INPLASY PROTOCOL

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Corresponding author:
Wang Xiaojie

499280551@qq.com

Author Affiliation:
The First Affiliated Hospital of Baotou Medical College of Inner Mongolia University of Science and Technology；Baotou Medical College；Baotou Eighth Hospital.

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Conflicts of interest:
None declared.

Colistin-associated acute kidney injury：A meta-analysis

Wang, XJ[1]；Dong, ZQ[2]；Dong, Y[3]；Cheng, J[4]；Zhang, L[5]；Chen CC[6]；Zhang, CX[7]；Chen, C[8]；Qi, J[9]；Tang, YC[10].

Review question / Objective: **Colistin is the last-resort antimicrobial agent against infections caused by multidrug-resistance Gram-negative bacteria (MDR-GNB). However, a differing risk of colistin-associated acute kidney injury (CA-AKI) has been demonstrated without affecting mortality, thus the association and its importance needs to be questioned. To assess the impact of this adverse effect, a meta-analysis comparing colistin with other antibiotics in treating MDR-GNB infections was conducted. The PubMed, Embase, Web of science and Cochrane Library electronic databases were searched up for cohort studies and randomised controlled trials with at least two arms with one arm containing colistin-based treatment. This study aimed to provide a more thorough understanding of CA-AKI, the influence of confounders, treatment strategies, and the overall clinical significance of CA-AKI in adult patients with GNB infections.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 December 2022 and was last updated on 15 December 2022 (registration number INPLASY2022120059).

INTRODUCTION

Review question / Objective: **Colistin is the last-resort antimicrobial agent against infections caused by multidrug-resistance Gram-negative bacteria (MDR-GNB). However, a differing risk of colistin-associated acute kidney injury (CA- AKI) has been demonstrated without affecting mortality, thus the association and its**

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importance needs to be questioned. To assess the impact of this adverse effect, a meta-analysis comparing colistin with other antibiotics in treating MDR-GNB infections was conducted. The PubMed, Embase, Web of science and Cochrane Library electronic databases were searched up for cohort studies and randomised controlled trials with at least two arms with one arm containing colistin-based treatment. This study aimed to provide a more thorough understanding of CA-AKI, the influence of confounders, treatment strategies, and the overall clinical significance of CA-AKI in adult patients with GNB infections.

Condition being studied: Colistin is one of the last-resort treatments for infections caused by multidrug-resistant (MDR) Gram-negative bacterial (GNB). Colistin was historically given as an intramuscular injection to manage GNB infections. Following the availability of amino-glycosides, this old drug was abandoned as a therapeutic choice owing to its nephrotoxicity, i.e. colistin-associated acute kidney injury (CA-AKI). However, it has been brought back to clinical use owing to its activity against MDR-GNB pathogens. Colistin has been shown to be effective in MDR-GNB infec- tions, but whether or not CA-AKI is clinically important is still in debate. Some meta-analyses showed that colistin therapy was associated with higher nephrotoxicity but similar mortality rates, whilst others showed neither higher nephrotoxicity nor mortality rates .

METHODS

Participant or population: Patients with multidrug-resistance Gram- negative bacteria (MDR-GNB) infection treated with colistin or other antibiotics will be addressed in the review.

Intervention: Antibacterial treatment with colistin or other antibiotics for multidrug-resistance Gram- negative bacteria (MDR-GNB) infected patients.

Comparator: The comparative intervention is to use other antibiotics than colistin, including ampicillin/sulbactam, tigecycline, carbapenem, imipenem, aminoglycoside and tobramycin.

Study designs to be included: Cohort studies and randomised controlled trials with at least two arms with one arm containing colistin-based treatment will be included to address the objective of the review.

Eligibility criteria: Studies were eligible for the meta-analysis if they met all of the following criteria: (i) parallel designed randomised controlled trial (RCT) or cohort study with comparator group; (ii) studies contain- ing at least two treatment arms and one of the arms contained colistin; and (iii) reported the incidence rate of nephrotoxicity or AKI in different intervention groups. Studies were excluded according to the following exclusion criteria: (i) letters, reviews, descriptive studies, case–control studies or irrelevant studies; (ii) paediatrics only; (iii) no full-text available; (iv) unable to retrieve data required for analysis; and (v) poor quality of cohort studies as assessed by the Newcastle–Ottawa Scale (NOS).

Information sources: The electronic databases including PubMed, Embase, Web of science and Cochrane Library.

Main outcome(s): The primary outcome was the occurrence of AKI within 14 days. CA-AKI was defined according to the definitions of the original studies. Increased serum creatinine (SCr) of 50% from baseline, in- creased SCr up to > 2 mg/dL in patients with normal renal func-tion, and new requirement for renal replacement therapy (RRT) were also defined as AKI.

Quality assessment / Risk of bias analysis: The Preferred Reporting Items for Systematic Review and Meta- analysis (PRISMA) guideline was used for screening and eligibility assessment of identified studies for systematic review and meta-

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analysis. Risk of bias was evaluated with the Cochrane risk of bias assessment tool. The quality of the eligible studies included in the analysis was assessed by the Jadad Scale for RCTs and the NOS for cohort studies. For RCTs, a total score out of 5 was determined for quality assessment. For cohort studies, a total score of < 5 out of 9 on the NOS scale were excluded.

Strategy of data synthesis: Study data were analysed using Review Manager (RevMan). All variables were pooled as dichotomous data to estimate the odds ratio (OR) and 95% confidence interval (CI) of AKI events using a random-effects model. Heterogeneity was assessed by the I 2 statistic. Substantial heterogeneity was defined as a P -value of < 0.10 and an I 2 value of > 50%. Publication bias was evaluated by funnel plot and Egger's linear regression.

Subgroup analysis: Subgroup analysis may be conducted between different antibiotic control groups, drug doses and diseases.

Sensitivity analysis: Sensitivity analysis may be conducted according to the size of heterogeneity.

Country(ies) involved: China.

Keywords: colistin; kidney; nephrotoxicity; polymyxin.

Contributions of each author:

Author 1 - Wang Xiaojie.
Email: 499280551@qq.com
Author 2 - Dong zhiqiang.
Author 3 - Dong yuan.
Author 4 - Cheng jie.
Author 5 - Zhang lei.
Author 6 - Chen congcong.
Author 7 - Zhang chunxia.
Author 8 - Chen chen.
Author 9 - Qi jun.
Author 10 - Tang yuchen.

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