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Systematic Review

Prolonged versus Intermittent Infusion of Antibiotics in Acute and Severe Infections: A Meta-analysis

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Abstract

Background: Acute and severe infections are an absolute indication for the use of intravenous broad-spectrum antibiotics. However, previous studies have found inconsistent clinical advantages of prolonged (extended [≥3-hour infusion] or continuous [24-hour fixed rate infusion]) over intermittent (6, or 8, or 12 interval hours infusion) infusion. The clinical superiority between prolonged and intermittent infusion in treating acute and severe infections thus continues to be elusive. We conducted a meta-analysis to summarize all published randomized controlled trials (RCTs), prospective and retrospective observational studies to determine whether prolonged infusion, compared to intermittent infusion, is correlated with lower mortality and better clinical outcome.

Methods: We performed a literature search using MEDLINE (source PubMed, January 1, 1966 to August 31, 2018) and EMBASE (January 1, 1980 to August 31, 2018) with no restrictions to collect RCTs and observational studies comparing prolonged infusion with intermittent infusion of the same intravenous administered antibiotics among adult hospitalized patients. A total of 43 studies including 30 RCTs, 5 prospective observational studies and 8 retrospective observational studies were identified.

Results: In comparison with intermittent infusion, prolonged infusion of antibiotics was associated with a reduction in all-cause mortality (pooled relative risk [RR] = 0.77, 95% confidence interval [CI] = 0.66–0.89) and improvement in clinical cure (RR = 1.11, 95% CI = 1.04–1.19), which was also observed in subgroups such as non-RCTs (mortality, RR = 0.63, 95% CI = 0.48–0.81; clinical cure RR = 1.33, 95% CI = 1.13–1.57) or studies with patients and APACHE II scores 15 (mortality, RR = 0.74, 95% CI 0.63–0.89; clinical cure RR = 1.19, 95% CI = 1.07–1.32). Moreover, in RCTs, mortality (RR = 0.86, 95% CI 0.72–1.03) between the two dosing strategies was not remarkably changed but clinical cure (RR = 1.07, 95% CI = 1.01–1.13) showed a significant advantage for prolonged infusion. Additionally, no significant differences in mortality between the two dosing strategies was found (RR = 0.87, 95% CI = 0.70–1.09) but a distinct improvement in clinical cure was observed (RR = 1.14, 95% CI = 1.02–1.28) in the prolonged infusion group for septic patients. Among two infusion modes, statistically significant severe adverse events were not reported (RR=0.83, 95% CI = 0.62–1.13).

Conclusion: Better outcomes in hospitalized patients, especially in those who were critical ill, were reported in prolonged infusion of intravenous antibiotics compared with traditional intermittent infusion.

Keywords: Antibiotics, Infections, Intermittent infusion, Prolonged infusion, Traditional infusion

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Introduction

Intravenous broad-spectrum antibiotics are comprehensively employed to treat acute and severe hospital-and community-acquired bacterial infections. However, the occurrence and spread of multiple-drug resistant infections caused by gram-negative and gram-positive bacteria have grown beyond control.[1-5] Despite deep global concerned and advanced pharmaceutical technology, very few new antibiotics have been developed in the past several decades to solve the problem of antibiotics-resistant infection. Consequently, two dosing strategies including prolonged (continuous or extended) and intermittent intravenous antibiotic infusions have been mutually compared to improve clinical efficacy.

Antibiotics are mainly categorized as either time-dependent or concentration-dependent antibiotics based on the pharmacokinetic and pharmacodynamic parameters related to antibacterial efficacy. Beta-lactams, carbapenem, clindamycin, and linezolid are time-dependent antibiotics which mean that they have antimicrobial efficacy only at serum concentration above the minimum inhibitory concentration (MIC).[6-8] Aminoglycosides, fluoroquinolones, and metronidazole are concentration-dependent antibiotics indicated that their antimicrobial efficacy depends on the peak plasma drug concentration over the MIC.[9,10]

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Since they are known for being short-lived, several time-dependent antibiotics are given with the concern that serum drug concentration will decrease below the MIC before the next infusion. To achieve optimal efficacy in time-dependent antibiotics such as β-lactam and vancomycin, extended (≥3-hour infusion) or continuous (24-hour fixed rate infusion) prolonged infusion are administrated aiming to extend serum drug concentration above MIC. Several studies have showed that the prolonged infusion mode of β-lactam maximally maintains serum drug concentration above MIC to potentially improve clinical outcomes.[11-14] In contrast, less attention has been given to the issue that alternative dosing strategies can be used to maximize bacterial killing in concentration-dependent antibiotics such as fluoroquinolones, azithromycin, or glycopeptides. Whether prolonged infusion in concentration-dependent antibiotics causes post-antibiotic effects and leads to better clinical outcomes, remains uncertain.

Previous studies have had some limitations in evaluating the clinical outcomes in prolonged and intermittent infusions, such as small sample size, clinical heterogeneity in participants and infections, study design, and single antibiotics or diseases.[13,15-21] The purpose of this analysis was to address the issue of which dosing strategy, prolonged or intermittent infusion, leads to better results for patients with acute and severe infections. Comparisons between prolonged and intermittent infusions in time- and concentration-dependent antibiotics were performed for all-cause mortality, clinical cure, side effects, nephrological damages, severe infections with Acute Physiology and Chronic Health Evaluation (APACHE II) (one of ICU scoring system) score ≥15, and septic infections.

Materials and Methods

Search Strategy

This meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[22] Relevant studies were identified via the electronic databases MEDLINE (source PubMed, January 1, 1966 to August 31, 2018) and EMBASE (January 1, 1980 to August 31, 2018) using the following key words in combination both as MeSH terms and text words; 'continuous', 'prolonged', 'extended', 'intermittent', 'bolus', 'administration', 'infusion', 'interval' , 'dosing', 'bolus', 'discontinuous'; with 'antibiotics', 'anti-microbial', 'anti-bacterial', 'beta-lactam', 'anti-microbial', 'penicillin', 'carbapenem', 'clindamycin', 'linezolid', 'carbapenem', 'aminoglycosides', 'fluoroquinolones', 'metronidazole'. We searched articles published in any language and scrutinized references from these articles to identify other relevant studies. A further citation search of each article was conducted.

Relevant Articles Selection

To minimize differences between studies, we imposed the following methodological restrictions for the following inclusion criteria; 1) Studies that contained the minimum necessary information to assess the clinical efficacy and outcomes of these two types of antibiotics infusion. 2) Studies investigating treatment of acute and severe infections in adult hospitalized patients admitted to the ICU and non-ICU. 3) Studies comparing prolonged (continuous or extended) infusion of antibiotics with intermittent infusion of same antibiotics. Both randomized controlled trials (RCTs) and prospective/retrospective observational studies were included. In the case of multiple publications, the most up-to-date or comprehensive information was used.

Data Extraction and Quality Assessment

Articles were reviewed and cross-checked independently. Standardized data extraction forms were completed for all included studies. The following data were extracted from each study, if available; study design, country, number of patients, gender, age, ethnicity, comorbidities, severity of illness, ICU or non-ICU patient, infection type, causative pathogen, type of antibiotic, dosing mode, administration duration, all-cause mortality, clinical cure, adverse effects, nephrological damage, and APACHE scores ICU patients. If applicable, we used the most comprehensively adjusted risk estimates. RCTs were appraised for methodological quality using the modified Jadad scale.[29,23] The nine-star Newcastle–Ottawa Scale (NOS), was used to assess the quality of non-randomized observational studies.[24]

Definitions and Outcomes

In our review, prolonged infusion was defined as administration of either continuous or extended infusion of antibiotics in all related publications. A continuous intravenous infusion is the infusion of a fixed rate drug over 24 hours and an extended infusion is an intermittent infusion with duration of more than 3 hours. An intermittent infusion is considered to be an infusion that lasts between 20 and 60 minutes each time.

The main outcomes of this review, to evaluate the effects of antibiotics on acute and severe infections, were all-cause mortality and clinical cure in patients. In this review, the heterogeneity of study population, infection sites, signs or symptoms of infections, and clinical (fever, vital signs, etc) and paraclinical (leukocyte counts, bacterial culture results, sputum production, etc) findings were considered to analyze the clinical cure. The secondary outcome of the analysis was the occurrence of antibiotics-related adverse effects and nephrotoxicity. Adverse effects included *Clostridium difficile* colitis, renal failure, confusion, tachycardia, tonic-clonic seizure, allergic reaction, phlebitis, thrombocytopenia, and red man syndrome. Nephrotoxicity was defined as a serum creatinine level that increased >0.5 mg/dL or >50% from the baseline value, as a 50% reduction in the calculated creatinine clearance in comparison to the baseline value, or as a need for renal

replacement therapy. In the subgroup analysis, the patients with APACHE II scores ≥15 or septic infection were evaluated and analyzed.

Data Analysis and Statistical Methods

This meta-analysis was performed using RevMan v.5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The heterogeneity between trials was appraised by χ^2 statistics. A P value of <0.01 was indicated statistical significance in the presence of heterogeneity. The I^2 statistic was used to characterize the extent of the inconsistencies. $I^2 > 50\%$ was indicated as considerable heterogeneity.[25] All reported outcomes were dichotomous. Pooled relative risks (RRs) and 95% confidence intervals (CIs) for mortality and clinical cure were calculated by using the Mantel-Haenszel fixed-or random-effects model based on the heterogeneity observed in the included studies. Outcome analyses were further stratified according to the following; A) RCTs or non-RCTs, B) studies performed in critically ill patients with APECHE II ≥15, C) studies conducted in patients with septic infection. A P-value of <0.05 was considered as statistically significant. Publication bias was evaluated visually using funnel plots of mortality and clinical cure.

Results

Study Selection and Characteristics

We identified potentially relevant published articles from a review of MEDLINE, and EMBASE. After removing duplicates, titles and abstracts were reviewed by three independent members of our study team. A total of 43 studies.[26-67] with 3,610 patients were identified as eligible for our meta-analysis study including 30 RCTs, 5 prospective comparative studies and 8 retrospective studies that were published between 1977 and August 2018. The selection process is depicted in Figure 1.

The characteristics of the eligible studies are presented in Table 1. Overall, in 28 of the 43 studies (65%), the patients were admitted to the intensive care unit for treatment. A mean/median APACHE II score of ≥15 was observed in 14 studies (33%). Infections and organism types were varied, for instance there were gram-positive infections in 4 studies (9%) and gram-negative infections in 19 studies (44%).

Table 2 describes the β-lactam antibiotic, dose and infusion schedule for each study. β-lactam antibiotics were used in 32 of the 43 studies included ceftazidime (7 studies), cefamandole (1 study), piperacillin/tazobactam (11 studies), meropenem (5 studies), temocillin (1 study), oxacillin (1 study), cefoperazone (1 study), ceftriaxone (1 study), imipenem (1 study), cefotaxime (1 study), piperacillin (1 studies), cefepime (1 study). Aminoglycosides included sisomicin (1 study), tobramycin (1 study), and gentamicin (1 study). Vancomycin and oxazolidinone (linezolid) were used in 3 studies and 1 study, respectively. Two studies contained patients administered with piperacillin/tazobactam, meropenem or ticarcillin/clavulanic acid. One study involved patients administered with piperacillin/tazobactam, meropenem or cefepime and another study enrolled the patients treated with piperacillin or meropenem. In all these studies, both study arms were shown to have comparable numbers for each group. Antibiotics were administered in the intervention arm via extended and continuous infusion in 6 and 36 studies, respectively as well as via extended and continuous infusion in 1 study. The 26 studies used equivalent total daily doses of antibiotics in both study arms.

All-Cause Mortality

A total of 32 studies reported all-cause mortality as an outcome. Among the 1436 patients enrolled in the prolonged infusion arm, there were 228 deaths compared to 295 deaths among the 1383 patients in the intermittent infusion arm, which indicated that there was a statistically significant mortality advantage to prolonged infusion (Figure 2A; RR = 0.77, 95% CI = 0.66–0.89). Stratification showed that a decreased mortality was associated with prolonged infusion in non-RCTs (Figure 2B; RR = 0.63, 95% CI = 0.48–0.81) but not in RCTs (RR = 0.86, 95% CI 0.72–1.03; Figure not shown). Subgroup analysis on time-dependent antibiotics and concentration-dependent antibiotics showed that prolonged infusion had a reduced mortality in the studies with time-dependent antibiotics and no significant difference was found between the two types of infusion in the studies with concentration-

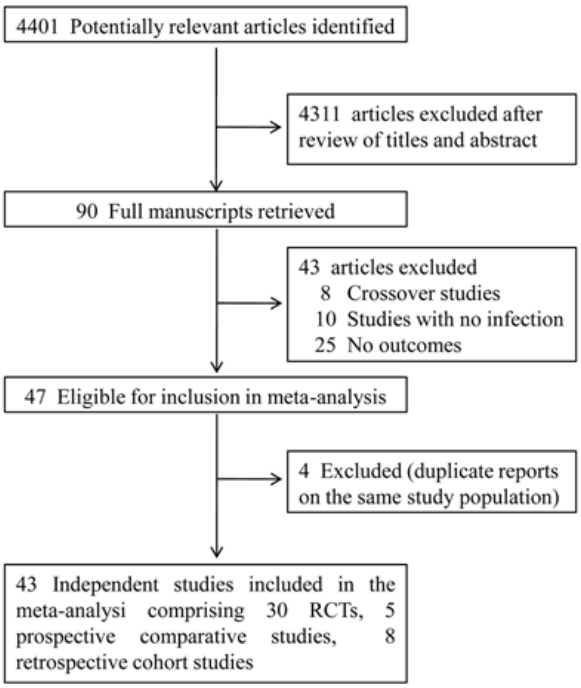


Figure 1. Flow Chart Depicting the Selection Process of Studies Included in the Meta-analysis.

Table 1. Characteristics of the Eligible Studies for Prolonged Infusion (PI) Versus Intermittent Infusion (II) of Antibitotics Included in the Meta-analysis

Study	Study Design	Patient Population (Country)	Infection Type	Organism Isolated	Sample Size (Clinically Evaluable)	PI	PI	II	II	Jadad or Newcastle-Ottawa scale
						Mean/Median Age (y)	Mean/Median APECHE II Score	Mean/ Median Age (y)	Mean/Median APECHE II Score	
Abdul-Aziz[26]	RCT	ICU (Malaysia)	Sepsis	Various	140	54	21	56	21	4
Abdul-Aziz[27]	Prospective study	ICU (Australia)	Various	Various	182	56	20	64	18	5
Adembri[28]	RCT	ICU (Italy)	Sepsis	Gram-positive	18	57	N/S	64	N/S	3
Angus[29]	RCT	N/S (Thailand)	Septicaemic melioidosis	Burkholderia pseudomallei	21	48	15	43	21	1
Bodey[30]	RCT	Non-ICU; cancer patients (USA)	Various	Various	204	N/S	N/S	N/S	N/S	3
Buck[31]	RCT	Non-ICU (Germany)	Various	N/S	24	61	N/S	60	N/S	2
Buijk[32]	Prospective study	Surgical ICU (The Netherlands)	IAI	Gram-negative	18	62	16	64	14	7
Chytra[33]	RCT	ICU (Czech Republic)	Various	Gram-negative	214	45	21	47	22	2
Cotrina-Luque[34]	RCT	Non-ICU (Spain)	Various	*Pseudomonas aeruginosa*	78	64.3	N/S	63.8	N/S	4
DeJongh[35]	RCT	N/S (Belgium)	Various	Various	12	58	12	56	13	2
Dow[36]	Retrospective cohort	ICU (USA)	Various	Gram-negative	121	58	24	60	25	8
Dulhunty[37]	RCT	ICU (Australia, Hong Kong)	Various; severe sepsis	Various	60	54	21	60	23	5
Dulhunty[38]	RCT	ICU (Australia, Hong Kong)	Sepsis	Various	432	64	130	65	135	5
Fahimi[39]	Prospective study	ICU (Iran)	VAP	Gram-negative	61	49	19	58	20	7
Feld[40]	RCT	Non-ICU; cancer patients (USA)	Pneumonia, septicemia, soft tissue infection	Gram-negative	120	43	N/S	46	N/S	2
Feld[41]	RCT	Non-ICU(Canada)	granulocytopenia	Gram-negative	70	56	N/S	50	N/S	2
Georges[42]	RCT	ICU (France)	Nosocomial pneumonia	Gram-negative	50	48	N/S	48	N/S	2
Grant[43]	Prospective study	N/S (USA)	Various	Various	98	66	12	65	12	7
Hanes[44]	RCT	ICU;trama patients (USA)	Pneumonia	Gram-negative	31	34	14	36	11	2
Hughes[45]	Retrospective cohort	N/S (USA)	Infective endocarditis	MSSA	107	40	N/S	45	N/S	7
Lagast[46]	RCT	N/S (Belgium)	Bacteraemia	Gram-negative	45	N/S	N/S	N/S	N/S	2
Lau[47]	RCT	ICU (USA)	Abdominal infection	Various	167	50	8	49	8	2
Lodise[11]	Retrospective cohort	Non-ICU (USA)	Various	*Pseudomonas aeruginosa*	194	63	15	64	16	7

Table 1. Continued

Study	Study Design	Patient Population (Country)	Infection Type	Organism Isolated	Sample Size (Clinically Evaluable)	PI	PI	II	II	Jadad or Newcastle-Ottawa scale
						Mean/Median Age (y)	Mean/Median APECHE II Score	Mean/ Median Age (y)	Mean/Median APECHE II Score	
Lorente[48]	Retrospective cohort	ICU (Spain)	VAP	Gram-negative	89	57	15	56	15	7
Lorente[49]	Retrospective cohort	ICU (Spain)	VAP	Gram-negative	121	63	16	63	16	8
Lorente[50]	Retrospective cohort	ICU (Spain)	VAP	Gram-negative	83	63	16	62	16	8
Lubasch[51]	RCT	N/S (Germany)	COPD exacerbation	Various	73	65	N/S	65	N/S	1
McNabb[52]	RCT	ICU (USA)	Nosocomial pneumonia	N/S	35	46	13.9	56	15.5	2
Nicolau[53]	RCT	ICU (USA)	Pneumonia	Various	35	46	14	56	16	3
Patel[54]	Retrospective cohort	N/S(USA)	Various	Gram-negative	129	70	11	72	11	7
Rafati[55]	RCT	ICU (Iran)	Various	Gram-negative	40	50	16	48	14	3
Roberts[56]	RCT	ICU (Australia)	Respiratory, IAI	Various	50	43	19	52	16	4
Roberts[57]	RCT	ICU (Australia)	Sepsis	N/S	10	57	N/S	55	N/S	3
Roberts[58]	RCT	ICU (Australia)	Sepsis	N/S	13	24.5	17.5	42	24	2
Roberts[59]	RCT	ICU (Australia)	N/S	N/S	16	30	20	41	24	2
Sakka[60]	RCT	Surgical ICU (Germany)	ICU-acquired pneumonia	Gram-negative	2	62	26	59	2	2
van Zanten[61]	RCT	ICU (The Netherlands)	COPD exacerbation	Various	83	65	N/S	69	N/S	2
Vuagnat[62]	Prospective study	Non-ICU (France)	Osteomyelitis	Staphylococcal infection	44	N/S	N/S	N/S	N/S	3
Wang[63]	Retrospective cohort	ICU (China)	HAP	*Acinetobacter baumannii*	30	44	20	40	17	7
Wright[64]	RCT	Non-ICU (South Africa)	Severe respiratory infection	N/S	36	N/S	N/S	N/S	N/S	1
Wysocki[65]	Retrospective study	Non-ICU (France)	Various	MRSA	26	61	N/S	67	N/S	3
Wysocki[66]	RCT	ICU (France)	Various	Staphylococcal infection	160	64	N/S	62	N/S	4
Zhao[67]	RCT	ICU (China)	Sepsis	Various	50	68	19.4	67	19.7	5

Table 2. Antibiotics Dosage Regimens of Eligible Studies for Prolonged Infusion (PI) Versus Intermittent Infusion (II) of Antibitotics Included in the Meta-analysis

Study	Antibiotics	Intervention	PI Daily Dose	II Daily Dose	Equivalent Daily Dose?	Concomitant Antibiotic?
Abdul-Aziz[26]	Cefepime (C)	Continuous	C: day 1:2 g LD over 30 min + 2 g over 8h q8h; day 2:2g over 8 h q8h.	C; 2 g over 30 min q8h.	Yes	Allowed: azithromycin; vancomycin; metronidazole; clindamycin; a minoglycosides; colistin
	Meropenem (M)		M: day 1:1g LD over 30 min+1g over 8h q8h;day 2:1g over 8h q8h.	M: 1g over 30 min q8h		
	Piperacillin/tazobactam (P)		P: day 1: 4 g/0.5 g LD over 30 min+4g/0.5g over 6h q6h;day 2:4g/0.5g over 6h q6h	P: 4 g/0.5 g over 30 min q6h		
Abdul-Aziz[27]	Piperacillin or Meropenem	Continuous and extended	N/S	N/S	Yes	N/S
Adembri[28]	Linezolid	Continuous	Day 1: 300 mg LD over 30 min; 900 mg over 2 4h; Day 2: 1200 mg/daily	600 mg q12h	Yes	N/S
Angus[29]	Ceftazidime	Continuous	12 mg/kg LD over 30 min; 4 mg/kg/h over 24h	4 mg/kg q8h	Yes	Allowed: amoxicillin/clavulanic acid or combination of doxycycline, trimethoprim/sulfamethoxazole and chloramphenicol
Bodey[30]	Cefamandole	Continuous	3g LD over 30 min; 12 g over 24h	3 g q6h	Yes	Allowed: carbenicillin
Buck[31]	Piperacillin/tazobactam	Continuous	2/0.5 g LD over 1h; 8/1 g over 24h	4/0.5 g q8h	No	N/S
Buijk[32]	Ceftazidime	Continuous	1 g LD;4.5 g over 24h	1 g LD; 1.5 g q8h	Yes	Allowed
Chytra[33]	Meropenem	Continuous	2 g LD over 30 min; 4 g over 24h	2 g q12h	Yes	Allowed
Cotrina-Luque[34]	Piperacillin/tazobactam	Continuous	2 g/0.25 g over 30 min + 8/1g over 24h	4 g/0.5g over 30 min q8h	No	N/S
DeJongh[35]	Temocillin	Continuous	2 g LD over 30 min;4 g over 24h	2 g q12h	Yes	Allowed: Flucloxacillin
Dow[36]	Piperacillin/tazobactam	Extended	3/0.375 g over 3-4 h q8h, 500mg q6h over 3-4h	3/0.375g q6h,500 mg q6h	Yes	Allowed
Dulhunty[37]	Piperacillin/tazobactam, Meropenem, Ticarcillin/ clavulanic acid	Continuous	13.5 g total daily dose over 24h, 3 g total daily dose over 24h, 12.4-13.5 g total daily dose over 24h	11.3-13.5 g given in divided doses, 3 g given in divided doses, 3 g given in divided doses	Yes	N/S
Dulhunty[38]	Piperacillin-tazobactam, ticarcillin-clavulanate, meropenem	Continuous	Prescribed antibiotic over 24h	Prescribed antibiotic q8h	Yes	N/S
Fahimi[39]	Piperacillin/tazobactam	Extended	3/0.375g over 4h q8h	3/0.375g q6h	No	Allowed
Feld[40]	Sisomicin	Continuous	30 mg/m2 LD over 30 min; 120 mg/m2 over 24h	30 mg/m2 over 30 min q6h	Yes	N/S
Feld[41]	Tobramycin	Continuous	60 mg/m2 LD over 30 min; 300 mg/m2 over 24h	75 mg/m2 over 30 min q6h	Yes	Allowed: Cefamandole nafate
Georges[42]	Cefepime	Continuous	4g over 24h	2g q12h	Yes	Allowed: amikacin
Grant[43]	Piperacillin/tazobactam	Continuous	8/1 g or 12/1. 5 g over 24h	3/0.375 g q6h or 4/0.5g q8h	No	N/S
Hanes[44]	Ceftazidime	Continuous	2 g LD over 30 min; 4 g over 24h	2 g q8h	No	N/S

Table 2. Continued

Study	Antibiotics	Intervention	PI Daily Dose	II Daily Dose	Equivalent Daily Dose?	Concomitant Antibiotic?
Hughes[45]	Oxacillin	Continuous	12 g over 24h	2 g q4h	Yes	Allowed: gentamicin
Lagast[46]	Cefoperazone	Continuous	1g LD over 15 min; 4g over 24h	2 g q12h	Yes	N/S
Lau[47]	Piperacillin/tazobactam	Continuous	2/0.25 g LD over 30 min; 12/1.5 g over 24h	3/0.375 g q6h	Yes	N/S
Lodise[11]	Piperacillin/tazobactam	Extended	3/0.375 g over 4h q8h	3/0.375 g q4h or q6h	No	Allowed: fluoroquinolone; gentamicin
Lorente[48]	Meropenem	Continuous	1 g LD over 30 min; 4 g over 24h	1 g q6h	Yes	Allowed: tobramycin
Lorente[49]	Ceftazidime	Continuous	1 g LD over 30 min; 4 g over 24h	2 g q12h	Yes	Allowed: tobramycin
Lorente[50]	Piperacillin/tazobactam	Continuous	4/0.5 g LD over 30 min; 16/2 g over 24h	4/0.5 g q6h	Yes	Allowed: tobramycin
Lubasch[51]	Ceftazidime	Extended	2 g LD over 30 min; 2 g over 7h q12h	2 g q8h	No	N/S
McNabb[52]	Ceftazidime	Continuous	3 g/d over 24h	2 g/d q8h	No	Allowed: tobramycin
Nicolau[53]	Ceftazidime	Continuous	1 g LD over 30 min; 3 g over 24h	2 g q8h	No	Allowed: tobramycin
Patel[54]	Piperacillin/tazobactam	Extended	3/0.375 g over 4h q8h	3/0.375 g or 4/0.5 g q6h-q8h	No	Allowed: a minoglycoside; fluoroquinolone
Rafati[55]	Piperacillin	Continuous	2 g LD over 30 min; 8 g over 24h	2 g LD;3g q6h	No	Allowed: amikacin
Roberts[56]	Ceftriaxone	Continuous	0.5 g LD; 2g over 24h	0.5 g LD;2g q24h	Yes	Allowed
Roberts[57]	Meropenem	Continuous	500 mg LD over 3 min; 3 g over 24h	1.5 g LD over 5 min;1g q8h	Yes	N/S
Roberts[58]	Piperacillin-tazobactam	Continuous	Day 1: 4 g/0.5 g over 20 min+ 8/1 g over 24 h ; Day2: 12g/1.5 g over 24h	4 g/0.5 g q6h or q8h	Yes	N/S
Roberts[59]	Piperacillin/tazobactam	Continuous	4/0.5g LD over 20 min; 12/1. 5g over 24h	4/0.5 g q6h-q8h	Yes	N/S
Sakka[60]	Imipenem/cilastatiin	Continuous	1/1 g LD over 40 min; 2/2g over 24h	1/1 g q8h	No	N/S
van Zanten[61]	Cefotaxime	Continuous	1g LD over 30 min; 2g over 24h	1 g q8 h	No	N/S
Vuagnat[62]	Vancomycin	Continuous	20 mg/kg LD over 60 min+40 mg/kg over 24h	20 mg/kg LD over 60 min+20 mg/kg over 60 min q12h	Yes	N/S
Wang[63]	Meropenem	Extended	500 mg over 3h q6h	1g q8h	No	N/S
Wright[64]	Gentamicin	Continuous	60 mg/m2 over 8 h q8h	60 mg/m2 over 30 min q8h	Yes	Allowed: penicillin
Wysocki[65]	Vancomycin	Continuous	15 mg/kg LD over 1h+30 mg/kg over 23h	15 mg/kg over 1h q12h	Yes	N/S
Wysocki[66]	Vancomycin	Continuous	15 mg/kg LD over 1h+30 mg/kg over 23h	15 mg/kg over 1h q12h	Yes	N/S
Zhao[67]	Meropenem	Continuous	0.5 g LD+ 3g over 24h	1.5 g LD+1g q8h	No	N/S

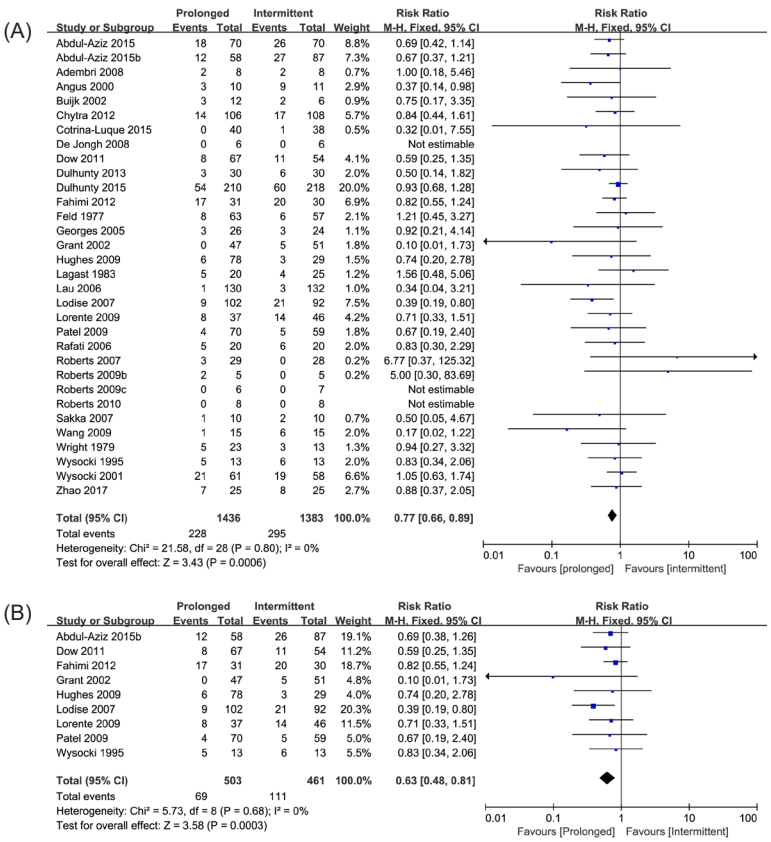


Figure 2. **A)** Forest plot summary of the pooled relative risks (RRs) of the studies comparing all-cause mortality in patients receiving prolonged and intermittent infusion. **B)** Forest plot summary of the pooled relative risks (RRs) of the non-RCTs comparing all-cause mortality in patients receiving prolonged and intermittent infusion.

dependent antibiotics (Figure S1 and S2, see online Supplementary file 1). Moreover, analysis with specific APACHE II scores indicated that the mortality rate was much more lower in critically ill patients with APACHE II scores ≥15 when prolonged infusion was used (Figure 3A; RR = 0.74, 95% CI = 0.63–0.89). Additionally, in the studies with septic patients, the mortality rate in the patients receiving prolonged infusion was not significantly lower than those receiving intermittent infusion (Figure 3B; RR = 0.87, 95% CI = 0.70–1.09). Overall, based on qualitative and quantitative exploration, no conclusive evidence of reporting bias was found.

Clinical Cure

Pooled outcomes of 27 studies (2460 patients) exhibited a statistically significant benefit in clinical cure in the patients with prolonged infusion, compared with intermittent infusion (Figure 4A; RR = 1.11, 95% CI = 1.04–1.19). Similar to the mortality results, a statistically significant advantage in clinical cure was detected in non-RCTs (Figure 4B; RR = 1.33, 95% CI 1.13–1.57) and in RTCs (RR = 1.07, 95% CI 1.01–1.13; Figure not shown). In the subgroups analysis, there was statistically significant a better clinical cure rate in patients with APACHE II score ≥15 receiving prolonged infusion than those receiving intermittent infusion (RR = 1.19, 95% CI = 1.07–1.32; Figure not shown). However, the clinical cure in studies with septic patients showed no difference between prolonged and intermittent infusion (RR = 1.14, 95% CI = 1.02–1.28; Figure not shown).

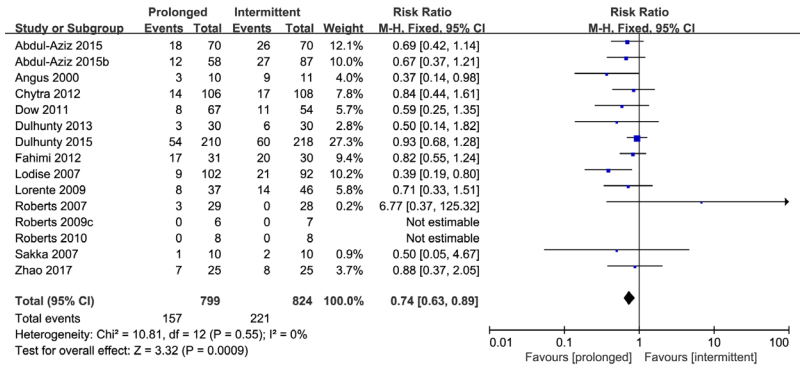
Serious Side Effects

Twelve studies reported serious side effects during antibiotic administration. Antibiotic- related adverse drug events were generally mild, and none were associated with mortality. Gastrointestinal manifestations were minor and included nausea, vomiting, diarrhea, and transient elevation in liver enzymes. Kidney injury also was also reported, including elevated serum creatinine and urea levels. No statistically significant differences in severe antibiotic side effects between the study arms were observed (Figure 5; RR = 0.83, 95% CI = 0.62–1.13).

Heterogeneity and Publication Bias

The included studies exhibited a large variation in sample sizes and clinical settings. There was no statistically significant heterogeneity among studies evaluating mortality ($I^2 = 0\%$, $P = 0.80$), among RCTs evaluating mortality ($I^2 = 0\%$, $P = 0.79$), among non-RCTs evaluating mortality ($I^2 = 0\%$, $P = 0.68$), among RCTs evaluating clinical cure ($I^2 = 2\%$, $P = 0.44$), among studies evaluating serious side effects ($I^2 = 19\%$, $P = 0.28$), among patients

(A)



(B)

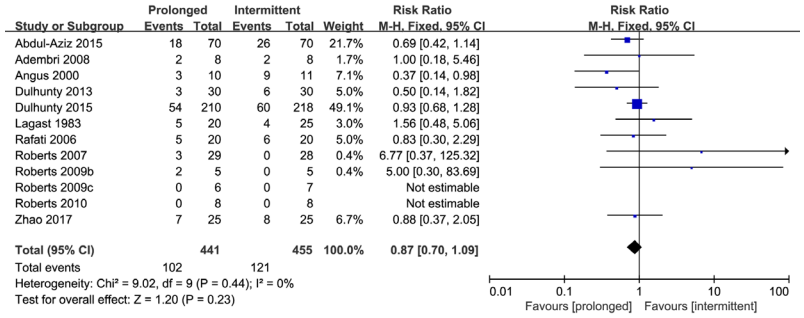
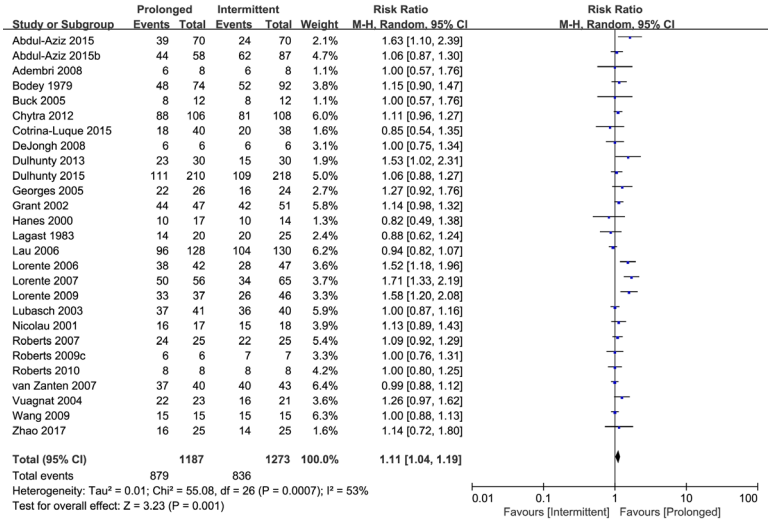


Figure 3. A) Forest plot summary of the pooled relative risks (RRs) of the studies with APACHE II score 15 comparing all-cause mortality in patients receiving prolonged and intermittent infusion. B) Forest plot summary of the pooled relative risks (RRs) of the studies with septic patients comparing all-cause mortality in patients receiving prolonged and intermittent infusion.

(A)



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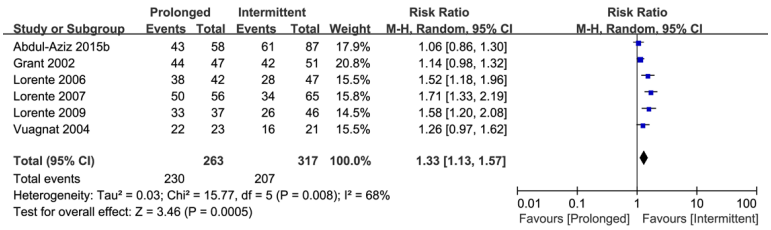

Figure 4. **A)** Forest plot summary of the pooled relative risks (RRs) of the studies comparing clinical cure in patients receiving prolonged and intermittent infusion. B) Forest plot summary of the pooled relative risks (RRs) of the non-RCTs comparing clinical cure in patients receiving prolonged and intermittent infusion.

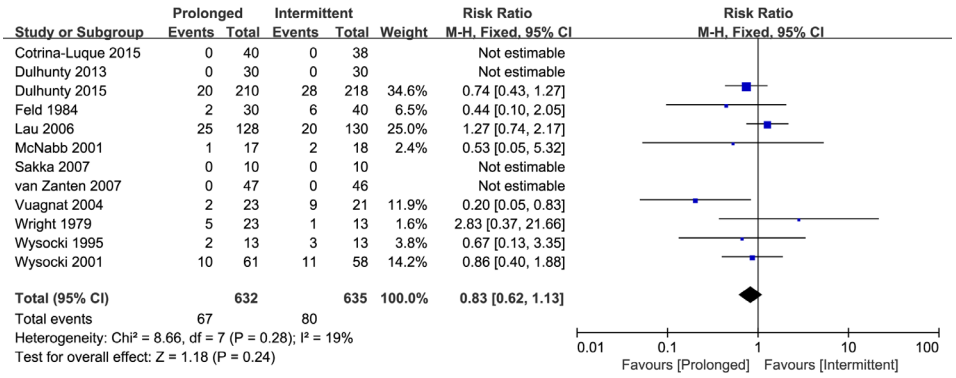

Figure 5. Forest Plot Summary of the Pooled Relative Risks (RRs) of the Studies Comparing Severe Adverse Events in Patients Receiving Prolonged and Intermittent Infusion.

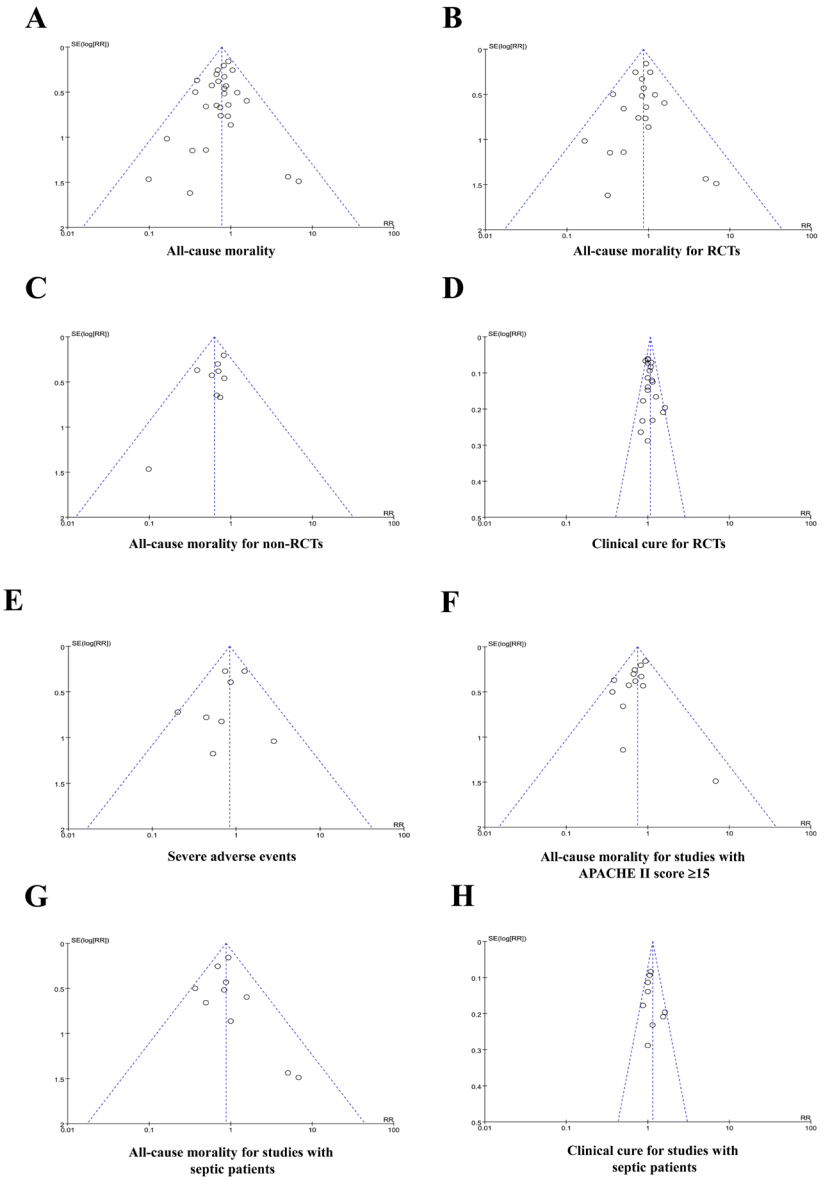

Figure 6. Funnel plots demonstrating low probability of publication bias in studies successively evaluating 1) all-cause mortality, 2) mortality for RCTs, 3) mortality for non-RCTs, 4) clinical cure, 5) severe adverse events, 6) mortality in patients with APACHE II score ≥ 15, 7) mortality in septic patients, and 8) clinical cure in septic patients.

with APACHE II score ≥ 15 evaluating mortality ($I^2 = 0\%$, $P = 0.55$), among septic patients evaluating mortality ($I^2 = 0\%$, $P = 0.87$), and among septic patients evaluating clinical cure ($I^2 = 26\%$, $P = 0.21$) (Figure 6). However, significant heterogeneity was observed among studies assessing clinical cure ($I^2 = 53\%$, $P = 0.0007$), among non-RCTs assessing clinical cure ($I^2 = 68\%$, $P = 0.008$), and among patients with APACHE II score ≥ 15 assessing clinical cure ($I^2 = 65\%$, $P = 0.0006$) (Figure 7). Visual inspection of the funnel plot comparing the effect measures of the primary outcomes for each study with its precision did not suggest asymmetry (Figure 6). No or little publication bias was detected.

Discussion

Several meta-analyses and reviews studies comparing prolonged and intermittent infusion of different antibiotics have been conducted previously.[15,16,21,68-76] Our present meta-analysis included 30 RCTs and 13 non-RCTs (5 prospective comparative studies and 8 retrospective cohort studies), which means it is the largest comprehensive analysis to date, and a wide range of antibiotics, infections, and organisms were also involved. The wide range of studies used in the present meta-analyses may allow the results to be broadly generalized. Our study is also one of the few studies showing a significant reduction in mortality and clinical cure improvement favor prolonged infusion of antibiotics in hospitalized patients over intermittent infusion. However, stratified analysis showed that the clinical benefits in all-cause mortality from prolonged infusion were attributable to the involved non-RCTs, because of the non-statistically significant results from the RCTs were as consistent as those of previous studies that involved RCTs alone.[19,68,669,73-75]

A possible explanation for the significant improvement in all-cause mortality from prolonged infusion among the non-RCTs (prospective and retrospective studies) compared with RCTs could be the difference in the sample size and specific organism in the study design. The average sample size of each non-RCTs was much larger than RCTs for all-cause mortality. There were 9 non-RCTs with 964 participants and 23 RCTs with 1855 participants (Figure 2A). Moreover, most solely gram-negative infections have been reported in non-RCTs compared to RCTs (Table 1). Gram-negative pathogen may be susceptible to β-lactins treatment. A previous study indicated that β-lactins with prolonged infusion had better clinical outcomes than intermittent infusion for gram-negative infections.[16,38] Since the non-RCTs with relatively large sample sizes and gram-negative infections were most likely to demonstrate the benefits of prolonged infusion, the influence may be detected in these studies. In addition, we also found that the prolonged infusion of time-dependent antibiotics had better outcome than intermittent infusion which was consistent with the previous studies,[11-14] suggesting that serum drug concentration above MIC can improve clinical outcomes. In the studies with concentration-dependent antibiotics, there were only two studies included in subgroup analysis which affected its statistical validity.

Previous studies have reported discrepant results in the clinical benefits of prolonged infusion in RCTs, which have been deeply discussed.[68,69,73,74,76] The potential effective factors to explain these inconsistency in the results of previous studies are small sample sizes, variation in clinical setting such as heterogeneous patients and disease severity, poor study quality, and renal dysfunction, which all can have an impact on the outcomes.[68,76] In our meta-analysis, the number of RCTs and non-RCTs included were 30 and 13 respectively, which are more compared to previous studies. Larger sample size could help to avoid the study bias as much as possible. Additionally, in some of the study population from the RCTs, who were composed of ICU patients, low mortality rates and low APACHE II scores may not be truly 'critically ill' and instead reflect participants with lower-risk. For example, study from Lau et al in the year 2006 exhibited a mortality rate of 1.5% and APACHE II score of 8,[47] whereas in a study by Chytra et al in 2012, the hospital mortality rates in critically ill participants was 15.5% and average of APACHE II score was 21.75.[33] The differences between study populations with heterogeneous clinical settings may affect the conclusions of different meta-analysis.

In our study, the critically ill patients and patients with APECHE II scores ≥15 who have been treated with

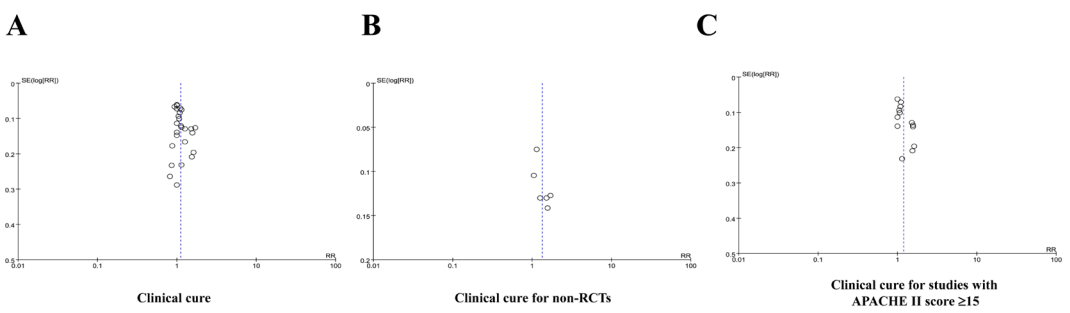

Figure 7. Funnel plots demonstrating relative high probability of publication bias in studies successively evaluating 1) clinical cure, 2) clinical cure in non-RCTs, and 3) clinical cure in patients with APACHE II score ≥ 15.

prolonged infusion had low mortality rates and better clinical cure. Augmented volume of integral distribution and accelerated drug clearance may elicit lower initial and reduced drug concentrations.[6] Extended and continuous infusion was more likely to maintain tough concentrations above the MIC in critically ill patients than intermittent infusion.[68] Increased MICs of organisms and decreased drug concentration may jointly reduce the probability of clinical cure when using intermittent infusion, which is further confirmed by our findings that septic patients with prolonged infusion had statistically significant clinical cure rates over intermittent infusion, although two dosing strategies had no significant difference in all-cause mortality rates in septic patients. Moreover, the two dosing strategies had no remarkable difference in severe adverse effects. Taken together, our results tend to support the choice of prolonged infusion of antibiotics for critically ill patients.

One limitation of the present study was that some involved clinical research did not provide infection-caused microbiological evidence and its susceptibility profiles, especially in older studies with low precision methodology in organism detection. It is inevitable that inappropriate antibiotic treatments and highly resistant organisms may be linked to increased mortality rates in some studies. Another limitation was our statistical analysis included retrospective studies which by nature have a risk of selection bias and make it difficult to control for confounding factors.

In conclusion, our meta-analysis data has shown that prolonged infusion of antibiotics may be associated with clinical benefits, less side effects, lower hospital mortality and higher rate of clinical cure than intermittent infusion. Critically illness patients, including patients with sepsis or APACHE II score ≥15, probably derive the most benefit from prolonged infusion.

Authors' Contribution

JY Luo and JL Liao contributed equally to this work; ZH Liu, Z Yang and YJ Cheng designed the research and analyzed the data; ZH Liu, JL Liao, RB Cai, JJ Liu, ZH Huang performed the retrieval; ZH Liu and JY Luo wrote the paper.

Conflict of Interest Disclosures

The authors have declared that no competing interests.

Ethical Statement

Not applicable.

Acknowledgments

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Supplementary Materials

Supplementary file 1 contains Figures S1-S2.

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