Administration of antimicrobials via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis

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Background: Aerosolized antibiotics are a widely recognized treatment for patients with cystic fibrosis (CF). We sought to clarify their role in the treatment of non-CF patients with nosocomial pneumonia by performing a meta-analysis of randomized controlled trials (RCTs) that compared administration of antimicrobials via the respiratory tract (with or without concurrent usage of systemic antibiotics) with control treatment.

Methods: An extensive search of PubMed, Scopus, Cochrane Central Register of Controlled Trials, Current Contents and bibliographies from retrieved publications was made.

Results: Five RCTs were included in the meta-analysis. Administration of antimicrobials via respiratory tract (either inhaled or endotracheally instilled) as opposed to control was associated with better treatment success in intention-to-treat (fixed effect model: odds ratio (OR) = 2.39, 95% confidence interval (CI) 1.29–4.44; random effects model: OR = 2.75, 95% CI 1.06–7.17) and in clinically evaluable patients (fixed effect model: OR = 3.14, 95% CI 1.48–6.70; random effects model: OR = 3.07, 95% CI 1.15–8.19). There were no statistically significant differences between therapeutic regimens regarding all-cause mortality (fixed effect model: OR = 0.84, 95% CI 0.43–1.64; random effects model: OR = 0.71, 95% CI 0.27–1.88), microbiological success (fixed effect model: OR = 2.06, 95% CI 0.91–4.68; random effects model: OR = 2.23, 95% CI 0.64–7.71) and toxicity (fixed effect model: OR = 0.34, 95% CI 0.04–2.53; random effects model: OR = 0.36, 95% CI 0.04–3.16).

Conclusions: The limited available evidence seems not to preclude a benefit from the administration of antimicrobial agents via the respiratory tract for treating nosocomial pneumonia.

Keywords: ICU-acquired pneumonia, healthcare-associated pneumonia, ventilator-associated pneumonia, respiratory tract infections

Introduction

Nosocomial and ventilator-associated pneumonia (VAP) have been recognized as important clinical problems with considerable mortality and morbidity.¹ Several of the currently administered antimicrobials for the treatment of these infections have been criticized for suboptimal penetration to the lung parenchyma, like vancomycin,² or for potentially severe toxicity, like aminoglycosides. Novel anti-infective agents would probably be the solution, given also the emergence of multidrug-resistant bacteria; however, the discovery rate of such agents has markedly declined.³ Along with these observations, the option of improving the bioavailability (and, hopefully, the effectiveness) of existing antimicrobial agents while eliminating their systemic toxicity by using alternative delivery methods appears almost compulsory. Among these alternatives, aerosolization has concentrated the interest of both researchers and clinicians.⁴

The father of aerosolized medicine was an ancient Greek botanist, Pedanius Dioscorides.⁵ Since then, the use of aerosolized drugs has been appreciated in many medical fields, such as asthma and chronic obstructive pulmonary disease. They have been used mainly as prophylaxis in certain types of lower respiratory tract infections (LRTIs) such as Pneumocystis jirovecii pneumonia and chronic Pseudomonas aeruginosa pulmonary infections in cystic fibrosis (CF) patients.⁶ However, existing data suggest that its prophylactic usage can be extended to
include other LRTIs as well, like intensive care unit-acquired pneumonia.7

Beyond their preventive usage, aerosolized antibiotics also served as a treatment modality in CF as they effectively eradicate early P. aeruginosa infection.5 Additionally, according to the recently published American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines for nosocomial pneumonia and VAP, aerosolized antibiotics in combination with systemically administered antibiotics may be beneficial in patients with VAP.8 We endeavoured to systematically examine the evidence related to the potential benefit from the administration of antimicrobial agents via the respiratory tract (with or without concurrent usage of systemic antibiotics) for the treatment of patients with nosocomial pneumonia by performing a meta-analysis of relevant randomized controlled trials (RCTs). We focused on treatment success, an outcome of clinical significance to patients affected by nosocomial pneumonia.

Methods

Data sources
Two investigators (E. I. and I. I. S.) independently sought to identify relevant RCTs from the PubMed database (from July 1950 to April 2007) by using the following search terms: inhaled antimicrobials, aerosolized or nebulized or endotracheal antibiotics. References from relevant studies were also scrutinized. In an effort to locate further reports, we repeated our search with the same keywords using the Scopus, Cochrane Central Register of Controlled Trials and Current Contents databases.

Study selection
Studies were considered eligible for inclusion in the present meta-analysis if they compared the effectiveness and toxicity of administration of antimicrobials via the respiratory tract (either inhaled or endotracheally instilled) with control for the treatment of patients with nosocomial pneumonia. Aerosolized antibiotics could be used as adjunctive or as solitary treatment. Studies conducted in populations with chronic microbial infection due to CF or bronchiectasis as well as in populations with viral or P. jirovecii pneumonia were excluded. Exclusion criteria regarding the language and time of publication were not implemented. Discrepancies between the two investigators regarding the eligibility of a trial were resolved in meetings of all authors.

Data extraction
The data extracted from the identified studies for further analysis were the study population, the definitions for treatment success used in each trial, the route of administration of antibiotics, the dosage and duration of the treatment regimens, the number of intention-to-treat (ITT) (i.e. the patients participating to the arm in which they were allocated regardless whether they received/completed treatment or their outcomes were collected) and clinically evaluable (CE) (i.e. the patients who received treatment and completed the trial) patients, the proportion of enrolled patients under mechanical ventilation and the type of cultures required for the microbiological diagnosis of pneumonia. Data referring to treatment success of ITT and CE patients as well as all-cause mortality in ITT patients, emergence of resistance in the aerosolized treatment group, eradication of initially isolated pathogens and adverse events in both treatment groups were also extracted. A quality evaluation of relevant trials was performed by examining the randomization, allocation concealment, exclusion criteria after randomization and assessor blinding. Allocation concealment was characterized as adequate, unclear, inadequate and non-existent according to Cochrane definitions.9

Definitions
Outcomes of the present meta-analysis: treatment success of ITT and CE patients was considered the primary outcome of this study. Treatment success was defined as the clinical (disappearance of fever, sputum reduction, improvement of auscultatory signs and extubation), laboratory (decrease in WBC) and radiological improvement of the patients according to the authors of the each of the included trials. On the other hand, all-cause mortality in ITT patients, microbiological success (defined as the eradication or elimination of the responsible pathogen assessed by qualitative or quantitative measures in endotracheal secretions/sputum and bronchoalveolar lavage/protected brush specimen, respectively) and drug-related toxicity served as secondary outcomes for this meta-analysis.

Nosocomial pneumonia refers to LRTIs in hospitalized patients. The presence of radiological findings (i.e. a new pulmonary infiltrate) was a prerequisite for the diagnosis in combination with compatible symptoms (fever, cough and purulent sputum production), laboratory (leucocytosis) and microbiological findings (positive cultures).

Data analysis and statistical methods
Data were analysed with the use of the ‘RevMan 4.2’ software. Small study effect was detected by the funnel plot method using Egger’s test; a P value lower than 0.05 denotes statistical significance. Statistical heterogeneity was assessed by employing both the $\chi^2$ test and I$^2$ statistic; a $\chi^2$ test’s P value lower than 0.10 and an I$^2$ value higher than 50% were defined to note statistical significance.4,9,10 When P was higher than 0.10 and I$^2$ was lower than 50% (i.e. statistically non-significant heterogeneity), pooled odds ratios (ORs) and 95% confidence intervals (CIs) for all outcomes were calculated by using both the Mantel–Haenszel4 fixed effect and the DerSimonian–Laird12 random effects models. This was done because the possible persistence of the statistical significance of our results even after the implementation of the conservative random effects model (along with the fixed effect model) presumably adds to the robustness of our findings. When $\chi^2$ test’s P was lower than 0.10 and I$^2$ was higher than 50% (i.e. statistically significant heterogeneity), OR and CI were calculated by using only the random effects model.

Results

Study selection
In Figure 1, we present the steps we followed in order to select the appropriate studies for the present meta-analysis. Out of the 685 articles that were identified through the initial PubMed search, the great majority of them was excluded for reasons dealing with the study design (i.e. retrospective or non-randomized), the study population (i.e. patients with viral pneumonia or tuberculosis) or because aerosolized antibiotics were prescribed for prophylaxis instead of treatment. In addition, the extensive search of Scopus (567 studies), Cochrane Central Register of Controlled Trials
Systematic review

685 potentially relevant articles identified in PubMed and screened for retrieval

↓ →

483 studies were excluded because they were
- animal studies (30)
- pharmacokinetic studies (55)
- histology–immunology studies (9)
- reviews (99)
- case reports/series (37)
- commentary–guidelines (4)
- irrelevant to our subject (186)

or they referred to:
- diagnosis–microbiology (22)
- epidemiology (14)
- adverse effects (27)

202 studies of several different prophylactic or therapeutic regimens for lower respiratory tract infections (LRTIs)

↓ →

92 studies were excluded because they referred to prophylaxis

110 studies examined any kind of LRTI

↓ →

86 studies were excluded because they examined patients with:
- cystic fibrosis (32)
- viral pneumonia (25)
- Pneumocystis jirovecii pneumonia (19)
- chronic suppurative lung disease (6)
- burn injury (1)
- endobronchial tuberculosis (3)

24 potentially evaluable studies

↓ →

19 studies were excluded as they were:
- retrospective (1)
- non-comparative (18)

Additional reports fulfilling our inclusion criteria and located by searches of:
- Scopus (n = 0, out of the 567 initially retrieved)
- Cochrane Central Register of Controlled Trials (n = 0 out of the seven initially retrieved)
- Current contents (n = 0 out of the 80 initially retrieved)

↓

Five randomized controlled trials were included in our meta-analysis

Figure 1. Flow diagram of retrieved reports.
Systematic review

In Table 1, we summarize the characteristics of the five RCTs, representing 176 patients with pneumonia, which were included in the current analysis. The mean sample size was 35 individuals (range 15–85) and two out of five of them were published after 2000. All the studies included in the meta-analysis enrolled patients with hospital-acquired pneumonia. The proportion of patients under mechanical ventilation was 100% in two, <50% in one, whereas the remaining two RCTs did not provide relevant data. In addition, in Table 1 we depict, in detail, the definitions for ‘treatment success’ used by the authors of the individual studies.

The methodological quality of the selected publications was assessed and depicted in Table 2. Allocation concealment was adequate in two out of five studies, whereas in the remaining studies it was unclear or non-existent. Regardless of the study quality, results concerning treatment success in both ITT and CE patients favoured aerosolized/endotracheally instilled antibiotics.

In three out of five RCTs, microbiological confirmation of pneumonia diagnosis was based on qualitative cultures (of sputum or tracheal aspirates), whereas in two RCTs quantitative cultures (of specimens obtained from bronchoalveolar lavage or protected brush) were required for this purpose.

Administration of study drugs

In Table 1, we show in detail the dosage, route and duration of administration of the used antimicrobials. Tobramycin, sisomycin or gentamicin was administered in three RCTs, one RCT and one RCT, respectively. In two reports, the investigators administered an inhaled antimicrobial, whereas in the remaining studies an endotracheally instilled antibiotic was used. Duration of administration via the respiratory tract was at least 5 days. In all the selected publications, the technique followed for drug delivery into lung parenchyma was described sufficiently. Four of the reports were placebo-controlled RCTs, whereas in the remaining study two different modes of gentamicin administration were compared (namely endotracheal instillation versus intramuscular injection).

Concurrent administration of systemic antimicrobials in the group of patients who received an aerosolized antibiotic was permitted in four out of the five trials included in the present meta-analysis. Concurrently used anti-infective medications were β-lactams, aminoglycosides and vancomycin in four trials, three trials and one trial, respectively. Systematic administration was accomplished intravenously or intramuscularly.

Treatment success in ITT patients

In Table 3, we summarize the outcome data of the RCTs included in the present meta-analysis. Data with regard to treatment success in ITT patients were provided for four selected trials. Small study effect was detected (Egger’s test $P = 0.034$; smaller reports favoured treatment), whereas statistically significant heterogeneity among the results was not identified ($P = 0.17, I^2 = 40.8\%$). Administration of antimicrobials via the respiratory tract was associated with better treatment success in ITT patients with pneumonia compared with control (fixed effect model: $OR = 2.39, 95\% CI 1.29–4.44$; random effects model: $OR = 2.75, 95\% CI 1.06–7.17$; 176 patients). The ORs for treatment success in ITT patients, as well as the pooled OR, are presented in Figure 2.

Treatment success in CE patients

The included studies in the meta-analysis reported on the treatment success in CE patients. Neither small study effect (Egger’s test $P = 0.14$) nor statistically significant heterogeneity ($P = 0.26, I^2 = 23.8\%$) was detected. Administration of antimicrobials via the trachea was associated with better treatment success in CE patients with pneumonia as opposed to control (fixed effect model: $OR = 3.14, 95\% CI 1.48–6.70$; random effects model: $OR = 3.07, 95\% CI 1.15–8.19$; 140 patients). The ORs for treatment success in CE patients in the individual RCTs, as well as the pooled OR, are presented in Figure 3.

All-cause mortality

Information dealing with the all-cause mortality during the study period was available for four of the RCTs that were included in the meta-analysis. Small study effect was detected (Egger’s test $P = 0.04$). Heterogeneity among the included comparisons was not statistically significant ($P = 0.17, I^2 = 41.1\%$). There was no significant difference between the compared groups regarding this outcome (fixed effect model: $OR = 0.84, 95\% CI 0.43–1.64$; random effects model: $OR = 0.71, 95\% CI 0.27–1.88$; 176 ITT patients).

Microbiological success

Data on the microbiological success were available for three studies. Small study effect (Egger’s test $P = 0.41$) was not found; in addition, no statistically significant heterogeneity ($P = 0.14, I^2 = 48.3\%$) was found among the identified studies. There was no statistically significant difference with regard to microbiological success between patients who received antimicrobial agents via the respiratory tract and control (fixed effect model: $OR = 2.06, 95\% CI 0.91–4.68$; random effect model: $OR = 2.23, 95\% CI 0.64–7.71$; 94 patients).

Emergence of resistance

With respect to development of resistance associated with the administration of an antimicrobial agent through the respiratory tract, three of the selected studies provided relevant data. In total, only 3 (6.5%) among the 46 individuals who received an endotracheal regimen with an initially susceptible pathogen had a resistant one after the completion of the treatment. In detail, one patient acquired a sisomycin-resistant Klebsiella spp., and the other two patients tobramycin- and gentamicin-resistant strains each (without the authors of the corresponding two RCTs specifically reporting on the pathogens involved).
Table 1. Main characteristics of the randomized controlled trials included in the meta-analysis (antimicrobial administered via the respiratory tract versus control)

<table>
<thead>
<tr>
<th>First author/ref. no.</th>
<th>Year of publication/country</th>
<th>Study design</th>
<th>Study population-setting</th>
<th>Treatment success definition</th>
<th>Treatment; duration</th>
<th>Technique for drug delivery</th>
<th>Control</th>
<th>Concurrent administration of systemic antimicrobials in the treatment group</th>
<th>Number of ITT patients, N; proportion of ITT patients who are under MV, %</th>
<th>Number of CE patients, N</th>
<th>Cultures required for the microbiological diagnosis of pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallal/13</td>
<td>2007/USA</td>
<td>SC RCT</td>
<td>mechanically ventilated for ≥96 h with VAP caused by <em>P. aeruginosa</em> or <em>Acinetobacter</em> spp./trauma ICU</td>
<td>extubation of patients or improved Multiple Organ Dysfunction Score, resolution of fever, pulmonary infiltrates and physical signs</td>
<td>inhaled tobramycin 300 mg every 12 h; 14 days</td>
<td>5 mL through jet nebulizer, fitted 30 cm from ET; flow rate &gt;6 mL/min; humidification discontinued during nebulization</td>
<td>placebo</td>
<td>iv piperacillin/tazobactam or imipenem/cilastatin; iv vancomycin (if necessary)</td>
<td>23; 100% 5 versus 5 quantitative; BAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le Conte/14</td>
<td>2000/France</td>
<td>MC RCT</td>
<td>patients intubated and mechanically ventilated with nosocomial pneumonia/ICU</td>
<td>extubation of patients</td>
<td>inhaled tobramycin 6 mg/kg/day; 5 days</td>
<td>aerosol delivered by a balloon with a valve, connected to ET. Ventilator parameters: RR, 16/min; FiO₂, 100%; tidal volume, 700 mL. Duration of aerosolization, 5 min</td>
<td>placebo</td>
<td>iv β-lactam; iv tobramycin 5 mg/kg/day every 12 h</td>
<td>38; 100% 20 versus 16 qualitative; PSB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown/15</td>
<td>1990/USA, Canada</td>
<td>MC RCT</td>
<td>patients (&gt;18 years) with either endotracheal or tracheostomy tubes in place and Gram-negative bacterial pneumonia/NA</td>
<td>resolution of fever, improvement of pulmonary infiltrates and physical signs</td>
<td>endotracheally instilled tobramycin 40 mg every 8 h; &gt;4 days</td>
<td>solutions were instilled by a small-bore plastic cannula with its tip distal to the carina</td>
<td>placebo</td>
<td>iv tobramycin 1.5 mg/kg every 8 h; iv cefazolin 2 g every 8 h; iv piperacillin 3 g every 4–6 h</td>
<td>85; NA 25 versus 16 qualitative; endotracheal secretions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>First author/ ref. no.</th>
<th>Year of publication/ country</th>
<th>Study design</th>
<th>Study population/ setting</th>
<th>Treatment success definition</th>
<th>Treatment; duration</th>
<th>Technique for drug delivery</th>
<th>Control</th>
<th>Concurrent administration of systemic antimicrobials in the treatment group</th>
<th>Number of ITT patients, N; proportion of ITT patients who are under MV, %</th>
<th>Number of CE patients, N</th>
<th>Cultures required for the microbiological diagnosis of pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klastersky/16 1979/Belgium</td>
<td>SC RCT</td>
<td>patients with either endotracheal or tracheostomy tubes in place and severe Gram-negative bronchopneumonia/ neurosurgical ICU</td>
<td>improvement of fever, pulmonary infiltrates and physical signs</td>
<td>endotracheally instilled sisomycin 25 mg every 8 h; 7.3 days (mean)</td>
<td>solution diluted in 5 mL of saline and administered over a 5 min period through a plastic catheter inserted deeply into the trachea</td>
<td>placebo</td>
<td>iv/im sisomycin 75 mg every 8 h; iv carbenicillin 10 mg every 8 h</td>
<td>38; 45%</td>
<td>18 versus 20 qualitative; sputum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klastersky/17 1972/Belgium</td>
<td>SC RCT</td>
<td>tracheostomized patients (&gt;18 years) with disseminated malignant disease or intracranial surgery and severe Gram-negative bronchial infection/ medical or neurosurgical ward</td>
<td>resolution of fever, diminution of WBC, decrease in purulence</td>
<td>endotracheally instilled gentamicin 40 mg every 4 h; 6–12 days</td>
<td>1 mL administered through a plastic catheter inserted deeply into the trachea</td>
<td>im gentamicin 80 mg every 8 h</td>
<td>none</td>
<td>15; NA</td>
<td>7 versus 8 qualitative; sputum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SC, single centre; MC, multicentre; VAP, ventilator-associated pneumonia; ICU, intensive care unit; iv, intravenous; im, intramuscular; BAL, bronchoalveolar lavage; PSB, protected specimen brush; ITT, intention-to-treat; CE, clinically evaluable; MV, mechanically ventilated; NA, not available/applicable; RR, respiratory rate; ET, endotracheal tube.
Hallal/13 unclear adequate 13 patients: negative BAL (n = 5); infection with an organism other than *P. aeruginosa* or *Acinetobacter* (n = 5); the *Acinetobacter* isolate was resistant to tobramycin (n = 3) double-blind: only the pharmacist was unblinded
Le Conte/14 unclear unclear 2 patients: death from the underlying disease during the first 5 days of treatment (n = 2) double-blind
Brown/15 unclear unclear 44 patients: physician decision to discontinue the protocol (n = 10); death in <48 h (n = 9); entry criterion exclusion (13 patients); protocol violation (n = 4 patients); perceived adverse effect (n = 13) double-blind
Klastersky/16 adequate adequate 0 patients double-blind
Klastersky/17 unclear non-existent 0 patients NA

**Adverse effects**

Data on adverse effects probably or possibly related to study medications were reported for four of the included RCTs. Small study effect (Egger’s test P = 0.88) was not detected and heterogeneity (P = 0.59, I² = 0%) was not statistically significant. There was no difference between patients who received antibiotics via the trachea and control with regard to the experience of any drug-related adverse effect (fixed effect model: OR = 0.34, 95% CI 0.04–2.53; random effects model: OR = 0.36, 95% CI 0.04–3.16; 102 patients).

With regard to the toxicity ascribed to the endotracheal administration of antimicrobials, at least 1 out of the 57 treated patients experienced adverse events from the respiratory system. In detail, desaturation appeared in one individual during the administration of nebulized tobramycin. In addition, in another patient, who was receiving sisomycin both endotracheally and intravenously, granular casts appeared in the urine; they disappeared after discontinuation of the aminoglycoside.

**Subgroup analysis**

We performed a subgroup analysis by excluding the RCT that enrolled patients in which the aerosolized antimicrobial was administered as a monotherapy. Four RCTs were included in this subanalysis. Administration of aerosolized antibiotics as opposed to placebo was associated with slightly higher treatment success in ITT (fixed effect model: OR = 1.98, 95% CI 1.03–3.79; random effects model: OR = 1.96, 95% CI 1.01–3.79) and CE (fixed effect model: OR = 2.44, 95% CI 1.09–5.49; random effects model: OR = 2.41, 95% CI 1.03–5.62) patients with hospital-acquired pneumonia. There was no difference between the compared groups regarding mortality (fixed effect model: OR = 0.98, 95% CI 0.48–1.98; random effects model: OR = 0.88, 95% CI 0.32–2.34).

**Discussion**

The main finding of our study is that patients with nosocomial pneumonia treated with inhaled or endotracheally instilled antibiotics experienced higher treatment success compared with control. This finding arose from the examination of both the CE and the ITT population. No differences between compared groups were revealed with regard to mortality, emergence of resistance and drug-related adverse events. It should be emphasized that in four of five RCTs included in this meta-analysis, the comparison between inhaled antibiotic and placebo was performed in patients who received concurrent systemic antimicrobial therapy.

Further examining the findings of this meta-analysis regarding treatment success, we should note that the statistically significant higher treatment success observed with aerosolized or endotracheally instilled antibiotics in the CE analysis remained in the ITT analysis which is more conservative in estimating significance in a treatment effect. Besides, even though the between-study heterogeneity observed in treatment success of ITT and CE patients was not statistically significant, both fixed and (a more conservative with regard to detection of significance) random effect models were used for the estimation of OR and CI. The statistically significant higher treatment success in the aerosolized/endotracheally instilled antibiotics arm persisted even after the implementation of the random effect model.

There are a number of observational studies that add support to the findings of this meta-analysis; they were very recently reviewed.
Table 3. Outcome data from the randomized controlled trials included in the meta-analysis (antimicrobial administered via the respiratory tract versus control)

<table>
<thead>
<tr>
<th>First author/ref. no.</th>
<th>Treatment success</th>
<th>Number of patients with treatment-related antibiotic-resistant organism isolation, n/N (%)</th>
<th>All-cause mortality in ITT patients, n/N (%)</th>
<th>Number of patients from whom the initially identified pathogens were eradicated, n/N (%)</th>
<th>Number of patients who experienced any drug-related adverse effect, n/N (%)</th>
<th>Adverse effects in the treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallal/13</td>
<td>NA</td>
<td>day 28*: 5/5 (100) versus 3/5 (60)</td>
<td>NA</td>
<td>NA</td>
<td>0/5 (0) versus 2/5 (40)</td>
<td>not observed</td>
</tr>
<tr>
<td>Le Conte/14</td>
<td>day 10: 7/21 (33) versus 3/17 (18)</td>
<td>NA</td>
<td>day 10: 7/20 (35) versus 3/16 (19)</td>
<td>NA</td>
<td>1/20 (5) versus 1/16 (6)</td>
<td>desaturation during nebulization</td>
</tr>
<tr>
<td>Brown/15</td>
<td>NA: 24/45 (53) versus 18/40 (45)</td>
<td>1/25 (4) versus 0/16 (0)</td>
<td>13/45 (29) versus 7/40 (18)</td>
<td>17/25 (68) versus 5/16 (31)</td>
<td>0/25 (0) versus 0/16 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Klastersky/16</td>
<td>NA: 14/18 (78) versus 9/20 (45)</td>
<td>1/14 versus NA</td>
<td>5/18 (28) versus 8/20 (40)</td>
<td>8/18 (44) versus 10/20 (50)</td>
<td>NA</td>
<td>granular casts appeared in the urine of 1 patient</td>
</tr>
<tr>
<td>Klastersky/17</td>
<td>NA: 7/7 (100) versus 2/8 (25)</td>
<td>1/7 versus NA</td>
<td>1/7 (14) versus 4/8 (50)</td>
<td>4/7 (57) versus 2/8 (25)</td>
<td>0/7 (0) versus 0/8 (0)</td>
<td>not observed</td>
</tr>
</tbody>
</table>

ITT, intention-to-treat; CE, clinically evaluable; NA, not available/applicable.

*After initiation of the aerosolized treatment.

In this RCT, the number of patients that experienced decrease (rather than total eradication) of the number of offending pathogens within the bronchial secretions was reported.
by Wood and Swanson. They regard mainly the aerosolized administration of aminoglycosides, colistin and β-lactams in the treatment of nosocomial pneumonia. The majority of studies have evaluated the effectiveness of inhaled antibiotics as adjuncts to systemic therapy. In small case series addressing this issue (3–5 patients), all patients were cured. In larger studies (maximum number of patients examined: 25), cure rates were encouragingly high ranging from 67% to 97%.21–24

It should be mentioned that studies evaluating aerosolized antibiotics as sole treatment in nosocomial respiratory tract infection are scarce. In one observational study,25 improvement reported in 12 patients with bronchitis treated with aerosolized gentamicin alone was markedly low (18%). However, in two studies focusing on bacteriological success, eradication of respiratory tract colonization or infection achieved by inhaled treatment alone was more than 90%.26,27

Existing data regarding the effectiveness of aerosolized antibiotics in LRTIs other than pneumonia are promising. In CF patients, aerosolized agents are used extensively as maintenance treatment aiming to suppress the P. aeruginosa lung population after chronic colonization has been established. Inhaled tobramycin or colistin administered for 28 days with subsequent 28 days resting periods (on–off therapy) seems to reduce exacerbations and delay the progression of lung disease.28 Additionally, aerosolized antibiotics seem to be beneficial in the eradication of early P. aeruginosa infection. Preliminary data from two studies on this topic suggested that eradication achieved by inhaled antibiotics was higher than placebo.29

Many studies30,31 have shown that aerosolized antibiotics achieve high sputum concentrations by directly reaching the site of inflammation. However, it is not clear whether they have adequate lung penetration to fight deep-seated infections like pneumonia.32 In this context, it is of critical importance to make sure that optimal delivery systems are used in order to achieve the maximum possible lung deposition. The ideal particle size of aerosolized antibiotics ranges between 1 and 5 μm. Smaller particles are likely to be exhaled, whereas larger particles might not reach alveoli.33 Endotracheal instillation used as delivery method by early studies included in our meta-analysis may have generated highly unpredictable concentrations of antibiotics in the lung parenchyma. It is impressive though that improvement rates reported by Klastersky et al.17 after endotracheal
instillation of sisomycin were significantly higher than those achieved by placebo.

Currently, the standardization of the inhaled antibiotic concentration deposited to the lung is still problematic. Modern ventilators do not incorporate regulatory standards regarding aerosol delivery. In addition, there are a number of parameters interfering with the sufficiency of aerosol lung deposition. An in vivo clinical study examining aerosol delivery via mechanical ventilator has shown that humidified aerosol delivery and continuous nebulization reduced the concentration of inhaled antibiotics detected in sputum. Other parameters affecting aerosolized nebulization reduced the concentration of inhaled antibiotics is associated with lower systemic absorption, renal toxicity. However, in the studies included in this meta-analysis, the examined studies, treatment duration ranged from 4 to 15 days. In fact, the selection of resistant pathogens has been reported by studies evaluating aerosolized antimicrobials as a long-term prophylactic measure against pneumonia. In CF, where there is the need for long-term administration of aerosolized antimicrobials in order to prevent infection or suppress colonizing pathogens, therapeutic protocols last for a maximum of 4 weeks, which represents the breakpoint for the emergence of resistance. However, it seems that even on–off treatment, when prolonged, can enhance the selection of resistant strains.

The most common adverse effects following antibiotic inhalation are bronchospasm and cough. In the studies analysed, significant differences between treatment groups regarding lung reactions were not noticed. Among inhaled antibiotics, colistin seems to be associated with a higher incidence of pulmonary adverse events. In a study conducted by Alothman et al., in children with CF treated with inhaled colistin, bronchoconstriction was more likely to happen in patients with pre-existent bronchial hyper-reactivity. Since local administration of antibiotics is associated with lower systemic absorption, renal toxicity is not a commonly anticipated adverse event. It should be noted that in the study conducted by Hallal et al., renal impairment was significantly lower in the inhaled tobramycin group compared with the systemic tobramycin group. However, there is a proportion of case reports suggesting a correlation between inhaled antibiotics and renal toxicity. Thus, clinicians should be aware that the use of inhaled antibiotics does not preclude renal toxicity.

The present meta-analysis has certain limitations. The quality of the studies included is moderate and this is mirrored in the allocation concealment methods used. The differences between studies regarding the interventions given (aerosolized or endotracheally instilled antibiotics, sole or adjunctive treatment) and the patient outcomes (improvement of clinical/physical/laboratory findings or extubation) might have increased the between-study clinical heterogeneity. However, the presence of clinical heterogeneity might also increase the generalizability of our results. A major concern when small studies are included in a meta-analysis is the presence of small study effect, which arises from publication, selection bias and low methodological quality of small studies.

In conclusion, the results of this meta-analysis seem to suggest that administration of antimicrobial agents via the respiratory tract might be beneficial for non-CF patients with nosocomial pneumonia and, thereby, they deserve further study to clarify its role. Most clinicians may hesitate to administer aerosolized antibiotics as monotherapy since penetration to deeply infected lungs is questionable. However, since lung penetration achieved by systemically administered antibiotics might be suboptimal as well, a combination of aerosolized and systematic treatment may be considered, especially in patients slowly responsive or unresponsive to standard therapy. Large, appropriately designed and conducted trials addressing this important issue appear to be urgently needed.

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References


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