"Nebulization of antimicrobial agents in mechanically ventilated adults in 2017: an international cross-sectional survey."

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ABSTRACT

2017 ESCMID practice guidelines reported safety concerns and weak evidence of benefit supporting use of aerosolized antibiotics in mechanically ventilated patients. Our primary goal was to assess current patterns of aerosolized antibiotic prescription in mechanically ventilated patients. A sequential global survey was performed prior to the release of the ESCMID guidelines, from the 1st of February to the 30th of April 2017, using an electronic platform. Responses were analyzed comparing geographical regions. A total of 410 units responded, with 261 (177 from Europe) being eligible for the full survey. 26.8% of units reported not using aerosolized antibiotics. The two major indications amongst prescribing units were ventilator-associated pneumonia and ventilator-associated tracheobronchitis (74.3% and 49.4%, respectively). 63.6% of units indicated prescription solely in response to multi-drug resistant organisms. In comparison with a survey undertaken in 2014, there was a significant reduction in use of aerosolized antibiotics for prophylaxis (50.6% vs 7.7%, $p<0.05$) and colonization (52.9% vs 25.3%, $p<0.05$). The large majority of units (91.7%) reported only prescribing in patients with positive pulmonary cultures. Asia appeared to be an outlier, with 53.3% of units reporting empirical use. The most commonly used device was the jet nebulizer. The most commonly prescribed drugs were colistin methanesulfonate (57.6%), colistin base (41.9%) and amikacin (31.4%), although there was considerable heterogeneity across geographical areas. A significant gap exists betw...

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ORIGINAL ARTICLE

Nebulization of antimicrobial agents in mechanically ventilated adults in 2017: an international cross-sectional survey

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Abstract

2017 ESCMID practice guidelines reported safety concerns and weak evidence of benefit supporting use of aerosolized antibiotics in mechanically ventilated patients. Our primary goal was to assess current patterns of aerosolized antibiotic prescription in mechanically ventilated patients. A sequential global survey was performed prior to the release of the ESCMID guidelines, from the 1st of February to the 30th of April 2017, using an electronic platform. Responses were analyzed comparing geographical regions. A total of 410 units responded, with 261 (177 from Europe) being eligible for the full survey. 26.8% of units reported not using aerosolized antibiotics. The two major indications amongst prescribing units were ventilator-associated pneumonia and ventilator-associated tracheobronchitis (74.3% and 49.4%, respectively). 63.6% of units indicated prescription solely in response to multi-drug resistant organisms. In comparison with a survey undertaken in 2014, there was a significant reduction in use of aerosolized antibiotics for prophylaxis (50.6% vs 7.7%, $p < 0.05$) and colonization (52.9% vs 25.3%, $p < 0.05$). The large majority of units (91.7%) reported only prescribing in patients with positive pulmonary cultures. Asia appeared to be an outlier, with 53.3% of units reporting empirical use. The most commonly used device was the jet nebulizer. The most commonly prescribed drugs were colistin methanesulfonate (57.6%), colistin base (41.9%) and amikacin (31.4%), although there was considerable heterogeneity across geographical areas. A significant gap exists between ESCMID clinical practice recommendations and the use of aerosolized antibiotics in clinical practice. Our findings indicate an urgent need for high-quality education to bring practice into line with evidence-based guidelines.

Introduction

Multi-drug resistant, Gram-negative bacteria (GNB) have risen to worrisome levels worldwide, resulting in increasingly difficult-to-treat infections. Ventilator-associated pneumonia (VAP), the most common infection amongst mechanically ventilated patients, is frequently caused by resistant GNB [1], which have a significant impact on patient outcomes [2, 3].

The pulmonary parenchymal penetration of intravenous antibiotics such as meropenem, amoxicillin and colistin is markedly inhibited, with alveolar levels reported to be around half of plasma levels [4–6]. Direct pulmonary delivery by aerosolization has been proposed as a potential solution to this problem.

The use of nebulized antibiotics for the treatment of VAP and ventilator-associated tracheobronchitis (VAT) has been hypothesized to result in improved clinical cure rate and better outcomes. This is suggested to be due to increased drug concentrations in the airways, with a potential reduction in side effects such as nephrotoxicity [7–9].

The use of aerosolized antibiotics is supported in the recent 2016 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) VAP guidelines [10]; however, this recommendation is only supported by expert opinion with low-grade evidence. By contrast, based on a meta-analyses of existing studies [11], a GRADE Assessment was conducted by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [12]. ESCMID do not support the use of nebulization of antibiotics in the eight most frequent

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scenarios based on PICO (Population-Intervention-Comparison-Outcome) questions due to the absence of evidence of benefit and risk of adverse respiratory effects.

In December 2014, a survey exploring the use of aerosolized antibiotics was undertaken, namely, the International Survey of Antimicrobial Nebulization in Mechanically ventilated patients (SANEME) [13]. We performed a new survey in 2017, the SANEME 2, with the following objectives:

1. Assess indications of nebulized agents in the real world, just prior to the publication of the ESCMID guidelines,
2. Characterize dose and frequency of the most common nebulized drugs and compare their use in VAP and VAT,
3. Assess the differences between geographical areas compared to results from the previous survey,
4. To identify the aerosolization devices and techniques which are in current use.

The hypothesis was that the lack of evidence to support the use of nebulized antibiotics would not prevent routine and widespread use.

Methods

This report describes the practices of prescription of aerosolized antibiotics in mechanically ventilated patients from participating units in 2017. An electronic platform survey was undertaken, based on a prior survey [13, 14] modified using the checklist rules suggested by Pulcini and Leibovici [15], between the 1st of February 2017 to the 30th of April 2017. The survey was developed and administered by CONELEC (Tarragona, Spain). The survey was distributed by invitation from members of the Steering Committee (Appendix 2). Only one professional per unit completed the questionnaire to avoid data duplication, although we did not specify the grade or seniority of respondents. No informed consent or ethical board authorization was required.

Questionnaire

Data were collected on the prescription of nebulized drugs, including the indications for use, the agents administered, dose, and aerosolization devices. Regarding dosing regimens, the questionnaire proposed pre-defined doses of colistin, tobramycin and amikacin for therapy of VAP and VAT. Respondents could record as many indications as they wished. The protocol and questionnaire of this project has been reported elsewhere [16].

Study population

Pediatric and neonatal ICUs were not eligible. Sites with five cases or fewer per month were considered ineligible. The study was designed to collect information on administration practices in units where nebulized antibiotics where used as "standard" prescription in ventilated adults.

Quality control assessment was performed by two investigators (MRR and JA) to ensure consistency and identify potential mistakes. In brief, reports with multiple missing data were identified (the clinical indications sections were mandatory) or major inconsistencies (such as contradictory responses). Unit responses which failed this assessment were excluded. National coordinators (steering committee) were informed, but individual investigators were not contacted. ICUs which reported no use of nebulized antibiotics were analyzed separately, with a focus on their reasons for avoiding nebulization therapy.

Definitions

VAT was defined as the presence of signs of systemic infection and changes in sputum characteristics without the presence of a new radiographic infiltrate in patients receiving mechanical ventilation for at least 48 h. VAP was defined as the presence of progressive, new radiographic infiltrate, signs of systemic infection, changes in sputum characteristics and detection of the causative agent in patients with mechanical ventilation for at least 48 h [10]. Adjunctive use was defined as nebulized antibiotics administered in addition to standard first-line IV antibiotics. Substitution was defined as nebulized antibiotics administered to patients instead of IV antibiotics.

Statistical analysis

Responses were analyzed by using descriptive statistics, reporting proportions (percentages). Data from 2014 have been extracted from reference [13]. Chi-square test was performed to evaluate a potential association between the geographical location of the participants and the particulars of the prescription of nebulized agents, such as their indications or the criteria for initiation of therapy [17].

Availability of data and materials The datasets supporting the conclusions of this article are available upon request.

Results

Respondents from 410 ICUs completed the survey, and the majority (69.7%) reported more than 10 years of clinical experience. After quality control (Fig. 1), 261 ICUs (177 from Europe), with more than five patients treated with nebulized antibiotics in the previous survey month, were eligible for the study (Fig. 2). The majority of ICUs were medical-surgical ($n = 210$, 80.5%). The remaining ICUs were pulmonary ($n = 27$, 10.3%), trauma ($n = 12$, 4.6%), neurosurgical ($n = 8$, 3.1%) and cardiac surgery ($n = 4$, 1.5%).

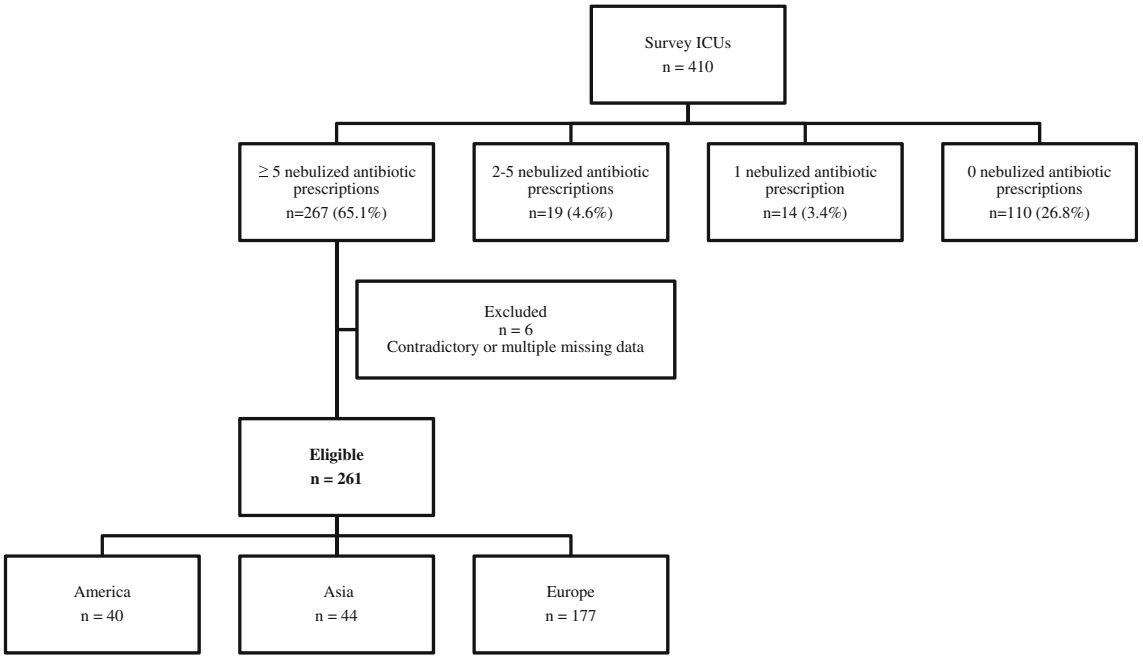

Fig. 1 Flow chart of ICU surveys

Aerosolized antibiotics were not prescribed in 110 (26.8%) ICUs. The main reasons for not using nebulized antibiotics were lack of appropriate material/resources (43.9%), lack of personal experience in their administration (35.1%), lack of local recommendation (15.8%), weak evidence to support indications (17.5%), and lack of clinical guidelines (12.3%). Even amongst prescribing units, only 25.7% have a specific protocol directing the use of aerosolized antibiotics and the majority (85.1%) believed in the necessity of further randomized control trials to support their use.

Aerosolization devices

Distribution of devices was heterogeneous, and 34 (13%) respondents were not aware of the brand or type of nebulizer used in their ICU. Amongst respondents ($n = 227$), jet nebulizer was the most commonly used (50.4%, $n = 114$), followed by ultrasonic nebulizer (30.7%, $n = 70$), and vibrating-mesh (13.8%, $n = 31$). The remaining 5.1% reported to use "other nebulizers". The majority of nebulizers ($n = 167$ respondents) were integrated in the ventilator circuit (71.9%, $n = 120$). Regarding ventilator circuit filter change ($n = 216$ respondents), 38.4% ($n = 83$) of units changed the nebulizer filters every day, 25.3% ($n = 55$) twice a week and 18.5% ($n = 40$) once a week. Only 18.1% ($n = 39$) changed filter after every nebulization, as recommended by the manufacturers and guidelines. Ventilator settings when prescribing aerosolized antibiotics are detailed in Table 1.

Antimicrobial prescription

The most common indications (Table 2) for nebulized therapy in respondents were VAP (74.3%, $n = 194$) and VAT (49.4%, $n = 129$), although 166 of 261 (63.6%) only treated in the presence of multi-drug resistant organisms (MDRO). In Asia, after VAP, colonization with MDRO was the second most common indication. Interestingly, the use of aerosolized antibiotics for the prevention of infections was almost exclusively restricted to Asia (29.5%, p value <0.05). In comparison to the 2014 survey (Table 3), respondents were more likely to use nebulized antibiotics for the treatment of VAP. In contrast, a significant reduction (p value <0.05) of use for prophylaxis (50.6% to 7.7%) and treatment of colonization (52.9% to 25.3%) was also reported.

Table 4 displays the use of aerosolized antibiotics for treatment (N = 230). Directed therapy with positive pulmonary specimen cultures was the most prevalent indication (91.7%, $n = 211$). However, respondents from Asia used empirical nebulized antibiotics more frequently than the other geographical regions. Empirical therapy was based on an increase of secretions, fever and leucocytosis, and a decrease in PaO2/FiO2 ratio or infiltrates on chest radiograph. Compared to 2014 (Table 5), guidance of prescription did not have any differences.

Of note, amongst the 129 units which reported using nebulized antibiotics for VAT therapy, 51.2% ($n = 66$) used nebulized antibiotics as adjunctive therapy only when MDRO were present, 26.4% ($n = 34$) used as adjunctive therapy without considering MDRO and only 17.1% ($n = 22$) used as

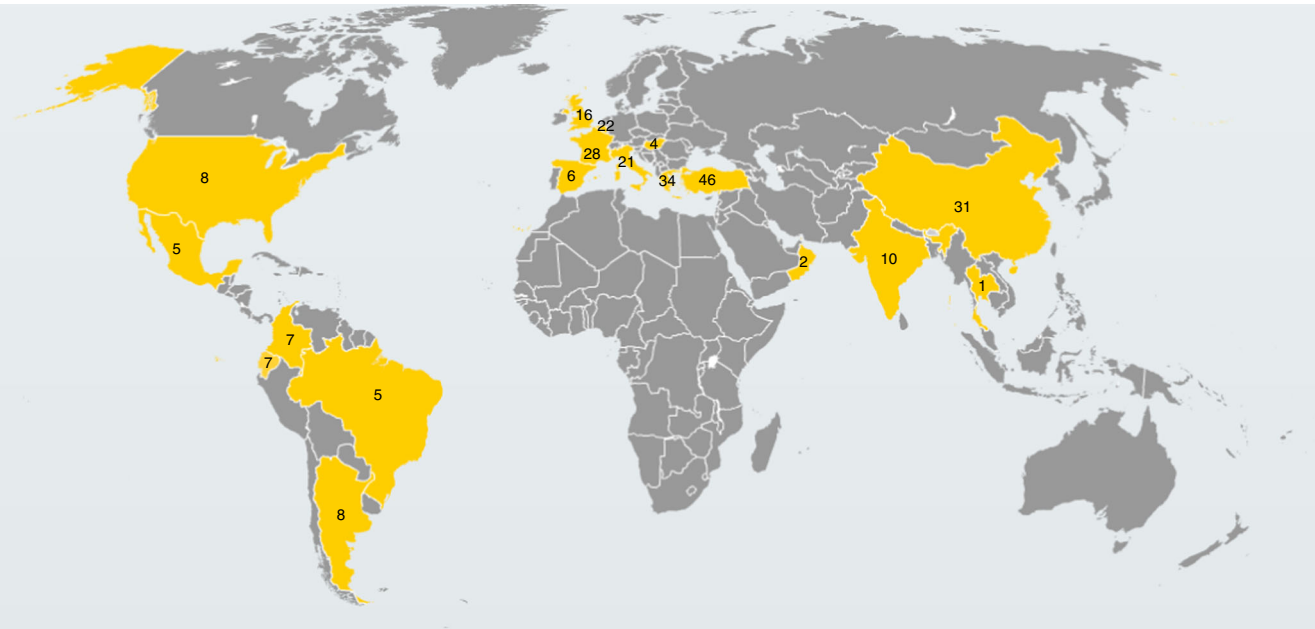

Fig. 2 Map of eligible ICUs *(map made on GunnMap)*

substitution therapy (seven non-respondents). Amongst the 132 respondents that did not select VAT as an indication, 56.1% ($n = 74$) never used nebulized antibiotics for VAT and 24.2% ($n = 32$) did not believe VAT should be treated.

Drugs and dosages

The most common prescribed drugs ($n = 236$) were colistin methanesulfonate (CMS) (57.6%, $n = 136$) and colistin base (41.9%, $n = 99$), followed by amikacin (31.4%, n = 74) and tobramycin (25.4%, $n = 60$). Use of other drugs was sporadic (see Table 6). Interestingly, there was considerable geographic differences in the use of specific drugs: CMS was the most frequent drug used in Europe, whilst colistin base was commonest in Asia and amikacin in the Americas (Table 6).

CMS doses tended to be used at higher median doses (6 and 9 million International Units (MIU), depending on the region) for VAP when compared with VAT (Online Resource Table 7), although there was considerable heterogeneity. For instance, the most commonly prescribed dose of CMS was 2 MIU every 8 h for VAP (28.4%, $n = 55$; total N = 194) compared with 1 MIU every 8 h for VAT (26.3%, $n = 30$; total $n = 114$). There was high regional heterogeneity in the most commonly prescribed doses. The most frequent dosage reported for VAP in the Americas (27 units) was 3 MIU 8/8 h ($n = 7$, 25.9%), compared with 2 MIU 8/8 h ($n = 45$, 30.8%) in Europe (146 units) and with 1 MIU 8/8 h ($n = 10$, 47.6%) in Asia (21 units) (Table 7). In contrast, the most commonly prescribed doses for VAP and VAT with amikacin ($n = 111/65$) were 15 mg/kg/12 h (35.1% and 43.1%, respectively) (see Online Resource Table 8). Regarding tobramycin (Online Resource Table 9) the most common doses used for VAP and VAT ($n = 91/61$) were 600 mg/day (44% and 34.4%, respectively).

During the assessment period (1 month), respondents reported the following adverse effects of nebulized antibiotics as common: bronchospasm (23.8%), cough (17.6%), moderate decrease in O2 saturation (16.9%), moderate increase in peak inspiratory pressure (14.6%), expiratory filter occlusion (8.8%), and nephrotoxicity (6.1%). More rarely encountered side effects (<5.4%) were: severe decrease in O2 saturation, severe increase in peak inspiratory pressure, arrhythmias, neurotoxicity and anaphylaxis.

Table 1 Ventilator settings when prescribing nebulized antibiotics

Ventilator changes	Total (N = 189)[a], *n* (%)[b]
Change characteristics of ventilator breath	48 (25.4)
Increase PEEP	21 (11.1)
Decrease inspiratory flow	20 (10.6)
Use a constant inspiratory flow	48 (25.4)
Increase inspiratory time	38 (20.1)
Insert an end-inspiratory pause	13 (6.9)
Increase tidal volume	21 (11.1)
Stop the active modifier	54 (28.6)
Place a filter on the expiratory limb	56 (29.6)
Use sedation to avoid discoordination with ventilator	26 (13.8)
Use continuous flow or breath actuation	19 (10.1)

PEEP positive end-expiratory pressure

[a] Non-responders eliminated

[b] Note that responders could indicate as many settings as they wanted, so the sum of results will be different from 100%

Table 2 Indications for the use of nebulized antibiotics

Characteristic	Asia (N = 44), *n* (%)[a]	Europe (N = 177), *n* (%)[a]	America (N = 40), *n* (%)[a]	Total (N = 261), *n* (%)[a]
VAP treatment	33 (75)	134 (75.7)	27 (67.5)	194 (74.3)
VAT treatment	13 (29.5)	93 (52.5)	23 (57.5)	129 (49.4)
MDRO colonization	15 (34.1)	43 (24.3)	8 (20)	66 (25.3)
Prophylaxis	13 (29.5)*	6 (3.4)	1 (2.5)	20 (7.7)

VAP ventilator-associated pneumonia, *VAT* ventilator-associated tracheobronchitis, *MDRO* Multi-drug resistant organisms

[a] Note that responders could denote as many indications as they wanted, so the sum of results will be different from 100%

*p value < 0.05, when compared with Europe

Discussion

The present study reports an extended (and heterogeneous) use of adjuvant nebulized antimicrobial agents in ICU patients receiving mechanical ventilation in 2017. Prescription remained restricted to two families of old drugs (colistin and aminoglycosides). Over 90% of units reported use only in response to positive cultures. Units in Asia were distinct in reporting a high rate of empirical use. Three in four ICUs prescribed aerosolized antibiotics for VAP and half for VAT, although 2/3 of respondents limited its use only in the presence of multi-drug resistant organisms. Most ICUs reported the use of devices that are suboptimal for the generation of appropriate particle size required to reach the distal airways. Moreover, a lack of standardization, with only a minority removing expiratory filters during nebulization raises concerns over both safety and efficacy.

Our survey demonstrates that practitioners continue to frequently use antibiotic nebulization in critically ill patients. It is clear from our survey that the absence of high-quality research in this area is associated with considerable heterogeneity of practice, and suggests significant scope for standardization and improvement of practice. Interestingly, the majority of units used nebulized antimicrobials for VAP and/or VAT therapy, whilst only 25% were using them for MDRO colonization and 8% as prophylaxis, a significant reduction since our last survey (53% and 51%, respectively). These data suggest a shift in the use of these agents to treat confirmed pulmonary infections relative to 2014, although further follow-up practice surveys will be required to confirm this apparent shift. This change may reflect several factors, including different practices in different geographical regions, the impact of stewardship strategies, emergence of resistance or an absence of high quality evidence and randomized control trials. Interestingly, a recent meta-analysis [18] reported that prophylactic aerosolized antibiotics in mechanically ventilated subjects reduced the occurrence of VAP, without a significant effect on ICU mortality or occurrence of VAP due to MDR pathogens. Considering geographical variations, Asian respondents continue to report the highest use of nebulized antibiotics for both MDRO colonization and prophylaxis, although our survey could not ascertain reasons for this variation in practice.

Regarding VAP and VAT, there was no significant change between 2014 and 2017. As suggested by a well-designed meta-analyses [11] and the 2017 ESCMID Guidelines [12], further high quality research is required. Given the recent nature of the ESCMID guidance, which was published after this survey was conducted, it will be interesting to see if practice changes again in the near future. The clinical challenges due to the increase in extremely- or pan-resistant Gram-negative organisms, create situations reminiscent of the pre-antibiotic era. Our findings confirm that clinicians tend to use aerosolized antibiotics with "old drugs" as 'salvage therapy' in patients with multi-resistant organisms in the face of limited therapeutic options, despite the weak evidence supporting efficacy and

Table 3 Comparison between 2014 survey and 2017 on indications for the use of nebulized antibiotics

Characteristic	2014 Total (N = 87), *n* (%)[a]	2017 Total (N = 261), *n* (%)[a]	*p* value
VAP treatment	58 (66.7)	194 (74.3)	0.166
VAT treatment	56 (64.4)	129 (49.4)	0.016
MDRO colonization	46 (52.9)	66 (25.3)	<0.001
Prophylaxis	44 (50.6)	20 (7.7)	<0.001

VAP ventilator-associated pneumonia, *VAT* ventilator-associated tracheobronchitis, *MDRO* Multi-drug resistant organisms

[a] Note that responders could denote as many indications as they wanted, so the sum of results will be different from 100%

Table 4 Guided prescription of nebulized antibiotics

Characteristic	Asia (N = 30)[a] *n* (%)[b]	Europe (N = 160)[a] *n* (%)[b]	America (N = 40)[a] *n* (%)[b]	Total (N = 230)[a] *n* (%)[b]
Directed	19 (63.3)*	155 (96.9)	37 (92.5)	211 (91.7)
Empirically	16 (53.3)*	25 (15.6)	4 (10)	45 (19.6)

[a] Non-responders eliminated

[b] Note that responders could denote as many indications as they wanted, so the sum of results will be different from 100%

*p value < 0.05, when compared with Europe

personal reports of significant respiratory and systemic adverse events. Recent trials with aerosolized fosfomycin or amikacin [19, 20] failed to demonstrate efficacy in severe pneumonia. Novel systemic therapies in clinical development or recently approved, such as ceftolozane-tazobactam, ceftazidime-avibactam, cefiderocol, or meropenem-vaborbactam, amongst others are alternative strategies which should hopefully improve the fight against MDR organisms.

Mechanically ventilated patients treated with nebulized antibiotics could be associated with shorter clinical resolution, using either adjunctive or substitution strategies, although it was supported by weak evidence with randomized clinical trials differing from observational studies. Moreover, this effect did not appear to translate into an improvement in mortality or mechanical ventilation duration [11]. Although adverse events were rarely reported in observational studies, respiratory and other adverse events were common in randomized trials. However, there is also the potential to reduce side effects, with a substitution strategy reported to significantly reduce nephrotoxicity (risk difference − 0.33 (95%CI —0.54 to −0.12)) when compared with systemic administration [11]. In terms of safety, a randomized, single-blind study [21] confirmed lower nephrotoxicity of aerosolized colistin versus systemic. Currently, there is no known optimum dose and considerable variability amongst the different reports [22–25], although the most commonly used doses are consistent with this survey [23, 25, 26].

The results from our survey reflect the uncertainty amongst clinicians and researchers regarding VAT, with 24% of respondents indicating that VAT should not be treated. This is an area which will need careful consideration in future randomized trials, as will uncertainty about the diagnostic criteria for VAP [10]. Although a wide number of nebulized antimicrobials were described in this study, only colistin and aminoglycosides were commonly used. There is lack of published pharmacokinetic, clinical outcome, or drug administration data supporting the use of many of these drugs via the inhaled route. From all the existing research [22–24, 27], colistin is the best-understood drug, and consequently the most frequently used in this survey.

To maximize therapeutic efficacy, aerosolization of antimicrobials in ventilated patients requires specific technical requirements [26]. When these requirements are not followed, there are risks of either adverse events or therapeutic failure in mechanically ventilated patients with pneumonia. Optimization of ventilator settings is required to decrease inspiratory flow turbulences and increase nebulization efficiency [27]. Table 1 reports ventilator settings and the findings suggest that educational measures are required to optimize administration. If adequate coordination between the patient and the ventilator is not achieved, implementing sedation with short acting sedative agents are required. A systematic review [28] reported variable aerosol delivery during mechanical ventilation, depending on the device used. For optimal nebulized drug delivery, vibrating-mesh type devices are the most efficient [24, 27], although these devices were used by only 14% of prescribers. Jet nebulizers were used by over half of prescribers, although these deliver less than 15% of the dose to the lung. Only 18% ($n = 39$) of units change filters after every nebulization, as recommended by the manufacturers and guidelines. Lack of removal has been associated with obstruction, increase in respiratory pressure and, if unrecognized, cardiac arrest [27]. These data highlight the need of further educational programmes to improve patient safety, and enhance the effective delivery of these drugs. It is possible that this lack of standardized, safe procedures is related to the high rate of adverse effects reported in this survey.

This survey has several limitations. First, we cannot be certain that all respondents answered questions in the same way.

Table 5 Comparison between 2014 survey and 2017 guided prescription of nebulized antibiotics

Characteristic	2014 Total (N = 76)[a], *n* (%)[b]	2017 Total (N = 230)[a], *n* (%)[b]	*p* value Total (N = 230), *n* (%)
Directed	69 (90.8)	211 (91.7)	0.797
Empirically	15 (19.7)	45 (19.6)	0.974

[a] Non-responders eliminated

[b] Note that responders could denote as many indications as they wanted, so the sum of results will be different from 100%

Table 6 Types of antibiotics nebulized and reported frequency of use by geographic location

Antibiotic type	Asia (N = 29)[a], *n* (%)[b]	Europe (N = 168)[a], *n* (%)[b]	America (N = 39)[a], *n* (%)[b]	Total (N = 236)[a], *n* (%)[b]
CMS	8 (27.6)*	110 (65.5)	18 (46.2)*	136 (57.6)
Colistin base	11 (37.9)	67 (39.9)	21 (53.8)	99 (41.9)
Amikacin	6 (20.7)	44 (26.2)	24 (61.5)*	74 (31.4)
Tobramycin	8 (27.6)	37 (22)	15 (38.5)*	60 (25.4)
Gentamicin	7 (24.1)*	17 (10.1)	6 (15.4)	30 (12.7)
Other	10 (34.5)	27 (16.1)	18 (46.2)	55 (23.3)

CMS colistimethate sodium

[a] Non-responders eliminated

[b] Note that responders could denote as many antibiotics as they wanted, so the sum of results will be different from 100%

*p value < 0.05, when compared with Europe

For instance, although we defined VAP and VAT we cannot be certain that respondents used those criteria when answering the questions. Second, data was not always complete from every unit and we cannot exclude this being the result of systematic bias. This questionnaire was only completed by one healthcare professional in each intensive care unit, and thus it was not able to evaluate possible intra-unit variation. Although we recruited a relatively large number of units, we did not achieve universal coverage and there is likely to be a degree of responder bias. We also urge caution in reading too much into variations between geographical regions, as these may reflect different sampling populations rather than genuine differences in practice. We also did not recruit from units in Africa and so cannot comment on practice in this continent. Finally, through our efforts to expand the scope of this survey, the comparison with previous iteration must again be treated with caution as the surveyed units were not identical and variation may result from this rather than genuine change in practice over time. This survey has a number of strengths, including its worldwide coverage of intensive care units from low, middle and high-income countries. We were able to recruit a reasonably large number of units, and through careful data quality control we maximized the quality of the data.

In summary, our findings confirm that nebulized antimicrobial agents in mechanically ventilated patient's remains a common clinical practice, particularly for MDRO in VAP (and VAT). Use for colonization and prevention is reported to be less common in most of the world and this is likely to reflect a change in clinical practice over the past few years. Although dosage of colistin used for VAP is double of that used for VAT, marked heterogeneity between geographical areas in terms of choice of antimicrobial agents and dosage regimens was noted. Of additional concern is the lack of standardization of nebulization devices and their safe integration into ventilator circuits. Interestingly, our study emphasizes the gap that exists between clinical practice and the evidence base underpinning it. The publication of well-designed meta-analysis [11] and guidelines, such as the 2017 ESCMID consensus statement and evidence-based guidelines [12, 27] are welcome but are limited by the current evidence gaps. Our findings suggest that a combination of improved education in the safe use of nebulized therapies and conducting high-quality randomized trials is an urgent need in an era of shortage of antimicrobials for MDRO.

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Compliance with ethical standards

Guarantor statement and author contribution The first author (JA) undertook the literature search, data analysis, first draft manuscript preparation and is the guarantor for this article. CSL, MRR and JR were responsible for the study design. MRR and JA performed quality assessment. A steering committee (Appendix 2) approved the protocol, provided advice and was responsible for dissemination of the survey. All authors contributed scientifically in subsequent drafts and have approved the final version of the manuscript.

Conflict of interest JR has received research grants and consulting fees from Bayer and Genentech. ZZ has received grants from Zhejiang provincial natural science foundation of China (LGF18H150005). ACM is supported by a Wellcome Trust Clinical Research Career Development Fellowship (WT 2055214/Z/16/Z). MB has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Cidara, Gilead, Menarini, MSD, Pfizer, The Medicine Company, Paratek, Tetraphase and Vifor. SE has received research grants and research support: Aerogen Ltd., Fisher and Paykel Healthcare, Hamiton Medical; and consulting, honoraria or lecture fees from Aerogen, La diffusion technique française, and Baxter. SB has received fees for advisory board activity from the Bayer advisory board on nebulized amikacin. The remaining authors did not disclose conflicts of interest.

Ethical approval Because this analysis was based on a clinical practice survey, institutional review board approval was not required.

Informed consent As this study does not have individual specific data of patients, informed consent was not applicable.

Appendix 1 - SANEME 2 Study Investigators (Collaborators)

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