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ORIGINAL ARTICLE

Effectiveness of adjunctive nebulized antibiotics in critically ill patients with respiratory tract infections

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Abstract

The purpose of the study was to analyze the effectiveness of adding nebulized antibiotics to systemic antimicrobials in critically ill patients with respiratory tract infections (pneumonia or tracheobronchitis) and the effect on renal function. A retrospective observational cohort study including critically ill patients with respiratory tract infections during a 2-year period was conducted. Intervention group included patients that received nebulized and systemic antimicrobials. Patients in the control group received only systemic antimicrobials. Clinical resolution was the primary endpoint. Secondary outcomes included change in fever, inflammatory parameters, and creatinine clearance; length of hospital stay, systemic therapy, and mechanical ventilation; hospital readmission; and mortality. Regression models were performed to estimate the effect of nebulized antibiotics on outcome variables adjusted by potential confounders. A total of 136 patients were included (93 in control group and 43 in intervention group). The intervention group had higher odds of clinical resolution (adjusted odds ratio (OR): 7.1; 95% confidence interval (95% CI): 1.2, 43.3). Nebulized antibiotic therapy was independently associated with reduction in procalcitonin (adjusted OR: 12.4; 95% CI: 1.4, 109.7). There were no significant differences in the rest of the secondary outcomes or in creatinine clearance reduction. Adding nebulized antibiotics for the management of respiratory tract infections has a positive impact on clinical resolution without increasing the risk of renal toxicity.

Keywords Respiratory infection · Inhalation · Nebulizer · Antimicrobial agent · Antiinfective agent · Critically ill · Critical care

Introduction

Respiratory tract infections have been recognized as an important clinical concern with a significant impact on patients' morbidity and mortality. At the present time, ventilator-associated pneumonia (VAP) remains the leading cause of death related to nosocomial infection in critically ill patients [1].

Given the limited penetration of some classes of antimicrobials into the lungs, eradication of microorganisms and improvement of symptoms frequently require high doses and long courses of systemic antibiotics, which are frequently accompanied with drug resistance and systemic toxicity, such as nephrotoxicity, ototoxicity, and/or general toxicity [2, 3]. Given this fact, nebulized antibiotic therapy is considered of high interest as it may provide high concentrations at the site of infection while minimizing systemic exposure and suppresses biofilm formation [1, 4].

The use of nebulized antibiotics in patients with bronchiectasis and cystic fibrosis is already established [5]. However, their role in intensive care unit (ICU) patients with respiratory tract infections is controversial. Currently, the Infectious

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Diseases Society of America and the American Thoracic Society guidelines for hospital-acquired and ventilator-associated pneumonia recommend the addition of inhaled antibiotics in patients with VAP due to Gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (very low-quality evidence) and consider reasonable the adjunctive inhaled therapy as a last-resort treatment in patients who are not responding to intravenous therapy alone, whether the infecting organism is or is not multidrug-resistant [6]. In contrast, the European Society of Clinical Microbiology and Infectious Diseases recommends avoiding the use of nebulized antibiotics for the treatment of respiratory infections in invasively mechanically ventilated adults due to a weak level of evidence of their efficacy and the high potential for underestimated risks of adverse events [7].

With regard to safety issues, published studies on nebulized antibiotics have reported local adverse effects, mainly bronchospasm, cough, and wheeze [3, 8–10]. In addition, patients with severe hypoxaemia are at higher risk of suffering respiratory complications [7]. As for systemic effects, a recent systematic review conducted in critically ill adults receiving invasive mechanical ventilation did not find an increased risk of nephrotoxicity when adding nebulized antibiotics to intravenous therapy in comparison with patients receiving only intravenous therapy [11].

The main objective of the study was to evaluate the effectiveness of adding nebulized antibiotics to systemic antimicrobial treatment in critically ill patients with respiratory tract infections in a real-world scenario. Secondly, we analyzed the effect of nebulized antibiotics on patients' renal function.

Materials and methods

Study design and population

A retrospective observational cohort study was conducted in an adult critical care area of a university hospital in Spain. The adult critical care area has 18 beds (12 in the ICU and 6 in the intermediate care unit). Inclusion criteria were adults admitted to the critical care area between 2014 and 2015 with respiratory tract infections (pneumonia or tracheobronchitis) treated in this setting with systemic antimicrobials in which sputum, bronchial aspirate, broncho-alveolar lavage, and/or pleural fluid samples were obtained. Pneumonia and tracheobronchitis diagnoses were determined by clinical, radiological, and/or microbiological findings attributed by physicians to these infections. The presence of a new and progressive or persistent infiltrate on chest radiography was the major distinguishing feature between pneumonia and tracheobronchitis, which was not present in the latter. A diagnosis of pneumonia or tracheobronchitis registered by a physician in the patient chart was mandatory for considering the inclusion of the patients in the study. Patients with airway colonization, consisting on the isolation of one or more microorganisms from respiratory samples without accompanying clinical signs of respiratory tract infection, were not included.

In a meta-analysis that compared nebulized antibiotics, with or without intravenous antibiotics, versus intravenous antibiotics for VAP treatment, 49% of the patients in the control group presented clinical cure [12]. Using a two-tailed test with an alpha of 0.05 and a power of 80%, we estimated that 41 patients in the intervention group and 82 patients in the control group would be necessary to detect as significant a 26% increase in clinical cure rate (75% versus 49%). We estimated that it would be possible to recruit that number of patients in a period of 2 years (2014 and 2015).

The intervention group included all patients who received nebulized antibiotics in addition to systemic antimicrobial treatment and fulfilled the inclusion criteria. The control group included patients that only received systemic antimicrobials without receiving nebulized antibiotics and met the inclusion criteria. Two controls per every patient in the intervention group were selected in ascending order from an anonymized list of potential controls provided by the department of Clinical Microbiology. The list included all patients with sputum, bronchial aspirate, broncho-alveolar lavage, and/or pleural fluid samples collected during the study period and ordered by microbial culture date. Patients that did not fulfill all the inclusion criteria were excluded.

Nebulized antibiotics

Treatment with nebulized antibiotics was established according to physicians' criteria and dose was selected according to the hospital protocol. Extemporaneous antibiotic solutions to administer by the respiratory route (tobramycin, gentamycin, amikacin, and/or colistimethate) were prepared in a horizontal air flow cabin of the hospital pharmacy services with aseptic techniques using antibiotics approved for systemic administration, with the exception of colistimethate that is also authorized for nebulization. The prescribed dose for tobramycin was 100–150 mg every 12 h, for gentamycin 100–200 mg every 12 h, for amikacin 250–500 mg every 12 h and for colistimethate 1 million international units every 8 h. The median duration of the nebulized antibiotic therapy in our study was 6 days (interquartile range: 4–10).

When administration was done by a jet nebulizer (Micro-Cirrus™-Intersurgical), the volume of the antibiotic solution was doubled (maintaining the same concentration) due to the residual volume of the device, and it was administered for 20–30 min, discarding the remaining solution. In patients under mechanical ventilation with the SERVO-i™ (Siemens) ventilator, the ultrasonic nebulizer integrated in that device was used. In this case, nebulization was maintained until the

solution was completely administered. After each administration, the nebulizer was cleaned.

Analyzed variables

For the current study, variables were extracted from patient electronic charts. These included patients' characteristics, comorbidities, variables related to hospital stay, clinical parameters, variables related to infectious disease diagnosis, and antimicrobial treatment. Bacterial isolates from the sputum, bronchial aspirate, broncho-alveolar lavage, and pleural fluid samples and their antibiograms were also analyzed. The use of bronchodilators, mucolytic agents, and expectorants during the nebulized therapy was determined by physicians and was also collected.

Clinical resolution was established as the primary endpoint and was defined as improvement of the patient´s general and clinical situation at the end of the systemic antimicrobial therapy in comparison with at the beginning, including resolution of the respiratory tract infection and improvement in lung function, registered by physicians in the patient clinical records. Secondary endpoints were resolution of fever; percentage of patients with reduction in C-reactive protein (CRP) and procalcitonin (PCT) at the end of the systemic antimicrobial treatment in comparison with at the beginning and the magnitude of the difference between these two values (end versus beginning of systemic therapy); resolution of leukocytosis; length of stay in the hospital, critical care area, and in ICU; length of systemic antimicrobial therapy; duration of intubation, and mechanical ventilation; hospital readmission; and mortality (all-cause in-hospital mortality and mortality within the following 30 days after hospital discharge). Patients with resolution of fever referred to those with more than 38 degrees Celsius (°C) at the beginning of systemic antimicrobial treatment and less than 38 °C at the end of the treatment. Patients with resolution of leukocytosis included those with white blood cell count above 12×10^9/L at the beginning of systemic therapy and below that value at the end of it.

The percentage of patients that had a reduction in creatinine clearance (CrCl) at the end of systemic therapy compared with at the beginning of it and the magnitude of CrCl reduction were compared between groups. CrCl was calculated using Cockroft–Gault equation [13]. When serum creatinine was lower than 0.6 mg/dl, a value of 0.6 mg/dl was assumed for CrCl calculation to limit the possibility of overestimating patients´ CrCl. Symptoms at respiratory level during the nebulized therapy were also collected.

Data analysis

Data were analyzed using STATA version 13.0. Normality of variables was analyzed using the Shapiro–Wilk normality test. Both patients' characteristics and outcome variables were compared between the intervention and control group using the Student's t test or Mann–Whitney U for continuous variables and chi-square for dichotomous data. In addition, regression models were performed to estimate the effect of nebulized antibiotics on outcome variables adjusted by confounding factors related to patients' comorbidities, infectious disease diagnosis, baseline inflammatory parameters, severity, requirement of ventilation, and/or intubation, etc. Multiple linear regressions were performed in the case of continuous outcome variables and logistic regressions in the case of dichotomous outcomes variables.

Results

Study population

A total of 52 patients that could potentially be eligible for the intervention group were identified; thus, 104 potentially eligible controls were selected. After a full review of patient charts, 9 patients from the intervention group and 11 controls were ineligible because they did not meet all the inclusion criteria: 8 patients from the intervention group and 11 from the control group received the antimicrobials outside the critical care area, and one additional patient from the intervention group received only nebulized antibiotics without systemic therapy. Therefore, 136 patients were finally included in the study, 43 in the intervention group, and 93 in the control group. Patient selection flow chart is shown in Figure S1 and patients´ characteristics in Table 1.

Patients in the intervention group presented significantly higher PCT values at the beginning of systemic antimicrobial therapy and worse sequential organ failure assessment (SOFA) values during hospital stay than patients in the control group. Cirrhosis, intubation during hospital stay, and mechanical ventilation and intubation prior to systemic therapy were more frequent in patients with nebulized antibiotics.

In 33.3% of the patients from the control group and in 55.8% from the intervention group the respiratory tract infection was acquired in the hospital ($p = 0.007$).

Bacterial isolates

A total of 47 bacterial isolates were identified in respiratory samples of the patients in the intervention group, which corresponded to 31 patients with target nebulized therapy (Table S1). No bacterial isolate was identified in patients with empiric nebulized therapy. A total of 65 bacterial isolates were identified in 45 patients in the control group (Table S2).

Significant differences were obtained in the percentage of patients with multidrug-resistant bacteria between both groups (27.9% in the intervention group versus 6.5% in the control group; $p = 0.001$).

Table 1 Patients' characteristics

Characteristic	Intervention group (n = 43)		Control group (n = 93)		p value
	No. obs.	Results	No. obs.	Results	
Age (years), mean (SD)	43	67.6 (9.3)	93	69.1 (13.4)	0.254[a]
Sex (males), no. (%)	43	28 (65.1%)	93	60 (64.5%)	0.946[b]
Body mass index, mean (SD)	43	24.5 (4.4)	93	24.3 (4.1)	0.590[a]
Comorbidities, no. (%)					
None	43	2 (4.7%)	93	8 (8.6%)	0.412[b]
Immunosupression	43	24 (55.8%)	93	47 (50.5%)	0.567[b]
Diabetes mellitus	43	10 (23.3%)	93	26 (28.0%)	0.563[b]
Chronic obstructive pulmonary disease	43	9 (20.9%)	93	15 (16.1%)	0.495[b]
Obstructive sleep apnea syndrome	43	0 (0%)	93	7 (7.5%)	0.065[b]
Oncologic diagnosis	43	20 (46.5%)	93	40 (43.0%)	0.702[b]
Metastasis	43	11 (25.6%)	93	18 (19.4%)	0.410[b]
Congestive heart failure	43	7 (16.3%)	93	29 (31.2%)	0.067[b]
Chronic kidney disease	43	12 (27.9%)	93	21 (22.6%)	0.500[b]
Cirrhosis	43	9 (20.9%)	93	8 (8.6%)	0.043[b]
Number of comorbidities, mean (SD)	43	2.4 (1.3)	93	2.3 (1.3)	0.620[a]
Type of stay in critical care area, no. (%)					
Intensive care unit	43	26 (60.5%)	93	53 (57.0%)	0.702[b]
Intermediate care unit	43	4 (9.3%)	93	15 (16.1%)	0.286[b]
Intensive care unit + intermediate care unit	43	13 (30.2%)	93	25 (26.9%)	0.686[b]
Reason for critical care area admission, no. (%)					
Acute respiratory distress syndrome	43	10 (23.3%)	93	43 (46.2%)	0.011[b]
Postoperative management	43	13 (30.2%)	93	11 (11.8%)	0.009[b]
Sepsis or septic shock	43	7 (16.3%)	93	16 (17.2%)	0.894[b]
Bleeding	43	5 (11.6%)	93	7 (7.5%)	0.433[b]
Respiratory tract infection	43	1 (2.3%)	93	3 (3.2%)	0.773[b]
Cardiopulmonary arrest	43	2 (4.7%)	93	1 (1.1%)	0.187[b]
Other	43	5 (11.6%)	93	12 (12.9%)	0.834[b]
Surgery during hospital stay, no. (%)	43	18 (41.9%)	93	24 (25.8%)	0.060[b]
Infectious disease diagnosis, no. (%)					
Sepsis or septic shock due to pneumonia or tracheobronchitis	43	10 (23.3%)	93	16 (17.2%)	0.404[b]
Pneumonia without sepsis	43	15 (34.9%)	93	41 (44.1%)	0.311[b]
Tracheobronchitis without sepsis	43	18 (41.9%)	93	36 (38.7%)	0.727[b]
BASAL fever, no. (%)	43	12 (27.9%)	93	24 (25.8%)	0.796[b]
BASAL inflammatory lab data, median (min., max.)					
White blood cell count (10^9/L)	41	8.8 (0.4, 25.3)	91	11.4 (0.7, 52.9)	0.204[c]
CRP	36	10.9 (0.1, 33.8)	89	9.5 (0.1, 44.8)	0.889[c]
PCT	27	2.1 (0.0, 83.4)	69	0.4 (0.1, 175.2)	0.015[c]
BASAL white blood cell count					
Leukopenia[d], no. (%)	41	6 (14.6%)	91	9 (9.9%)	0.427[b]
Leukocytosis[e], no. (%)	41	17 (41.5%)	91	41 (45.1%)	0.700[b]
Worst SOFA during hospital stay, median (min., max.)	42	10 (1, 20)	88	6 (0, 20)	< 0.001[c]
Mechanical ventilation or intubation, no. (%)					
Mechanical ventilation during hospital stay	43	35 (81.4%)	93	71 (76.3%)	0.509[b]
Intubation during hospital stay	43	24 (55.8%)	93	23 (24.7%)	< 0.001[b]
Mechanical ventilation prior to systemic antibiotics	43	14 (32.6%)	93	10 (10.8%)	0.002[b]

Table 1 (continued)

Characteristic	Intervention group (n = 43)		Control group (n = 93)		p value
	No. obs.	Results	No. obs.	Results	
Mechanical ventilation prior to nebulized antibiotics	43	28 (65.1%)	--	--	NA
Intubation prior to systemic antibiotics	43	9 (20.9%)	93	2 (2.2%)	< 0.001[b]
Intubation prior to nebulized antibiotics	43	16 (37.2%)	--	--	NA
Creatinine clearance (ml/min), median (min., max.)	39	58.7 (12.3, 141.4)	92	57.0 (14.3, 168.1)	0.782[c]

BASAL, at the beginning of systemic antimicrobial therapy; *CRP*, C-Reactive protein; *max.*, maximum; *min.*: minimum; *NA*, not applicable; *no.*: number; *no. obs.*, number of available observations; *p*, probability in the comparison test; *PCT*, procalcitonin; *SD*, standard deviation; *SOFA*, sequential organ failure assessment value

[a] Student's *t* test

[b] Chi-square

[c] Mann–Whitney *U* test

[d] White blood cell count < 4×10^9 /L

[e] White blood cell count > 12×10^9 /L

Antimicrobial treatment

Systemic antimicrobial therapy was initiated empirically (not as targeted therapy) in 96.8% of patients from the control group and in 83.7% from the intervention group (p = 0.007). In contrast, nebulized antibiotics were placed as targeted treatments (not as empirical therapies) in 72.1% of the cases.

Four patients in the intervention group received different non-simultaneous nebulized antibiotics, making a total of 50 nebulized treatments in 43 patients. Half of the nebulized treatments were tobramycin, 20% gentamycin, 16% amikacin, and 14% colistimethate.

The majority of the nebulized treatments were administered by a jet nebulizer (n = 43), except for 7 treatments that were administered through an ultrasonic nebulizer. In general, a bronchodilator was administered prior to administration of the nebulized antibacterial, except for 3 cases in which a bronchodilator was not prescribed as an adjunct to nebulized antibiotic treatment. A total of 15 patients received oral acetylcysteine (600–1200 mg per day) during the nebulized therapy.

Outcome variables

Results of the univariate and multivariate analyses are shown in Table 2. After controlling for confounders, the nebulized antibiotic therapy was independently associated with clinical resolution (adjusted odds ratio: 7.1; 95% confidence interval (95% CI): 1.2, 43.3; p = 0.033). Regarding secondary outcomes, the intervention group had higher odds of reduction in PCT at the end of systemic treatment after controlling for confounders (adjusted odds ratio: 12.4; 95% CI: 1.4, 109.7; p = 0.023). No significant differences were found in the rest of the secondary endpoints or in CrCl reduction.

Fourteen patients in the intervention group (32.6%) had respiratory symptoms during the nebulized therapy, which consisted on atelectasis, wheezing, and cough. None of these symptoms were directly attributed by physicians to nebulized antibiotics, though contribution of nebulized therapy cannot be excluded. Nevertheless, no nebulized treatment had to be discontinued due to this issue. There were no significant differences in the incidence of respiratory symptoms during the nebulized therapy according to the patients' PaO_2/FiO_2 ratio (37% of the patients with PaO_2/FiO_2 ratio ≥ 200 and 28% of the patients with PaO_2/FiO_2 ratio < 200; p = 0.557).

Discussion

The addition of nebulized antibiotic therapy was associated with higher odds of achieving clinical resolution after controlling for confounding factors. Nebulized treatment also led to a greater probability of PCT reduction. Since the intervention group included more severe or complicated cases, regression models were carried out to adjust the effect of the intervention by this imbalance.

Nebulized therapy did not increase the risk of nephrotoxicity, supporting the idea that nebulized antibiotics have no effect on general system. As for local symptoms, there were identified cases of atelectasis, wheezing or cough during nebulization therapy, but none of the nebulized treatment was discontinued due to safety issues. However, data on local adverse events have to be interpreted with caution as they might be underreported in the patient charts.

Overall, our findings are similar to those observed in a systematic review conducted in invasively mechanically ventilated adults with ventilator-associated tracheobronchitis

Table 2 Results of the univariate and multivariate analyses

Outcome variable	Univariate analyses					Multivariate analyses	
	Intervention group (n = 43)		Control group (n = 93)		p value	Adjusted effect estimate intervention vs. control (95% CI)[a]	Adjusted p value[a]
	No. obs.	Result	No. obs.	Result			
Primary endpoint							
Clinical resolution, no. (%)	43	31 (72.1%)	93	65 (69.9%)	0.793[b]	OR: 7.1 (1.2, 43.3)	0.033[c]
Secondary endpoints							
Resolution of fever, no. (%)	12	12 (100.0%)	24	22 (91.7%)	0.303[b]	--[d]	--[d]
Inflammatory lab data							
Patients with reduction in PCT, no. (%)	25	21 (84.0%)	63	40 (63.5%)	0.060[b]	OR: 12.4 (1.4, 109.7)	0.023[c]
Change in PCT, median (min., max.)[e]	25	− 2.4 (− 82.8, 2.0)	63	− 0.1 (-174.3, 194.2)	0.009[f]	Coef.: − 12.7 (− 30.6, 5.2)	0.164[g]
Patients with reduction in CRP, no. (%)	35	27 (77.1%)	89	69 (77.5%)	0.963[b]	OR: 1.8 (0.3, 10.0)	0.486[c]
Change in CRP, median (min., max.)[e]	35	− 3.4 (− 22.6, 13.1)	89	− 5.6 (− 38.1, 26.3)	0.439[f]	Coef.: − 0.6 (− 4.2, 3.1)	0.764[g]
Resolution of leukocytosis, no. (%)	17	8 (47.1%)	40	25 (62.5%)	0.280[b]	OR: 0.8 (0.03, 19.1)	0.883[c]
Length of stay (days), median (min., max.)							
Hospital	43	23 (3, 160)	93	19 (2, 167)	0.064[f]	Coef.: 6.6 (− 0.7, 13.8)	0.076[g]
Critical care area	43	12 (2, 70)	93	7 (1, 46)	0.011[f]	Coef.: 1.9 (− 1.5, 5.4)	0.267[g]
Intensive care unit	39	10 (2, 48)	78	5 (1, 46)	0.003[f]	Coef.: 2.7 (− 0.8, 6.1)	0.130[g]
Length of therapy, median (min., max.)							
Systemic antimicrobials (days)	43	17 (2, 133)	93	13 (2, 52)	0.032[f]	Coef.: 3.8 (− 1.6, 9.1)	0.165[g]
Intubation (hours)	22	77 (8, 355)	21	49 (3, 265)	0.489[f]	Coef.: 24.8 (− 57.6, 107.1)	0.556[g]
Mechanical ventilation, including intubation (hours)	31	75 (1, 570)	51	59 (2, 552)	0.450[f]	Coef.: 8.4 (− 67.8, 84.5)	0.830[g]
In-hospital mortality, no. (%)	43	12 (27.9%)	93	23 (24.7%)	0.694[b]	OR: 0.4 (0.05, 2.9)	0.347[c]
Hospital readmission within 30 days[h], no. (%)	43	6 (14.0%)	93	11 (11.8%)	0.727[b]	OR: 27.1 (0.04, 18543.9)	0.322[c]
Mortality within 30 days[h], no. (%)	30	1 (3.3%)	69	8 (11.6%)	0.189[b]	OR: 0.2 (0.01, 2.7)	0.215[c]
Patients with creatinine clearance reduction, no. (%)	26	4 (15.4%)	80	25 (31.3%)	0.115[b]	OR: 0.3 (0.01, 7.6)	0.463[c]
Reduction in creatinine clearance (ml/min)[e], median (min., max.)	4	− 11.3 (− 18.0, − 1.7)	25	− 16.2 (− 54.9, − 1.5)	0.184[f]	Coef.: 14.4 (− 1.6, 30.3)	0.073[g]

95% CI, 95% confidence interval; *CRP*, C-Reactive protein; *Coef.*, regression coefficient; *max.*, maximum; *min.*, minimum; *no.*: number; *no. obs.*, number of available observations; *OR*, odds ratio; *p*, probability of the comparison test; *PCT*, procalcitonin

[a] Adjusted by: sex; age; body mass index; presence of comorbidities (immunosuppression, diabetes mellitus, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, oncologic diagnosis, metastasis, congestive heart failure, chronic kidney disease, cirrhosis); total number of comorbidities; type of stay in the critical care area; reason for admission to the critical care area; surgery during hospital stay; infectious disease diagnosis; fever, white blood cell count, CRP, and PCT at the beginning of the systemic antimicrobial therapy; worst sequential organ failure assessment (SOFA) value during hospital stay; and mechanical ventilation, and intubation previous to the beginning of systemic antimicrobials

[b] Chi-square

[c] Logistic regression

[d] It was not possible to develop a regression model since all the patients in the intervention group resolved fever at the end of the systemic antimicrobial therapy

[e] Difference between values at the end of the systemic antimicrobial therapy and values at the beginning of it. A negative value denotes that the patient had lower values at the end of systemic antimicrobial treatment in comparison with values at the beginning of it

[f] Mann–Whitney *U* test

[g] Multiple linear regression

[h] After hospital discharge

(VAT) or VAP that included studies up to 2016 [11]. The addition of nebulized therapy was associated with higher clinical resolution rates in VAT and VAP caused by resistant pathogens, but not in VAP due to susceptible pathogens. However, this was not consistently translated into significant differences in duration of mechanical ventilation, ICU stay, or all-cause mortality. As for safety results, nebulized therapy did not lead to an increased risk of nephrotoxicity [11].

With respect to antimicrobial resistance, the limited data available suggest that the use of nebulized antibiotics would not be associated with an increased resistance [1, 14]. In the review mentioned before, the risk of developing new resistant strains was significantly lower with adjunctive nebulized therapy in comparison with receiving only systemic antibiotics in patients with VAT [11]. In our case, it was not possible to analyze microbial outcomes since samples are rarely collected after clinical resolution of infections in the clinical practice.

As for the device used for nebulization, in our study, antibiotics were mostly administered by a jet nebulizer, which coincides with previous publications [15, 16]. However, the efficiency of drug delivery into distal airways and alveoli appears to be higher for vibrating mesh and ultrasonic devices, and future investigations should take this into account [5].

The present study must be considered exploratory due to its observational nature and the limited sample size; therefore, the obtained results must be taken with caution. In addition, as with retrospective studies based on electronic records, variables not recorded in electronic patient charts could not be analyzed. With respect to the primary endpoint, even if clinical resolution is frequently used as an outcome variable, its definition is not standardized. Nevertheless, each physician evaluated patients' clinical situation under his responsibility without knowing that this study was going to be conducted. In addition, the study also included various objective outcomes, such as reduction in CRP and PCT, and resolution of leukocytosis and fever, reducing the risk of bias. In future studies, objective and uniform scales such as the clinical pulmonary infection score have to be implemented. Furthermore, there is a need for standardizing practices and for developing guidelines regarding the use of nebulized antibiotics. Despite these limitations, our study represents the clinical practice and real-world scenarios scarcely collected in the scientific literature. Further studies are warranted to confirm the obtained results.

Authorship All the authors contributed to:

- The conception and design of the study; or the acquisition, analysis, or interpretation of data; and
- Drafting the article or revising it for critically important intellectual content; and
- Final approval of the version to be published; and
- All the authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest Leire Leache: Merck Sharp & Dohme financed her attendance to the 22nd Congress of the European Association of Hospital Pharmacists in 2017.

Rest of the authors: none to declare.

Ethical approval Ethical approval was received from the Clinical Research Ethics Committee of Navarra (Spain) in June 2016.

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