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Prolonged infusion with β-lactam antibiotics for treatment of infection caused by less-sensitive bacteria: a proposed meta-analysis protocol

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Huadong Chen and Zhenwei Yu contributed equally to this paper.

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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 less sensitive microorganisms. The efficiency of prolonged infusion in severe infection was well illustrated recently, but still confusing in less sensitive microbial infection. The objective of this meta-analysis is to determine the clinical effects of prolonged infusion with β-lactam for patients infected by microbes not sensitive to the given drug.

Methods and analysis

Literature searches will be performed with Medline, the Cochrane database, EMBASE database, the Chinese National Knowledge Infrastructure (CNKI), and Wanfang database. Two reviewers will screen and select studies according to settled 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 randomized 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 efficiency of prolonged infusion with β-lactams for infections caused by microbes with reduced sensitivity to β-lactam treatment.

This protocol has been conducted according to the Preferred Reporting Items for Systemic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement.

The strength of the results 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 efficiency 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[7], and hence patient outcomes are optimized. The target fT > MIC for β-lactam is recognized as 40–60%. For severe infection patients, the target fT > MIC needs to be elevated to 100%. And for patients infected by less-sensitive 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 antibacterial activity towards sever infection and infection caused by less-sensitive microbes.[8,9]

Recent studies have investigated the clinical value of prolonged infusion with β-lactam with randomized controlled trials (RCTs), which suggest the potential advantage of prolonged infusion for patients with severe sepsis.[10–12] However, some meta-analyses comparing prolonged infusion and an intermittent bolus of β-lactam have conflicting results.[13–17] The probable reason is that most of these studies have not been

stratified for patients with severity or infections that have reduced sensitivity. With the evidence accumulates, the efficiency of prolong infusion of β-lactam in severe infection patients or critic ill patients was well illustrated recently.[16,17] However, the efficiency in less sensitive infection is still confusing. The MIC ranges of the infecting pathogens are very important to the outcomes; patients infected by microorganisms with low MICs obtained target PK/PD thresholds using a standard intermittent infusion of antibiotics.[18] This indicates that prolonged infusion with a β-lactam has no advantage for treating infections caused by sensitive microbes. Meta-analysis evaluating the effect of prolonged infusion in patient stratified with sensitivity is needed.

To address this shortcoming, we carried out a meta-analysis to assess the clinical effects of prolonged infusion with β-lactam for patients infected by less-sensitive 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 conducted according to the Preferred Reporting Items for Systemic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement[19] and registered in PROSPERO (CRD42018105111).

The PRISMA-P checklistis 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. Experimental studies, animal studies, and case reports will be excluded.

Participants

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

Interventions

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

Type of outcome measures

Studies to evaluate the clinical efficiency 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 be included. If the reviewer obtains the required information from the authors, studies published in other languages will also be included.

Information sources

The following electronic databases will be searched from their inception to July 31, 2018: Medline, Cochrane database, EMBASE database, the Chinese National Knowledge Infrastructure (CNKI), and the Wanfang database.

Search strategy and selection of studies

The aforementioned electronic databases will be searched using a combination of following items: β-lactam, penicillin, cephalosporin, carbapenem, monobactam, prolonged, extended, continuous, intermittent, bolus, pulse, discontinuous, infusion,

administration, dosing. A detailed search strategy example is shown in online supplementary appendix 2.

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 (CHD and YLY) independently and cross-checked. Any inconsistency will be solved by discussion with a third reviewer (YZW).

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 microorganisms, results of a sensitivity analysis, β-lactams administered and dosing regimen, co-administrated antibiotics, and clinical outcomes including adverse events. The data will be extracted by two reviewers (CHD and YLY) independently using an electronic data table and cross-checked. Any inconsistency will be solved by discussion with a third reviewer (YZW).

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 analyzed if the reviewers fail to obtain data from any corresponding author

Measurement of outcomes

Primary outcome

Effective rate. Effective rate is defined as clinical improvement, clinical cure, or eradication of the infecting bacteria.

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,[20] respectively. Two reviewers will evaluate the quality independently (CHD and YLY). Conflicting results will be judged by a third reviewer (YZW).

Data synthesis

Data synthesis will be carried out with Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The odds ratio and 95%

confidential interval will be calculated for discontinuous outcomes. The mean difference and 95% confidential interval will be calculated for continuous outcomes. 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 effect model will be used when no significant heterogeneity exists among studies; otherwise, a random model will be used.

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 microorganism; (3) site of infection.

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 summarized using the Grading of Recommendations Assessment, Development and Evaluation approach.[21]

DISCUSSION

We believe that this meta-analysis will provide valuable information for clinicians with respect to treating infections caused less-sensitive bacteria. Importantly, the results may prompt the individualized 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-lactam are not well designed, and therefore bias may exist. The strength of the obtained results will be affected by the quality of the included studies. Missing data is a common occurrence in these types of studies, and dealing with missing data is time consuming. Heterogeneity of outcome definitions may vary among studies.

Contributors

CHD and YZW had the original idea for a meta-analysis. All authors designed the protocol. CHD and YZW reviewed the search strategy. CHD and YLY drafted the protocol. YZW registered in PROSPERO and is the guarantor of the protocol. All authors read and approved the final version.

Funding

There is no specific funding for this study.

Competing of interests

None declared.

Patient consent

Not required.

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Search strategy for Medline

1# beta lactam

2# penicillin

3# cephalosporin

4# carbapenem

5# monobactam

6# 1# OR 2# OR 3# OR 4# OR 5#

7# prolonged

8# extended

9# continuous

10# intermittent

11# bolus

12# pulse

13# discontinuous

14# 7# OR 8# OR 9# OR 10# OR 11# OR 12# OR 13#

15# infusion

16# administration

17# dosing

18# 15# OR 16# OR 17#

19# 6# AND 14# AND 18#

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item no.	Checklist item	Reported line number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Line 40
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Line 3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Line 218
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			Not applicable
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Line 52
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Line 88
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Line 103
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Line 131
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Line 136
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Line 154
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Line 145
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Line 154
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Line 150
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Line 165
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Line 173
Data synthesis	15a	Describe criteria under which study data will be quantified	Line 181
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Line 181
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Line 189 and 194
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Line 194
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as with GRADE)	Line 201

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution License 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Evidence based practice, Infectious diseases, Pharmacology and therapeutics
Keywords:	MICROBIOLOGY, INFECTIOUS DISEASES, Infection control < INFECTIOUS DISEASES, CLINICAL PHARMACOLOGY

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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Huadong Chen and Zhenwei Yu contributed equally to this paper.

Word count:2633

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 microorganisms. The efficacy of prolonged infusion in severe infection was well illustrated recently, but still confusing in non-susceptible microbial infection. The objective of this meta-analysis is to determine the clinical effects of prolonged infusion with β-lactam 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 (CINAHL) database, the Chinese National Knowledge Infrastructure (CNKI), 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 randomized 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 Systemic Review and Meta-Analysis Protocols (PRISMA-P) 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

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Recent studies have investigated the clinical value of prolonged infusion with β-lactam with randomized controlled trials (RCTs), which suggest 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 was 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 microorganism 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-lactam 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.

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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-lactam will be included. Prolonged infusion is defined as infusion of a β-lactam of no less than 3 hours. Continuous infusion is recognized 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 minutes.

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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.

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

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 microorganisms, 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 (CHD and YLY) independently using an electronic data table and cross-checked. Any inconsistency will be solved by discussion with a third reviewer (YZW).

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 analyzed 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 (CHD and YLY). Conflicting results will be judged by a third reviewer (YZW).

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Subgroup analysis

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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 summarized 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 non-susceptible bacteria. Importantly, the results may prompt the individualized 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-lactam 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 is a common occurrence in these types of studies. And there is a variability of outcome definitions across studies.

Contributors

CHD and YZW had the original idea for a meta-analysis. All authors designed the protocol. CHD and YZW reviewed the search strategy. CHD and YLY drafted the protocol. YZW registered in PROSPERO and is the guarantor of the protocol. All authors read and approved the final version.

Funding

There is no specific funding for this study.

Competing of interests

None declared.

Patient consent

Not required.

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1. Collignon P. Antibiotic resistance: Are we all doomed? *Intern Med J* 2015; 45: 1109–15.

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Search strategy for Medline

1# beta lactam

2# penicillin

3# cephalosporin

4# carbapenem

5# monobactam

6# 1# OR 2# OR 3# OR 4# OR 5#

7# prolonged

8# extended

9# continuous

10# intermittent

11# bolus

12# pulse

13# discontinuous

14# 7# OR 8# OR 9# OR 10# OR 11# OR 12# OR 13#

15# infusion

16# administration

17# dosing

18# 15# OR 16# OR 17#

19# 6# AND 14# AND 18#

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item no.	Checklist item	Reported line number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Line 42
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Line 3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Line 218
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			Not applicable
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Line 52
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Line 88
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Line 103
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Line 131
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Line 137

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Line 155
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Line 144
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Line 155
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Line 151
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Line 166
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Line 173
Data synthesis	15a	Describe criteria under which study data will be quantified	Line 181
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Line 181
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Line 189 and 195
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Line 195
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as with GRADE)	Line 202

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution License 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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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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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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Huadong Chen and Zhenwei Yu contributed equally to this paper.

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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 microorganisms. The efficacy of prolonged infusion in severe infection was well illustrated recently, but still confusing in non-susceptible microbial infection. The objective of this meta-analysis is to determine the clinical effects of prolonged infusion with β-lactam 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 (CINAHL) database, the Chinese National Knowledge Infrastructure (CNKI), 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 randomized 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 Systemic Review and Meta-Analysis Protocols (PRISMA-P) 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 optimized.[7] The target fT > MIC for β-lactam is recognized 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 sever infection and infection caused by non-susceptible microbes.[9,10]

Recent studies have investigated the clinical value of prolonged infusion with β-lactam with randomized controlled trials (RCTs), which suggest 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 was 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 microorganism 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-lactam 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 Systemic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement and registered in PROSPERO (CRD42018105111). [23]

The PRISMA-P checklistis 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-lactam will be included. Prolonged infusion is defined as infusion of a β-lactam of no less than 3 hours. Continuous infusion is recognized 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 minutes.

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 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 July 31, 2018: Medline, Cochrane database, EMBASE database, Cumulative Index to Nursing and Allied Health Literature (CINAHL) database, the Chinese National Knowledge Infrastructure (CNKI), 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 (CHD and YLY) independently and cross-checked. Any inconsistency will be solved by discussion with a third reviewer (YZW).

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 microorganisms, 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 (CHD and YLY) independently using an electronic data table and cross-checked. Any inconsistency will be solved by discussion with a third reviewer (YZW).

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 analyzed 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 (CHD and YLY). Conflicting results will be judged by a third reviewer (YZW).

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 synthesized separately. The odds ratio and 95% confidential interval will be calculated for categorical outcomes. The mean difference and 95% confidential interval 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 effect 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 enrollment 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 microorganism; (3) site of infection; (4) folds of increased MIC; (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 summarized 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 non-susceptible bacteria. Importantly, the results may prompt the individualized 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-lactam 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 is a common occurrence in these types of studies. And there is a variability of outcome definitions across studies.

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Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Line 42
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Line 3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Line 218
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			Not applicable
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Line 52
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Line 88
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Line 103
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Line 131
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Line 137

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Line 155
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Line 144
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Line 155
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Line 151
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Line 166
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Line 173
Data synthesis	15a	Describe criteria under which study data will be quantified	Line 181
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Line 181
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Line 189 and 195
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Line 195
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as with GRADE)	Line 202

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution License 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 2

Search strategy for Cochrane Library（https://www.cochranelibrary.com/）

#1 (beta lactam):ti,ab,kw OR (penicillin):ti,ab,kw OR (cephalosporin):ti,ab,kw OR (carbapenem):ti,ab,kw OR (monobactam):ti,ab,kw (Word variations have been searched)
#2 MeSH descriptor: [beta-Lactamases] explode all trees
#3 MeSH descriptor: [Penicillins] explode all trees
#4 MeSH descriptor: [Cephalosporins] explode all trees
#5 MeSH descriptor: [Carbapenems] explode all trees
#6 MeSH descriptor: [Carbapenems] explode all trees
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 (prolonged):ti,ab,kw OR (extended):ti,ab,kw OR (continuous):ti,ab,kw OR (intermittent):ti,ab,kw OR (bolus):ti,ab,kw (Word variations have been searched)
#9 (pulse):ti,ab,kw OR (discontinuous):ti,ab,kw (Word variations have been searched)
#10 MeSH descriptor: [Pulse Therapy, Drug] explode all trees
#11 #8 or #9 or #10
#12 (infusion):ti,ab,kw OR (administration):ti,ab,kw OR (dosing):ti,ab,kw (Word variations have been searched)
#13 MeSH descriptor: [Drug Administration Schedual] explode all trees
#14 #12 or #13
#15 #7 and #11 and #14

Search strategy for Medline (http://apps.webofknowledge.com/MEDLINE)

1 ((((TS: (beta lactam) OR TS: (penicillin)) OR TS: (cephalosporin)) OR TS: (carbapenem)) OR TS: (monobactam))
2 ((((TI: (beta lactam) OR TI: (penicillin)) OR TI: (cephalosporin)) OR TI: (carbapenem)) OR TI: (monobactam))
3 ((((((TS: (prolonged) OR TS: (extended)) OR TS: (continuous)) OR TS: (intermittent)) OR TS: (bolus)) OR TS: (pulse)) OR TS: (discontinuous))
4 ((((((TI: (prolonged) OR TI: (extended)) OR TI: (continuous)) OR TI: (intermittent)) OR TI: (bolus)) OR TI: (pulse)) OR TI: (discontinuous))
5 (((((MH: (prolonged) OR MH: (extended)) OR MH: (continuous)) OR MH: (intermittent)) OR MH: (bolus)) OR MH: (pulse)) OR MH: (discontinuous)
6 ((TS: (infusion) OR TS: (administration)) OR TS: (dosing))
7 ((TI: (infusion) OR TI: (administration)) OR TI: (dosing))
8 #2 OR #1
9 #5 OR #4 OR #3
10 #7 OR #6
11 #10 AND #9 AND #8