INPLASY PROTOCOL

To cite: Huang et al. Aerosolized antibiotics for the treatment of pneumonia in mechanically ventilated patients: a systematic review and meta-analysis of randomised controlled trials. Inplasy protocol 202070039. doi: 10.37766/inplasy2020.7.0039

Received: 11 July 2020

Published: 11 July 2020

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Support: **None.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
The authors have no conflicts of interest to disclose.

Aerosolized antibiotics for the treatment of pneumonia in mechanically ventilated patients: a systematic review and meta-analysis of randomised controlled trials

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Review question / Objective: **We sought to perform a systemic review and meta-analysis, by pooling available RCTs and stratifying different aerosolized antibiotics strategies, to investigate the efficacy and safety of aerosolized antibiotics in the treatment of critically ill ventilated patients with pneumonia.**
Condition being studied: **The research team comes from the Department of Critical Care Medicine of a tertiary hospital in China, and all the team members have perfect clinical experience in treatment of nebulized antibiotics. Moreover, our team members have published nearly 10 meta-analysis, which can guarantee the successful completion of the current research.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 July 2020 and was last updated on 11 July 2020 (registration number INPLASY202070039).

INTRODUCTION

Review question / Objective: **We sought to perform a systemic review and meta-analysis, by pooling available RCTs and stratifying different aerosolized antibiotics strategies, to investigate the efficacy and safety of aerosolized antibiotics in the treatment of critically ill ventilated patients with pneumonia.**

Rationale: **Treatment of pneumonia in ventilated patients is often unsuccessful. Meanwhile, the constantly developing drug**

resistance makes treatment extremely difficult. One of the potential causes is intravenous antibiotics do not penetrate well into the lungs. Therefore, aerosolized antibiotics are attaching more and more interesting by clinicians. However, previous meta-analysis and guidelines differ on this issue for significant heterogeneity among study designs and treatment strategies. Recently, several RCT studies have been published.

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METHODS

Search strategy: Search terms include “aerosols”, “nebulizers” ,"vaporizers, pulmonary delivery" "critical care", "intensive care", "critically ill", "ventilated", "ventilator-associated pneumonia", VAP, "nosocomial pneumonia", "hospital-acquired pneumonia", HAP, "viral respiratory infection", "intubation", and "intubated". Language was restricted in English and Chinese. Study type is limited in RCT.

Participant or population: Adult (≥18 years old) ICU patients with mechanical ventilation and confirmed pneumonia.

Intervention: These patients received aerosolized antibiotics treatment used as adjunctive therapy strategy (aerosolized antibiotics added to standard IV antibiotics) or substitute therapy strategy (aerosolized targeted antibiotics added to standard IV antibiotics).

Comparator: These comparator received aerosolized antibiotics treatment used as adjunctive therapy strategy (aerosolized placebo or no use added to standard IV antibiotics) or substitute therapy strategy (IV targeted antibiotics added to standard IV antibiotics).

Study designs to be included: We will include only randomised controlled trials in the current study.

Eligibility criteria: We include RCT focusing adult (≥18 years old) ICU patients with mechanical ventilation and confirmed pneumonia. These patients received aerosolized antibiotics treatment used as adjunctive therapy strategy or substitute therapy strategy. IV targeted antibiotics added to standard IV antibiotics). No types of aerosolized antibiotics restriction were imposed. Ventilation could be provided through any kind of invasive artificial airway.

Information sources: The references in the included studies and personal files were also searched. In addition, we will request advice from experts in the field; search associated articles from critical care, surgical, infection meetings; and contacted the authors of included trials, if need.

Main outcome(s): Primary outcome are clinical response (defined as complete or partial resolution of clinical signs and symptoms of pneumonia) and mortality (considering the longest follow-up reported by each study author). Secondary outcomes include pneumonia associated mortality, microbiologic eradication, changes of clinical pulmonary infection score from baseline after treatment, length of stay in ICU, duration of MV and adverse events of bronchospasm and nephrotoxicity.

Quality assessment / Risk of bias analysis: For methodological quality, we will use the “risk of bias tool” recommended by the Cochrane Collaboration. For each RCT, risk of bias was evaluated for six domains (i.e., random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; or other bias and an “overall” risk of bias will be estimated. For each domain, risk of bias was categorized

as "low," "unclear," or "high." Disagreement for all methodological steps will be resolved by discussion.

Strategy of data synthesis: An overall effect estimate for all data as risk ratio (RR) / mean difference (MD) with 95% CI will be calculated. The presence of statistical heterogeneity among the studies by using the Q statistics and the heterogeneity by using the I2 statistic was addressed. A p value of less than 0.10 or an I2 value of greater than 50% as indicative was considered of substantial heterogeneity. A random-effects model or a fixed-effects mode (DerSimonian-Laird) will be chosen when significant heterogeneity or non-significant heterogeneity was not observed, respectively.

Subgroup analysis: Subgroup analyses: (a) type of antibiotics; (b) type of nebulizers; (c) patients with or without drug resistant pathogens; (d) study design (blinded or unblinded); and (e) literature quality.

Sensibility analysis: We conducted sensitivity analyses by removing any single study in turn to test the robustness of the pooled estimate of each outcome.

Country(ies) involved: China.

Keywords: Aerosolized antibiotics; mechanical ventilation; pneumonia; mortality; meta-analysis.

Contributions of each author:

Author 1 - Hui-Bin Huang - Dr. Huang will contribute to the conception of the study, data collection, analysis and drafting of the article.

Author 2 - Jun-Ping Qin - Dr. Qin will contribut to data collection, literature search and writing of the manuscript.

Author 3 - Yuan Xu - Dr. Xu will be responsible for the integrity of the work as a whole, from inception to publication of the article.

Author 4 - Bin Du - Dr. Du will be responsible for the integrity of the work as a whole, from inception to publication of the article.