

# INPLASY PROTOCOL

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The authors have no conflicts of interest to disclose.

## Ceftazidime-avibactam for the treatment of infections: a protocol of systematic and meta-analysis

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**Review question / Objective:** The aim of this meta-analysis of randomized controlled trials is to evaluate the efficacy and safety of Ceftazidime-avibactam for the treatment of infections.

**Condition being studied:** Ceftazidime/avibactam, a novel  $\beta$ -lactam/  $\beta$ -lactamase inhibitor combination, displays in vitro activity against bacteria producing class A [including *Klebsiella pneumoniae* carbapenemase (KPC)] as well as some class D carbapenemases and has been approved by the European Medicines Agency (EMA) for infections due to Gram-negative bacteria with limited treatment options. However, no conclusive data are available in the literature regarding whether ceftazidime/avibactam can be used alone or in combination therapy against carbapenem-resistant Gram-negative bacteria. In fact, although combination therapy may be associated with a greater selective pressure and thus the development of antimicrobial resistance, in clinical practice several clinicians have used it in combination, also considering recent data on the selection of mutations in bla KPC genes conferring resistance to ceftazidime/avibactam.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 October 2020 and was last updated on 09 October 2020 (registration number INPLASY2020100029).

### INTRODUCTION

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approved by the European Medicines Agency (EMA) for infections due to Gram-negative bacteria with limited treatment options. However, no conclusive data are available in the literature regarding whether ceftazidime/avibactam can be used alone or in combination therapy against carbapenem-resistant Gram-negative bacteria. In fact, although combination therapy may be associated with a greater selective pressure and thus the development of antimicrobial resistance, in clinical practice several clinicians have used it in combination, also considering recent data on the selection of mutations in bla KPC genes conferring resistance to ceftazidime/avibactam.

## METHODS

**Participant or population:** Adults with infection (as diagnosed by a clinician, or using any recognized diagnostic criteria) will be included.

**Intervention:** Ceftazidime-avibactam was the main intervention.

**Comparator:** Other antibiotic.

**Study designs to be included:** Only randomized controlled trials will be considered.

**Eligibility criteria:** According to our aims, we designed the following inclusion criteria: (a) all randomized controlled trials (RCTs) which were performed to investigate the comparative efficacy and safety of CAZ-AVI versus other antibiotic in GNB infection patients will be considered for eligibility; (b) adult GNB infection patients regardless sex are diagnosed with definitive diagnosis standards which must be introduced in details; (c) the information of at least one of effectiveness and safety can be accessed; (d) only studies published in English and Chinese language will be eligible for our inclusion criteria.

**Information sources:** We will assign two independent reviewers to perform a systematic search in several electronic databases including PubMed, Web of

science, Cochrane library, Embase, Clinical Trials, China National Knowledge Infrastructure (CNKI), Wanfang database, Chinese sci-tech periodical full-text database (VIP), and China Biology Medicine disc. We will also check reference lists of all included studies and reviews which were performed to summarize the evidences of CAZ-AVI for the treatment of GNB infection in order to capture any potentially eligible studies.

**Main outcome(s):** The efficacy outcomes of this meta-analysis were clinical treatment success (defined as “clinical cure”), and microbiological response, respectively assessed at the test-of-cure (TOC) visit, late-follow-up (LFU) visit and end-of-treatment (EOT) visit based on modified intent-to-treat (MITT) population, microbiologically modified intent-to-treat (mMITT) population, clinically evaluable (CE) population, microbiological evaluable (ME) population or extended microbiologically valuable (EME) population in each individual study.

**Additional outcome(s):** All included patients at incidence of adverse events (AEs).

**Quality assessment / Risk of bias analysis:** The overall quality of all included studies is associated with the reliability and robustness of pooled results. Therefore, we will critically evaluate the quality of included study with Cochrane risk of bias assessment tool. Each included study will be assessed from the following six domains including randomization sequence generation, allocation concealment, blinding of participants, blinding of study personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other bias. According to the actual information of each study in terms of risk of bias, individual study will be labeled with ‘low risk of bias’, ‘unclear risk of bias’, and ‘high risk of bias’. The overall level of all included studies will be determined according to the results of assessing the risk of bias of individual study.

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**Strategy of data synthesis:** In our systematic review and meta-analysis, we will calculate the relative risk (RR) with 95% confidence intervals (CIs) to express dichotomous data, and the mean difference (MD) with 95% CIs to express continuous data. Before performing statistical analysis, we will firstly use the Cochrane Q test to qualitatively assess the heterogeneity across included studies, and then we will use I<sup>2</sup> statistic to quantitatively estimate heterogeneity. We will consider included studies for individual outcome as heterogeneity if I<sup>2</sup> >50% and P < 0.10. In contrast, studies will be considered as homogeneous when a I<sup>2</sup> ≤ 50% and a P ≥ 0.10 was estimated. We will perform all statistical analyses based on a random effect model because no homogeneous studies will be found in the real world.

**Subgroup analysis:** In order to exclude the impact of important confounding factors on all statistical analyses, we will perform several subgroup analyses according to the different visit time.

**Sensibility analysis:** We will conduct sensitivity analysis based on study quality.

**Country(ies) involved:** China.

**Keywords:** ceftazidime-avibactam; efficacy; safety; meta-analysis.

**Contributions of each author:**

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Author 2 - Xiaoran Zhang.

Author 3 - Yali Wang.

Author 4 - Chunhui Li.