Continuous Infusion Compared with Intermittent Intravenous Infusion of Beta-Lactam Antibiotics for Critically Ill Patients: A Systematic Review and Meta-Analysis of Randomized Trials

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Research

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Abstract

Background: The pathophysiologic changes during critical illness and high minimal inhibitory concentration (MIC) pathogens are important risk factors of mortality and bacterial eradication in critical care. Beta-lactam antibiotics have a time-dependent effect on bactericidal activity. The continuous infusion (CIF) of beta-lactam antibiotics achieves sufficient drug concentration above the MIC, especially for critically ill patients. However, the superiority of CIF over intermittent infusion (IIF) of beta-lactam antibiotics is yet to be clearly established. Thus, we aimed to investigate the effects on mortality of CIF of beta-lactams antibiotics in comparison to those of IIF of beta-lactams antibiotics in patients with sepsis admitted to the intensive care unit (ICU).

Methods: We systematically searched PUBMED, MEDLINE, Cochrane Library, EMBASE, Web of Science, and ICTRP for randomized controlled trials (RCTs) comparing CIF with IIF of beta-lactam antibiotics in critically ill populations. All RCTs published until October 2019 were eligible. The primary outcome measure was the relative risk (RR) of mortality, while the secondary outcome measures were bacterial eradication rate, length of ICU stay, and length of admission.

Results: In total, 6 RCTs comprising 974 patients were analyzed. We found a significantly lower mortality for critically ill patients on CIF (RR: 0.79; 95% CI: 0.63, 0.98) compared with those on IIF of beta-lactam antibiotics. The pooled RR for the bacterial eradication rate was 1.16 (95% CI: 1.03, 1.29) for CIF compared with IIF administration.

Conclusion: CIF of beta-lactam antibiotics for critically ill patients significantly reduces mortality and yields a better bacterial eradication rate than IIF. These findings support the clinical and bacterial eradication benefits in adult critically ill patients, and may guide clinical discussions and decisions.

Background

Intermittent infusion (IIF) of antibiotics is a common strategy in the treatment of patients with infection. In the past decade, the development of novel antibiotics has slowed down, and different dosing strategies based on the pharmacokinetic properties of antibiotics have been attempted instead to improve clinical outcomes or to reduce adverse drug reactions. For example, once-daily dosing of aminoglycosides, a concentration-dependent antibiotic, has demonstrated similar clinical outcomes to conventional-dosing but with lower renal toxicity.[1] Compared with IIF, continuous infusion (CIF) as a newer method of drug administration, especially for beta-lactam antibiotics, can maintain sufficient drug concentrations above the minimum inhibitory concentration (MIC) and also have better clinical outcomes.

Beta-lactam antibiotics have a time-dependent effect on bactericidal activity, which is related to the duration of the antibiotic concentration above the MIC. Patients in the intensive care unit (ICU) have restricted activity, and thus CIF is easier to perform in the ICU than in the general ward. However, evidence concerning the effectiveness of CIF of beta-lactam antibiotics is still inconclusive. An earlier systematic review reported no difference in mortality between the CIF groups and the IIF groups.[2] A Cochrane review published in 2013 also failed to demonstrate the benefit of CIF for all-cause mortality.[3] However, another study found an almost statistically significant reduction in mortality rates with CIF.[4] These conflicting findings might be because different types of antibiotics, such as aminoglycosides, glycopeptides (mostly vancomycin), and beta-lactam antibiotics, were included in the above systematic review. Neither the CIF of vancomycin has been shown to substantially improve patient outcomes when compared to IIF,[5] nor are aminoglycosides suitable for use in CIF according to their pharmacokinetic properties. Including those antibiotics in the systematic review could diminish the actual effects of CIF of beta-lactam antibiotics.

To our best knowledge, no current systematic reviews have clearly focused on the outcomes of CIF of beta-lactam antibiotics in critically ill patients with sepsis. As such, this study aimed to investigate the effects on mortality of CIF in comparison to those of IIF of beta-lactams antibiotics of patients with sepsis in the ICU.

Methods

Literature search

We systematically reviewed randomized controlled trials (RCTs) in PubMed, MEDLINE, Cochrane Library, EMBASE, Web of Science, and ICTRP. All RCTs published until October 2019 were eligible. The following search strategy was implemented: [(intensive care unit OR ICU OR critically ill) AND (carbapenem OR meropenem OR imipenem OR doripenem OR piperacillin OR ticarcillin OR cephalosporins OR cefepime OR ceftazidime OR ceftolozane OR cefoperazone OR monobactam OR aztreonam) AND (extended OR prolonged OR continuous OR discontinuous OR intermittent OR short OR bolus) AND (mortality OR survival)]. The detailed list of keywords, synonyms, truncation, and controlled vocabularies are listed in the appendix [see Additional file 1]. We also manually searched the reference lists of the identified systematic reviews for additional RCTs. There were no exclusions made for language or publication. The search was performed independently by two reviewers, and duplicate studies were deleted before selection.

Study selection

CIF was defined as an infusion duration of > 3 h or a 24-h CIF, whereas IIF was defined as a bolus administration or infusion duration of < 60 min. As such, eligible studies were those comparing the clinical outcomes between CIF and IIF of beta-lactam antibiotics in patients who received intensive care or were admitted to the ICU. Non-RCTs, studies that used varying antibiotics in their study arms, with cross-over study designs, only reporting pharmacokinetic or pharmacodynamic outcomes, with less than 10 patients, those that only used antibiotics for surgical prophylaxis, or those that included patients aged younger than 18 years were excluded.

Data extraction and quality assessment

Two authors independently extracted data from the included studies using a standardized form. The data were the main characteristics of the study (author, year of publication, study countries, and year), number of included patients and those that were clinically evaluated, type of infection and causative bacteria, intravenous dosage, and the regimen of beta-lactam antibiotics. In addition, the clinical outcomes of mortality and bacterial eradication rates and other outcomes (i.e., length of ICU stay and length of hospital admission) in each treatment group were recorded. Discrepancies between the two authors were resolved by consensus.

The quality of each study was evaluated using the Cochrane Collaboration tool to evaluate the risk of bias. Specifically, the tool was used to assess whether there was adequate generation of randomization sequences, concealment of treatment allocation, masking of assessors, and appropriate methods for addressing missing data. Two researchers independently conducted quality assessments and a third author was consulted for final categorization if disagreements occurred.

Definitions and outcome measures

The primary outcome measure was all-cause mortality. If multiple mortality rates with differing follow-up lengths were reported, the one with the longer follow-up was selected. As such, in a study reporting 14-day and 30-day mortality, the latter would be included in the meta-analyses. Meanwhile, the secondary outcome measures were the bacterial eradication rate, length of ICU stay, and length of admission.

Statistical analysis

The meta-analysis was performed with Review Manager for Windows version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). Statistical heterogeneity among studies was assessed using the Cochran's q test, with significant heterogeneity defined as $p < 0.10$ and the *I* square (I^2) test. We expected variations in the demographics of the patients in the ICU. Thus, we used the Mantel–Haenszel random effects model to calculate the pooled risk ratio (RR) and 95% CI for the primary outcome and bacterial eradication rate. For other secondary outcomes, the random effects model was used to calculate the mean difference and 95% CI for the length of ICU stay, and standardized mean difference and 95% CI for length of admission. For studies that reported medians and interquartile ranges (IQRs) for the secondary outcomes, we extrapolated the mean and standardized difference (SD) by assuming the width of the IQR to be 1.35 SD.[6] We tested for publication bias by examining a funnel plot created by using the trim-and-fill procedure with the Review Manager for Windows version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark).

Results

Study characteristics

We identified 1964 articles through the database search and 35 articles from the review of the reference lists of other relevant systematic reviews. After removing duplicates, 1398 articles remained. Of these, 1341 were further excluded after reviewing the titles and abstracts. From the remaining 57 articles that were assessed for eligibility through a full-text review, 51 studies were excluded because they were non-RCTs or only included pharmacokinetic/dynamic data. Finally, six studies[7–12] were included in this meta-analysis (Fig. 1).

The sample sizes ranged from 50 to 432 patients, and the year of publication ranged from 2012 to 2018. All six studies were performed in different countries, but most of them were performed in Asia. All studies were carried out in the ICU, with the majority of patients having sepsis. The antibiotics administered included piperacillin-tazobactam, ticarcillin-clavulanate, meropenem, and cefepime. CIF time varied from 3 to 24 hours, whereas IIF was performed within 30 minutes (Table 1).

Table 1
Study characteristics

	Study period	Countries	Exclusion criteria	Patients enrolled	Age (mean ± SD)	APACHE II (mean ± SD)	Infection focus	Bacteria	Antibiotic
Abdul-Aziz 2016	2013/04-2014/07	Malaysia	Renal replacement therapy, impaired hepatic function, palliative treatment , imminent death	140	54 (42–63) vs 56 (41–68)	21 (17–26) vs 21 (15–26)	Lung, intraabdominal, skin and soft tissue, UTI, bacteremia, CNS	NA	Cefepime ,Meropenem Piperacillin/tazobactam
Chytra 2012	2007/09-2010/05	Czech	Acute or chronic renal failure(eGFR < 30 ml/min),immune-deficiency, immunosuppressant medication, neutropenia	214	44·9 ± 17.8·vs 47·2 ± 16·3	21.4 ± 7.9 vs 22.1 ± 8.79	Lung, intraabdominal, skin and soft tissue, UTI, bacteremia, others, unknown	Gram(-): 92.5%	Meropenem
Dulhunty 2013	2010/04-2011/11	Australia, Hong Kong	Palliative or supportive treatment, continuous renal replacement therapy	60	54 ± 19 vs 60 ± 19	21 ± 8.6 vs 23 ± 7.6	Lung, intraabdominal, skin and soft tissue, UTI, bacteremia, CNS, unknown	Gram(+): 33.4% Gram(-): 67.6%	Piperacillin/Tazobactam Meropenem Ticarcillin/clavulanate
Dulhunty 2015	2012/7/2-2014/4/10	Australia, New Zealand, Hong Kong	Palliative or Supportive treatment, imminent death	432	64 (54–72) vs 65 (53–72)	21 (17–26) vs 20 (16–25)	Lung, intraabdominal, skin and soft tissue, UTI, bacteremia, others,unknown	Gram(+): 26.5% Gram(-): 72.3%	Piperacillin/tazobactam Meropenem Ticarcillin/clavulanate
Wang 2014	2012/9/1-2013/9/30	China	Immunosuppression, neutropenia, pregnancy, concomitant severe infection, renal insufficiency (Crcl < 50 ml/min)	78	63·5 ± 15·3 vs 57·2 ± 19·5	20.7 ± 7.4 vs 19.2 ± 7.0	Hospital acquired pneumonia	NA	Meropenem
Zhao 2017	2012/06-2014/12	China	Acute or chronic renal failure (eGFR < 50 ml/min), immunodeficiency, Immunosuppressant medication	50	68.0 ± 15.4 vs 67.0 ± 12.2	19.4 ± 5.0 vs 19.7 ± 5.9	Lung, intraabdominal, skin and soft tissue, UTI, bacteremia, others	Gram(-): 86.0%	Meropenem

Risk of bias

All included studies were RCTs, but there were two studies with unclear methods of randomization as well as allocation concealment. In the assessment of performance and detection bias, four studies showed low bias, while the rest showed high or unclear bias. All studies had a low risk of attrition bias, and the risk of selection bias was unclear in only one study. However, only one study reported other sources of potential bias (Figs. 2 and 3). No obvious asymmetry was found in the funnel plot for the primary outcome, indicating minimal publication bias (Fig. 4).

Primary outcome

Mortality

The pooled outcome of the six studies showed that there was a statistically significant mortality advantage in the CIF group (RR: 0.79, 95% CI: 0.63, 0.98; $p = 0.03$). No significant heterogeneity was found among the studies ($I^2 = 0\%$, $p = 0.57$) (Fig. 5).

Secondary outcomes

Bacterial eradication rate

Of the six RCTs included in this meta-analysis, only three trials[8, 11, 12] reported data on the bacterial eradication rate. There was no statistically significant heterogeneity among the identified comparisons (I^2 = 0%, p = 0.84). The estimated pooled RR for bacterial eradication rate was 1.16 (95% CI: 1.03, 1.29) for CIF compared with IIF of antibiotics (p = 0.01) (Fig. 6a).

Length of ICU stay

All six studies reported the length of ICU stay. Of these, five studies reported the length of ICU stay by median[7, 9–12], while one used mean[8]. There was no significant difference in the length of ICU stay between the CIF group and the IIF group (mean difference = 0.03, 95% CI: -1.44, 1.50 days, p = 0.97). Significant heterogeneity was found among all studies (I^2 = 51%, p = 0.07) (Fig. 6b).

Length of admission

Two studies[9, 12] reported the length of admission as an outcome in median [IQR] days. There was no significant heterogeneity between these studies (I^2 = 0%, p = 0.68). The duration of admission was slightly longer in the IIF group (mean difference = 0.17, 95% CI: 0.02, 0.32 days; p = 0.03) (Fig. 6c).

Discussion

This meta-analysis showed that CIF of beta-lactam antibiotics for critically ill patients is associated with lower hospital mortality and higher bacterial eradication rate than the traditional method of IIF.

Sepsis is an important public health issue owing to its considerable impact on in-hospital mortality and the high economic burden.[13] The major factors influencing sepsis-associated mortality are the patient's characteristics and comorbidities, including advanced age, male sex, liver cirrhosis, and chronic renal disease.[14–17] The APACHE II score is positively associated with mortality, with higher scores indicating higher mortality rates.[18] Thus, our study could control for the disease severity to measure the mortality rate in sepsis patients with different administration regimens.

The strength of our study is that we included a homogenous population of sepsis patients admitted in the ICU, with mean APACHE II scores of ≥ 19. Further, all antibiotics administered belonged to the beta-lactam class. Meanwhile, our meta-analysis also has some limitations. First, we could not evaluate the safety of CIF because none of the studies reported the safety outcomes. Second, we could not analyze the effects of CIF on renal impairment patients due to the lack of subgroup analyses or related data from the included studies. There was also a lack of microbiologically proven infections in our studies, mostly due to a profound variation in the infection focus and pathogen of sepsis in patients with differing critical status.

In contrast to the previous meta-analysis and systematic review performed by Chen *et al.*[19], we only included adult ICU patients treated with beta-lactam antibiotics. We consider this to be important because the disease status and patient characteristics are correlated with mortality, and healthcare support systems are profoundly different between ICU and non-ICU patients.[20] Consequently, Chen *et al.* might not have provided sufficient evidence for a homogenous population because they included both adult patients in the ICU and ward.

Compared with other studies [21–23] that showed no significant benefit in clinical cure rate, our study findings indicate that the CIF of beta-lactam antibiotics has better efficacy and achieves better outcomes than IIF, especially for critically ill patients with sepsis. There are two possible explanations. First, severe disease causes pathophysiologic changes that lead to a more profound difference in drug levels under CIF or IIF of antibiotics [24]. Two, due to a higher prevalence of pathogens with higher MIC levels in the ICU or critically ill population, CIF, rather than the traditional IIF, may be required to achieve the effective therapeutic concentration level [25–27].

Our study showed that compared to IIF, CIF reduced the risk of hospital mortality by 21%. The secondary outcome of bacterial eradication rate was significantly higher in the CIF group than in the IIF group. These findings correlate with the mechanism of the time-dependent effect that beta-lactam antibiotics have on bacterial eradication. This, in turn, should be enhanced by maintaining the duration of a sustained concentration above the MIC (time > MIC), which can be achieved with CIF.[28] Drug pharmacokinetic parameters change due to the hyperdynamic state of sepsis, such as hypovolemia, hypoalbuminemia, and organ hypoperfusion (liver, kidney).[29] In addition, pathophysiological changes in critical status also affect the volume distribution and drug clearance. This might lead to a lower-than-expected drug plasma concentration.[29] Consequently, an important consideration in the medical treatment of critically ill patients with sepsis is how to attain the optimal concentration of antibiotics. Roberts *et al.* found that in the PK data, the CIF group had significantly higher Css (steady state) concentrations than the Cmin (minimum) of the IIF group. The same results were also found in plasma data.[30] However, few studies have explored the effectiveness of CIF of concentration-dependent antibiotics. Tan *et al.* showed that CIF of colistin, which is a concentration-dependent antibiotic, has no pharmacodynamic benefits for treating an infection with a multidrug-resistant pathogen, such as *Acinetobacter baumannii* species.[31]

Nonetheless, there are a few limitations to consider when interpreting for clinical use. First, although all included studies were RCTs, two of the studies belonged to the same author, and half of the studies had a smaller sample size, with fewer than 100 people. Second, most of the countries where these studies were conducted are developing countries, whose capacity to care for critically ill patients may not be comparable to European and American countries. Therefore, it is unknown whether the same effect might be observed in regions with higher levels of medical care. Third, although meropenem was used in all included studies, its stability might be of concern as the infusion should be completed within a certain period of time after meropenem has been diluted. However, in our review, this has not been well addressed in any studies, with varying infusion rates or protocols documented. Thus, this issue should be taken into consideration when applying CIF of meropenem to critically ill patients.

Despite the limitations of the studies included, this systematic review and meta-analysis provides summary information on the efficacy of CIF in comparison to that of IIF of beta-lactam antibiotics. The results support the clinical and bacterial eradication benefits in adult critically ill patients, and these findings may guide clinical discussions and decisions. It should be noted that disease severity in the included studies was generally moderate to severe, with the patients having a mean APACHE II score of ≥ 19.

As noted earlier, there is no censuses on the infusion rates or protocols among the studies reviewed, neither were the deficiency well-addressed. Future studies should focus on a standardized infusion regimen of beta-lactam antibiotics in the general or specific (e.g., those with renal impairment) population or when multidrug-resistant pathogens such as *Acinetobacter baumannii* species are present.

Conclusions

Compared with IIF, CIF of beta-lactam antibiotics could achieve greater clinical and bacterial eradication benefits in critically ill patients primarily due to the time-dependent characteristics of CIF. These findings support the clinical and bacterial eradication benefits in adult critically ill patients, and may guide clinical discussions and decisions.

List Of Abbreviations

CIF continuous infusion

ICU intensive care unit

IIF intermittent infusion

IQRs interquartile ranges

MIC minimal inhibitory concentration

RCTs randomized controlled trials

RR relative risk

SD standardized difference

Declarations

- Ethics approval and consent to participate: Not applicable
- Consent for publication: Not applicable
- Availability of data and materials: Not applicable
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Figures

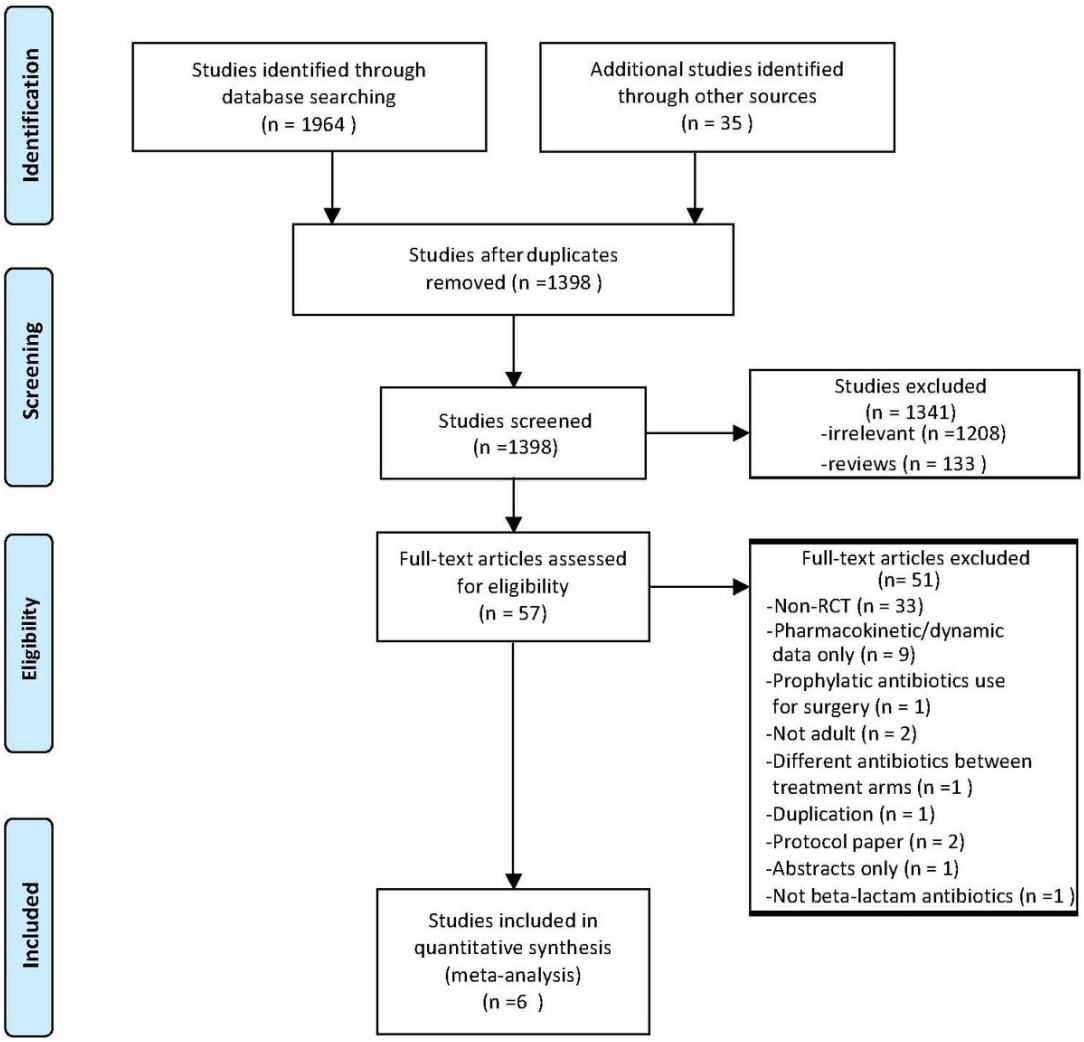

Figure 1

Study selection flowchart

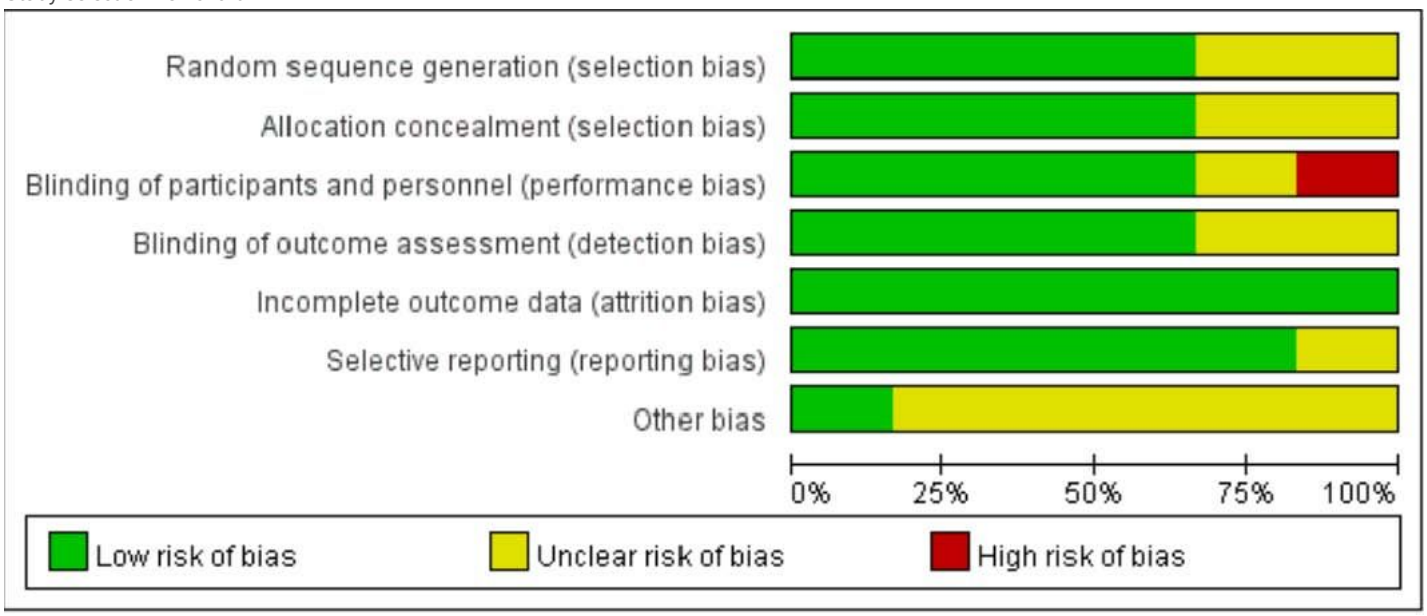

Figure 2

Risk of bias assessment in the overall studies

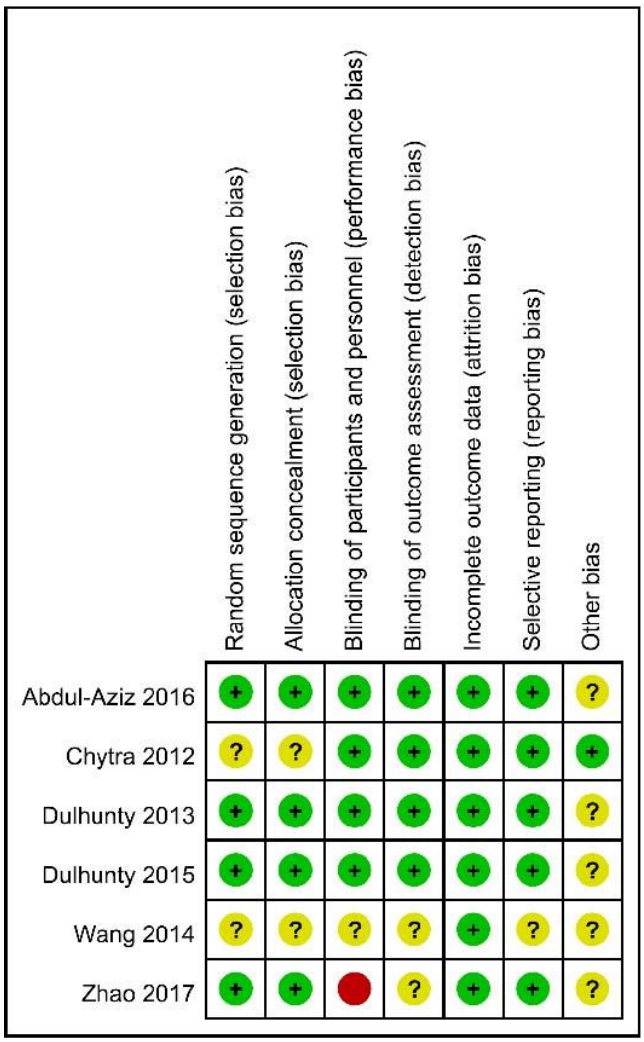

Figure 3

Risk of bias assessment by studies.

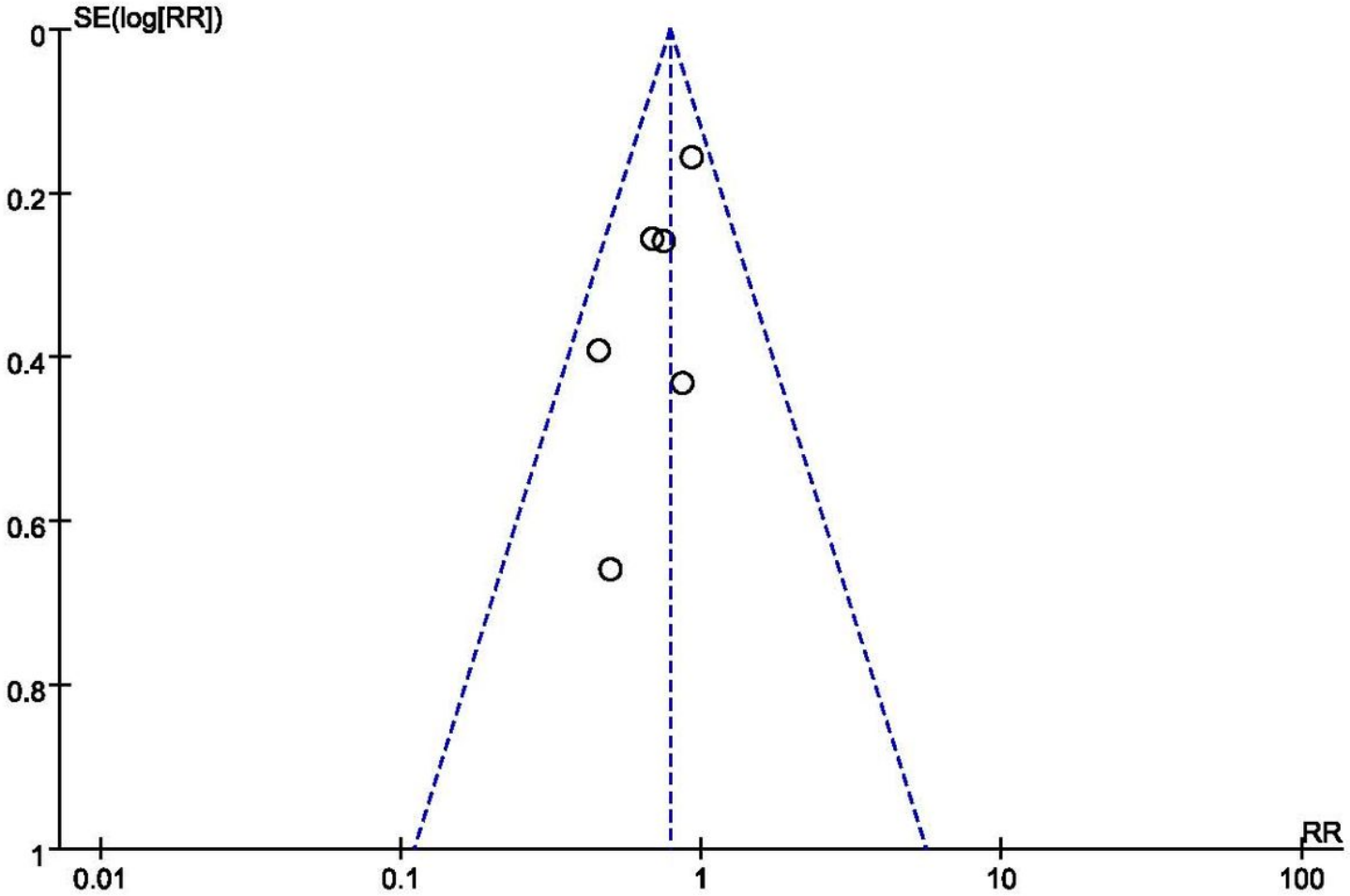

Figure 4

Funnel plot of the six trials for comparison of mortality between continuous and intermittent infusion

Study or Subgroup	Continuous infusion Events	Total	Intermittent infusion Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abdul-Aziz 2016	18	70	26	70	18.0%	0.69 [0.42, 1.14]
Chytra 2012	21	120	28	120	17.7%	0.75 [0.45, 1.24]
Dulhunty 2013	3	30	6	30	2.7%	0.50 [0.14, 1.82]
Dulhunty 2015	56	212	62	220	47.7%	0.94 [0.69, 1.28]
Wang 2014	7	38	16	40	7.7%	0.46 [0.21, 0.99]
Zhao 2017	7	25	8	25	6.3%	0.88 [0.37, 2.05]
Total (95% CI)		**495**		**505**	**100.0%**	**0.79 [0.64, 0.98]**
Total events	112		146			

Heterogeneity: Tau² = 0.00; Chi² = 3.93, df = 5 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.16 (P = 0.03)

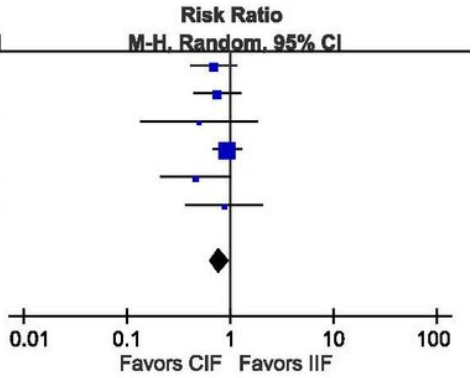

Figure 5

Comparison of mortality outcomes between continuous infusion and intermittent infusion

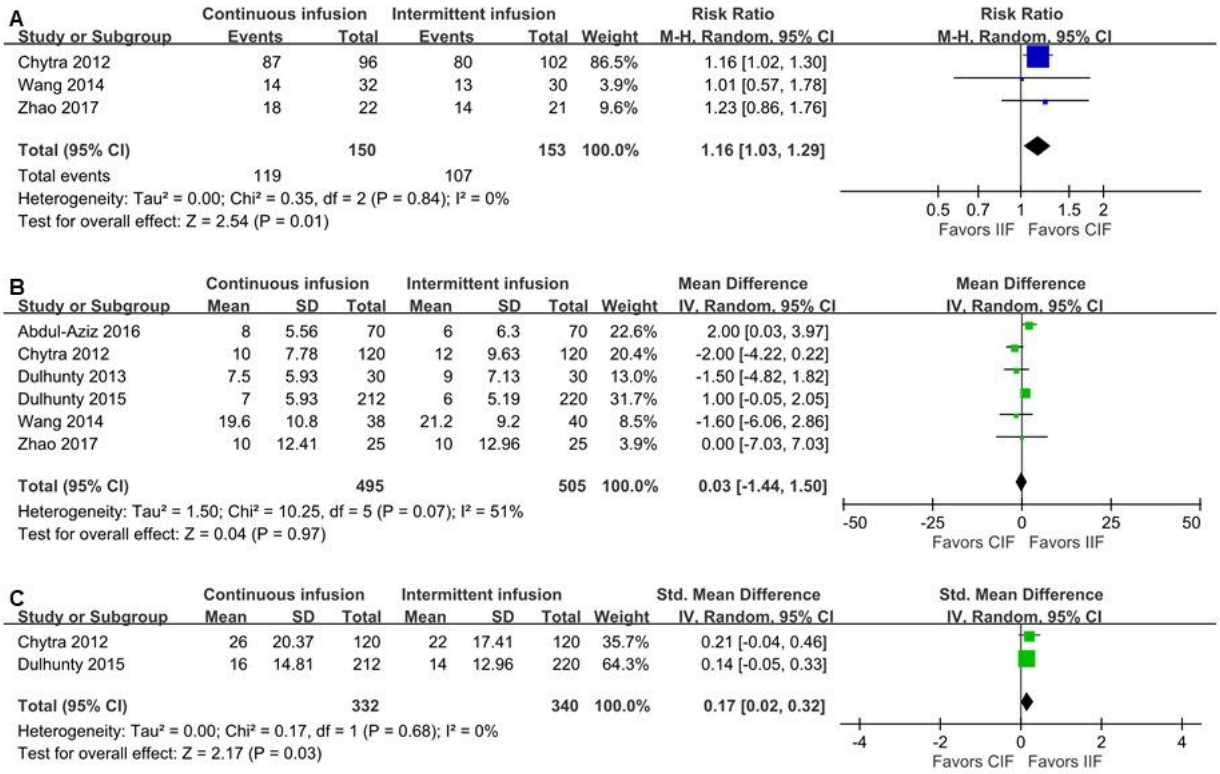

Figure 6

Comparison of secondary outcomes between continuous infusion and intermittent infusion. (a) Bacterial eradication rate. (b) Length of ICU stay. (c) Length of admission.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfilelan.docx