Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults

A Systematic Review and Meta-analysis

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ABSTRACT

Background: Nebulization of antiinfective agents is a common but unstandardized practice in critically ill patients.

Methods: A systematic review of 1,435 studies was performed in adults receiving invasive mechanical ventilation. Two different administration strategies (adjunctive and substitute) were considered clinically relevant. Inclusion was restricted to studies using jet, ultrasonic, and vibrating-mesh nebulizers. Studies involving children, colonized-but-not-infected adults, and cystic fibrosis patients were excluded.

Results: Five of the 11 studies included had a small sample size (fewer than 50 patients), and only 6 were randomized. Diversity of case-mix, dosage, and devices are sources of bias. Only a few patients had severe hypoxemia. Aminoglycosides and colistin were the most common antibiotics, being safe regarding nephrotoxicity and neurotoxicity, but increased respiratory complications in 9% (95% CI, 0.01 to 0.18; I^2 = 52%), particularly when administered to hypoxemic patients. For tracheobronchitis, a significant decrease in emergence of resistance was evidenced (risk ratio, 0.18; 95% CI, 0.05 to 0.64; I^2 = 0%). Similar findings were observed in pneumonia by susceptible pathogens, without improvement in mortality or ventilation duration. In pneumonia caused by resistant pathogens, higher clinical resolution (odds ratio, 1.96; 95% CI, 1.30 to 2.96; I^2 = 0%) was evidenced. These findings were not consistently evidenced in the assessment of efficacy against pneumonia caused by susceptible pathogens.

Conclusions: Performance of randomized trials evaluating the impact of nebulized antibiotics with more homogeneous populations, standardized drug delivery, predetermined clinical efficacy, and safety outcomes is urgently required. Infections by resistant pathogens might potentially have higher benefit from nebulized antiinfective agents. Nebulization, without concomitant systemic administration of the drug, may reduce nephrotoxicity but may also be associated with higher risk of respiratory complications. **(Anesthesiology 2017; 126:890-908)**

AEROSOLIZED administration of antibiotics to treat respiratory infections in critically ill patients was described more than 40 yr ago.[1] Supported by experimental studies,[2,3] several clinical studies demonstrated that the endotracheal administration of polymyxin B or gentamicin prevented ventilator-associated pneumonia (VAP).[4–7] However, when it was prophylactically administered beyond 1 week, the incidence of VAP caused by polymyxin B-resistant pathogens increased,[8] leading the critical care community to abandon this administration method. During the 1990s, an enhanced understanding of conditions required for reaching the deep lung during mechanical ventilation,[9] together with the development of new-generation nebulizers,[10–13] contributed to its reemergence. In 1998, a study performed in tracheostomized patients suggested that the

What We Already Know about This Topic

- In critically ill patients, nebulized antibiotics are increasingly used; however, the safety and efficacy of these are unknown

What This Article Tells Us That Is New

- A systematic review reports that the data are sparse; however, nebulization may be more effective in cases of resistant organisms and less nephrotoxic (if replacing nephrotoxic systemic agents) but may compromise mechanical ventilation especially in hypoxemic patients

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nebulization of aminoglycosides using a jet nebulizer, producing appropriate mass median aerodynamic diameter aerosol particles, was appropriate for treating ventilator-associated tracheobronchitis (VAT).[14] Between 2000 and 2010, experimental studies on pharmacokinetics/pharmacodynamics using ultrasonic or vibrating-mesh nebulizers in mechanically ventilated piglets[15–18] increased the understanding of several factors influencing nebulization performance, which renewed the interest for antibiotic nebulization.[19–23] Respiratory infections have also become more difficult to treat due to greater levels of host immunosuppression and an increasing prevalence of drug-resistant pathogens.[24,25] These factors make daily clinical practice highly challenging, with intensivists considering alternative treatment strategies, including nebulization. However, aerosol administration might lead to a potential increased risk of severe adverse events, such as cardiorespiratory or nephrotoxicity.[23,26] Given this background, our main aim was to determine the efficacy and safety of this widely extended but yet unstandardized practice by performing a systematic review and meta-analysis of the existing literature. Recent reports describe the complexity and variability of administration practices,[27] evidencing the differences in management for VAT and VAP. Our hypothesis was that nebulized antibiotics are safe and effective for therapy of nosocomial respiratory infections in invasively mechanical ventilation adults.

Materials and Methods

This report describes the results of the systematic review and meta-analyses under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[28] A list of clinical questions under the PICO framework (Population-Intervention-Comparison-Outcome) format was created (table 1). The selected population was adult critically ill patients, receiving support with invasive mechanical ventilation, defined as ventilatory support through a nasotracheal tube, orotracheal tube, or tracheostomy. Noninvasive mechanical ventilation or other respiratory support devices such as high-flow nasal therapy were not considered in our study. The respiratory infections considered were VAT, VAP, or severe hospital-acquired pneumonia. Patients who were colonized, with colonization defined as the presence of purulent tracheal secretions without infectious signs and radiologic infiltrate, were excluded from our analyses. The susceptibility pattern of the pathogens was simplified as susceptible or resistant, the latter including bacteria with any type of resistance criteria (multidrug-, extensively drug-, or pandrug-resistant bacteria) defined by the Centers for Disease Control and Prevention (Atlanta, Georgia).[29] Nebulization of the antibiotic had to be performed with any device generating particles sufficiently small to reach the lung parenchyma (jet, ultrasonic, or vibrating-mesh nebulizers).

Two different strategies for the administration of nebulized antibiotics were considered clinically relevant for the treatment of VAP:

1. Adjunctive strategy: nebulized colistin or aminoglycosides administered to patients already receiving IV colistin or aminoglycosides, added to standard first-line IV antibiotics (in comparison to patients also receiving the same IV therapy, but no nebulized antibiotics).
2. Substitution strategy: nebulized colistin or aminoglycosides administered to patients not receiving IV colistin or aminoglycosides, but only standard first-line IV antibiotics (in comparison to patients receiving IV colistin or aminoglycosides—not nebulized—added to the first-line IV antibiotics).

In agreement with the current trends of personalized medicine,[30] we postulated that similar interventions (nebulization of antibiotics) might have divergent effects in different subsets, justifying the formulation of multiple PICO questions with predetermined outcomes. Therefore, the evaluated safety and efficacy predefined outcomes (table 2) were determined as enclosed: (1) adverse events (nephrotoxicity, neurotoxicity and cardiorespiratory complications); (2) emergence of resistance and superinfection; (3) clinical resolution and mortality; and (4) length of intensive care unit stay and mechanical ventilation.

Efficacy outcomes were evaluated according to both the susceptibility pattern of the pathogen and the administration's strategy. None of the safety outcomes was considered to be possibly influenced by the susceptibility pattern of the pathogen; therefore, this factor was not taken into consideration in their analysis. Evaluation of systemic toxicity was performed according to the administration strategy for better discrimination of their impact. Occurrence of cardiorespiratory complications was considered not to be influenced by the specified administration strategies, therefore this factor was not taken into consideration in its analysis. The effect of nebulized antiinfective agents against viral and fungal infections was also assessed.

Information Sources

A global search strategy was systematically performed in three different databases: MEDLINE database through the PubMed search engine, EMBASE, and the Cochrane Library Database. Search terms are detailed in appendix 1. No restrictions of study design, time, or language were imposed. The first search was performed in June 2014, and it was repeated

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Table 1. Population-Intervention-Comparison-Outcome Framework

Population	Intervention	Comparator	Outcome
Bacterial respiratory infections			
Regarding VAT			
MV patients with VAT	Addition of nebulized antibiotics to their conventional IV antibiotic therapy	Conventional IV antibiotic therapy	Improvement of clinical outcome*
MV patients with VAT	Treatment with nebulized antibiotics (alone, no IV therapy)	Conventional IV antibiotic therapy	Improvement of clinical outcome*
Regarding HAP or VAP			
Resistant pathogens			
MV patients with VAP caused by resistant pathogens	Adjunctive strategy: addition of nebulized colistin or aminoglycosides to IV colistin or aminoglycosides plus standard first-line IV antibiotics	IV colistin or aminoglycosides plus the standard first-line IV antibiotics	Improvement of clinical outcome*
MV patients with VAP caused by resistant pathogens	Substitution strategy: nebulized colistin or aminoglycosides plus standard first-line IV antibiotics	IV colistin or aminoglycosides plus the standard first-line IV antibiotics	Improvement of clinical outcome*
Susceptible pathogens			
MV patients with VAP caused by susceptible pathogens	Adjunctive strategy: addition of nebulized colistin or aminoglycosides to IV colistin or aminoglycosides plus standard first-line IV antibiotics	IV colistin or aminoglycosides plus the standard first-line IV antibiotics	Improvement of clinical outcome*
MV patients with VAP caused by susceptible pathogens	Substitution strategy: nebulized colistin or aminoglycosides plus standard first-line IV antibiotics	IV colistin or aminoglycosides plus the standard first-line IV antibiotics	Improvement of clinical outcome*
Viral respiratory infections			
MV patients with viral respiratory infection	Nebulized antivirals	Conventional antiviral therapy	Improvement of clinical outcome*
Fungal respiratory infections			
MV patients with fungal respiratory infection (including *Pneumocystis jirovecii*)	Nebulized antifungals	Conventional antifungal therapy	Improvement of clinical outcome*

* Defined by the efficacy outcomes (table 2).

HAP = hospital-acquired pneumonia; IV = intravenous; MV = mechanically ventilated; VAP = ventilator-associated pneumonia; VAT = ventilator-associated tracheobronchitis.

in March 2015 and July 2016. No other eligible studies were identified by evaluating previous reviews, abstracts from meetings or under suggestion of the panel of experts.

Statistical Analysis

The eligibility criteria, study selection, data collection, and risk of bias assessment are described in detail in the appendix 2. The main characteristics and quality of the studies are summarized in detail in appendix 3. Analysis of all outcomes was performed according to the design of the study, being either randomized controlled trials (RCTs) or observational studies, and their results are also presented accordingly. As the majority of the included studies had a small sample size, a pooled evaluation of all studies was also performed for each outcome, in order to detect a potential presence of clinically significant trends. This approach was considered acceptable due to the lack of large-scale data.

All statistical analyses were performed using Review Manager (RevMan) version 5.3. (Nordic Cochrane Centre, Cochrane Collaboration, Denmark, 2014). The summary statistic measures used for the evaluation of binary outcomes were the risk ratio for RCTs and the odds ratio (OR) for the observational study and pooled evaluation. Risk difference was also used where necessary. The summary statistic measure used for the evaluation of continuous outcomes was the mean difference. All statistical measures were calculated with 95% CI. Random-effects meta-analysis using the Mantel–Haenszel model approach was chosen to obtain pooled study results. The Higgins I^2 test was predefined to quantify heterogeneity ($I^2 \leq 25\%$ for low, $25\% < I^2 < 50\%$ for moderate, and $I^2 \geq 50\%$ for high). Metaregression was not performed given the low number of studies included in the analysis. Assessment of publication bias using a funnel plot[31,32] was planned when considered meaningful (*i.e.*, at least 10 studies available).

Results

Study Selection

A total of 1,435 studies were identified: 898 studies in the MEDLINE database (PubMed), 327 in EMBASE, and 210 in the Cochrane Library Database. After assessment for inclusion, manually adjusting for duplicates, and revision of the articles, 11 studies were finally included in the meta-analysis. The PRISMA flow diagram[33] of the studies' selection is presented in figure 1.

No RCTs or observational studies were found to evaluate the efficacy and/or safety of nebulized antivirals or antifungals for the treatment of respiratory viral and fungal

Table 2. Predefined Evaluated Outcomes

Efficacy outcomes
Clinical resolution (yes/no; after 8 days of treatment) if one or more of the following occurred:
Removal of vital support (ventilation, vasopressors)
Improvement of daily organ failure score
Improvement of Pao_2/Fio_2 ratio
Inflammatory parameters decrease (C-reactive protein and/or procalcitonin)
30-day mortality (yes/no)
Duration of MV, days
Duration of ICU stay, days
Occurrence of superinfection (yes/no)
Emergence of resistant strains (yes/no)
Safety outcomes
Systemic toxicity (yes/no; especially nephrotoxicity)
Cardiorespiratory complications (yes/no; including hypoxemia; cough, bronchoconstriction, lung injury or acute respiratory distress syndrome; problems with the nebulization system such as obstruction of the expiratory filter; arrhythmias, cardiorespiratory arrest)

Fio_2 = fraction of inspired oxygen; ICU = intensive care unit; MV = mechanically ventilated; Pao_2 = arterial oxygen partial pressure.

infections in mechanically ventilated patients. Characteristics and results on efficacy and safety of their use are detailed in appendixes A4 and A5.

Six RCTs and five observational studies assessed the efficacy and safety of nebulized antibiotics for the treatment of bacterial infections, involving 826 patients. Five of the studies had a small sample size (fewer than 50 patients). The largest study was an observational study involving 208 patients. Five studies administered aminoglycosides, four administered colistin, and two administered both. Four studies used jet nebulizers, three studies used vibrating-mesh nebulizers, and three studies used different devices indistinctively (jet and ultrasonic nebulizers were used in two studies; the other study used jet and vibrating-mesh nebulizers). One of the studies did not detail the type of nebulizer used, but they did specify having used a device generating optimal-size droplets with diameter between 1 and 5 μm. The risk of bias of the included studies was globally low. The main characteristics of the included studies and the administration strategy to which they belong are described in table 3. A summary of their risk of bias of the included RCT is detailed in figure 2.

Treatment of VAT. Only two RCT by Palmer *et al.*[34] and Palmer and Smaldone[35] involving 85 patients evaluated the efficacy and safety of nebulized antibiotics. Both studies assessed efficacy, but neither of them did so in our predefined terms (both considered reduction of the Clinical Pulmonary Infection Score as a sign of clinical resolution). Meta-analysis of the results showed a greater reduction of the Clinical Pulmonary Infection Score, with a high heterogeneity (mean difference, −3.11 points; 95% CI from −6.18 to −0.04; I^2 = 90%), and significantly less emergence of resistant strains in patients receiving nebulized antibiotics (70 patients; risk ratio = 0.18; 95% CI, 0.05 to 0.64; I^2 = 0%). The forest plot is shown in figure 3. No significant differences were found in mortality and duration of mechanical ventilation. No significant difference in systemic toxicity (nephrotoxicity, indirectly measured by serum creatinine concentration) was found.

Efficacy of Nebulized Antibiotics for the Treatment of VAP Caused by Resistant Pathogens. Six studies were included in the analysis of the efficacy of nebulized antibiotics for the treatment of VAP caused by resistant pathogens.

Adjunctive Administration Strategy. Four studies administered nebulized antibiotics under this strategy; one RCT, Niederman *et al.*[36] (administering nebulized amikacin in patients who could already be receiving IV aminoglycosides), and three observational studies: Kofteridis *et al.*,[37] Doshi *et al.*,[38] and Tumbarello *et al.*[39] Efficacy was assessed by all of the included studies.

No significant difference in clinical resolution was evidenced in the RCT (48 patients; OR, 1.30; 95% CI, 0.22 to 7.55), but it was significantly higher in patients receiving nebulized antibiotics in the meta-analysis of the observational study included (389 patients; OR, 0.51; 95% CI, 0.34 to 0.77; I^2 = 0%). Pooled meta-analysis of all studies (437 patients) also showed significantly better clinical resolution rates in patients receiving nebulized antibiotics (OR, 0.53; 95% CI, 0.36 to 0.80; I^2 = 0%). The forest plot, stratified according to the study design, is shown in figure 4.

Two observational studies[37,38] reported VAP-related mortality, which was found to decrease in patients receiving nebulized antibiotics (181 patients; OR, 0.5; 95% CI, 0.26 to 0.96; I^2 = 0%). All-cause mortality was reported by two observational studies[37,39] with no difference in the mortality rates (294 patients; OR, 0.68; 95% CI, 0.33 to 1.37; I^2 = 46%), with moderate heterogeneity. The forest plot for mortality is shown in figure 5.

A significant decrease in the length of mechanical ventilation support to patients receiving nebulized antibiotics was also evidenced (303 patients; 3.72 days fewer; 95% CI from −5.86 to −1.59 days; I^2 = 0%) in the meta-analysis of the two observational studies that assessed it.[38,39] The forest plot is shown in figure 6. No other significant differences were found in the rest of the efficacy outcomes assessed (duration of intensive care unit stay and development of superinfection).

Substitution Administration Strategy. One observational study administered nebulized antibiotics under this strategy: Ghannam *et al.*,[40] involving 32 patients. Higher rates of clinical resolution in patients receiving nebulized antibiotics were reported (OR, 9.53; 95% CI, 1.85 to 49.2). Duration of mechanical ventilation and intensive care unit stay were similar, independently of the use of nebulized agents.

Efficacy of Nebulized Antibiotics for the Treatment of VAP Caused by Susceptible Pathogens. One RCT, Lu *et al.*,[26] was analyzed. In this trial, both aminoglycosides and ceftazidime were administered either by nebulization or IV, with no other IV antibiotics being administered concomitantly, which was considered to be equivalent to the substitution administration strategy.

No significant differences were apparent for clinical resolution, mortality, duration of mechanical ventilation (median of 11 more days; P = 0.13), intensive care unit

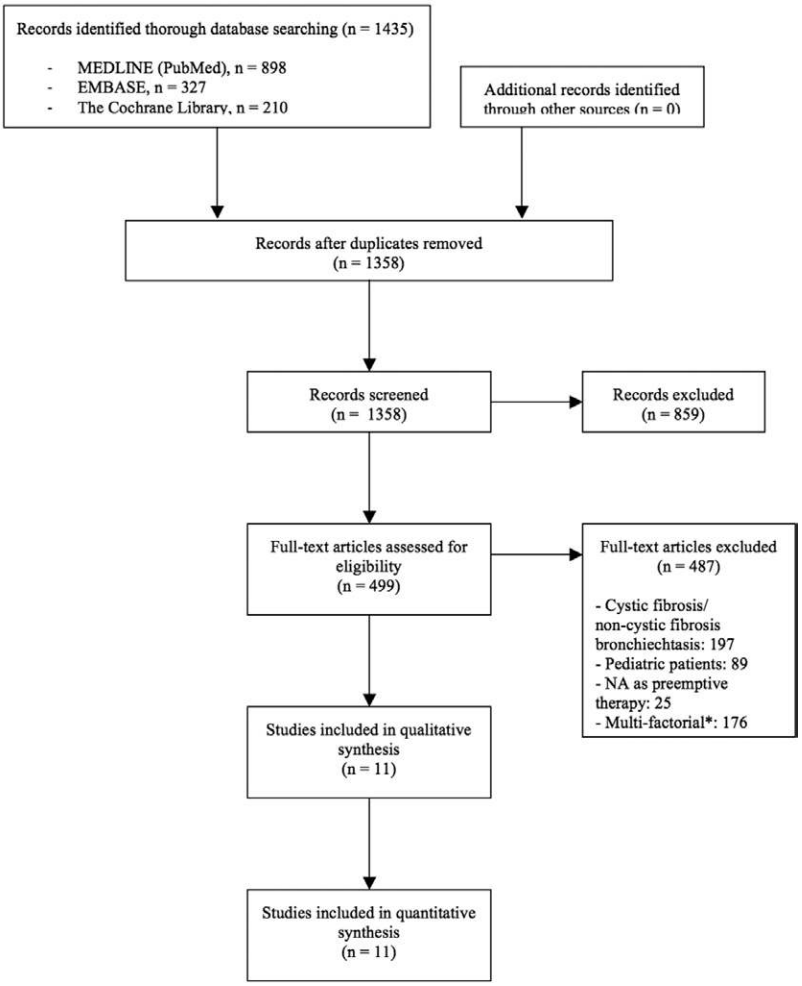

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the study selection. *Articles with one or more of the exclusion criteria detailed in appendix 2. NA = nebulized antibiotics.

stay (median of 9 more days; $P = 0.08$), and development of superinfection between the patients receiving nebulized antibiotics and the patients receiving systemic therapy. However, per-treatment emergence of resistant strains was considered to be potentially prevented by antibiotics nebulization, as new growth or persistence of infection was caused exclusively by susceptible strains in patients treated with nebulized antibiotics, while 50% of the strains became intermediate or resistant in the group of patients treated systemically.

Safety of Nebulized Antibiotics for the Treatment of VAP. Three additional studies were included in the meta-analysis for safety: two RCT, Hallal *et al.*[41] and Rattanaumpawan *et al.*,[42] and one observational study, Arnold *et al.*[43]

Evaluation of Systemic Toxicity of Nebulized Antibiotics Administered according to the Adjunctive Strategy. Two types of systemic toxicity were reported: nephrotoxicity[36,37,39,42,43] and neurotoxicity.[37,42] No significant difference was evidenced in the occurrence of nephrotoxicity (fig. 7A) or neurotoxicity between patients receiving nebulized antibiotics and patients without intratracheal therapy.

Evaluation of Systemic Toxicity of Nebulized Antibiotics Administered according to the Substitution Strategy. Two studies reported nephrotoxicity events.[40,41] The RCT[40] did not show any difference in the risk of nephrotoxicity (risk difference, −0.40; 95% CI, −0.85 to 0.05), but the analysis of the observational study[41] did show less occurrence of nephrotoxicity when nebulized antibiotics were administered (risk difference, −0.31; 95% CI, −0.55 to −0.08). The pooled analysis of both (involving 42 patients) also showed significantly less occurrence of nephrotoxicity in patients receiving treatment with nebulized antibiotics (risk difference, −0.33; 95% CI, −0.54 to −0.12; $I^2 = 0\%$; fig. 7B).

All studies reporting data on cardiorespiratory complications were analyzed together, according to the study design, but independently of the administration strategy. The meta-analysis of two observational studies[37,43] showed no differences in the occurrence of cardiorespiratory adverse events, with no heterogeneity (risk difference, 0.00; 95% CI from −0.04 to 0.04; $I^2 = 0\%$). Meta-analysis of the four RCTs included[26,36,41,42] showed

Table 3. Main Characteristics and Administration Strategy of the Included Studies

Study and Year	Country	Characteristics	No. of Patients	Infection	Device	Administration Strategy
Randomized controlled trials						
Palmer *et al*. 2008[34]	USA	Phase III study, double-blinded, placebo-controlled, single center	43	VAT, mixed susceptibility	Jet nebulizer	
Palmer and Smaldone 2014[35]	USA	Phase III study, double-blinded, placebo-controlled, single center	47	VAT, mixed susceptibility	Jet nebulizer	
Niederman *et al*. 2012[36]	USA, France, Spain	Phase II study, double-blinded, placebo-controlled, parallel group, multicentric	67	VAP, resistant pathogens	Vibrating-mesh nebulizer (PDDS Clinical®, Nektar Therapeutics, USA)	Adjunctive strategy
Lu *et al*. 2011[26]	France	Phase II study, single center	46	VAP, susceptible pathogens	Vibrating-mesh nebulizer	Substitution strategy
Hallal *et al*. 2007[41]	USA	Phase III study, double-blinded, pilot study, single center	10	VAP†	Jet nebulizer	Substitution strategy*
Rattanaumpawan *et al*. 2010[42]	Thailand	Phase III study, open label, single center	102	VAP†	Jet and ultrasonic nebulizers	Adjunctive strategy*
Observational trials						
Ghannam *et al*. 2009[40]	USA	Matched case–control study, retrospective, single center	32	VAP, resistant pathogens	Jet nebulizer	Substitution strategy
Kofteridis *et al*. 2010[37]	Greece	Matched case–control study (ratio 1:1), retrospective, single center	86	VAP, resistant pathogens	Vibrating-mesh nebulizer (information obtained after contacting the author)	Adjunctive strategy
Doshi *et al*. 2013[38]	USA	Cohort analysis, retrospective, multicentric	95	VAP, resistant pathogens	Jet nebulizer (in two centers), vibrating-mesh nebulizer (in one center)	Adjunctive strategy
Tumbarello *et al*. 2013[39]	Italy	Matched case–control study (ratio 1:1), retrospective, single center	208	VAP, resistant pathogens	Jet and ultrasonic nebulizers indistinctively	Adjunctive strategy
Arnold *et al*. 2012[43]	USA	Cohort study, retrospective, single center	90	VAP†	Not defined but they specified using a nebulizer generating optimal droplet sizes (1–5 μm)	Adjunctive strategy*

*Studies included only in the evaluation of adverse effects. †The susceptibility pattern of the pathogens is not specified as they are not relevant for the analysis of their adverse effects.

PDDS = pulmonary drug delivery system; VAP = ventilator-associated pneumonia; VAT = ventilator-associated tracheobronchitis.

a 9% increase in incidence of respiratory complications in patients receiving nebulized antibiotics (risk difference, 0.09; 95% CI from −0.01 to 0.18; I^2 = 52%), but high heterogeneity between studies was observed (fig. 8). The combined analysis of all studies was similar but with higher heterogeneity (risk difference, 0.04; 95% CI, from −0.02 to 0.11; I^2 = 75%). The study that registered more cardiorespiratory complications[26] detailed that no bronchospasms were evidenced. Three patients with an initial severe hypoxemia ($Pa_{O_2}/F_{I_{O_2}}$ ratio of less than 200) suffered a 25% decrease in their Pa_{O_2} after the nebulization. Three other complications were related to obstruction of the expiratory filter, detected in two of the cases by an increase in the peak airway pressure. The other patient suffered a secondary cardiac arrest. Finally, one patient had to be excluded in an early phase of the study due to severe hypoxemia secondary to alveolar derecruitment induced by the nebulization.

Discussion

Our study provides new information on the efficacy and safety of antibiotic nebulization in mechanically ventilated patients. This is important because despite its administration being increasingly common practice worldwide,[27] our study demonstrates limited available evidence for its use.

According to our analysis, in terms of efficacy, the administration of nebulized antibiotics might increase the likelihood of clinical resolution (particularly in VAP caused by resistant pathogens), but this is not consistently translated into a significant improvement in mortality or mechanical ventilation duration. Antibiotic nebulization also appears to have a protective effect against the emergence of resistant strains when used for the treatment of VAT or even VAP caused by susceptible pathogens. This contrasts with previous studies, reported before 1985,[1–6] probably due to technical limitations in the delivery of the drug and the prolonged administration periods at that time. In terms of safety, our

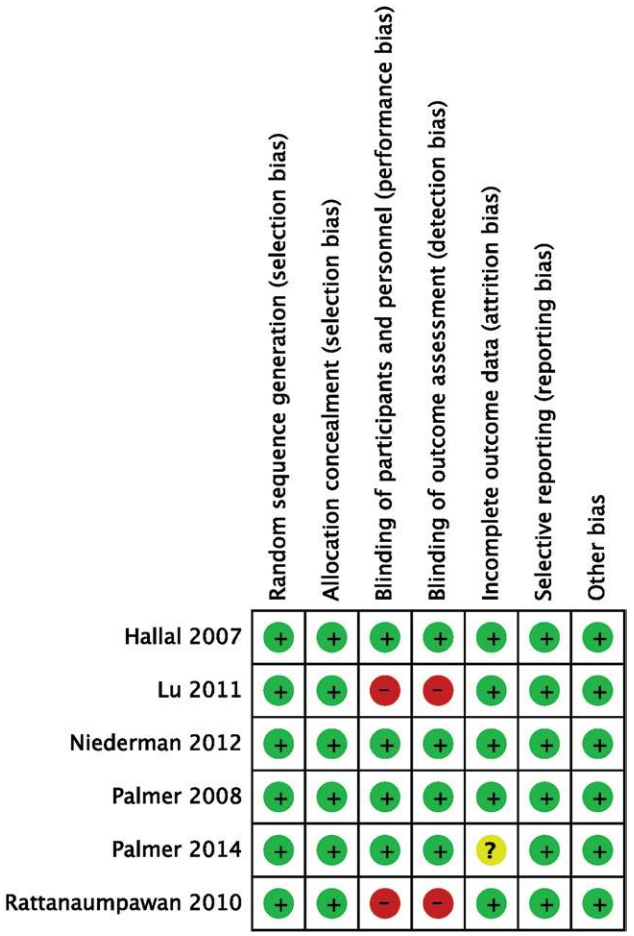

Fig. 2. Risk of bias summary for the randomized clinical trials.

analysis reveals that the risk of nephrotoxicity might be lower when the antibiotics are nebulized instead of administered IV. In July 2016, a new systematic search of the literature was performed, identifying one new RCT by Abdellatif *et al.*,[44] performing colistin nebulization under a strategy equivalent to the substitution strategy. Due to limitations in its design, it did not meet our eligibility criteria for its efficacy evaluation, but we evaluated their data regarding safety (nephrotoxicity), which was consistent with the results of our analysis (fig. 7B), suggesting less occurrence of nephrotoxicity when nebulized antibiotics are administered (for both RCT included: Risk difference, −0.23; 95% CI, −0.37 to −0.10; I^2 = 0%; for pooled analysis of all: Risk difference, −0.25; 95% CI, −0.37 to −0.14). Finally, our study also reveals a 9% increase in risk of respiratory complications, especially when they are administered to severely hypoxemic patients, such as severe acute respiratory distress syndrome patients.

The main limitations of our study are its small sample size and the fact that only half of the included studies were RCTs. Due to the small sample size of the studies, no subgroup analyses could be performed, such as a comparison of the efficacy among the three different types of devices used or between the different drugs administered. As the number of RCTs included in the meta-analysis was also very small, a meta-regression could not be performed. Two of the RCTs were not blinded and for the analysis of one of the PICO questions (regarding treatment of VAT), all the included studies were from the same investigator, which introduces a possibility of bias on the results of that specific analysis. However, this is not only a limitation, but an interesting denouement, as it evidences the lack of RCTs in this field.[32,45]

Another limitation is the fact that all of the included studies in our meta-analysis were published between 2007 and 2015. Clinical studies published before 2014 may have used infratherapeutic doses of the drugs, as the recommended doses of colistin and aminoglycosides have markedly increased the last years based on pharmacokinetics/pharmacodynamics studies.[23,46,47] Also, continuous renal replacement therapy might be a confounder, requiring a substantial modification in the administered doses.[48,49]

It is also likely that some overlap is present between VAT and VAP in the analyzed studies, given the difficulty in their diagnosis.[50] Moreover, for the analysis of one PICO question (regarding VAT), the Clinical Pulmonary Infection Score used as an outcome for clinical resolution in the included studies was not a predefined outcome of our analysis. However, as the Pao_2/Fio_2 is a predictor of mortality and clinical resolution in VAP,[51] and as both entities—VAP and VAT—are closely linked and overlapping, we considered that a decrease in Clinical Pulmonary Infection Score in patients treated for VAT was fulfilling the third criteria of our predefined terms of clinical resolution (table 2) and included these studies in the analysis. Another limitation was that some of the outcomes were surrogated, and some of the included studies had heterogeneous populations, with potentially higher risk of mortality and/or morbidities than the average population included (*e.g.*, oncologic patients, delayed targeted antibiotic therapy). Finally, our study protocol was not previously published or registered in a platform like PROSPERO (International Prospective Register of Systematic

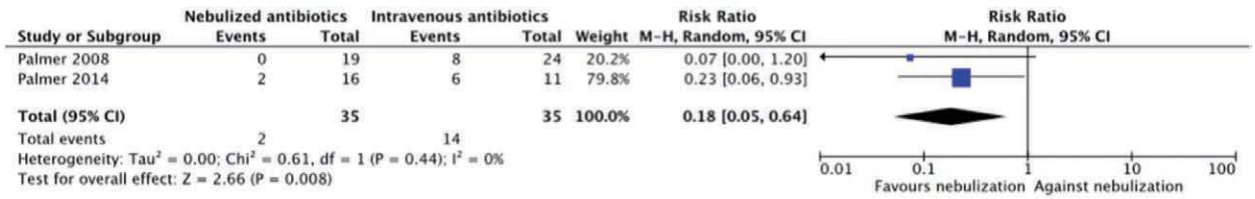

Fig. 3. Emergence of resistant strains in patients treated with nebulized antibiotics for ventilator-associated tracheobronchitis. I = heterogeneity index; M–H = Mantel–Haenszel.

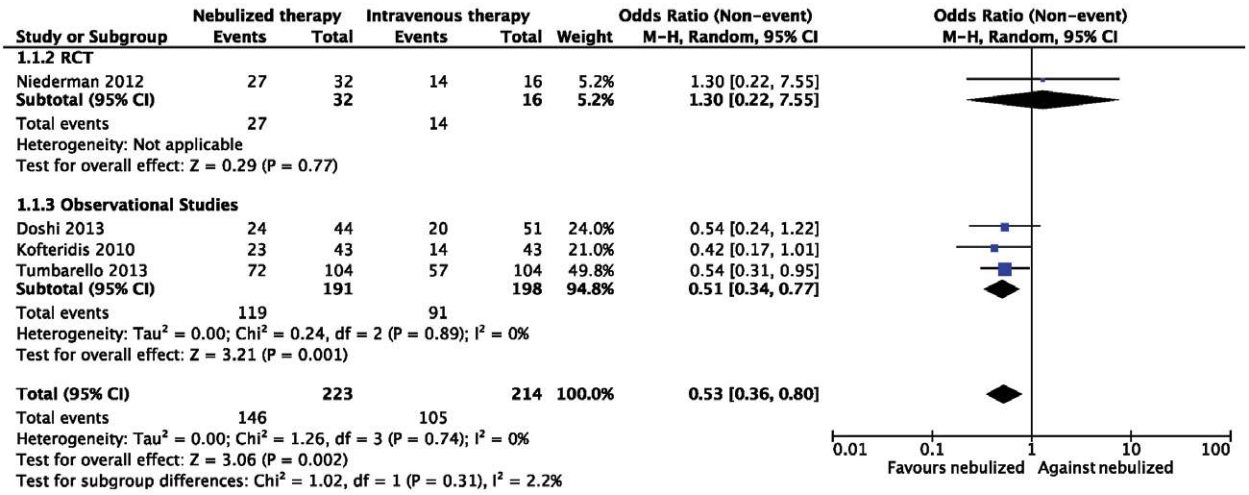

Fig. 4. Clinical resolution of patients treated with nebulized antibiotics for ventilator-associated tracheobronchitis caused by resistant pathogens—adjunctive administration strategy. I = heterogeneity index; M–H = Mantel–Haenszel; RCT = randomized controlled trial.

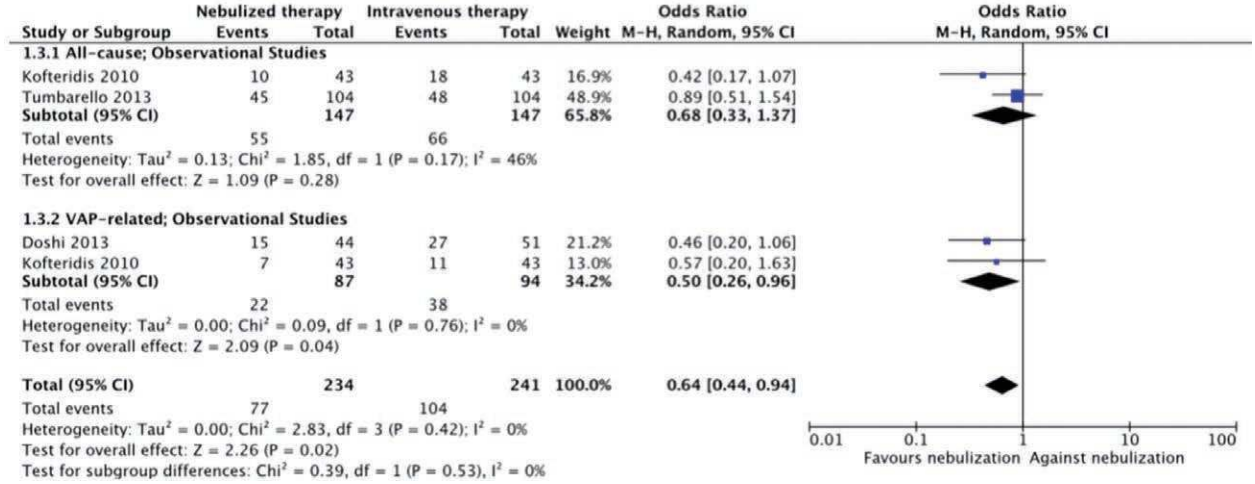

Fig. 5. Mortality of patients treated with nebulized antibiotics for ventilator-associated pneumonia (VAP) caused by resistant pathogens—adjunctive administration strategy. I = heterogeneity index; M–H = Mantel–Haenszel.

Reviews, https://www.crd.york.ac.uk/PROSPERO/). However, all clinically relevant questions were identified and defined *a priori*, using the PICO format, and the initial protocol was never modified. Meta-analyses may result in type I errors owing to an increase of random error when sparse data are analyzed.[52]

The main strength of our meta-analysis is our strict inclusion of studies. The nebulization devices used in the included studies were restricted to the ones providing sufficiently small particles to reach the lung parenchyma (jet, ultrasonic, and vibrating-mesh nebulizers). Similarly, the population of the included studies was also strictly selected (*e.g.*, only studies involving invasively mechanically ventilated patients were included, studies with colonized-but-not-infected patients were also excluded). Our strict selection limited the study size as a drawback, but also makes our results more robust and generalizable to the study population, in contrast with previous reviews[53–57] that had highly heterogeneous results and a potential overestimation of the effects. This is the reason why VAT and VAP were analyzed separately, contrasting with recent systematic review and meta-analysis.[53–57] Our study is also the first to analyze different administration strategies (adjunctive and substitution) separately. Finally, our analysis adds value regarding important information on safety aspects such as respiratory or nephrotoxicity adverse events.

In conclusion, our study shows that very limited evidence exists on the use of nebulized antibiotics in mechanically ventilated patients. Improvement in clinical resolution does not translate to improvements in other significant outcomes, which should be enclosed in further studies as predetermined outcomes. Patients with resistant pathogen-related infections might potentially derive greater benefit from nebulized antibiotic therapy. Its use, without the concomitant IV administration of the drug, may reduce nephrotoxicity associated with systemic colistin or aminoglycosides. Administration of

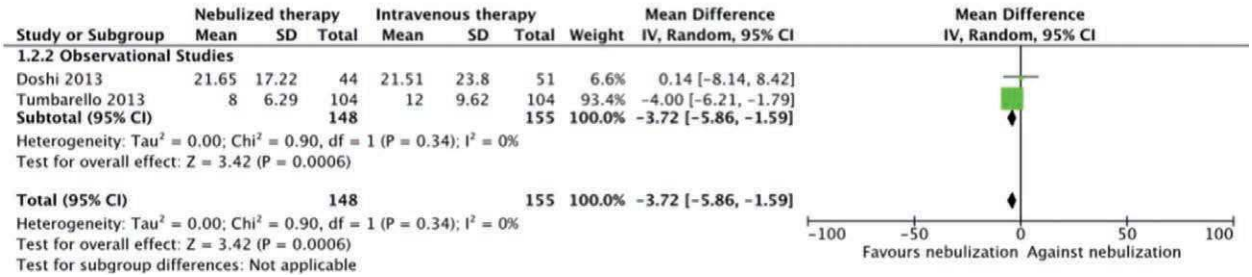

Fig. 6. Mechanical ventilation duration in patients treated with nebulized antibiotics for ventilator-associated pneumonia caused by resistant pathogens—adjunctive administration strategy. I = heterogeneity index.

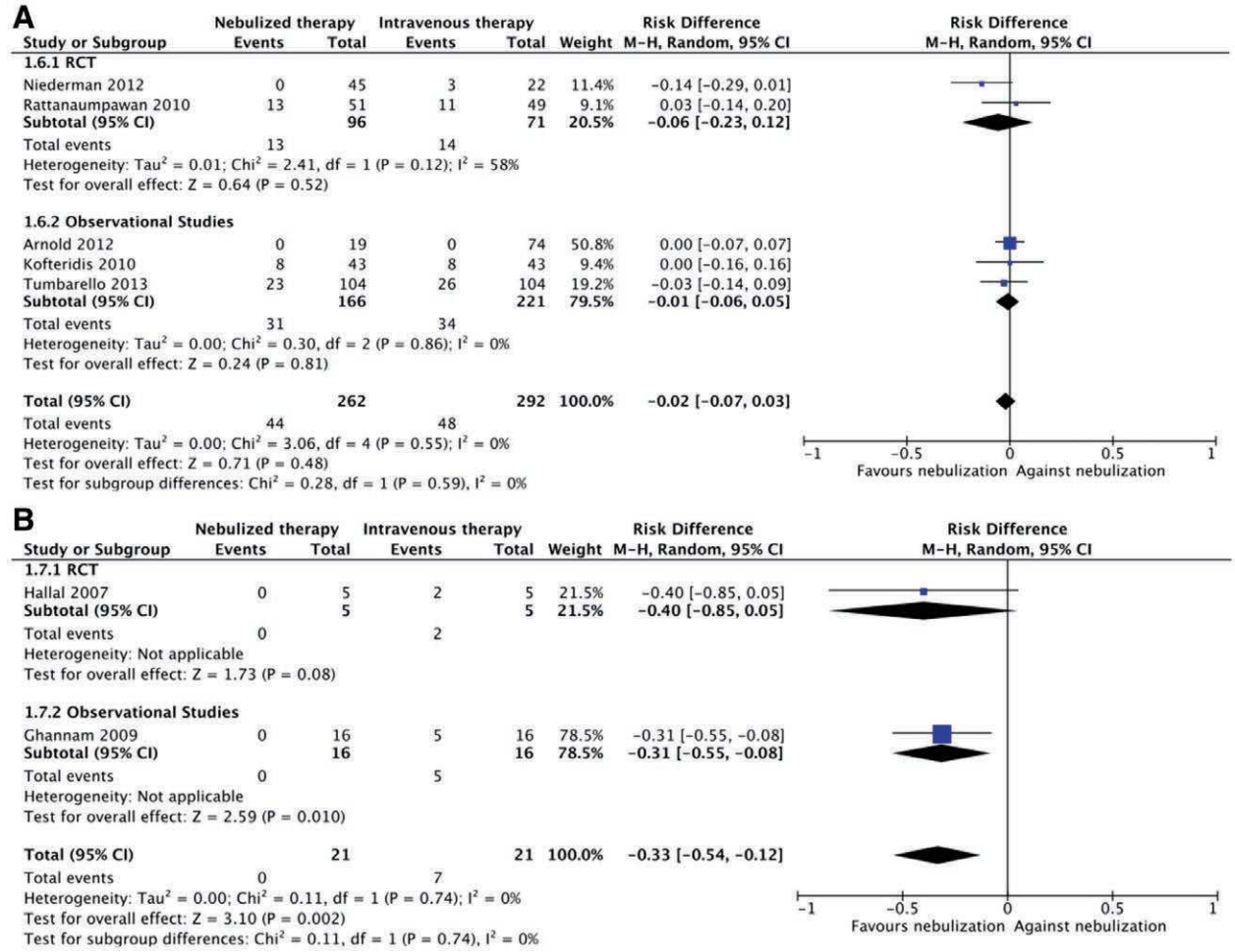

Fig. 7. Nephrotoxicity in patients treated with nebulized antibiotics for ventilator-associated pneumonia—(*A*) adjunctive administration strategy and (*B*) substitution administration strategy. I = heterogeneity index; M–H = Mantel–Haenszel; RCT = randomized controlled trial.

nebulized antibiotics seems to be associated with a higher risk of respiratory complications, particularly in severely hypoxemic patients. Therefore, future studies should stratify patients based on the degree of hypoxemia. Our findings evidence that in an era of emerging Gram-negative–resistant organisms, further research with larger RCT including more homogeneous populations, standardized drug delivery, and clinically relevant predetermined outcomes is an urgent and unmet clinical need.

Acknowledgments

The results of the systematic review and meta-analysis will be translated into recommendations following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system as part of an Institutional Position Paper convened by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID, Basel, Switzerland) Study Group for Infections in Critically Ill Patients (Basel, Switzerland) under the support of the ESCMID and in collaboration with the Iberoamerican Cochrane Center in Barcelona, Spain.

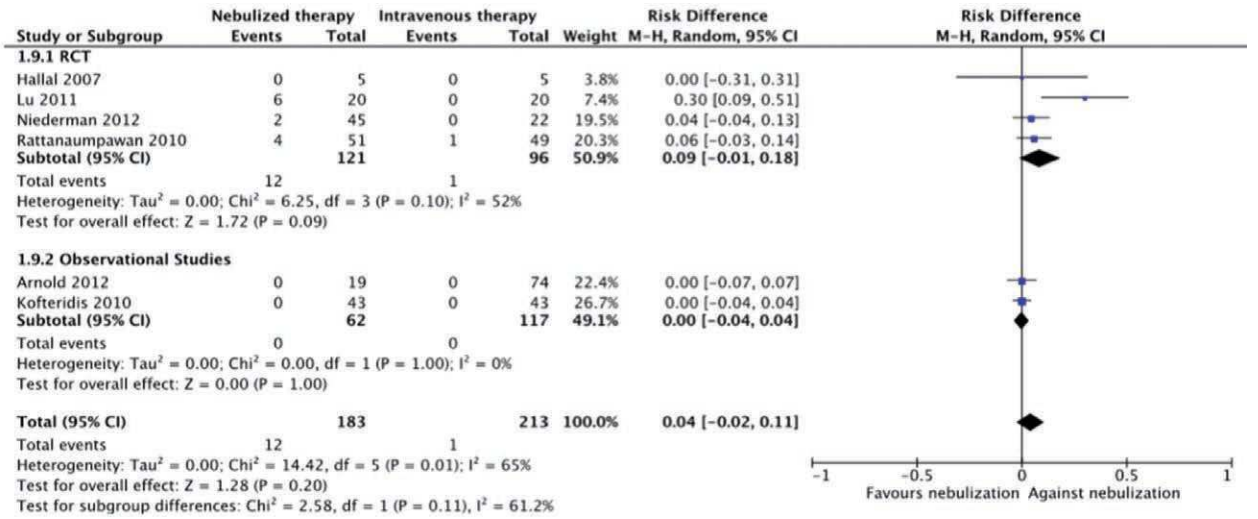

Fig. 8. Forest plot on respiratory complications due to the administration of nebulized antibiotics. I = heterogeneity index; M–H = Mantel–Haenszel; RCT = randomized controlled trial.

The authors acknowledge Pablo Alonso, M.D., Ph.D., Ivan Solà, M.D., and Sandra Pequeño, M.D., of the Iberoamerican Cochrane Center, for their assessment on methodology. Ivan Solà, M.D., also acted as an independent reviewer for the inclusion of studies, and Sandra Pequeño, M.D., acted as an independent reviewer for the bias risk assessment.

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Competing Interests

Dr. Rello received research grants and consulting fees from Bayer (Leverkusen, Germany) and Genentech (San Francisco, California). Dr. Roberts received consulting fees from Infectopharm (Heppenheim, Germany). Dr. Chastre received honoraria for lecture or advisory board from Bayer, Pfizer (New York, New York), Basilea (Basel, Switzerland), Astra-Zeneca (London, United Kingdom), Cubist-MSD (Lexington, Massachusetts), MSD (Kenilworth, New Jersey), Kenta-Aridis (San Jose, California), and Medimmune (Gaithersburg, Maryland). Dr. Palmer received research grants from Nektar Therapeutics (San Francisco, California) and consulting fees from Bayer and holds patents for the endobronchial delivery of antibiotics in ventilated patients through the Research Foundation of Stony Brook (Stony Brook, New York) and participated in the 2016 Infectious Diseases Society of America/American Thoracic Society Guidelines Committee for ventilator-associated pneumonia/hospital-acquired pneumonia. Dr. Luyt received honoraria for lecture or advisory board from Bayer, MSD (Kenilworth, New Jersey), ThermoFisher Brahms (Waltham, Massachusetts), and Astellas (Tokyo, Japan). The other authors declare no competing interests.

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Address correspondence to Dr. Rello: Pg Vall d'Hebron, 129–AMI 14. E08035 Barcelona, Spain. jrello@crips.es. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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Appendix 1: List of Terms of the Search Strategy

#1	"Aerosols" [Mesh]
#2	"Nebulizers and Vaporizers" [Mesh]
#3	nebul*[tiab]
#4	aerosol*[tiab]
#5	vaporiz*[tiab]
#6	inhal*[tiab]
#7	pulmonary delivery*[tiab]
#8	atomiz*[tiab]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	"Anti-Bacterial Agents" [Mesh]
#11	antimicrobial*[tiab]
#12	antibacterial*[tiab]
#13	anti-bacterial*[tiab]
#14	antibiotic*[tiab]
#15	bacterio*[tiab]
#16	antiviral*[tiab]
#17	antifungal*[tiab]
#18	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	"Pneumonia, Ventilator-Associated" [Mesh]
#20	ventilator associated pneumonia*[tiab]
#21	vap[tiab]
#22	nosocomial pneumonia*[tiab]
#23	Hospital-acquired pneumonia*[tiab]
#24	hap[tiab]
#25	respiratory tract*[tiab]
#26	ventilator associated tracheobronchitis*[tiab]
#27	vat[tiab]
#28	viral respiratory infection*[tiab]
#29	fungal respiratory infection*[tiab]
#30	ventilat*[tiab]
#31	intubat*[tiab]
#32	lung infect*[tiab]
#33	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34	#9 AND #18 AND #33
#35	colistin*[ti]
#36	polymyxin*[ti]
#37	amikacin*[ti]
#38	gentamicin*[ti]
#39	tobramycin*[ti]
#40	aminoglycoside*[ti]
#41	ciprofloxacin*[ti]
#42	ribavirin*[ti]
#43	zanamivir*[ti]
#44	oseltamivir*[ti]
#45	amphotericin*[ti]
#46	pentamidin*[ti]
#47	caspofungin*[ti]
#48	fluconazole*[ti]
#49	posaconazole*[ti]
#50	voriconazole*[ti]
#51	vancomycin*[ti]
#52	meropenem[ti]
#53	ertapenem[ti]
#54	imipenem*[ti]
#55	doripenem*[ti]
#56	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
#57	#18 OR #56
#58	#9 AND #33 AND #57
#59	#34 OR #58

Appendix 2: Appendix to "Materials and Methods"

Eligibility Criteria

Randomized controlled trials, observational studies, and case series evaluating efficacy and/or safety of nebulized antiinfective agents for the treatment of respiratory infections in invasively mechanically ventilated adult patients were eligible if the delivery of the drug was performed with devices generating particles smaller than 5 μm of diameter: jet nebulizers, ultrasonic nebulizers, or vibrating-mesh nebulizers.

Exclusion criteria included studies involving pediatric patients, patients without invasive mechanical ventilation support, patients diagnosed as being colonized but not infected, and patients with particular characteristics such as burn-injured patients or patients receiving support with renal replacement therapies and/or cardiopulmonary support with extracorporeal life support devices such as extracorporeal membrane oxygenation, due to the lack of knowledge on the impact these techniques might have in the technique being evaluated. Studies involving patients with cystic fibrosis or other non-cystic fibrosis were also excluded as they were considered to have particular characteristics deserving a separate evaluation. Studies reporting delivery with other devices, or other practices such as tracheal instillation (either manually or with a pneumatic pump), were rejected as they produce larger particles that may not sufficiently reach the lung parenchyma.

A list of efficacy and safety outcomes to be evaluated (table 2) was independently rated by all authors according to their potential clinical relevance or impact on answering the Population-Intervention-Comparison-Outcome questions. Outcomes were classified as being "nonimportant" (rated 1 to 3), "important" (4 to 6), or "critical" (7 to 9). Only critical outcomes (with a mean score equal to or more than 7) will be evaluated under the Grading of Recommendations Assessment, Development and Evaluation methodology.

Study Selection

Three authors (S.B., G.P., and C.S.-L.) independently assessed all the studies identified in the literature search by screening their titles and abstracts. Disagreements between reviewers were resolved by consensus. In case of disagreement, a fourth independent reviewer (I.S.) determined the eligibility. Authors of articles considered for rejection due to lack of information (*e.g.*, type of device used) were contacted to provide further details.

Data Collection Process

Full texts of the selected studies were obtained. A data sheet, based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions,[23] was developed for data extraction, which was performed by one author (C.S.-L.) and afterward checked by a second independent reviewer (S.P.). Authors of articles with relevant nonreported or unclear data were contacted to provide further information.

Data Items

For each included study, the following data were extracted: general information regarding the study design, inclusion/exclusion criteria, *etc*.; type of intervention performed (including the type of device for delivery); main and secondary outcomes evaluated and adverse events reported.

Risk of Bias Assessment

Risk of bias was assessed for every included study by one author (C.S.-L.) and afterward checked by a second independent reviewer (S.P.) from the Iberoamerican Cochrane Center, Barcelona, Spain. Assessment was performed based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[31]: bias regarding selection, performance, detection, attrition, and reporting was assessed for all randomized controlled trials. Bias risk was also assessed for observational studies under the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions,[31] evaluating selection and representativity of the cohorts, presence of confounding factors, and adequacy of both the outcomes and their following process.

Appendix 3: Main Characteristics and Quality of the Included Studies

Table A3.1. Studies Regarding the Use of Nebulized Antibiotics for the Treatment of Ventilator-associated Tracheobronchitis: Main Characteristics

Study and Year	Country	Characteristic	No. of Patients	Type of Nebulizer	Nebulized Drug and Dosage	IV Drugs
Randomized controlled trials						
Palmer *et al*. 2008[34]	United States	Double-blinded, placebo-controlled, single center	43 patients (19 receiving NA and 24 not receiving local therapy)	Jet nebulizer	Vancomycin and/or gentamicin Dose: vancomycin: 120 mg/8 h; gentamycin: 80 mg/8 h	According to clinician's decision. Targeted IV antibiotics at randomization: 17 patients receiving NA (89.5%), 15 patients not receiving local therapy (62.5%); no significant difference between both groups ($P = 0.08$)
Palmer and Smaldone 2014[35]	United States	Double-blinded, placebo-controlled, single center	47 patients (24 receiving NA and 23 not receiving local therapy)	Jet nebulizer	Vancomycin and/or gentamicin-sulfate or amikacin Dose: vancomycin: 120 mg/8 h; gentamycin sulfate: 80 mg/8 h; amikacin: 400 mg/8 h	According to clinician's decision. Targeted IV antibiotics at randomization: 16 patients receiving NA (66%), 14 patients not receiving local therapy (77%); no significant difference between both groups ($P = 0.51$)

IV = intravenous; NA = nebulized antibiotics.

Table A3.2. Studies Regarding the Use of Nebulized Antibiotics for the Treatment of VAT: Evaluated Outcomes and Quality

Study and Year	Efficacy Outcomes	Safety Outcomes	Global Bias Risk	Particularities
Randomized controlled trials				
Palmer *et al*. 2008[34]	Clinical resolution (reduction in CDC-NNIS and CPIS scores) Secondary: Leukocyte count (day 14) Systemic antibiotic use Weaning from MV Mortality Emergence of new resistant strains Bacterial growth in semiquantitative tracheal aspirate cultures	None evaluated	Low risk of bias	Most patients had criteria for VAP diagnose at randomization (five in the group receiving NA; six in the group not receiving local therapy). Authors were contacted to clarify this particularity. They considered to be treating only VAT due to the characteristics of the device used for nebulization
Palmer and Smaldone 2014[35]	Primary: Eradication of MDRO Secondary: Emergence of new resistant strains Clinical resolution (CPIS score, leukocyte count, fever, volume of secretions, *etc*.) Duration of MV Mortality	Nephrotoxicity	Low risk of bias (uncertain risk on losts in the monitoring: five patients in the placebo group were removed from the study by their family or were transferred to another facility)	There can be a quantity of patients included in the NA group having criteria for a VAP diagnose, as initial APACHE score was significantly higher in this group, in comparison to the APACHE score in the group receiving no local therapy. Authors were contacted to clarify this particularity. They considered to be treating only VAT due to the characteristics of the device used for nebulization

APACHE = Acute Physiology and Chronic Health Evaluation; CDC-NNIS = Centers for Disease Control-National Nosocomial Infections Surveillance; CPIS = Clinical Pulmonary Infections Score; MDRO = multiple drug-resistant organisms; MV = mechanical ventilation; NA = nebulized antibiotics; VAP = ventilator-associated pneumonia; VAT = ventilator-associated tracheobronchitis.

Table A3.3. Studies Regarding the Use of NA for the Treatment of Ventilator-associated Pneumonia Caused by Resistant Pathogens: Main Characteristics

Study and Year	Country	Characteristic	No. of Patients	Type of Nebulizer	Nebulized Drug and Dosage	IV Drugs
Randomized controlled trials						
Niederman *et al*. 2012[36]	United States, France, Spain	Double-blinded, placebo-controlled, parallel group, phase II study, multicentric	67 patients (45 receiving NA and 22 not receiving local therapy)	Vibrating-mesh nebulizer (PDDS Clinical®)	Amikacin with a drug-device combination (BAY41-6551) Two different dosage groups: 400 mg/12 h and 400 mg/24 h	IV aminoglycosides could be administered At day 1, the mean number of IV antibiotics per patient per day was 1.4 and 1.5 for the groups receiving NA and 1.6 for patients not receiving local therapy. No significant difference was observed between the groups ($P = 0.91$)
Observational trials						
Ghannam *et al*. 2009[40]	United States	Matched case–control study, retrospective, single center	32 patients	Jet nebulizer	Colistin or aminoglycosides Dose: colistin: 100 mg/8 h, tobramycin: 30 mg/12 h, amikacin: 100 mg/8 h, and gentamicin: 100 mg/8 h	IV colistin or aminoglycosides. All patients in both groups received other concomitant IV antibiotics (detailed in table 2 of the study). Both groups had also a similar duration of antibiotherapy: 11 days in the NA group (with a range from 3 to 26) and 10 days in the IV group (range from 2 to 21 days), $P > 0.8$
Kofteridis *et al*. 2010[37]	Greece	Matched case–control study (ratio 1:1), retrospective, single center	86 patients	Vibrating-mesh nebulizer (information obtained after contacting the author)	Colistin Dose: two MIU per day, divided into two doses	All patients received IV colistin (both cases and controls). Dose: nine MIU per day, divided in three doses No references to other IV antibiotics being administered
Doshi *et al*. 2013[38]	United States	Cohort analysis, retrospective, multicentric	95 patients	Jet nebulizer (in two centers), vibrating-mesh nebulizer (in one center)	Colistin Two different doses: 75 mg/12 h (in two centers) and 150 mg/12 h (in one center, via jet)	All patients received IV colistin (both cohorts). Doses detailed in table 1 of the study. Globally, if CrCl > 80 ml/min, two centers administered 5 mg · kg^{-1} · day^{-1} of colistin (divided in two doses). The other center administered the same dose if CrCl > 70 ml/min. Additional IV antibiotics administered in 43.2% of patients receiving adjunctive NA and in 64.7% of patients receiving IV therapy alone ($P = 0.036$)
Tumbarello *et al*. 2013[39]	Italy	Matched case–control study (ratio 1:1), retrospective, single center	208 patients	Jet and ultrasonic nebulizers indistinctively	CMS Dose: three MIU per day divided in three doses	All patients received IV colistin (both cases and controls) Dose: 100.000 IU · kg^{-1} · day^{-1}, every 8 to 12 h No references to other IV antibiotics being administered (but their patients were infected by colistin-only–susceptible pathogens)

CMS = colistimethate sodium; CrCl = creatinine clearance; IU = international units; IV = intravenous; MIU = millions of international units; NA = nebulized antibiotics; PDDS = Pulmonary Drug Delivery System.

Table A3.4. Studies Regarding the Use of NA for the Treatment of VAP Caused by Resistant Pathogens: Evaluated Outcomes and Quality

Study and Year	Efficacy Outcomes	Safety Outcomes	Global Bias Risk	Particularities
Randomized controlled trials				
Niederman *et al*. 2012[36]	Primary: PK/PD analysis in the tracheal aspirates Secondary: Clinical resolution (complete/partial resolution of pneumonia signs and symptoms, improvement/lack of progression of all abnormalities on chest x-ray and no additional IV antibiotics since completion of study treatment) Microbiologic eradication New infections/superinfecion rates	Nephrotoxicity, respiratory complications	Low risk of bias	Inclusion of patients with HCAP Secondary outcomes were evaluated in the *efficacy population* (completing ≥ 7 days of study drug/placebo: 16 patients in each group, 48 patients in total) Adverse events were evaluated in the *safety population* (patients who had been screened, randomized, and had received at least one dose of treatment, a total of 67 patients: 45 patients receiving NA and 22 in placebo group)
Observational trials				
Ghannam *et al*.[40]	Primary: Clinical resolution of VAP (improvement of clinical parameters, ventilator parameters, laboratory findings and/or receding pulmonary infiltrates on a chest x-ray at the end of therapy) Secondary: Bacterial eradication. Duration of antibiotic therapy	Systemic toxicity (nephrotoxicity) Respiratory complications	Low risk of bias	The population of the study is oncologic patients. Therefore, this is a selected population with probably higher risk of mortality and morbidities All patients received prophylaxis with β-agonist bronchodilators before and after the aerosolization. Therefore, this study was excluded for the analysis of this particular outcome
Kofteridis *et al*. 2010[37]	Primary: Clinical resolution of VAP (resolution of signs and symptoms of infection by the end of the treatment) Secondary: VAP-related mortality All-cause mortality Microbiologic outcome	Systemic toxicity (nephrotoxicity and neurotoxicity) Respiratory complications	Low risk of bias	
Doshi *et al*. 2013[38]	Primary: Clinical resolution of VAP (resolution of signs and symptoms of infection by the end of the treatment) Secondary: Mortality Duration of MV Duration of ICU stay Microbiologic cure	None	Low risk of bias	Not all the included patients were MV: a 4.5% in the adjunctive therapy with NA and a 3.9% in the systemic therapy alone, were not under MV Even though, as the MV patients were more than 95% in both groups, and there was no statistically significant difference between them due to this factor ($P > 0.999$), the experts committee decided not to exclude this article
Tumbarello *et al*. 2013[39]	Primary: Clinical resolution of VAP (resolution of signs and symptoms of infection and improvement/lack of progression of chest x-ray abnormalities by the end of the treatment) Secondary: Mortality Duration of MV Duration of ICU stay Microbiologic cure	Nephrotoxicity	Low risk of bias	

HCAP = healthcare-associated pneumonia; ICU = intensive care unit; IV = intravenous; MV = mechanical ventilation; NA = nebulized antibiotics; PD = pharmacodynamics; PK = pharmacokinetics; VAP = ventilator-associated pneumonia.

Table A3.5. Studies Regarding the Use of Nebulized Antibiotics for the Treatment of Ventilator-associated Pneumonia Caused by Susceptible Pathogens: Main Characteristics

Study and Year	Country	Characteristic	No. of Patients	Type of Nebulizer	Nebulized Drug and Dosage	IV Drugs
Randomized controlled trials						
Lu *et al*. 2011[26]	France	Phase II trial, single center	46 patients	Vibrating-mesh nebulizer	Amikacin plus ceftazidime Dose: amikacin: 25 mg kg^{-1} day^{-1}; single dose; duration: 3 days. ceftazidime: 120 mg kg^{-1} day^{-1}; divided in 8 doses of 15 mg/kg each; duration: 8 days	IV amikacin plus ceftazidime Amikacin: 15 mg · kg^{-1} · day^{-1}; single dose; duration: 3 days. Ceftazidime: initial bolus of 30 mg/kg more than 30 min plus continuous infusion of 90 mg · kg^{-1} · day^{-1}; duration: 8 days Patients infected with *Pseudomonas aeruginosa* with an intermediate susceptibility to ceftazidime and/or amikacin (3 patients out of 20), were treated in with ciprofloxacin

IV = intravenous.

Table A3.6. Studies Regarding the Use of Nebulized Antibiotics for the Treatment of VAP Caused by Susceptible Pathogens: Evaluated Outcomes and Quality

Study and Year	Efficacy Outcomes	Safety Outcomes	Global Bias Risk	Particularities
Randomized controlled trials				
Lu *et al*. 2011[26]	Primary: Clinical and bacteriologic cure of VAP after 8 complete days of antibiotic therapy (association of reduction of clinical and biologic signs of infection, decrease in the modified CPIS score < 6, significant lung CT improvement, and lower respiratory tract specimens either sterile or with nonsignificant concentrations of *Pseudomonas aeruginosa).* Secondary: Antibiotic-induced changes in lung aeration and lung-inflammation (assessed by CT scan) Per-treatment emergence of resistant strains	Respiratory complications	Low risk of bias except for a high risk of bias in the blinding (a nonblinded investigator evaluated curation and possibility of superinfection after the treatment)	The majority of the global selected population in the study had an inadequate initial antibiotic treatment. Therefore, this is a selected population that may have a higher risk of mortality and morbidities

CPIS = Clinical Pulmonary Infection Score; CT = computed tomography; VAP = ventilator-associated pneumonia.

Table A3.7. Studies Regarding the Use of NA for the Treatment of Ventilator-associated Pneumonia Independently of the Pathogen's Susceptibility Pattern: Main Characteristics

Study and Year	Country	Characteristic	No. of Patients	Type of Nebulizer	Nebulized Drug and Dosage	IV Drugs
Randomized controlled trials						
Hallal *et al*. 2007[41]	United States	Double-blinded, pilot study, single center	10 patients	Jet nebulizer	Tobramycin Dose: 300 mg/12 h	IV tobramycin on a single daily dose, adjusted according to the renal function (creatinine clearance) Patients in both groups could also receive other IV therapy with pipercilin–tazobactam or imipenem–cilastatin. No information was provided on potential significantly different distribution of these antibiotics between both groups
Rattanaumpawan *et al*. 2010[42]	Thailand	Open label, single center	102 patients	Jet and ultrasonic nebulizers	CMS Dose equivalent to 75 mg of colistin base, every 12 h	Regimen and duration of IV antibiotics decided by the patient's responsible physician Table 1 in the study shows no significant differences in the distribution of the different types of antibiotics between both groups
Observational trials						
Arnold *et al*. 2012[43]	United States	Cohort study, retrospective, single center	90 patients	Not defined but they specified using a nebulizer generating optimal droplet sizes (1–5 μm).	Colistin or tobramycin Dose: colistin: 150 mg/12 h, tobramycin: 300 mg/12 h *Patients infected with *Pseudomonas aeruginosa* with an intermediate susceptibility to ceftazidime and/or amikacin (4 of 20 patients) were treated with both nebulized ceftazidime and amikacin	Regimen and duration of IV antibiotics decided by the patient's responsible physician Significantly higher rate of IV colistin and aminoglycosides in the group receiving adjunctive NA

CMS = colistimethate sodium; IV = intravenous; NA = nebulized antibiotics.

Table A3.8. Studies Regarding the Use of NA for the Treatment of VAP Independently of the Pathogen's Susceptibility Pattern: Evaluated Outcomes and Quality

Study and Year	Efficacy Outcomes	Safety Outcomes	Global Bias Risk	Particularities
Randomized controlled trials				
Hallal *et al*. 2007[41]	Primary: Resolution of VAP (extubation within the study period/still MV but with improval of Multiple Organ Dysfunction Scores, fever, pulmonary infiltrates and physical signs of pneumonia resolved). Secondary: Superinfection by *Pseudomonas aeruginosa* or *Acinetobacter* spp. Bacteremia *by P. aeruginosa* or *Acinetobacter* spp. Need to change the therapy regimen	Systemic toxicity (nephrotoxicity)	Low risk of bias	As the distribution of other antibiotics administered (piperacilin–tazobactam or imipenem–cilastatin) was not provided (a potential significantly different distribution may exist between both groups) the experts committee decided to exclude this study for efficacy evaluation. It was only included for safety evaluation
Rattanaumpawan *et al*. 2010[42]	Primary: Clinical resolution (complete resolution of all signs and symptoms of VAP, and improvement/lack of progression of all abnormalities on the chest x-ray Microbiologic outcome (days 3 and 7).	Systemic toxicity (nephrotoxicity) Respiratory complications (bronchospasm)	High risk of bias of blinding (open label) Low risk of bias in the rest of the evaluation	They mixed both MDRO pathogens and susceptible microorganisms. Prevalence of MDRO was 58.8% in the adjunctive nebulized therapy group and 40.8% in the placebo group ($P = 0.11$)
Observational trials				
Arnold *et al*. 2012[43]	Mortality (30 days and in-hospital) Duration of MV Duration of ICU stay Length of IV therapy Recurrence of VAP	They report no adverse effects related to nebulized colistin Authors were contacted for clarification, and reported having monitored: nephrotoxicity respiratory adverse events	Low risk of bias except for a high risk of bias for confounding factors; the group receiving adjunctive NA had significantly higher rate of MDRO pathogens ($P < 0.001$), significantly higher APACHE II score ($P = 0.004$), significantly higher rate IV aminoglycosides ($P = 0.001$), and significantly higher rate of IV colistin ($P = 0.02$)	Risk of overestimation of nephrotoxicity and respiratory complications in the group receiving adjunctive NA due to the confounding factors previously described in the table

APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; IV = intravenous; MDRO = multiple drug-resistant organisms; MV = mechanical ventilation; NA = nebulized antibiotics; spp. = species; VAP = ventilator-associated pneumonia.

Appendix 4: Study Characteristics and Meta-analysis on Efficacy and Safety of Nebulized Antivirals for the Treatment of Viral Infections

No randomized trials or observational studies were found to evaluate the efficacy and/or safety of nebulized antivirals for the treatment of viral infections; therefore, no evidence can be provided on their use. Only some case series and reports on nebulization of zanamivir were found.[58] Zanamivir is not approved for nebulization, and the Food and Drugs Administration alerted in October 2009 (http://www.medscape.com/viewarticle/710336) of the death of a person with influenza who had received its powder for inhalation formulation through a nebulizer. According to the manufacturer, lactose sugar in the formulation increases the risk of obstruction of the mechanical ventilator circuit.

Appendix 5: Study Characteristics and Meta-analysis on Efficacy and Safety of Nebulized Antifungals for the Treatment of Fungal Infections

No randomized controlled trials or observational studies were found to evaluate the efficacy and/or safety of nebulized antifungals for the treatment of fungal infections. Only one case series[59] reported their experience on nebulization of Amphotericin B Lipid Complex (Sigma Tau Pharmaceuticals, USA) to 32 immunosuppressed oncology patients as adjunctive therapy to systemic antifungals. Only eight patients were under mechanical ventilation support and had a demonstrated fungal infection. Only one of the patients was reported to have survived. They also reported respiratory complications (modest cough, mild bronchospasm, and transient chest pain) in three patients although it was not specified if those patients were under mechanical ventilation or not. No other evidence was found for the use of nebulized antifungals for the treatment of fungal respiratory infections.