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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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Manuscripts

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

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13

14 Word count:2455

15

16 **ABSTRACT**

17 Introduction

18 Prolonged infusion with β -lactam antibiotics should theoretically produce a better clinical
19 efficacy than intermittent infusion in severe infection and infection caused by less
20 sensitive microorganisms. The efficiency of prolonged infusion in severe infection was
21 well illustrated recently, but still confusing in less sensitive microbial infection. The
22 objective of this meta-analysis is to determine the clinical effects of prolonged infusion
23 with β -lactam for patients infected by microbes not sensitive to the given drug.

25 Methods and analysis

26 Literature searches will be performed with Medline, the Cochrane database, EMBASE
27 database, the Chinese National Knowledge Infrastructure (CNKI), and Wanfang
28 database. Two reviewers will screen and select studies according to settled eligibility
29 criteria, and then the data from the included studies will be extracted. The quality will be
30 evaluated based on a modified Jadad score and the Newcastle-Ottawa system for
31 randomized controlled trials and observational studies, respectively. Data synthesis will
32 be performed with Review Manager 5.3 software. Sensitivity analysis and publication
33 bias will also be investigated.

35 Ethics and dissemination

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4 36 No ethics approval is required. The full article will be published in a peer-reviewed
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7 37 journal and presented at international conferences.
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12 39 PROSPERO registration number

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15 40 CRD42018105111
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20 42 **Strength and limitation of this study**
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22
23 43 This meta-analysis will evaluate the clinical efficiency of prolonged infusion with
24
25
26 44 β -lactams for infections caused by microbes with reduced sensitivity to β -lactam
27
28 45 treatment.
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31 46 This protocol has been conducted according to the Preferred Reporting Items for
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34 47 Systemic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement.
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36 48 The strength of the results may be affected by the quality of the included studies.
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42 50 **INTRODUCTION**
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45 51 Global effects are taken to account the antibiotic resistance issue, although the
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48 52 development of new antibiotics cannot keep up with the occurrence of resistance, and the
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51 53 treatment of infections caused by resistant microbes is becoming increasingly
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53 54 challenging.^{1,2} To obtain the maximum antimicrobial effect of existing drugs, clinicians
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56 55 and scientists have turned to the rational use of antibiotics, including administration
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4 56 under the guidance of pharmacokinetic/pharmacodynamics (PK/PD) models.^{3,4}
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7 57 β -lactams are a broad class of antibiotics widely used to treat infections, especially
8
9 58 those that are caused by Gram-negative microbes.⁵ β -lactams exhibit primary
10 59 time-dependent antimicrobial activity, and the best PK/PD index predicts clinical
11
12 60 efficiency according to the duration of the maintenance of the drug concentration above
13
14 61 the minimum inhibitory concentration (MIC) for the pathogen (referred as $fT > MIC$)
15
16 62 during each dosing interval.⁶ When PK/PD targets are achieved, β -lactams have their
17
18 63 maximal antibiotic effect⁷, and hence patient outcomes are optimized. The target $fT >$
19
20 64 MIC for β -lactam is recognized as 40–60%. For severe infection patients, the target $fT >$
21
22 65 MIC needs to be elevated to 100%. And for patients infected by less-sensitive microbes,
23
24 66 the $fT > MIC$ decreases owing to the elevated MIC. Treatment failure will occur when
25
26 67 administered by traditional intermittent infusion. According to in vitro and in vivo
27
28 68 simulations, prolonged infusion with β -lactams can enhance the $fT > MIC$ and thus
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30 69 improve antibacterial activity towards severe infection and infection caused by
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32 70 less-sensitive microbes.^{8,9}
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45 71 Recent studies have investigated the clinical value of prolonged infusion with
46
47 72 β -lactam with randomized controlled trials (RCTs), which suggest the potential
48
49 73 advantage of prolonged infusion for patients with severe sepsis.^{10–12} However, some
50
51 74 meta-analyses comparing prolonged infusion and an intermittent bolus of β -lactam have
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53 75 conflicting results.^{13–17} The probable reason is that most of these studies have not been
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4 76 stratified for patients with severity or infections that have reduced sensitivity. With the
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7 77 evidence accumulates, the efficiency of prolong infusion of β -lactam in severe infection
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10 78 patients or critic ill patients was well illustrated recently.^{16,17} However, the efficiency in
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12
13 79 less sensitive infection is still confusing. The MIC ranges of the infecting pathogens are
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15
16 80 very important to the outcomes; patients infected by microorganisms with low MICs
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19 81 obtained target PK/PD thresholds using a standard intermittent infusion of antibiotics.¹⁸
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22 82 This indicates that prolonged infusion with a β -lactam has no advantage for treating
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25 83 infections caused by sensitive microbes. Meta-analysis evaluating the effect of prolonged
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28 84 infusion in patient stratified with sensitivity is needed.

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31 85 To address this shortcoming, we carried out a meta-analysis to assess the clinical
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34 86 effects of prolonged infusion with β -lactam for patients infected by less-sensitive
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37 87 microbes. To our knowledge, this is the first study to assess meta-data from other studies
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40 88 of patients with infections that have reduced susceptibility to β -lactam treatment.

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43 90 **METHODS**

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45 91 This protocol has been conducted according to the Preferred Reporting Items for
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48 92 Systemic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement¹⁹ and
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50
51 93 registered in PROSPERO (CRD42018105111).

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53 94 The PRISMA-P checklist is shown in online supplementary appendix 1.

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4 96 Patient and public involvement

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7 97 Patients or the public are not involved.

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12 99 Eligibility criteria

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15 100 Study design

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17 101 RCTs, quasi-RCTs, and observational studies (retrospective and prospective) will be
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20 102 included. Experimental studies, animal studies, and case reports will be excluded.

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23 103 Participants

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25 104 Patients who are infected by bacteria that are not sensitive to β -lactams will be included.

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27
28 105 The sensitivity of the infecting microbes should be tested and established to be not
29
30
31 106 sensitive (intermediate or resistant) to the administered β -lactam in the study. There is no
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34 107 restriction regarding the site of infection or other patient characteristics.

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37 108 Interventions

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39 109 Studies evaluating the clinical efficiency of prolonged infusion with β -lactam will be
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41
42 110 included. Prolonged infusion is defined as infusion of a β -lactam of no less than 3 hours.

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45 111 Continuous infusion is defined as a special type of prolonged infusion and can be
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47
48 112 included.

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50 113 Comparators

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53 114 The study will compare conventional, intermittent infusion of the same β -lactams as used
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56 115 in the intervention group. Intermittent infusion is defined as infusion of drug in less than

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4 116 30 minutes.
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7 117 Type of outcome measures
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9 118 Studies to evaluate the clinical efficiency of prolonged infusion will be included. The
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11
12 119 clinical effective rate must be evaluated. The effect is defined as a clinical cure, clinical
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15 120 improvement, or eradication of infected bacteria.
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17 121 Language
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19
20 122 Studies published in English and Chinese will be included. Studies published in other
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23 123 languages but with a full information abstract in English or Chinese will be included. If
24
25
26 124 the reviewer obtains the required information from the authors, studies published in other
27
28
29 125 languages will also be included.
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34 127 Information sources
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36 128 The following electronic databases will be searched from their inception to July 31, 2018:
37

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39 129 Medline, Cochrane database, EMBASE database, the Chinese National Knowledge
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41
42 130 Infrastructure (CNKI), and the Wanfang database.
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44
45 131
46

47 132 Search strategy and selection of studies
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49
50 133 The aforementioned electronic databases will be searched using a combination of
51
52
53 134 following items: β -lactam, penicillin, cephalosporin, carbapenem, monobactam,
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56 135 prolonged, extended, continuous, intermittent, bolus, pulse, discontinuous, infusion,
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4 136 administration, dosing. A detailed search strategy example is shown in online
5
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7 137 supplementary appendix 2.

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9 138 Relevant publications such as references within the included studies will be searched
10
11
12 139 manually. The yielded studies will be selected by reading the title, abstract, and full text
13
14
15 140 to determine whether the eligibility criteria are met.

16
17 141 The literature searches and study selections will be carried out by two reviewers
18
19
20 142 (CHD and YLY) independently and cross-checked. Any inconsistency will be solved by
21
22
23 143 discussion with a third reviewer (YZW).

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26 144

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28 145 Data extraction

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31 146 Data for the following attributes will be extracted: author and publication year of the
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33
34 147 study, study design, study duration and region, number of participating patients, patient
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36
37 148 age, gender, infection site, isolated microorganisms, results of a sensitivity analysis,
38
39
40 149 β -lactams administered and dosing regimen, co-administrated antibiotics, and clinical
41
42
43 150 outcomes including adverse events. The data will be extracted by two reviewers (CHD
44
45
46 151 and YLY) independently using an electronic data table and cross-checked. Any
47
48
49 152 inconsistency will be solved by discussion with a third reviewer (YZW).

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53 154 Dealing with missing data

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56 155 When required data are not available in the literature or not published in an extractable
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4 156 form, the corresponding author of the published study will be contacted by e-mail to
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7 157 request additional information. Only available data will be analyzed if the reviewers fail
8
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10 158 to obtain data from any corresponding author

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15 160 Measurement of outcomes

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17 161 Primary outcome

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20 162 Effective rate. Effective rate is defined as clinical improvement, clinical cure, or
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23 163 eradication of the infecting bacteria.

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26 164 Secondary outcomes

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28 165 Mortality rate, microbial eradication rate, adverse effect rate, and length of hospital stay.

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34 167 Quality (risk of bias) of individual studies

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37 168 The quality of RCTs and observational studies will be assessed using a modified Jadad
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39 169 score and the Newcastle-Ottawa system,²⁰ respectively. Two reviewers will evaluate the
40
41
42 170 quality independently (CHD and YLY). Conflicting results will be judged by a third
43
44
45 171 reviewer (YZW).

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50 173 Data synthesis

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53 174 Data synthesis will be carried out with Review Manager 5.3 software (Copenhagen: The
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56 175 Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The odds ratio and 95%

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4 176 confidential interval will be calculated for discontinuous outcomes. The mean difference
5
6
7 177 and 95% confidential interval will be calculated for continuous outcomes. Heterogeneity
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9
10 178 among studies will be investigated using the I^2 test before data synthesis ($I^2 > 50\%$ is
11
12 179 defined to indicate significant heterogeneity). The Mantel-Haenszel fixed effect model
13
14
15 180 will be used when no significant heterogeneity exists among studies; otherwise, a random
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18 181 model will be used.

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23 183 Subgroup analysis

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26 184 Subgroup analysis will be carried out if a sufficient number of studies can be included in
27
28 185 our analysis. The subgroups will include: (1) type of β -lactam; (2) type of infecting
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31 186 microorganism; (3) site of infection.

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36 188 Sensitivity analysis and assessment of publication bias

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39 189 Sensitivity analysis will be performed by excluding each study one by one to evaluate the
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42 190 stability of the results without estimation of bias from the individual study. This process
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45 191 allows for identification of any single article that may have a great influence on the final
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48 192 result. Publication bias will be evaluated by funnel plots if the number of studies included
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51 193 in the analysis is sufficient.

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55 195 Summary of data

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4 196 The results of the main outcomes will be summarized using the Grading of
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7 197 Recommendations Assessment, Development and Evaluation approach.²¹
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10 11 12 199 **DISCUSSION**

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15 200 We believe that this meta-analysis will provide valuable information for clinicians with
16
17 201 respect to treating infections caused less-sensitive bacteria. Importantly, the results may
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20 202 prompt the individualized use of β -lactams. The results will also help physicians devise
21
22
23 203 dosing regimens for antibiotics under the guidance of PK/PD knowledge.

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25 204 Some limitations of this meta-analysis are apparent. Most studies evaluating
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27
28 205 prolonged infusion with β -lactam are not well designed, and therefore bias may exist.
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31 206 The strength of the obtained results will be affected by the quality of the included studies.
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34 207 Missing data is a common occurrence in these types of studies, and dealing with missing
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36
37 208 data is time consuming. Heterogeneity of outcome definitions may vary among studies.

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40 41 42 210 **Contributors**

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44
45 211 CHD and YZW had the original idea for a meta-analysis. All authors designed the
46
47 212 protocol. CHD and YZW reviewed the search strategy. CHD and YLY drafted the
48
49
50 213 protocol. YZW registered in PROSPERO and is the guarantor of the protocol. All authors
51
52
53 214 read and approved the final version.

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55 215

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4 **216 Funding**

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7 217 There is no specific funding for this study.

8
9 **218 Competing of interests**

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12 219 None declared.

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15 **220 Patient consent**

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17 221 Not required.

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34 235 Pharmacokinetic/pharmacodynamic (PK/PD) Index Map for Selecting an Optimal PK/PD35
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4 Search strategy for Medline
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6 1# beta lactam
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8
9 2# penicillin
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11
12 3# cephalosporin
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14 4# carbapenem
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16
17 5# monobactam
18

19 6# 1# OR 2# OR 3# OR 4# OR 5#
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21
22 7# prolonged
23

24 8# extended
25

26
27 9# continuous
28

29
30 10# intermittent
31

32 11# bolus
33

34
35 12# pulse
36

37
38 13# discontinuous
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40 14# 7# OR 8# OR 9# OR 10# OR 11# OR 12# OR 13#
41

42
43 15# infusion
44

45 16# administration
46

47
48 17# dosing
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50 18# 15# OR 16# OR 17#
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53 19# 6# AND 14# AND 18#
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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:			
Sources	5a	Indicate sources of financial or other support for the review	Not applicable
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 participant, 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:			

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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), and 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.**

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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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Manuscripts

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4 1 Prolonged infusion with β -lactam antibiotics for treatment of infection caused by non-
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7 2 susceptible bacteria: a study protocol for a systemic review and meta-analysis
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9 3 Huadong Chen¹, Lingyan Yu², Zhenwei Yu³
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34 12 Huadong Chen and Zhenwei Yu contributed equally to this paper.
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39 14 Word count:2633
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4 **16 ABSTRACT**
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6
7 **17 Introduction**
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9 **18** Prolonged infusion with β -lactam antibiotics should theoretically produce a better
10
11
12 **19** clinical efficacy than intermittent infusion in severe infection and infection caused by
13
14
15 **20** non-susceptible microorganisms. The efficacy of prolonged infusion in severe infection
16
17
18 **21** was well illustrated recently, but still confusing in non-susceptible microbial infection.
19
20
21 **22** The objective of this meta-analysis is to determine the clinical effects of prolonged
22
23
24 **23** infusion with β -lactam for patients infected by microbes non-susceptible to the given
25
26
27 **24** drug.
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29 **25**

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31 **26 Methods and analysis**
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34 **27** Literature searches will be performed with Medline, the Cochrane database,
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37 **28** EMBASE database, Cumulative Index to Nursing and Allied Health Literature
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40 **29** (CINAHL) database, the Chinese National Knowledge Infrastructure (CNKI), and
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43 **30** Wanfang database. Two reviewers will screen and select studies according to a priori
44
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46 **31** defined eligibility criteria, and then the data from the included studies will be
47
48
49 **32** extracted. The quality will be evaluated based on a modified Jadad score and the
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51
52 **33** Newcastle-Ottawa system for randomized controlled trials and observational studies,
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54
55 **34** respectively. Data synthesis will be performed with Review Manager 5.3 software.
56
57
58 **35** Sensitivity analysis and publication bias will also be investigated.
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60 **36**

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4 37 Ethics and dissemination

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6 38 No ethics approval is required. The full article will be published in a peer-reviewed

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9 39 journal and presented at international conferences.

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14 41 PROSPERO registration number

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17 42 CRD42018105111

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23 44 **Strength and limitation of this study**

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25 45 This meta-analysis will evaluate the clinical efficacy of prolonged infusion with β -

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28 46 lactams for infections caused by microbes with reduced susceptibility to β -lactam

29
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31 47 treatment.

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34 48 This protocol has been written following the Preferred Reporting Items for Systemic

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36
37 49 Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement.

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39
40 50 The credibility of the findings may be affected by the quality of the included studies.

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45 52 **INTRODUCTION**

46
47 53 Global effects are taken to account the antibiotic resistance issue, although the

48
49
50 54 development of new antibiotics cannot keep up with the occurrence of resistance, and

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52
53 55 the treatment of infections caused by resistant microbes is becoming increasingly

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55
56 56 challenging.^{1,2} To obtain the maximum antimicrobial effect of existing drugs, clinicians

57
58
59 57 and scientists have turned to the rational use of antibiotics, including administration

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3
4 58 under the guidance of pharmacokinetic/pharmacodynamics (PK/PD) models.^{3,4}
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6

7 59 β -lactams are a broad class of antibiotics widely used to treat infections, especially
8
9 60 those that are caused by Gram-negative microbes.⁵ β -lactams exhibit primary time-
10
11 61 dependent antimicrobial activity, and the best PK/PD index predicts clinical efficacy
12
13 62 according to the duration of the maintenance of the drug concentration above the
14
15 63 minimum inhibitory concentration (MIC) for the pathogen (referred as $fT > MIC$)
16
17 64 during each dosing interval.⁶ When PK/PD targets are achieved, β -lactams have their
18
19 65 maximal antibiotic effect, and hence patient outcomes are optimized.⁷ The target $fT >$
20
21 66 MIC for β -lactam is recognized as 40–60%. For severe infection patients, the target fT
22
23 67 $> MIC$ needs to be elevated to 100%.⁸ And for patients infected by non-susceptible
24
25 68 microbes, the $fT > MIC$ decreases owing to the elevated MIC. Treatment failure will
26
27 69 occur when administered by traditional intermittent infusion. According to in vitro and
28
29 70 in vivo simulations, prolonged infusion with β -lactams can enhance the $fT > MIC$ and
30
31 71 thus improve probability of target attainment towards severe infection and infection
32
33 72 caused by non-susceptible microbes.^{9,10}
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45 73 Recent studies have investigated the clinical value of prolonged infusion with β -
46
47 74 lactam with randomized controlled trials (RCTs), which suggest the potential advantage
48
49 75 of prolonged infusion for patients with severe sepsis.^{11–13} However, some meta-analyses
50
51 76 comparing prolonged infusion and an intermittent bolus of β -lactam have conflicting
52
53 77 results.^{14–18} The probable reason is that most of these studies have not been stratified
54
55 78 for patients with severity or infections that have reduced susceptibility. With the
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4 79 evidence accumulates, the efficacy of prolong infusion of β -lactam in severe infection
5
6 80 patients or critically ill patients was well illustrated recently.^{17,18} However, the efficacy
7
8
9 81 in non-susceptible infection is still confusing. The MIC ranges of the infecting
10
11
12 82 pathogens are very important to the outcomes; target PK/PD thresholds will be obtained
13
14
15 83 using a standard intermittent infusion of antibiotics in susceptible microorganism
16
17
18 84 infection, but not in non-susceptible infection.¹⁹ This indicates that prolonged infusion
19
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21 85 with a β -lactam has less advantage for treating infections caused by sensitive
22
23 86 microbes.²⁰⁻²² Meta-analysis evaluating the effect of prolonged infusion in patient
24
25
26 87 stratified with susceptibility is needed.

27
28 88 To address this shortcoming, we carried out a meta-analysis to assess the clinical
29
30
31 89 effects of prolonged infusion with β -lactam for patients infected by non-susceptible
32
33
34 90 microbes. To our knowledge, this is the first study to assess meta-data from other
35
36
37 91 studies of patients with infections that have reduced susceptibility to β -lactam treatment.
38

39 92

40 41 42 93 **METHODS**

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44
45 94 This protocol has been written following the Preferred Reporting Items for Systemic
46
47
48 95 Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement and registered in
49
50
51 96 PROSPERO (CRD42018105111).²³

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53 97 The PRISMA-P checklist is shown in online supplementary appendix 1.

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56 98

57 58 99 **Patient and public involvement**

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4 100 Patients or the public are not involved.
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9 102 **Eligibility criteria**

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11
12 103 *Study design*

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14
15 104 RCTs, quasi-RCTs, and observational studies (retrospective and prospective) will be
16
17 105 included. *In vitro* studies, animal studies, and case reports will be excluded.

18
19
20 106 *Participants*

21
22
23 107 Patients who are infected by bacteria that are not susceptible to β -lactams will be
24
25 108 included. The susceptibility of the infecting microbes should be tested and established
26
27 109 to be non-susceptible (intermediate or resistant) to the administered β -lactam in the
28
29 110 study. There is no restriction regarding the method used to determine the susceptibility.
30
31
32
33 111 There is also no restriction regarding the site of infection or other patient characteristics.

34
35
36 112 *Interventions*

37
38
39 113 Studies evaluating the clinical efficacy of prolonged infusion with β -lactam will be
40
41
42 114 included. Prolonged infusion is defined as infusion of a β -lactam of no less than 3 hours.
43
44
45 115 Continuous infusion is recognized as a special type of prolonged infusion and can be
46
47 116 included.

48
49
50 117 *Comparators*

51
52
53 118 The study will compare conventional, intermittent infusion of the same β -lactams as
54
55 119 used in the intervention group. Intermittent infusion is defined as infusion of drug in
56
57
58 120 less than 30 minutes.
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4 121 *Type of outcome measures*
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6 122 Studies to evaluate the clinical efficacy of prolonged infusion will be included. The
7
8
9 123 clinical effective rate must be evaluated. The effect is defined as a clinical cure, clinical
10
11
12 124 improvement, or eradication of infected bacteria.
13

14
15 125 *Language*
16

17 126 Studies published in English and Chinese will be included. Studies published in other
18
19
20 127 languages but with a full information abstract in English or Chinese will be included.
21
22
23 128 If the reviewer obtains the required information from the authors or translators, studies
24
25
26 129 published in other languages will also be included.
27

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31 131 **Information sources**
32

33 132 The following electronic databases will be searched from their inception to July 31,
34
35
36 133 2018: Medline, Cochrane database, EMBASE database, Cumulative Index to Nursing
37
38
39 134 and Allied Health Literature (CINAHL) database, the Chinese National Knowledge
40
41
42 135 Infrastructure (CNKI), and the Wanfang database.
43

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47 137 **Search strategy and selection of studies**
48

49
50 138 The aforementioned electronic databases will be searched using a combination of
51
52
53 139 following items: β -lactam, penicillin, cephalosporin, carbapenem, monobactam,
54
55
56 140 prolonged, extended, continuous, intermittent, bolus, pulse, discontinuous, infusion,
57
58
59 141 administration, dosing. A detailed search strategy example is shown in online
60

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4 142 supplementary appendix 2.
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7 143 Relevant publications such as references within the included studies will be
8
9 144 searched manually. The yielded studies will be selected by reading the title, abstract,
10
11
12 145 and full text to determine whether the eligibility criteria are met.
13

14
15 146 The literature searches and study selections will be carried out by two reviewers
16
17 147 (CHD and YLY) independently and cross-checked. Any inconsistency will be solved
18
19
20 148 by discussion with a third reviewer (YZW).
21

22
23 149

24 25 150 **Data extraction**

26
27
28 151 Data for the following attributes will be extracted: author and publication year of the
29
30
31 152 study, study design, study duration and region, number of participating patients, patient
32
33
34 153 age, gender, infection site, isolated microorganisms, methods and results of
35
36
37 154 susceptibility analysis, β -lactams administered and dosing regimen, co-administrated
38
39
40 155 antibiotics, and clinical outcomes including adverse events. The data will be extracted
41
42
43 156 by two reviewers (CHD and YLY) independently using an electronic data table and
44
45
46 157 cross-checked. Any inconsistency will be solved by discussion with a third reviewer
47
48 158 (YZW).

49
50 159

51 52 160 **Dealing with missing data**

53
54
55 161 When required data are not available in the literature or not published in an extractable
56
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58 162 form, the corresponding author of the published study will be contacted by e-mail to
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4 163 request additional information. Only available data will be analyzed if the reviewers
5
6
7 164 fail to obtain data from any corresponding author
8

9 165

12 166 **Measurement of outcomes**

15 167 *Primary outcome*

17 168 Effective rate. Outcomes defined as clinical cure, clinical improvement and eradication
18
19
20 169 of the infecting bacteria by original study are regarded as effective in this meta-analysis.
21

23 170 *Secondary outcomes*

25 171 Mortality rate, microbial eradication rate, adverse effect rate, and length of hospital stay.
26
27

28 172

31 173 **Quality (risk of bias) of individual studies**

33 174 The quality of RCTs and observational studies will be assessed using a modified Jadad
34
35
36 175 score and the Newcastle-Ottawa system, respectively.²⁴ Two reviewers will evaluate
37
38
39 176 the quality independently (CHD and YLY). Conflicting results will be judged by a third
40
41
42 177 reviewer (YZW).
43
44

45 178

47 179 **Data synthesis**

49
50 180 Data synthesis will be carried out with Review Manager 5.3 software (Copenhagen:
51
52
53 181 The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The odds ratio and
54
55
56 182 95% confidential interval will be calculated for categorical outcomes. The mean
57
58
59 183 difference and 95% confidential interval will be calculated for continuous outcomes.
60

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4 184 Heterogeneity among studies will be investigated using the I^2 test before data synthesis
5
6 185 ($I^2 > 50\%$ is defined to indicate significant heterogeneity). The Mantel-Haenszel fixed
7
8
9 186 effect model will be used when no significant heterogeneity exists among studies;
10
11
12 187 otherwise, a random effect model will be used.
13
14

15 188

17 189 **Subgroup analysis**

19 190 Subgroup analysis will be carried out if a sufficient number of studies can be included
20
21
22
23 191 in our analysis. The subgroups will include: (1) type of β -lactam; (2) type of infecting
24
25
26 192 microorganism; (3) site of infection; (4) folds of increased MIC; (5) type of included
27
28
29 193 studies.
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33 195 **Sensitivity analysis and assessment of publication bias**

35 196 Sensitivity analysis will be performed by excluding each study one by one to evaluate
36
37
38
39 197 the stability of the results without estimation of bias from the individual study. This
40
41
42 198 process allows for identification of any single article that may have a great influence
43
44
45 199 on the final result. Publication bias will be evaluated by funnel plots if the number of
46
47
48 200 studies included in the analysis is sufficient.
49

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52 202 **Summary of data**

54
55 203 The results of the main outcomes will be summarized using the Grading of
56
57
58 204 Recommendations Assessment, Development and Evaluation approach.²⁵
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6 206 **DISCUSSION**

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8
9 207 We believe that this meta-analysis will provide valuable information for clinicians with
10
11
12 208 respect to treating infections caused non-susceptible bacteria. Importantly, the results
13
14
15 209 may prompt the individualized use of β -lactams. The results will also help physicians
16
17
18 210 devise dosing regimens for antibiotics under the guidance of PK/PD knowledge.

19
20 211 Some limitations of this meta-analysis are apparent. Most studies evaluating
21
22
23 212 prolonged infusion with β -lactam are not well designed, and therefore bias may exist.
24
25
26 213 The credibility of the findings will be affected by the quality of the included studies.
27
28
29 214 Missing data is a common occurrence in these types of studies. And there is a variability
30
31
32 215 of outcome definitions across studies.

33
34 216

35
36 217 **Contributors**

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39 218 CHD and YZW had the original idea for a meta-analysis. All authors designed the
40
41
42 219 protocol. CHD and YZW reviewed the search strategy. CHD and YLY drafted the
43
44
45 220 protocol. YZW registered in PROSPERO and is the guarantor of the protocol. All
46
47
48 221 authors read and approved the final version.

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50 222

51
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53
54
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58 225 **Competing of interests**

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4 226 None declared.
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7 227 **Patient consent**
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9 228 Not required.
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For peer review only

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4 Search strategy for Medline
5

6 1# beta lactam
7

8
9 2# penicillin
10

11 3# cephalosporin
12

13
14 4# carbapenem
15

16
17 5# monobactam
18

19 6# 1# OR 2# OR 3# OR 4# OR 5#
20

21
22 7# prolonged
23

24 8# extended
25

26
27 9# continuous
28

29
30 10# intermittent
31

32 11# bolus
33

34
35 12# pulse
36

37
38 13# discontinuous
39

40 14# 7# OR 8# OR 9# OR 10# OR 11# OR 12# OR 13#
41

42
43 15# infusion
44

45 16# administration
46

47
48 17# dosing
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50 18# 15# OR 16# OR 17#
51

52
53 19# 6# AND 14# AND 18#
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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:			
Sources	5a	Indicate sources of financial or other support for the review	Not applicable
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 author, 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 (note 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.**

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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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4 1 Prolonged infusion with β -lactam antibiotics for treatment of infection caused by non-
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7 2 susceptible bacteria: a study protocol for a systemic review and meta-analysis
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34 12 Huadong Chen and Zhenwei Yu contributed equally to this paper.
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4 **16 ABSTRACT**
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6
7 **17 Introduction**
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9 **18** Prolonged infusion with β -lactam antibiotics should theoretically produce a better
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11
12 **19** clinical efficacy than intermittent infusion in severe infection and infection caused by
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14
15 **20** non-susceptible microorganisms. The efficacy of prolonged infusion in severe infection
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17
18 **21** was well illustrated recently, but still confusing in non-susceptible microbial infection.
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20
21 **22** The objective of this meta-analysis is to determine the clinical effects of prolonged
22
23
24 **23** infusion with β -lactam for patients infected by microbes non-susceptible to the given
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26
27 **24** drug.
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31 **26 Methods and analysis**
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34 **27** Literature searches will be performed with Medline, the Cochrane database,
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37 **28** EMBASE database, Cumulative Index to Nursing and Allied Health Literature
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40 **29** (CINAHL) database, the Chinese National Knowledge Infrastructure (CNKI), and
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42
43 **30** Wanfang database. Two reviewers will screen and select studies according to a priori
44
45
46 **31** defined eligibility criteria, and then the data from the included studies will be
47
48
49 **32** extracted. The quality will be evaluated based on a modified Jadad score and the
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51
52 **33** Newcastle-Ottawa system for randomized controlled trials and observational studies,
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54
55 **34** respectively. Data synthesis will be performed with Review Manager 5.3 software.
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58 **35** Sensitivity analysis and publication bias will also be investigated.
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60 **36**

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4 37 Ethics and dissemination

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6 38 No ethics approval is required. The full article will be published in a peer-reviewed

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9 39 journal and presented at international conferences.

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14 41 PROSPERO registration number

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23 44 **Strength and limitation of this study**

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25 45 This meta-analysis will evaluate the clinical efficacy of prolonged infusion with β -

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28 46 lactams for infections caused by microbes with reduced susceptibility to β -lactam

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31 47 treatment.

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34 48 This protocol has been written following the Preferred Reporting Items for Systemic

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37 49 Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement.

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40 50 The credibility of the findings may be affected by the quality of the included studies.

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45 52 **INTRODUCTION**

46
47 53 Global effects are taken to account the antibiotic resistance issue, although the

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50 54 development of new antibiotics cannot keep up with the occurrence of resistance, and

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53 55 the treatment of infections caused by resistant microbes is becoming increasingly

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56 56 challenging.^{1,2} To obtain the maximum antimicrobial effect of existing drugs, clinicians

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58
59 57 and scientists have turned to the rational use of antibiotics, including administration

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4 58 under the guidance of pharmacokinetic/pharmacodynamics (PK/PD) models.^{3,4}
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6

7 59 β -lactams are a broad class of antibiotics widely used to treat infections, especially
8
9 60 those that are caused by Gram-negative microbes.⁵ β -lactams exhibit primary time-
10
11 61 dependent antimicrobial activity, and the best PK/PD index predicts clinical efficacy
12
13 62 according to the duration of the maintenance of the drug concentration above the
14
15 63 minimum inhibitory concentration (MIC) for the pathogen (referred as $fT > MIC$)
16
17 64 during each dosing interval.⁶ When PK/PD targets are achieved, β -lactams have their
18
19 65 maximal antibiotic effect, and hence patient outcomes are optimized.⁷ The target $fT >$
20
21 66 MIC for β -lactam is recognized as 40–60%. For severe infection patients, the target fT
22
23 67 $> MIC$ needs to be elevated to 100%.⁸ And for patients infected by non-susceptible
24
25 68 microbes, the $fT > MIC$ decreases owing to the elevated MIC. Treatment failure will
26
27 69 occur when administered by traditional intermittent infusion. According to in vitro and
28
29 70 in vivo simulations, prolonged infusion with β -lactams can enhance the $fT > MIC$ and
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31 71 thus improve probability of target attainment towards severe infection and infection
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33 72 caused by non-susceptible microbes.^{9,10}
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45 73 Recent studies have investigated the clinical value of prolonged infusion with β -
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47 74 lactam with randomized controlled trials (RCTs), which suggest the potential advantage
48
49 75 of prolonged infusion for patients with severe sepsis.^{11–13} However, some meta-analyses
50
51 76 comparing prolonged infusion and an intermittent bolus of β -lactam have conflicting
52
53 77 results.^{14–18} The probable reason is that most of these studies have not been stratified
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55 78 for patients with severity or infections that have reduced susceptibility. With the
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4 79 evidence accumulates, the efficacy of prolong infusion of β -lactam in severe infection
5
6 80 patients or critically ill patients was well illustrated recently.^{17,18} However, the efficacy
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9 81 in non-susceptible infection is still confusing. The MIC ranges of the infecting
10
11
12 82 pathogens are very important to the outcomes; target PK/PD thresholds will be obtained
13
14
15 83 using a standard intermittent infusion of antibiotics in susceptible microorganism
16
17
18 84 infection, but not in non-susceptible infection.¹⁹ This indicates that prolonged infusion
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21 85 with a β -lactam has less advantage for treating infections caused by sensitive
22
23 86 microbes.²⁰⁻²² Meta-analysis evaluating the effect of prolonged infusion in patient
24
25
26 87 stratified with susceptibility is needed.

27
28 88 To address this shortcoming, we carried out a meta-analysis to assess the clinical
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30
31 89 effects of prolonged infusion with β -lactam for patients infected by non-susceptible
32
33
34 90 microbes. To our knowledge, this is the first study to assess meta-data from other
35
36
37 91 studies of patients with infections that have reduced susceptibility to β -lactam treatment.
38

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40 41 42 93 **METHODS**

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45 94 This protocol has been written following the Preferred Reporting Items for Systemic
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47
48 95 Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement and registered in
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51 96 PROSPERO (CRD42018105111).²³

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53 97 The PRISMA-P checklist is shown in online supplementary appendix 1.

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56 98

57 58 99 **Patient and public involvement**

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4 100 Patients or the public are not involved.
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9 102 **Eligibility criteria**

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11
12 103 *Study design*

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15 104 RCTs, quasi-RCTs, and observational studies (retrospective and prospective) will be
16
17 105 included. *In vitro* studies, animal studies, and case reports will be excluded.

18
19
20 106 *Participants*

21
22
23 107 Patients who are infected by bacteria that are not susceptible to β -lactams will be
24
25 108 included. The susceptibility of the infecting microbes should be tested and established
26
27 109 to be non-susceptible (intermediate or resistant) to the administered β -lactam in the
28
29 110 study. There is no restriction regarding the method used to determine the susceptibility.
30
31
32 111 There is also no restriction regarding the site of infection or other patient characteristics.
33
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35

36 112 *Interventions*

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38
39 113 Studies evaluating the clinical efficacy of prolonged infusion with β -lactam will be
40
41 114 included. Prolonged infusion is defined as infusion of a β -lactam of no less than 3 hours.
42
43 115 Continuous infusion is recognized as a special type of prolonged infusion and can be
44
45 116 included.
46
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50 117 *Comparators*

51
52
53 118 The study will compare conventional, intermittent infusion of the same β -lactams as
54
55 119 used in the intervention group. Intermittent infusion is defined as infusion of drug in
56
57 120 less than 30 minutes.
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4 121 *Type of outcome measures*
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6 122 Studies to evaluate the clinical efficacy of prolonged infusion will be included. The
7
8
9 123 clinical effective rate must be evaluated. The effect is defined as a clinical cure, clinical
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11
12 124 improvement, or eradication of infected bacteria.
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15 125 *Language*
16

17 126 Studies published in English and Chinese will be included. Studies published in other
18
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20 127 languages but with a full information abstract in English or Chinese will be included.
21
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23 128 If the reviewer obtains the required information from the authors or translators, studies
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25
26 129 published in other languages will also be included.
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31 131 **Information sources**
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33
34 132 The following electronic databases will be searched from their inception to July 31,
35
36 133 2018: Medline, Cochrane database, EMBASE database, Cumulative Index to Nursing
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39 134 and Allied Health Literature (CINAHL) database, the Chinese National Knowledge
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42 135 Infrastructure (CNKI), and the Wanfang database.
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47 137 **Search strategy and selection of studies**
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50 138 The aforementioned electronic databases will be searched electronically. We will
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53 139 develop search strategies for each database, based on the search strategy developed for
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56 140 Cochrane database and Medline (online supplementary appendix 2), with appropriate
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59 141 reversions.
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4 142 Relevant publications such as references within the included studies will be
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6
7 143 searched manually. The yielded studies will be selected by reading the title, abstract,
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10 144 and full text to determine whether the eligibility criteria are met.

11
12 145 The literature searches and study selections will be carried out by two reviewers
13
14
15 146 (CHD and YLY) independently and cross-checked. Any inconsistency will be solved
16
17
18 147 by discussion with a third reviewer (YZW).

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22 23 149 **Data extraction**

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25
26 150 Data for the following attributes will be extracted: author and publication year of the
27
28
29 151 study, study design, study duration and region, number of participating patients, patient
30
31
32 152 age, gender, infection site, isolated microorganisms, methods and results of
33
34
35 153 susceptibility analysis, β -lactams administered and dosing regimen, co-administrated
36
37
38 154 antibiotics, and clinical outcomes including adverse events. The data will be extracted
39
40
41 155 by two reviewers (CHD and YLY) independently using an electronic data table and
42
43
44 156 cross-checked. Any inconsistency will be solved by discussion with a third reviewer
45
46
47 157 (YZW).

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51 159 **Dealing with missing data**

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53 160 When required data are not available in the literature or not published in an extractable
54
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56 161 form, the corresponding author of the published study will be contacted by e-mail to
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59 162 request additional information. Only available data will be analyzed if the reviewers
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4 163 fail to obtain data from any corresponding author
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9 165 **Measurement of outcomes**
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12 166 *Primary outcome*
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15 167 Effective rate. Outcomes defined as clinical cure, clinical improvement and eradication
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18 168 of the infecting bacteria by original study are regarded as effective in this meta-analysis.
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20 169 *Secondary outcomes*
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23 170 Mortality rate, microbial eradication rate, adverse effect rate, and length of hospital stay.
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28 172 **Quality (risk of bias) of individual studies**
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31 173 The quality of RCTs and observational studies will be assessed using a modified Jadad
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34 174 score and the Newcastle-Ottawa system, respectively.²⁴ Two reviewers will evaluate
35

36
37 175 the quality independently (CHD and YLY). Conflicting results will be judged by a third
38

39 176 reviewer (YZW).
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44 178 **Data synthesis**
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47 179 Data synthesis will be carried out with Review Manager 5.3 software (Copenhagen:
48

49
50 180 The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The results of RCTs
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53 181 and observational studies will be synthesized separately. The odds ratio and 95%
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56 182 confidential interval will be calculated for categorical outcomes. The mean difference
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59 183 and 95% confidential interval will be calculated for continuous outcomes. A random
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4 184 effects model will be used to obtain a summary estimate of the average effect with its
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7 185 95% CI. Heterogeneity among studies will be investigated using the I^2 test before data
8
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10 186 synthesis ($I^2 > 50\%$ is defined to indicate significant heterogeneity). The Mantel-
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12 187 Haenszel fixed effect model will be used when no significant heterogeneity exists
13
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15 188 among studies. Otherwise, additional *a priori* defined subgroup analysis will be
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18 189 triggered: type of study design, place of enrollment and level of risk of bias.
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23 191 **Subgroup analysis**

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26 192 Subgroup analysis will be carried out if a sufficient number of studies can be included
27
28
29 193 in our analysis. The subgroups will include: (1) type of β -lactam; (2) type of infecting
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31
32 194 microorganism; (3) site of infection; (4) folds of increased MIC; (5) type of included
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35 195 studies.
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39 197 **Sensitivity analysis and assessment of publication bias**

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42 198 Sensitivity analysis will be performed by excluding each study one by one to evaluate
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45 199 the stability of the results without estimation of bias from the individual study. This
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48 200 process allows for identification of any single article that may have a great influence
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51 201 on the final result. Publication bias will be evaluated by funnel plots if the number of
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54 202 studies included in the analysis is sufficient.
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58 204 **Summary of data**

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4 205 The results of the main outcomes will be summarized using the Grading of
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6 206 Recommendations Assessment, Development and Evaluation approach.²⁵
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11 208 **DISCUSSION**

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15 209 We believe that this meta-analysis will provide valuable information for clinicians with
16
17 210 respect to treating infections caused non-susceptible bacteria. Importantly, the results
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19 211 may prompt the individualized use of β -lactams. The results will also help physicians
20
21 212 devise dosing regimens for antibiotics under the guidance of PK/PD knowledge.
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24
25 213 Some limitations of this meta-analysis are apparent. Most studies evaluating
26
27 214 prolonged infusion with β -lactam are not well designed, and therefore bias may exist.
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29 215 The credibility of the findings will be affected by the quality of the included studies.
30
31 216 Missing data is a common occurrence in these types of studies. And there is a variability
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33 217 of outcome definitions across studies.
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41 219 **Contributors**

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44 220 CHD and YZW had the original idea for a meta-analysis. All authors designed the
45
46 221 protocol. CHD and YZW reviewed the search strategy. CHD and YLY drafted the
47
48 222 protocol. YZW registered in PROSPERO and is the guarantor of the protocol. All
49
50 223 authors read and approved the final version.
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4 226 There is no specific funding for this study.
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6
7 227 **Competing of interests**
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9 228 None declared.
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11
12 229 **Patient consent**
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15 230 Not required.
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For peer review only

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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:			
Sources	5a	Indicate sources of financial or other support for the review	Not applicable
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 author, 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 Schedules] 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