# Basic Treatment Combined With Atomized Inhalation of Amikacin for Ventilator-associated Pneumonia: A Meta-analysis of Randomized Controlled Trials

**Qihui Huang**
Hefei City First People's Hospital
**Xiaojia Feng**
: First Affiliated Hospital of Bengbu Medical College
**Huihui Guo**
Hefei City First People's Hospital
**Lin Zhang** ( 2005202zhl@sina.com )
Hefei City First People's Hospital

**Research**

**Keywords:** Atomization, Amikacin, ventilator associated pneumonia

**Posted Date:** April 14th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-418355/v1

## Abstract

**Background:** Compared with single intravenous therapy, nebulized amikacin combined with intravenous therapy can significantly benefit ventilator-associated pneumonia (VAP). However, the existing literature provides controversial conclusions.

**Methods:** We systematically searched PubMed, Embase, Cochrane, CNKI, VIP, and Wanfang databases (without language restriction) for randomized controlled trials (RCTs) involving atomization inhalation of amikacin in the treatment of VAP published before October 2020. Literature screening, data extraction, and quality evaluation were performed according to the preferred reporting items for systematic reviews and meta-analyses guidelines.

**Results :** A total of 9 RCTs were found eligible and included in our analysis (1162 patients with VAP). The results of this meta-analysis showed a significant benefit of combination treatment for improving the clinical cure (odds ratio, 2.40; 95% CI, 1.50–3.84; p = 0.006), Pathogen clearance rate (odds ratio, 3.46; 95% CI, 2.41–4.97; p <0.001), bronchospasm rate (odds ratio, 2.82; 95% CI, 1.38–5.78; p = 0.005) and Clinical pulmonary Infection Score (CPIS) (MD,-0.90; 95% CI, -1.23 to -0.57; p<0.001), No significant difference was found in 28-day mortality (odds ratio, 1.15; 95%CI, 0.81–1.63; p = 0.45) and renal impairment (odds ratio, 0.88; 95% CI, 0.60–1.30; p = 0.53).

**Conclusion :** The addition of atomization inhalation of amikacin to intravenous antibiotics treatment in VAP patients significantly improves the clinical cure rate and pathogen clearance rate, t can also help reduce the 28-day mortality, bronchospasm rate and CPIS outcome. In addition, the combination has no significant difference in the rate of renal impairment over the conventional intravenous treatment.


## 1. Background

Ventilator-associated pneumonia (VAP), defined as parenchymal infection in patients exposed to invasive mechanical ventilation for at least 48 hours, is an important cause of nosocomial pneumonia in the intensive care unit (ICU)[1, 2]. The incidence of VAP in mechanically ventilated patients is reported to be 5–40%, and the crude mortality rate can reach 20–70%[3–5]. The onset of VAP complicates the patient's original condition and consequently makes the treatment more difficult. This can significantly increase the duration of mechanical ventilation, length of hospital stay, and mortality of patients[6].

The current first-line treatment for VAP is intravenous and intramuscular administration of antibiotics. However, multidrug-resistant bacteria and gram-negative bacilli, such as *Acinetobacter baumannii*, *Pseudomonas aeruginous*, and *Klebsiella pneumoniae*, which are the main causative pathogens of VAP, are often insensitive to commonly used antibiotics, and the efficacy of the basic intravenous antibiotic therapy is often poor. While these pathogens may be sensitive to polymyxins and aminoglycosides, these antibiotics are associated with adverse effects[7]. Moreover, it is difficult to achieve an effective drug concentration in the lung tissue with conventional intravenous antibiotics, because an increase in the drug dose could increase the incidence of adverse reactions[8].

Compared to basic treatment, that is, intravenous antibiotics treatments alone, aerosol antibiotic therapy is a popular therapy widely used in respiratory diseases at present. In this method, the drug is added into an atomization device so that it forms fog drops and delivers the drug directly to the lungs, thereby achieving a 20–200-fold higher drug concentration in the target organ[9, 10]. At the same time, due to the presence of an alveolar-capillary barrier, the amount of drug reaching the systemic circulation is low with atomization inhalation, and consequently, the risk of systemic adverse effects is also significantly reduced. While the benefits of nebulized antibiotics in the treatment and prognosis of patients with VAP in the ICU ward are clear, The European Society for Clinical Microbiology and Infectious Diseases also states that[11] there is currently insufficient evidence on the effectiveness of using inhalational therapy. Therefore, this systematic review and meta-analysis study was conducted to updated the efficacy and safety of amikacin aerosol therapy(AAT).

## 2. Methods

## 2.1 Database and search strategy

This systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[12].A statement was made and registered in the International Prospective System Review (No.CRD42021230429). A systematic literature search was performed on PubMed, Cochrane, Embase, CNKI, VIP, and Wanfang. The search string used was as follows: (Pneumonia, Ventilator-AssociatedTitle"[Mesh]) OR (VentilatorAssociatedPneumonia [Title/Abstract]) OR (VAP [Title/Abstract]), ((amikacin [Title/Abstract]) OR (Amikacina Medical [Title/Abstract])) OR (Medical, Amikacina [Title/Abstract]) OR (Amikacina Normon [Title/Abstract])) OR (Abstron, Amikacina [Title/Abstract])) OR (Amikin [Title/Abstract]) OR (Biklin [Title/Abstract])) OR (Amiklin [Title/Abstract])) OR (BB-K8 [Title/Abstract]) OR (BBK8 [Title/Abstract]) OR (BB K 8 [Title/Abstract])) OR (Gamikal [Title/Abstract])) OR (Kanbine [Title/Abstract])) OR (Oprad [Title/Abstract]) OR (Amikacin [Title/Abstract])))). There were no restrictions on search language, date, region, or publication status. The reference lists of relevant reviews were also searched to ensure a thorough search of the included articles.

## 2.2 Selection criteria and study selection

Our meta-analysis included studies involving adult patients (over 18 years of age and of either sex) diagnosed with VAP who underwent mechanical ventilation in the ICU and randomized controlled studies of the efficacy of nebulized amikacin in comparison with basic treatment strategies with at least 1 week of intervention, details of intervention measures such as treatment duration and application methods, and dose. The studies were included only if data on definite outcome variables were available. Studies comparing different routes of administration; animal experiments; studies less than 7 days; observational and retrospective studies; and articles with insufficient data were excluded. The initial screening was based on the titles and abstracts of all search results to exclude ineligible studies. The full text was browsed to assess whether the study met the inclusion criteria. Then, study selection was performed independently by two authors (Q.H.Huang and X.J.Feng)according to the search strategy, and any differences were resolved by discussion or consensus with a third author(H.H.Guo).

## 2.3 Data extraction

We extracted the following data from each selected study: total number of participants, age, sex, treatment duration, underlying treatment, literature source, randomization method, concealment of allocation, investigator blinding, patient blinding, completeness, follow-up, and outcome measures. Clinical outcomes included clinical cure rate, pathogen clearance rate, Clinical Pulmonary Infection Score(CPIS)(mean [SD]), and adverse reactions included mortality, bronchospasm rate, and renal damage rate.

## 2.4 Assessment for risk of bias

Two reviewers(Q.H.Huang and X.J.Feng)assessed the risk of bias for each study using the Cochrane risk of bias tool. Factors such as random sequence generation, allocation concealment, blinding of participants and investigators, blinding of analysts, incomplete result data, selective reporting, and conflict of interest were considered in the assessment. Disagreements about risk assessment were resolved by discussion between two other reviewers.

## 2.5 Data synthesis

Data analysis was performed using RevMan software (version 5.3) provided on the Cochrane website. Continuous variables are presented as differences in the mean with a 95% confidence interval (95% CI). The odds ratio (OR) was used as the influencing index for dichotomous variables. Heterogeneity was assessed by the Cochrane Q statistic and the $I^2$statistic. A P value $\leq 0.10$ together with an $I^2$value $\geq 50\%$ indicates significant heterogeneity. $I^2$values $\leq 50\%$ represented acceptable between-study heterogeneity, and the fixed-effects model was selected. Otherwise, the random-effects model was selected[13, 14]. Heterogeneous causes can be analyzed, such as age, sex, course of treatment, dose or other factors, etc. The Stata software was used for We used the STATA program (Stata Corporation, College Station, Texas) for sensitivity analysis, which was used to eliminate possible heterogeneity factors.

# 3 Results

## 3.1 Retrieval of basic information and evaluation of quality

According to the search strategy, we retrieved a total of 90 relevant articles and finally included 9 [15–23] RCTs involving atomization inhalation of amikacin in VAP patients. The basic treatment in those 9 studies was conventional ventilator support and treatment with systemic antibiotics. The experimental group received atomized inhalation of amikacin on the basis of intravenous antibiotics, and we called it the AAT group. The quality scores of the 9 included studies were above 4, which means high-quality RCTs. The literature screening flowchart and basic information of a total of 1162 patients included are shown in Fig. 1 and Table 1. The quality evaluation results are shown in Fig. 2.

## 3.2 Meta-analysis results

### 3.2.1 Clinical cure rate

Nine RCTs including 1162 patients reported data on the in-hospital clinical cure ,The results showed that the cure rate was 75%(431/582) in the AAT group and 61%(357/578) in the basic treatment group. There was a significant difference between the two groups using the randomed effect model (OR = 2.40;95% CI,1.50–3.84; p = 0.0002), with high heterogeneity ($\chi 2 = 21.49$, I2 = 63%). Sensitivity analysis concluded that the study by Niederman M was the main reason affecting this heterogeneity. After excluding this study, the heterogeneity was found to be low ($I^2 = 0\%$, P = 0.99). (Fig. 3–4).

### 3.2.2 Pathogen clearance rate

Seven RCTs including 586 patients reported data on the pathogen clearance rate, The results showed that the rate was 65.2%(191/293) in the AAT group and 38.1%(111/291) in the basic treatment group. Meta-analysis using the randomed-effects model showed that the AAT group significantly reduced the pathogen clearance rate(OR = 3.46; 95% CI, 2.41–4.97,p < 0.001; p for heterogeneity 0.89, $I^2 = 0\%$). A significant difference was observed upon comparing the results of the two groups, indicating that addition of atomization inhalation of amikacin to the basic treatment can improve the pathogen clearance rate in VAP patients (Fig. 5).

### 3.2.3 28-day mortality

Four RCTs including 758 patients reported data on the in-hospital mortality with overall incidence of 21.2%(85/380 in AAT group,76/378 in basic treatments group). There was statistically significant between the two groups with the random effects model (OR = 1.15;95% CI, 0.81–1.63;p = 0.45; p for heterogeneity = 0.60,I2 = 0%). The difference suggesting that combining atomized amikacin with basic treatment could not reduce the 28-day mortality of VAP patients (Fig. 6).

### 3.2.4 CPIS

In 5 RCTs including 346 subjects,Clinical pulmonary infection score (CPIS) was reported. The did not show any difference in the two groups with the random effects model either (MD=-1.71; 95% CI, -3.30 to -0.12; p = 0.04) with high heterogeneity ($\chi 2 = 120.91$, $I^2 = 97\%$). In order to reduce heterogeneity in the study design or intervention maneuver, We first adopted the method of one-item elimination, and after excluding the study by Yue, the heterogeneity was found to be low ($\chi 2 = 2.89$, $I^2 = 0\%$,). Analysis of CPIS in 5 groups showed that the CPIS of patients in the AAT group was lower than that of patients in the basic treatments group (Fig. 7).

### 3.2.5 Rate of bronchospasm

Four RCTs including 794 patients reported data on the bronchospasm rate, The results showed that the rate was 7.5%(30/398) in the AAT group and 2.8%(11/396) in the basic treatment group. The difference was statistically significant between the two groups with random effects model(OR = 2.89; 95% CI, 1.42–5.87; p = 0.003; p for heterogeneity = 0.84,$I^2 = 0\%$)(Fig. 8).

### 3.2.6 Rate of renal impairment

Amikacin is a semisynthetic aminoglycoside antibiotic, and intravenous administration of amikacin in the ICU is limited by its main adverse effect of renal damage. Four RCTs including 794 patients reported data on the renal impairment rate, The results showed that the rate was 14.6%(58/398) in the AAT group and 16.2%(64/396) in the basic treatment group. There was no significant difference between the two groups with random effects model(OR = 0.88;95% CI, 0.60–1.30;p = 0.53;p for heterogeneity = 0.85,$I^2 = 0\%$)(Fig. 9).

## 3.3 Publication bias

Outcome measures of the clinical cure rate after combined atomization inhalation of amikacin compared with basic treatment were analyzed to detect publication bias. The funnel plot was slightly asymmetric between the study groups, suggesting a high possibility of publication bias. Other relevant treatment outcome measures, due to the small number of included studies, were not tested for publication bias.

## 4. Discussion

We included 10 trials that presented at least one of the primary outcomes in the updated meta-analysis. In VAP patients, The findings revealed an improvement with the addition of atomizatied amikacin compared with intravenous treatments alone in the disease's outcomes. The results showed that the combined medication group improved the clinical cure rate and pathogen clearance rate, and reduced the bronchospasm rate and CPIS outcome. Simultaneous, the combination therapy had no effect on the outcome of 28-day mortality rate and renal damage rate. Our main outcome endpoint is the clinical cure rate. In the sensitivity analysis, Michael's study is the main reason. In Michael's study, aerosolized antibiotics cannot relieve pneumonia symptoms faster. Consider the following reasons for this heterogeneity: First of all, this study is only aimed at mechanically ventilated patients with gram-negative pneumonia, while the bacteria detected in patients with ventilator pneumonia are the existence of widespread flora, and aminoglycoside antibiotics also have a certain sterilization effect on the positive flora. effect. Second, the observation in the figure shows that the large sample data of Michael's study is the cause of this heterogeneity, but the result of the large sample study with negative results is still positive after the inclusion of the negative result, and the sensitivity analysis is also stable. After comprehensive consideration, atomization The clinical cure rate of amikacin is a definite improvement. Same as CPIS, although the results in the figure show that the five included studies have high heterogeneity, the lung infection scores after combined treatment with nebulized amikacin in all studies showed a downward trend after treatment, while the yue study declined more significant.

The current first-line treatment for ventilator-associated pneumonia (VAP) is intravenous administration of antibiotics, which are associated with systemic adverse effects. Aerosol inhalation of aminoglycoside antibiotics has been proposed as a treatment strategy for ventilator pneumonia in mechanically ventilated patients in intensive care units. Intravenously administered aminoglycoside antibiotics and vancomycin do not effectively cross the alveolar-capillary barrier and have a low concentration at the site of pulmonary lesions, reducing their antibacterial effectiveness. In recent years, the application of aerosol inhaled antibiotics has become a research hotspot. Aerosol antibiotics can reach a higher concentration in the lesion area to avoid adverse system reactions[24]. Animal experiments and related clinical studies have shown that aerosol inhalation of amikacin can reach the far end of the most severe infection, and is effective in clinical cure rate and signs of pneumonia[25, 26]. The 2016 VAP guidelines of the American Thoracic Society/American Society of Infectious Diseases recommended that patients with VAP caused by aminoglycosides or polymyxin-sensitive Gram-negative bacilli should use inhaled and systemic avidin instead of systemic antibiotics alone[6]. Nebulized antibiotics can increase the concentration of local antibiotics and significantly enhance the antibacterial effect. At the same time, nebulization makes the antibiotics confined in the lungs, which can reduce the occurrence of systemic toxicity[27]. According to current clinical practical applications, the choice of nebulizer, the setting of the pipeline, and the setting of the ventilator parameters will affect the concentration of the drug in the lung tissue, the loss of drug delivery, and systemic side effects. The safety, effectiveness and clinical effects of nebulized inhalation will also be affected by

factors such as patient age, different underlying diseases, and human-machine cooperation[28]. Therefore, we further research is required before advocating the application of atomization inhalation of amikacin in the treatment of VAP.

This study has certain limitations: This study included a total of 9 RCTs and a total of 1162 patients, indicating that the number of included studies and patients was relatively small. 7 of the 9 included RCTs did not adequately describe the blinding method; therefore, this may lead to some selection bias. Because of the delay in the diagnosis of VAP due to the timeliness and the interference of various parameters such as the complex condition, it is difficult to accurately locate the treatment effect. Meta-analysis is essentially an observational study, and every step may produce some deviations. However, the 9 RCTs included in this study were of high quality, with scores above 4 and low statistical heterogeneity, which increased the reliability of the results to a certain extent.

In summary, the combination of aeroseurol inhalation of amikacin and basic treatment can improve the clinical cure and removal of pathogens. It also helps to reduce the bronchospasm rate and CPIS outcomes in patients with VAP, but there is no significant difference in the rate of 28-day mortality and renal damage. Analysis of many prospective, large-sample, multicenter RCTs is needed to establish the efficacy and safety of combining atomization inhalation of amikacin with the basic treatment in VAP patients.

VAP: ventilator associated pneumonia; RCT: randomized controlled trials; CPIS: Clinical pulmonary Infection Score; ICU: intensive care unit; AAT: amikacin aerosol therapy; 95% CI: 95% confidence interval.

## Declarations

### Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Anhui Medical University.

### Consent for publication

Written informed consent for publication was obtained from all participants.

### Availability of data and materials

Not applicable.

### Competing interests

All authors have no conflicts of interest to declare.


### Funding

This study supported by Hefei Key Discipline Construction Project (No: Hefei Science and Education No. 2019-160), and Hefei Famous Doctor Studio (NO: Hefei Talents Work No. 2019-1).


### Authors' contributions

Conceptualization: Qihui Huang, Xiaojia Feng.

Data retrieval: Qihui Huang, Xiaojia Feng, Huihui Guo.

Project administration: Huihui Guo, Lin Zhang.

Supervision: Lin Zhang.

Validation: Lin Zhang.

Writing – original draft: Qihui Huang, Xiaojia Feng.

Writing – review and editing: Qihui Huang, Lin Zhang.


### Acknowledgements

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. QH and JJ had the idea for the study. QH, JJ , and HH selected studies for inclusion and abstracted data. QH did the statistical analyses. QH, JJ, HH and LZ interpreted the data. QH, JJ and HH wrote the first draft. QH, JJ, HH and LZ critically revised the paper for important intellectual content. All authors read and approved the final manuscript.

**Authors' information**

Lin Zhang, Director of Intensive Care Department, The Third Affiliated Hospital of Anhui Medical University

Qihui Huang, Master of Critical Care Medicine, The Third Affiliated Hospital of Anhui Medical University

Xiaojia Feng, Master of Breast Surgery, The First Affiliated Hospital of Bengbu Medical University

Huihui Guo, Master of Critical Care Medicine, The Third Affiliated Hospital of Anhui Medical University

## References

1. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Resp Crit Care. 2005;171(4):388–416.
2. Charles MP, Kali A, Easow JM, Joseph NM, Ravishankar M, Srinivasan S, et al. Ventilator-associated pneumonia. Austr Med J. 2014;7(8):334–44.
3. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Infect Dis. 2013;13(8):665–71.
4. Muscedere JG, Day A, Heyland DK. Mortality, attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and hospital-acquired pneumonia. Clin Infect Dis. 2010;51(Suppl 1):120–5.
5. Mehta AB, Syeda SN, Wiener RS, Walkey AJ. Epidemiological trends in invasive mechanical ventilation in the United States: A population-based study. J Crit Care. 2015;30(6):1217–21.
6. Kalil AC, Metersky ML, Klompas M. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–111.
7. Zampieri FG, Nassar AP Jr, Gusmao-Flores D, Taniguchi LU, Torres A, Ranzani OT. Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis. Crit care. 2015;19(1):150.
8. Sandiumenge A, Rello J. Ventilator-associated pneumonia caused by ESKAPE organisms: cause, clinical features, and management. Curr Opin Pulm Med. 2012;18(3):187–93.
9. Montgomery AB, Vallance S, Abuan T. A randomized double-blind placebo-controlled dose-escalation phase 1 study of aerosolized amikacin and fosfomycin delivered via the PARI investigational eFlow® inline nebulizer system in mechanically ventilated patients. Journal of Aerosol Medicine Pulmonary Drug Delivery. 2014;27(6):441–8.
10. Poulakou G, Siakallis G, Tsiodras S, Arfaras-Melainis A, Dimopoulos G. Nebulized antibiotics in mechanically ventilated patients: roadmap and challenges. Expert Rev Anti-Infect Ther. 2017;15(3):211–29.
11. Rello J, Solé-Lleonart C, Rouby JJ. Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. Clin Microbiol Infect. 2017;23(9):629–39.
12. Preferred reporting items for. systematic reviews and meta-analyses: the PRISMA statement-PubMed. https://pubmed.ncbi.nlm.nih.gov/19622551/ (2021). Accessed 18 Mar 2021.
13. Du F, Jiang P, He S, Song D, Xu F. Antiplatelet Therapy for Critically Ill Patients: A Pairwise and Bayesian Network Meta-Analysis. Shock. 2018;49(6):616–24.
14. Gu XM, Yao SB, He Z, Wang YG, Li ZH. Meta-analysis of the success rate of heartbeat recovery in patients with prehospital cardiac arrest in the past 40 years in China. Mil Med Res. 2020;7(1):34.
15. Li H, Yang CH, Xue YY. Clinical efficacy of nebulized amikacin in the treatment of ventilator-associated pneumonia caused by pseudomonas. Journal of Internal Medicine Critical Care. 2016;22(05):335–7.
16. Meng FL. Evaluation of the clinical efficacy of nebulized amikacin in the treatment of ventilator-associated pneumonia. Bengbu Medical College, 2013.
17. Yang CH, Xue YY, Xie J. Observation on the clinical efficacy of nebulized antibiotics in the treatment of ventilator-associated pneumonia. Chinese Journal of Respiratory Critical Care. 2015;14(03):273–7.
18. Yue XZ. Study on the efficacy and feasibility of nebulized inhalation of amikacin in the treatment of ventilator-associated pneumonia. Journal of Clinical Rational Use. 2016;9(15):38–9 + 42.
19. Zhu JD, Jiang HT, Luo JG. Analysis of the value of amikacin in the treatment of Acinetobacter baumannii ventilator-associated pneumonia. Chinese Journal of Microecology. 2015;27(11):1319–21 + 1331.
20. Liu C, Zhang YT, Peng ZY, Zhou Q, Hu B, Zhou H, et al. Aerosolized Amikacin as Adjunctive Therapy of Ventilator-associated Pneumonia Caused by Multidrug-resistant Gram-negative Bacteria: A Single-center Randomized Controlled Trial. Chin Med J. 2017;130(10):1196–201.

21. Chen S. Effect of nebulized amikacin on blood gas indexes and inflammatory factors in elderly patients with ventilator-associated pneumonia. Anhui Medicine. 2018;22(05):965–7.
22. Niederman MS, Alder J, Bassetti M, Boateng F, Cao B, Corkery K, et al. Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial. Lancet Infect Dis. 2020;20(3):330–40.
23. Tong K. Evaluation of the clinical efficacy of nebulized amikacin in the treatment of ventilator-associated pneumonia. Journal of Clinical Pulmonology. 2016;21(10):1862–5.
24. Niederman MS. Adjunctive Nebulized Antibiotics: What Is Their Place in ICU Infections? Front Med. 2019;6:99.
25. Goldstein I, Wallet F, Robert J, Becquemin MH, Marquette CH, Rouby JJ. Lung tissue concentrations of nebulized amikacin during mechanical ventilation in piglets with healthy lungs. Am J Resp Crit Care. 2002;165(2):171–5.
26. Lu Q, Luo R, Bodin L, Yang J, Zahr N, Aubry A, et al. Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. Anesthesiology. 2012;117(6):1335–47.
27. Zhang C, Berra L, Klompas M. Should Aerosolized Antibiotics Be Used to Treat Ventilator-Associated Pneumonia? Resp Care. 2016;61(6):737–48.
28. Aerosol Therapy for Pneumonia in the Intensive Care Unit - PubMed. https://pubmed.ncbi.nlm.nih.gov/30390752/ (2021). Accessed 18 Mar 2021.

## Tables

**Table 1** Characteristics of the studies included in the meta-analysis

| Source | Sample (T/C) | Age (year) | Sex (male /female) | Intervention | | Treat-ment period (week) | Outcome measure |
|---|---|---|---|---|---|---|---|
| | | | | Treatment Group(T) | Control group(C) | | |
| Meng,2011[16] | 29/27 | T:50.38±15.34C:49.26±15.96 | - | Atomized amikacin 600mg,qd | Intravenous antibiotics | 2 | CCR+PCR+CPIS |
| Zhu,2015[19] | 34/34 | T:42.4±6.8 C:41.9±5.9 | T:18/16 C:20/14 | Atomized amikacin (7.5mg/kg,qd) | Intravenous antibiotics + nebulized saline | 1 | CCR+CPIS |
| Yang,2015[17] | 60/60 | T:54±15 C:58±15 | T:36/24 C:27/33 | Atomized amikacin 400mg,bid | Intravenous antibiotics + nebulized saline | 1 | CCR+PCR+MR |
| Li,2016[15] | 38/38 | T:64±10 C:61±24 | T:22/16 C:30/8 | Atomized amikacin 400mg/,qd | Intravenous antibiotics | 1 | CCR+CPIS+MR |
| Yue,2016[18] | 39/39 | T:49.6±2.3 C:50.2±2.5 | T:21/18 C:22/17 | Atomized amikacin 600mg,qd | Intravenous antibiotics | 2 | CCR+PCR+CPIS |
| Tong,2016[23] | 45/45 | T:44.5±19.5 C:47.2±17.8 | T:26/19 C:29/16 | Atomized amikacin 600mg,qd | Intravenous antibiotics | 2 | CCR+PCR+CPIS |
| Liu,2017[20] | 27/25 | T: 68.1 ± 16.7 C: 64.7 ± 10.6 | T:16/11 C:16/9 | Atomized amikacin 400mg,bid | Intravenous antibiotics + nebulized saline | 1 | CCR+PCR+CPIS+MR |
| Chen,2018[21] | 55/55 | T:73.2±5.9 C:73.4±7.2 | T:33/22 C:32/23 | Atomized amikacin 400mg,bid | Intravenous antibiotics + nebulized saline | 2 | CCR+PCR+MR |
| Niederman2019[22] | 255/253 | T:66(56~76) C:66(54~78) | T:182/73 C:178/75 | Atomized amikacin 400mg,qd | Intravenous antibiotics | 4 | CCR+PCR+MR |

CCR: Clinical cure rate;  PCR: Pathogen clearance rate MR: Mortality rate

## Figures

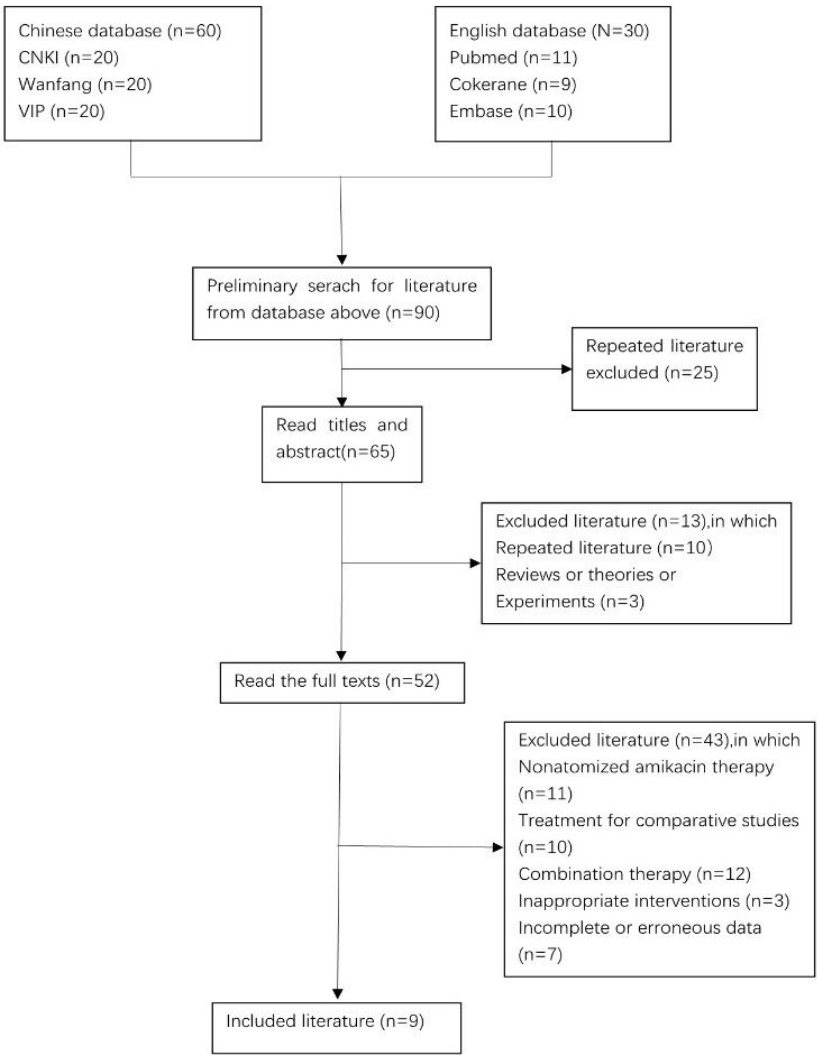


**Figure 1**

Flowchart of the literature review


Figure 2

Assessment of risk bias for RCTs. a. A graph with percentages for all included studies. b. A summary of bias for each included study

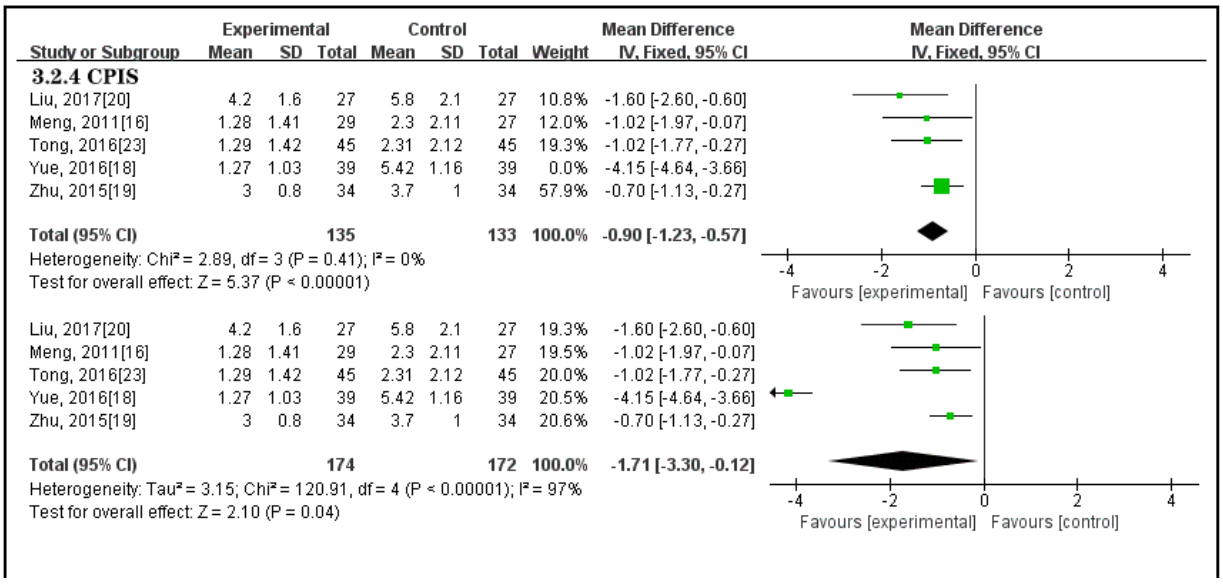


Figure 3

Forest plot of Clinical cure rate between the two groups

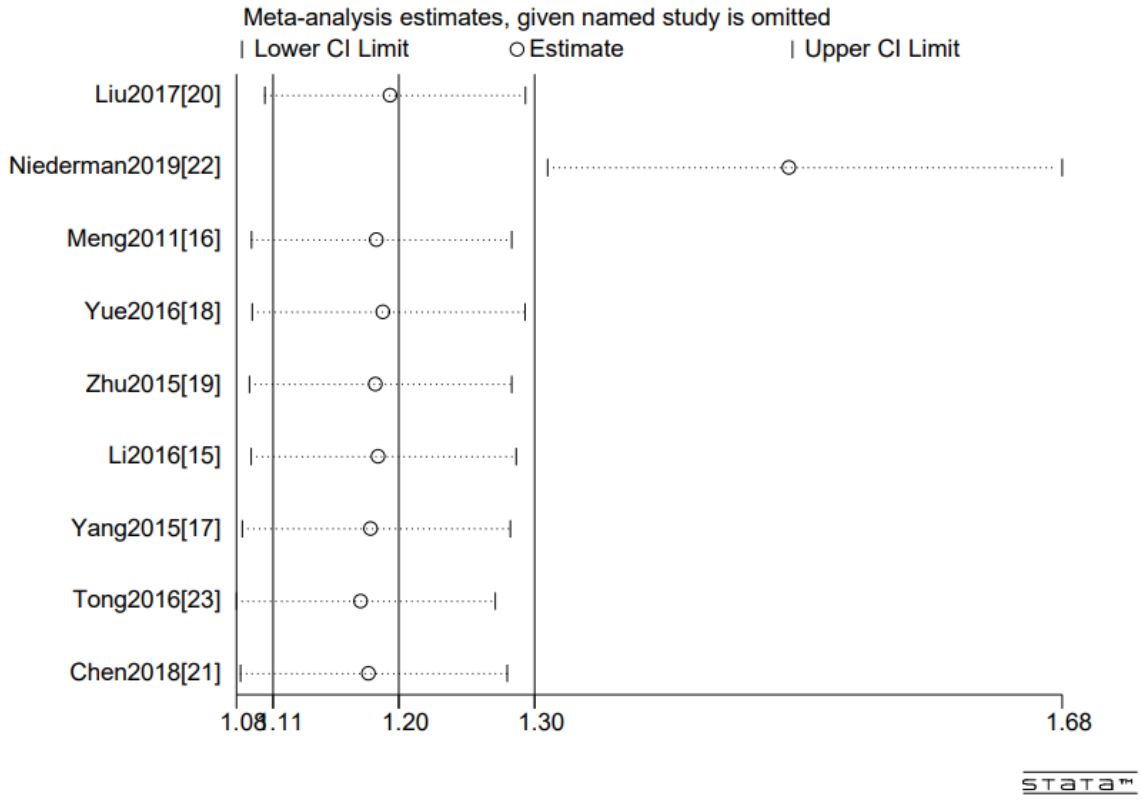


**Figure 4**

Sensitivity analysis of cure rate heterogeneity

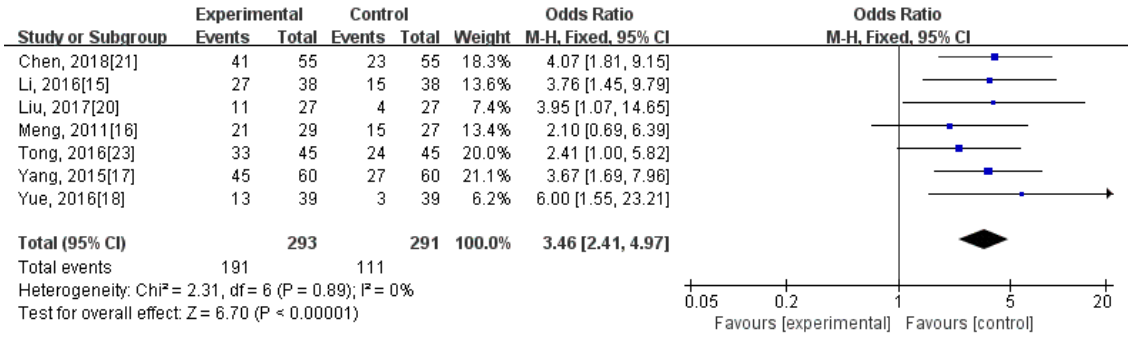


**Figure 5**

Forest plot of pathogen clearance between the two groups

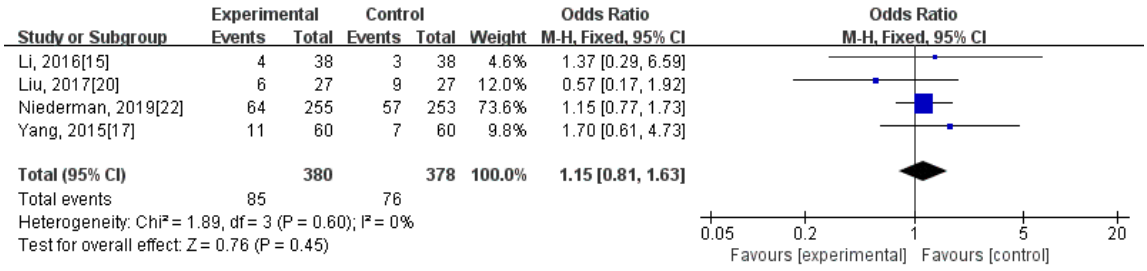


**Figure 6**

Forest plot of 28-day mortality between the two groups

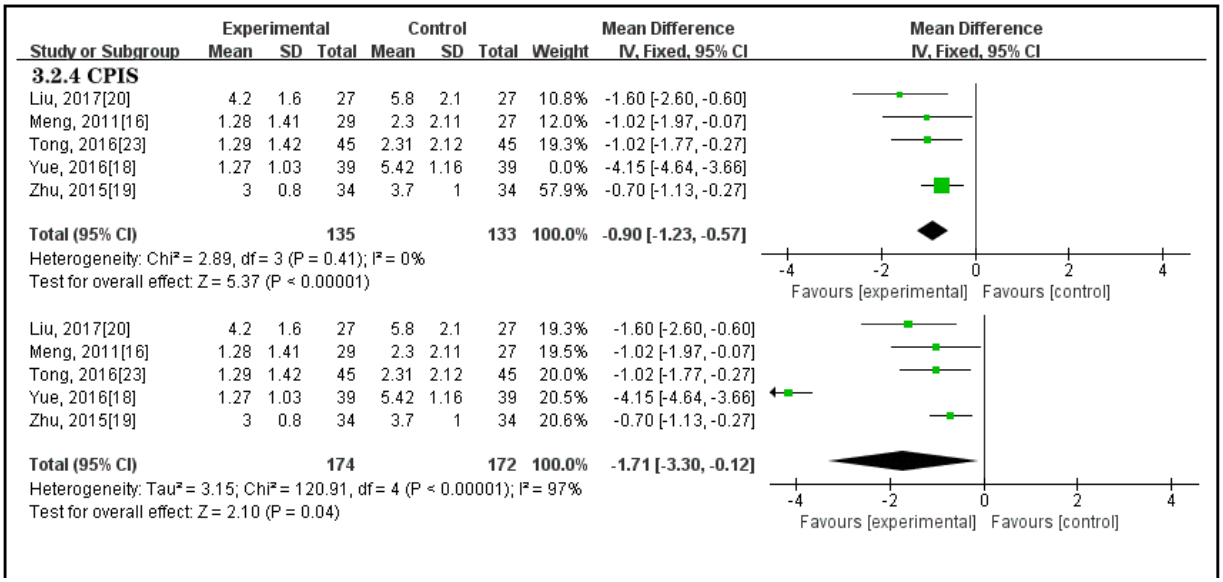


**Figure 7**

Forest plot of Clinical cure rate between the two groups

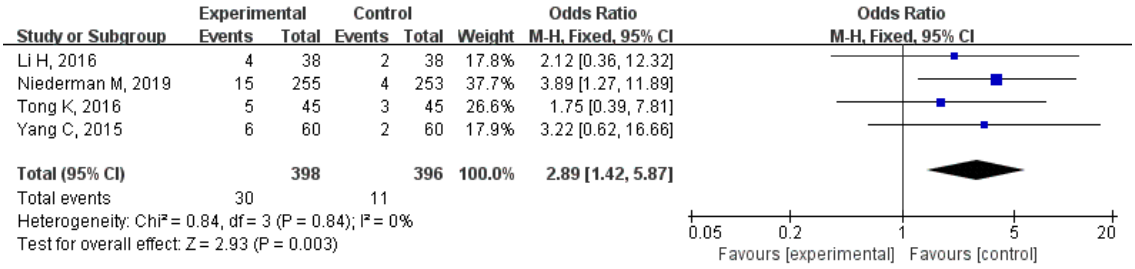


**Figure 8**

Forest plot of bronchospasm rate between the two groups

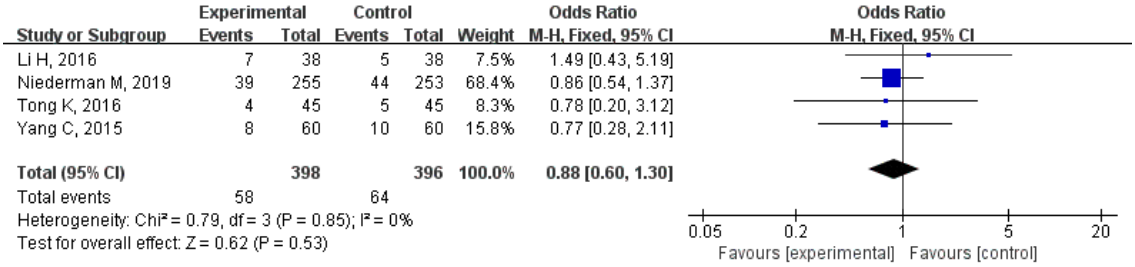


**Figure 9**

Forest plot of renal impairment rate between the two groups