonary infection population. A possible explanation for the better effectiveness in the continuous group is the higher tissue concentrations of β-lactam in this patient group than in the intermittent group[8,9];

Table 4

Subgroup analysis of odds ratio based on study designs and antibiotic types and disease types for pulmonary infection.

Subgroup	Odds ratio	95% Confidence interval
Disease type		
Pneumonia only		
Randomized controlled trials	0.875	0.364–2.101
Nonpneumonia only		
Randomized controlled trials	0.832	0.519–1.332
Antibiotic type		
Carbapenem only		
Randomized controlled trials	0.880	0.479–1.617
Noncarbapenem only		
Randomized controlled trials	0.805	0.454–1.429
Retrospective study	0.872	0.454–1.673

patients with pneumonia in particular experience persistent maintenance and low penetration of most β-lactams into lung tissue.[28] Other studies had similar outcomes that showed an improved bacteriological efficacy associated with the continuous application of meropenem[11] and β-lactams.[20] In the current study, the overall OR of pulmonary infection comparing continuous group and intermittent group was 0.834 (95% CI: 0.542–1.282), and no significant difference was found in the pulmonary infection between participants in the continuous and intermittent groups. The continuous group tended to show more favorable results in pulmonary infection. We want to focus on continuous application of effective antibiotics for patients with ventilator-associated pneumonia. In addition, our subgroup analysis showed that different study designs or disease types or antibiotic types showed no discrepancies of treatment effectiveness in the continuous group (Table 3). Since only few studies were enrolled in the subgroup, the sample size was too small to assess that heterogeneity of effectiveness.

The overall OR of antibiotic duration comparing continuous and intermittent groups was 1.055 (95% CI: 0.659–1.689). No significant difference was found in the antibiotic duration between participants in the continuous and intermittent groups. The continuous group tended to show more favorable results in antibiotic duration. Our result showed a significantly shorter

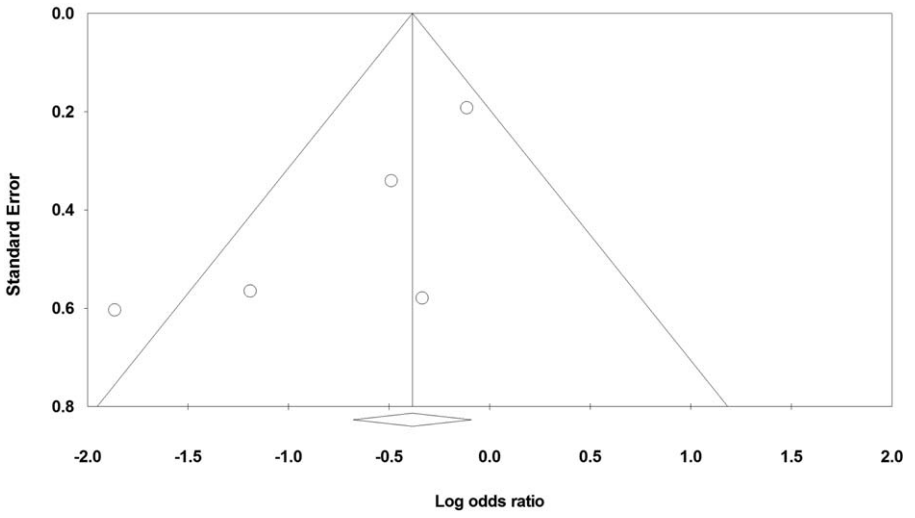

Figure 6. Funnel plot of the odds ratio of clinical success.

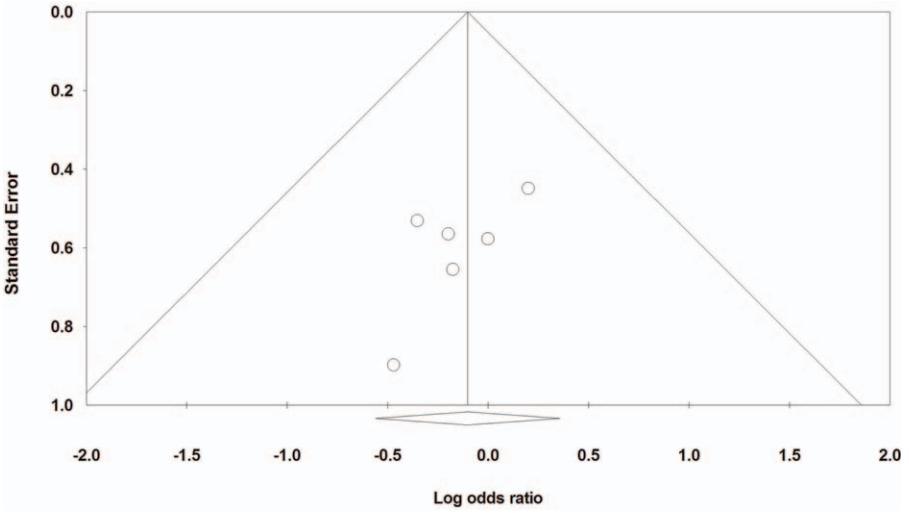

Figure 7. Funnel plot of the odds ratio of intensive care unit stay.

duration of antibiotic treatment in the continuous group, and this result is the same as that obtained by Zhao et al.[24]

The overall OR of ICU stay comparing continuous and intermittent groups was 0.834 (95% CI: 0.542–1.282). No significant difference was found in the ICU stay between participants in the continuous and intermittent groups. The continuous group tended to show more favorable results in ICU stay. Our result showed a significantly shorter duration of ICU stay in the continuous group, and similar results were observed in the study by Chytra et al.[11] However, Zhao et al[24] reported no differences in ICU mortality rate, length of stay, and values of white blood cell count and procalcitonin. Zhao et al's results[24] are concurrent with those of Dulhunty et al,[22] although previous studies had conflicting results.[29] Meta-analyses by Roberts et al[30] and Shiu et al[7] found no significant differences in cumulative mortality between the 2 groups. By contrast, Falagas et al[31] found a significant mortality difference between continuous and intermittent infusion in their meta-analysis of observational studies and RCTs comparing infusion methods of carbapenems and piperacillin-tazobactam. Such studies have not been conducted in patients with severe sepsis and pneumonia; their mortality rates were much lower than that in our patients.

Majorly, the results of present meta-analysis were not significant due to the limited number of enrolled trials. The present meta-analysis has other limitations. First, the primary outcome was clinical results and microbiological results. The principal reason for this was that only a minority of included trials recorded clinical and microbiological results. Second, we did not serially investigate the detailed confounders of mortality rate, length of stay, and antibiotic duration due to lack of the most commonly documented in the results of the retrieved

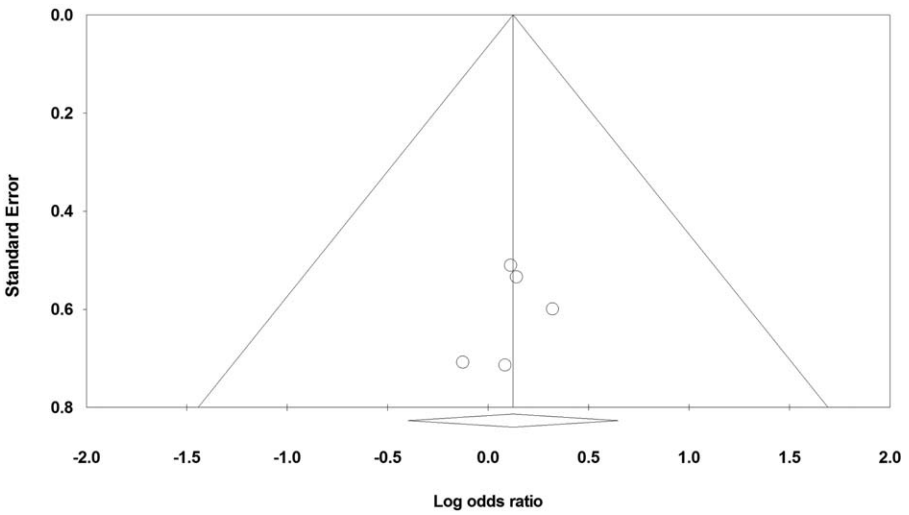

Figure 8. Funnel plot of the odds ratio of antibiotic duration.

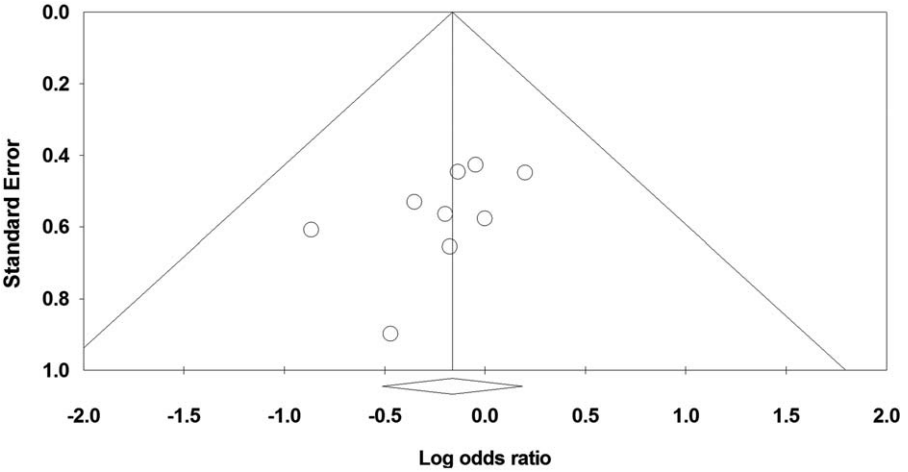

Figure 9. Funnel plot of the odds ratio of pulmonary infection.

studies. Third, the outcome of the 2 antibiotic administration types can be modified. Therefore, we also analyzed the OR of the most prevalent clinical major events to examine whether inconsistency exists between all outcomes. Fourth, because ORs are derived from the between-group difference divided by the number, the value of OR may be overestimated. Hence, researchers should consider the influence of measurement precision when reporting treatment effectiveness by using ORs. Finally, due to the above-mentioned limitations, we suggest that future similar studies should record serial changes in continuous infusions of intravenous antibiotics and infection status to warrant clinical effectiveness.

5. Conclusions

The results of present meta-analysis were insufficient to recommend continuous infusion of intravenous antibiotics better than traditional intermittent infusions of antibiotics at routine clinical care. Hope large-scale RCT to provide more rebuts evidence for making recommendations to warrant continuous infusions of intravenous antibiotics at clinical practice.

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Writing – review & editing: Hua-Cheng Yen, Chang-Hua Chen.
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