BMJ Open

Prolonged infusion with β-lactam antibiotics for treatment of infection caused by non-susceptible bacteria: a study protocol for a systemic review and meta-analysis

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ABSTRACT

Introduction Prolonged infusion with β-lactam antibiotics should theoretically produce a better clinical efficacy than intermittent infusion in severe infection and infection caused by non-susceptible micro-organisms. The efficacy of prolonged infusion in severe infection has been well illustrated recently, but is still confusing in non-susceptible microbial infection. The objective of this meta-analysis is to determine the clinical effects of prolonged infusion with β-lactams for patients infected by microbes non-susceptible to the given drug.

Methods and analysis Literature searches will be performed with Medline, the Cochrane database, EMBASE database, Cumulative Index to Nursing and Allied Health Literature database, the Chinese National Knowledge Infrastructure and Wanfang database. Two reviewers will screen and select studies according to a priori defined eligibility criteria, and then the data from the included studies will be extracted. The quality will be evaluated based on a modified Jadad score and the Newcastle-Ottawa system for randomised controlled trials and observational studies, respectively. Data synthesis will be performed with Review Manager 5.3 software. Sensitivity analysis and publication bias will also be investigated.

Ethics and dissemination No ethics approval is required. The full article will be published in a peer-reviewed journal and presented at international conferences.

PROSPERO registration number CRD42018105111.

Strength and limitation of this study

► This meta-analysis will evaluate the clinical efficacy of prolonged infusion with β-lactams for infections caused by microbes with reduced susceptibility to β-lactam treatment.
► This protocol has been written following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.
► The credibility of the findings may be affected by the quality of the included studies.

INTRODUCTION

Global effects are taken to account the antibiotic resistance issue, although the development of new antibiotics cannot keep up with the occurrence of resistance, and the treatment of infections caused by resistant microbes is becoming increasingly challenging.[1 2] To obtain the maximum antimicrobial effect of existing drugs, clinicians and scientists have turned to the rational use of antibiotics, including administration under the guidance of pharmacokinetic/pharmacodynamics (PK/PD) models.[3 4]

β-lactams are a broad class of antibiotics widely used to treat infections, especially those that are caused by Gram-negative microbes.[5] β-lactams exhibit primary time-dependent antimicrobial activity, and the best PK/PD index predicts clinical efficacy according to the duration of the maintenance of the drug concentration above the minimum inhibitory concentration (MIC) for the pathogen (referred as fT >MIC) during each dosing interval.[6] When PK/PD targets are achieved, β-lactams have their maximal antibiotic effect, and hence patient outcomes are optimised.[7] The target fT >MIC for β-lactam is recognised as 40%–60%. For severe infection patients, the target fT >MIC needs to be elevated to 100%.[8] And for patients infected by non-susceptible microbes, the fT >MIC decreases owing to the elevated MIC. Treatment failure will occur when administered by traditional intermittent infusion. According to in vitro and in vivo simulations, prolonged infusion with β-lactams can enhance the fT >MIC and thus improve probability of target attainment towards severe infection and infection caused by non-susceptible microbes.[9 10]

Recent studies have investigated the clinical value of prolonged infusion with β-lactams with randomised controlled trials (RCTs),

which suggests the potential advantage of prolonged infusion for patients with severe sepsis.[11–13] However, some meta-analyses comparing prolonged infusion and an intermittent bolus of β-lactam have conflicting results.[14–18] The probable reason is that most of these studies have not been stratified for patients with severity or infections that have reduced susceptibility. With the evidence accumulates, the efficacy of prolong infusion of β-lactam in severe infection patients or critically ill patients has been well illustrated recently.[17 18] However, the efficacy in non-susceptible infection is still confusing. The MIC ranges of the infecting pathogens are very important to the outcomes; target PK/PD thresholds will be obtained using a standard intermittent infusion of antibiotics in susceptible micro-organism infection, but not in non-susceptible infection.[19] This indicates that prolonged infusion with a β-lactam has less advantage for treating infections caused by sensitive microbes.[20–22] Meta-analysis evaluating the effect of prolonged infusion in patient stratified with susceptibility is needed.

To address this shortcoming, we carried out a meta-analysis to assess the clinical effects of prolonged infusion with β-lactams for patients infected by non-susceptible microbes. To our knowledge, this is the first study to assess meta-data from other studies of patients with infections that have reduced susceptibility to β-lactam treatment.

METHODS
This protocol has been written following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement and registered in PROSPERO.[23]

The PRISMA-P checklist is shown in online supplementary appendix 1.

Patient and public involvement
Patients or the public are not involved.

Eligibility criteria
Study design
RCTs, quasi-RCTs and observational studies (retrospective and prospective) will be included. In vitro studies, animal studies and case reports will be excluded.

Participants
Patients who are infected by bacteria that are not susceptible to β-lactams will be included. The susceptibility of the infecting microbes should be tested and established to be non-susceptible (intermediate or resistant) to the administered β-lactam in the study. There is no restriction regarding the method used to determine the susceptibility. There is also no restriction regarding the site of infection or other patient characteristics.

Interventions
Studies evaluating the clinical efficacy of prolonged infusion with β-lactams will be included. Prolonged infusion is defined as infusion of a β-lactam of no less than 3 hours.

Continuous infusion is recognised as a special type of prolonged infusion and can be included.

Comparators
The study will compare conventional, intermittent infusion of the same β-lactams as used in the intervention group. Intermittent infusion is defined as infusion of drug in less than 30 min.

Type of outcome measures
Studies to evaluate the clinical efficacy of prolonged infusion will be included. The clinical effective rate must be evaluated. The effect is defined as a clinical cure, clinical improvement or eradication of infected bacteria.

Language
Studies published in English and Chinese will be included. Studies published in other languages but with a full information abstract in English or Chinese will also be included. If the reviewer obtains the required information from the authors or translators, studies published in other languages will also be included.

Information sources
The following electronic databases will be searched from their inception to 31 July 2018: Medline, Cochrane database, EMBASE database, Cumulative Index to Nursing and Allied Health Literature database, the Chinese National Knowledge Infrastructure and the Wanfang database.

Search strategy and selection of studies
The aforementioned electronic databases will be searched electronically. We will develop search strategies for each database, based on the search strategy developed for Cochrane database and Medline (online supplementary appendix 2), with appropriate reversions.

Relevant publications such as references within the included studies will be searched manually. The yielded studies will be selected by reading the title, abstract and full text to determine whether the eligibility criteria are met.

The literature searches and study selections will be carried out by two reviewers (HC and LY) independently and cross-checked. Any inconsistency will be solved by discussion with a third reviewer (ZY).

Data extraction
Data for the following attributes will be extracted: author and publication year of the study, study design, study duration and region, number of participating patients, patient age, gender, infection site, isolated micro-organisms, methods and results of susceptibility analysis, β-lactams administered and dosing regimen, co-administrated antibiotics and clinical outcomes including adverse events. The data will be extracted by two reviewers (HC and LY) independently using an electronic data table and cross-checked. Any inconsistency will be solved by discussion with a third reviewer (ZY).

Dealing with missing data

When required data are not available in the literature or not published in an extractable form, the corresponding author of the published study will be contacted by e-mail to request additional information. Only available data will be analysed if the reviewers fail to obtain data from any corresponding author.

Measurement of outcomes

Primary outcome

Effective rate. Outcomes defined as clinical cure, clinical improvement and eradication of the infecting bacteria by original study are regarded as effective in this meta-analysis.

Secondary outcomes

Mortality rate, microbial eradication rate, adverse effect rate and length of hospital stay.

Quality (risk of bias) of individual studies

The quality of RCTs and observational studies will be assessed using a modified Jadad score and the Newcastle-Ottawa system, respectively.[24] Two reviewers will evaluate the quality independently (HC and LY). Conflicting results will be judged by a third reviewer (ZY).

Data synthesis

Data synthesis will be carried out with Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The results of RCTs and observational studies will be synthesised separately. The OR and 95% CI will be calculated for categorical outcomes. The mean difference and 95% CI will be calculated for continuous outcomes. A random effects model will be used to obtain a summary estimate of the average effect with its 95% CI. Heterogeneity among studies will be investigated using the I^2 test before data synthesis (I^2 >50% is defined to indicate significant heterogeneity). The Mantel-Haenszel fixed-effects model will be used when no significant heterogeneity exists among studies. Otherwise, additional a priori defined subgroup analysis will be triggered: type of study design, place of enrolment and level of risk of bias.

Subgroup analysis

Subgroup analysis will be carried out if a sufficient number of studies can be included in our analysis. The subgroups will include (1) type of β-lactam; (2) type of infecting micro-organism; (3) site of infection; (4) folds of increased MIC and (5) type of included studies.

Sensitivity analysis and assessment of publication bias

Sensitivity analysis will be performed by excluding each study one by one to evaluate the stability of the results without estimation of bias from the individual study. This process allows for identification of any single article that may have a great influence on the final result. Publication bias will be evaluated by funnel plots if the number of studies included in the analysis is sufficient.

Summary of data

The results of the main outcomes will be summarised using the Grading of Recommendations Assessment, Development and Evaluation approach.[25]

DISCUSSION

We believe that this meta-analysis will provide valuable information for clinicians with respect to treating infections caused by non-susceptible bacteria. Importantly, the results may prompt the individualised use of β-lactams. The results will also help physicians devise dosing regimens for antibiotics under the guidance of PK/PD knowledge.

Some limitations of this meta-analysis are apparent. Most studies evaluating prolonged infusion with β-lactams are not well designed, and therefore bias may exist. The credibility of the findings will be affected by the quality of the included studies. Missing data are a common occurrence in these types of studies. And there is a variability of outcome definitions across studies.

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