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Use of Nebulized Antimicrobials for the Treatment of Respiratory Infections in Invasively Mechanically Ventilated Adults: A Position Paper from the European Society of Clinical Microbiology and Infectious Diseases.

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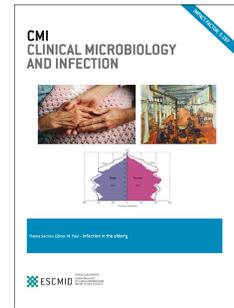
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Use of Nebulized Antimicrobials for the Treatment of Respiratory Infections in Invasively Mechanically Ventilated Adults:

A Position Paper from the European Society of Clinical Microbiology and Infectious Diseases.

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## ABSTRACT

With an established role in cystic fibrosis and bronchiectasis, nebulized antibiotics are increasingly being used to treat respiratory infections in critically ill invasively mechanically ventilated adult patients. Although there is limited evidence describing their efficacy and safety, in an era of need for new strategies to enhance antibiotic effectiveness because of a shortage of new agents and increases in antibiotic resistance, the potential of nebulization of antibiotics to optimize therapy is considered of high interest, particularly in patients infected with multidrug-resistant (MDR) pathogens. This Position Paper of the European Society of Clinical Microbiology and Infectious Diseases provides recommendations based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology regarding the use of nebulized antibiotics in invasively mechanically ventilated adults, based on a systematic review and meta-analysis of the existing literature (last search July 2016). Overall, the panel recommends to avoid use of nebulized antibiotics in clinical practice, due to a weak level of evidence of their efficacy and the high potential for underestimated risks of adverse events (particularly, respiratory complications). Higher quality evidence is urgently needed to inform clinical practice. Priorities of future research are detailed in the second part of the Position Paper as a guidance for researchers in this field. In particular, the panel identified an urgent need for randomized clinical trials of nebulized antibiotic therapy as part of a substitution approach to treatment of pneumonia due to MDR pathogens.

## INTRODUCTION

The administration of nebulized antibiotics is formally approved by regulatory bodies for the management of patients with bronchiectasis or cystic fibrosis (CF) [1]. However, the clinical challenges posed by extremely- or pan-drug resistant pathogens Gram-negative pathogens are causing significant concern for clinicians, creating situations reminiscent of the pre-antibiotic era. Therefore, despite lacking high-quality efficacy and safety data, clinicians worldwide are increasingly using antibiotic nebulization to optimize the treatment of respiratory infections in critically ill invasively mechanically ventilated adult patients [2, 3].

The recommendations of this document, based on the highest-level available evidence, are intended to provide guidance for clinicians, nurses and respiratory therapists caring for adults under mechanical ventilation, as well as for antibiotic stewardship doctors and pharmacists. This Position

Paper consists of two parts: a) evidence-based recommendations developed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [4]; and b) discussion on future research priorities.

## METHODS

### Consensus Statement

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Critically Ill Patients (ESGCIP) received approval from the ESCMID Executive Committee to develop a Position Paper regarding the nebulization of antibiotics in critically ill invasively mechanically ventilated adult patients, using GRADE methodology to evaluate the available evidence.

A Task Force was convened to develop this document, including critical care, respiratory and internal medicine physicians, anesthesiologists, clinical microbiologists, nurses, pharmacists and medical education specialists. Panel expert participants were suggested by the chair of the ESGCIP (JRe) and approved by the ESCMID Executive Committee, based on their prior clinical experience or on their expertise in clinical trials and publications, ensuring a true multidisciplinary approach. The systematic search of the literature, the meta-analysis and the application of the GRADE methodology were conducted in collaboration with the Iberoamerican Cochrane Centre (Barcelona, Spain). No industry input occurred into the development of this Position Paper and no industry representatives were present at any meeting. There was no industry funding for any aspect of this project.

As a complement to this Position Paper providing evidence-based recommendations, another document compiling the key practical considerations of antibiotic nebulization was also written by a panel of experts [5] to help standardisation in their delivery in order to improve the safety in their administration.

### Definition of the review questions

Every member of the panel of experts was asked to independently create a list of clinically-relevant questions to evaluate the effects of nebulized antibiotics. All questions were discussed and re-evaluated by the panel until a consensus of review questions was reached. Eight questions were finally formulated by the panel, under the PICO (Population-Intervention-Comparison-Outcome) structure.

### Definition of the Population

The targeted population was defined as adult critically ill patients with a respiratory infection, receiving support with invasive mechanical ventilation. The respiratory infections considered were ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP). The panel of experts considered severe hospital-acquired pneumonia (HAP) requiring invasive mechanical ventilation to be equivalent to VAP for the purposes of evaluating the use of nebulized antibiotic

therapy. The susceptibility pattern of the pathogens was simplified to being susceptible or resistant (including multidrug- (MDR), extensively drug- or pandrug-resistant bacteria, as defined by the Center of Disease Control and Prevention [6]). Mechanical ventilation could be provided through any kind of invasive artificial airway (nasotracheal tube, orotracheal tube or tracheostomy).

#### Definition of the Intervention

The intervention was defined as the administration of nebulized antibiotics, such as ceftazidime, colistin or aminoglycosides. Antibiotic delivery needed to be performed with devices generating particles smaller than 5 $\mu$ m of diameter (jet nebulizers, ultrasonic nebulizers or vibrating-mesh nebulizers) as is required to reach the lung parenchyma.

Two different strategies of administration were considered clinically relevant (Table 1):

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

#### Definition of the Comparison

The comparison was defined as the administration of IV antibiotics such as colistin or aminoglycosides, added to standard first-line IV antibiotics.

#### Definition of the Outcomes

In order to reach the most accurate evidence-based recommendations, the panel of experts considered it vital to evaluate both the efficacy and the safety of antibiotic nebulization. Therefore, they were asked to independently create a list of potentially relevant outcomes regarding both efficacy and safety. After a unique extensive list of outcomes was created, the panel were asked to rate all the proposed outcomes through a DELPHI questionnaire. Outcomes were classified as being “non-important” (rated 1 to 3), “important” (4 to 6) or “critical” (7 to 9). Only the “critical” outcomes (with a mean score equal to or more than 7), were evaluated in the systematic review and meta-analysis [7]; the list of outcomes evaluated can be found in Appendix 1.

To reach the maximal accuracy, each efficacy outcome was evaluated according to both the susceptibility pattern of the pathogen and the administration strategy. This contrasted the approach for evaluating the safety outcomes, as none of these were considered to be influenced by the susceptibility pattern of the pathogen, and as such, it was not taken into account for the safety analysis. Occurrence of cardio-respiratory complications was also not considered to be influenced by the administration’s strategy.

### Inclusion & Exclusion Criteria

Inclusion criteria were directly derived from the definitions of PICO components. The following population or types of intervention were excluded:

- Population: neonatal and pediatric patients; adult patients without invasive mechanical ventilation support (therefore including non-invasive mechanical ventilation and high-flow oxygenotherapy); colonised patients, where colonisation was defined as presence of purulent tracheal secretions without infectious clinical signs and radiological infiltrates; patients with cystic fibrosis or other non-cystic fibrosis bronchiectasis were excluded as they were considered to have particular characteristics deserving a separate evaluation; patients with particular characteristics such as burned patients, patients receiving support with renal replacement therapies and/or cardiopulmonary support with extracorporeal life support devices were also excluded from the study, due to the lack of knowledge on the impact these techniques might have in the technique being evaluated.
- Intervention: nebulisation delivered with devices other than jet nebulisers, ultrasonic nebulisers and/or vibrating-mesh nebulisers, where the device would be likely to produce particles larger than 5  $\mu$ m in diameter and therefore less likely to reach the lung parenchyma; other practices such as tracheal instillation (either manually or with a pneumatic pump) were also rejected.

### Systematic Review & Meta-analysis

Herewith, we provide general information on the methodology used. For further detail on the characteristics of the included studies, and evaluation of quality and risk of bias, etc., we suggest referring to the systematic review and meta-analysis reported elsewhere [7].

### Systematic search of the literature

After the definition of the PICO questions and exclusion criteria, a search strategy was created (list of terms detailed in the Appendix 2). A systematic search was conducted in three different databases (MEDLINE Database, EMBASE and The Cochrane Library) in June 2014 and repeated in March 2015 and in July 2016. No restrictions of language, time or type of publication were imposed. A total of 1435 studies were identified.

### Study selection

Three authors (SB, GP and CSL) independently assessed all the studies identified in the literature search by screening their titles and abstracts. Disagreements between reviewers were resolved by consensus. In case of persistent disagreement, a fourth independent reviewer (IS) determined the eligibility of the study. Authors of articles considered for rejection due to lack of information (e.g. type of device used), were contacted to provide further details. Only randomized-controlled trials (RCT), observational studies and case series evaluating efficacy and/or safety of the technique were eligible to be included in the meta-analysis. Review articles, expert opinion articles, and other articles having not undergone a peer-review process, like abstracts from congresses, were manually rejected. After assessment for inclusion, manual adjusting for duplicates and revision of the

manuscripts in relation to our inclusion and exclusion criteria, only 11 studies were included in the meta-analysis [8-18].

A final search was repeated in July 2016, finding only one additional RCT [19] that met the criteria for its inclusion in our meta-analysis. This paper was only considered eligible for inclusion in the analysis of safety outcomes (and not in the analysis of efficacy outcomes) due to its high risk of bias: an intention-to-treat analysis of a non-inferiority study, single blinded and with a loss of patients to follow up of 18.7 %.

#### Data Items & Collection

Based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [20], a data sheet was developed for data extraction for each included study. Study design, inclusion & exclusion criteria of patients, administration strategy, drugs and type of nebulizer used, main and secondary outcomes evaluated and adverse events reported were all collected for each study in an individual data sheet. Data extraction was performed by one of the authors (CSL) and checked by an independent reviewer (SP). Authors of articles with relevant non-reported or unclear data were contacted to provide further information.

#### Risk of bias assessment

Risk of bias for randomized controlled trials and observational studies was evaluated based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [20] by one of the authors (CSL) and checked by a second independent reviewer (SP). Details are reported elsewhere [7].

#### Statistical analysis

Analysis of all outcomes was performed according to the design of the study, as reported in March 2017 [7]. Pooled evaluation of RCT and observational studies was also performed for each outcome due to the small sample size of included studies, so a potential existence of clinically significant trends could be detected. Risk ratio (RR) and odds ratio (OR) were used for the evaluation of binary outcomes for RCTs and observational studies respectively. Risk difference (RD) was also used whenever necessary. Mean difference (MD) was used for the evaluation of continuous outcomes. All statistical measures were calculated with a 95% confidence interval (CI). Random-effects meta-analysis through the Mantel-Haenszel model approach was performed to obtain pooled study results of RCTs and observational studies. Higgins I<sup>2</sup> test was predefined to quantify heterogeneity (I<sup>2</sup> ≤ 25% for low heterogeneity; 25% ≤ I<sup>2</sup> ≤ 50% for moderate heterogeneity; I<sup>2</sup> ≥ 50% for high heterogeneity). Meta-regression was not performed given the low number of studies included in the meta-analysis. All statistical analyses were performed using Review Manager (RevMan) version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Denmark, 2014).

#### Development of Recommendations

The results of the systematic review and meta-analysis were evaluated under the GRADE methodology [4] to achieve an evidence-based recommendation for each one of the initial PICO questions.

Values and preferences relating to both patients and costs were taken into account by the panel of experts. Regarding the values and preferences of the patients, the Task Force considered that none of the interventions (nebulized or IV administration) could be considered particularly uncomfortable or invasive for the patients. Therefore, given the non-significant difference, this scenario was considered not value-sensitive. Regarding the costs and resource use, no economic studies were identified assessing the cost of antibiotic nebulization. The panel of experts estimated the cost of nebulized antibiotics to be similar to the cost of average intravenous antibiotic therapy. However, nebulized antibiotics are usually added to systemic therapy, therefore the cost of the total therapy would be higher.

## EVIDENCE-BASED RECOMMENDATIONS

### Ventilator-associated Pneumonia (VAP)

#### 1. VAP caused by Resistant Pathogens

1.1. **Adjunctive Strategy:** In mechanically ventilated patients already receiving conventional IV therapy, including colistin or aminoglycosides, for a VAP caused by resistant pathogens, should nebulized antibiotics such as colistin or aminoglycosides be used, as adjunctive therapy to systemic antibiotics, as compared to absence of local treatment, to improve clinical outcome?

#### Summary of the Evidence

Our systematic review identified one RCT [8] and three observational studies [9, 10, 11], involving a total of 458 patients, evaluating the efficacy of nebulized antibiotics under this administration strategy for the treatment of VAP caused by resistant organisms. Two studies [8, 9] employed a vibrating mesh nebulizer, one [10] used both jet and vibrating-mesh devices, and one [11] both jet and ultrasonic devices.

No significant difference in clinical resolution rates were observed in the RCT (48 patients; OR=1.30; 95%CI 0.22-7.55). The meta-analysis of the observational studies showed higher rates of clinical resolution in the group of patients receiving nebulized antibiotics (389 patients; OR=0.51; 95%CI 0.34-0.77; I<sup>2</sup>=0%), significantly shorter duration of MV support (303 patients; 3.72 days less; 95%CI from -5.86 to -1.59 days; I<sup>2</sup>=0%) and significantly lower VAP-related mortality (181 patients; OR=0.5; 95%CI 0.26-0.96; I<sup>2</sup>=0%), even though all-cause mortality did not differ significantly. No significant differences were seen for duration of ICU stay or development of superinfections. No evidence was provided for the emergence of resistant strains.

The overall quality of evidence is very low, due to serious imprecision and indirectness of the results for the majority of the outcomes. The safety analysis evidenced a higher incidence of respiratory

complications (low quality of evidence) associated with nebulization, and no differences in systemic toxicity (nephrotoxicity and neurotoxicity; very low quality of evidence).

#### Recommendation

We suggest avoiding the use of nebulized antibiotics such as colistin or aminoglycosides, added to conventional IV antibiotic therapy already including IV colistin or aminoglycosides for the treatment of VAP caused by resistant pathogens as standard clinical practice.

Weak recommendation. Very low quality of evidence.

Remark: We recommend avoiding their use particularly in patients with severe hypoxemia (PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 200) or having shown signs of poor pulmonary reserve, tending to rapid lung de-recruitment.

#### Rationale for the Recommendation

Evidence obtained from observational studies suggested that the addition of nebulized antibiotics such as colistin or aminoglycosides to a conventional IV antibiotic therapy already involving these antibiotics, might be effective against VAP caused by resistant pathogens, mainly in terms of clinical resolution and duration of mechanical ventilation support. The weak quality of this evidence was balanced against the fact that nebulisation of antibiotics was associated with higher risk of respiratory complications. As a conclusion, the panel of experts decided to recommend their avoidance in clinical practice.

1.2. Substitution Strategy- In mechanically ventilated patients already receiving conventional IV therapy, for a VAP caused by resistant pathogens, should nebulized antibiotics such as colistin or aminoglycosides be exclusively used, as compared to conventional IV therapy with additional IV colistin or aminoglycosides, to improve clinical outcome?

#### Summary of the Evidence

Only one observational study [12] addressed the administration of nebulized antibiotics under this strategy, in cancer patients. A jet nebulizer was the device used in this study involving 32 patients. Higher rates of clinical resolution were associated with the administration of nebulized antibiotics (OR=9.53; 95%CI 1.85-49.2), but no significant differences were found for the rest of the efficacy outcomes analysed, duration of mechanical ventilation support and ICU stay. The overall quality of the evidence was very low due to the serious indirectness and very serious imprecision of the results for all the outcomes. The safety evaluation determined that nebulized antibiotic administration was associated with a higher incidence of respiratory complications (low quality of evidence) and reduced nephrotoxicity (low quality of evidence) associated to their use under the substitution strategy. No differences were observed in terms of other systemic toxicities.

## Recommendation

We suggest avoiding the use of nebulized antibiotics such as colistin or aminoglycosides instead of their IV administration for the treatment of VAP caused by resistant pathogens as standard clinical practice

Weak recommendation. Very low quality of evidence.

Remark: We recommend avoiding their use particularly in patients experiencing severe hypoxemia (PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 200) or demonstrating signs of poor pulmonary reserve, tending to rapid de-recruitment.

## Rationale for the Recommendation

Despite the weak evidence suggesting that the administration of nebulized antibiotics such as colistin or aminoglycosides instead of the administration of those IV antibiotics might be a good option for the treatment of VAP caused by resistant pathogens mainly in terms of clinical resolution and less occurrence of nephrotoxicity, the recommendation of the guideline panel was to avoid their use in standard clinical practice. The rationale for this recommendation was balancing the higher rates of respiratory complications associated with the use of nebulized antibiotics against the low quality evidence suggesting potential benefits of their use.

## 2. VAP caused by Antibiotic-Susceptible Pathogens

2.1. Adjunctive Strategy: In mechanically ventilated patients already receiving conventional IV therapy, including colistin or aminoglycosides, for a VAP caused by antibiotic-susceptible pathogens, should nebulized antibiotics such as colistin or aminoglycosides be used, as adjunctive therapy to systemic antibiotics, as compared to absence of local treatment, to improve clinical outcome?

## Summary of the Evidence

No evidence was found regarding the use of nebulized antibiotics such as colistin or aminoglycosides, added to conventional IV antibiotic therapy already including IV colistin or aminoglycosides for the treatment of VAP caused by susceptible pathogens in invasively mechanically ventilated patients, in comparison to the use of conventional IV antibiotic therapy alone.

## Recommendation

We recommend avoiding the use of nebulized antibiotics such as colistin or aminoglycosides, added to conventional IV antibiotic therapy already including IV colistin or aminoglycosides for the treatment of VAP caused by antibiotic-susceptible pathogens in clinical practice.

Strong recommendation. No evidence available.

#### Rationale for the Recommendation

Due to the lack of available evidence, no recommendation should be made on the use of nebulized antibiotics such as colistin or aminoglycosides, added to conventional IV antibiotic therapy already including IV colistin or aminoglycosides for the treatment of VAP caused by susceptible pathogens in invasively mechanically ventilated patients. However, balancing this absence of evidence versus evidence causing a higher risk of respiratory adverse effects, the panel considers it to be consistent and responsible to recommend the avoidance of this treatment strategy against VAP caused by susceptible pathogens.

2.2. Substitution Administration Strategy- In mechanically ventilated patients with VAP caused by antibiotic-susceptible pathogens, should nebulized antibiotics such as colistin or aminoglycosides be used, instead of systemic IV therapy, to improve clinical outcome?

#### Summary of the Evidence

One RCT [13] evaluating the use of nebulized antibiotics (aminoglycosides and ceftazidime, without other concomitant IV antibiotics) to treat VAP caused by antibiotic-susceptible pathogens, in comparison to the use of those IV antibiotics, was considered to have an administration strategy equivalent to the substitution strategy, and therefore included in our analysis. A vibrating-mesh nebulizer was the device used in this trial of 40 patients.

No significant differences were observed for clinical resolution, mortality, duration of mechanical ventilation or ICU stay, and occurrence of superinfection. The fact that 50% of the pathogens in the group receiving IV antibiotics became intermediate or resistant, in contrast to the susceptible strains that caused new growth or persistence of the infection in the group receiving nebulized antibiotics, might lead one to consider nebulization of antibiotics for preventing the emergence of resistant strains, but no further evidence is available on this particular outcome. The overall quality of the evidence is very low due to serious indirectness and very serious imprecision of the results for all the efficacy outcomes. The safety evaluation of nebulization was associated with a higher incidence of respiratory complications (low quality of evidence) and a reduced occurrence of nephrotoxicity (low quality of evidence). No differences were observed in terms of other systemic toxicities.

#### Recommendation

We suggest avoiding the use of nebulized antibiotics such as colistin or aminoglycosides instead of their IV administration for the treatment of VAP caused by antibiotic-susceptible pathogens in clinical practice.

Weak recommendation. Very low quality of evidence.

Remark: We recommend avoiding their use particularly in patients undergoing a severe hypoxemia (PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 200) or having shown signs of poor pulmonary reserve, tending to rapid de-recruitment.

#### Rationale for the Recommendation

Due to the lack of evidence supporting efficacy of nebulized antibiotics such as colistin or aminoglycosides administered in place of those same IV antibiotics for the treatment of VAP caused by antibiotic-susceptible pathogens, and balancing this lack of efficacy with the evidence on higher rates of respiratory complications associated to their use, the guideline panel agreed to suggest avoiding use of nebulized antibiotics in this context.

#### Ventilator-associated Tracheobronchitis (VAT)

1.1. Adjunctive Strategy: In mechanically ventilated patients already receiving conventional IV antibiotic therapy for ventilator-associated tracheobronchitis (VAT), should nebulized antibiotics be used, as compared to absence of local treatment, to improve clinical outcome?

#### Summary of the Evidence

Our systematic review identified only 2 RCTs [14-15], involving a total of 85 patients. The device used for nebulization was a jet nebulizer in both studies. Both trials defined clinical resolution only as an improvement of the Clinical Pulmonary Infection Score, and included also patients meeting clinical criteria for the diagnosis of a VAP.

No significant differences were found either in mortality or duration of mechanical ventilation nor in the occurrence of systemic adverse events such as nephrotoxicity. No evidence was provided for the remaining predefined outcomes (clinical resolution, length of ICU stay, emergence of superinfection, existence of other adverse events such as respiratory complications).

The meta-analysis of the trials showed a significant reduction in the emergence of resistant strains in surveillance cultures in patients receiving nebulized antibiotics added to the conventional IV therapy (70 patients; RR=0.18; 95% CI, 0.05 -0.64; I<sup>2</sup>=0%; 328 for every 1000 treated patients, with a range from 144 to 380; moderate quality of evidence), as well as an increase in the clinical resolution as per improvement of the Clinical Pulmonary Infection Score (high heterogeneity: I<sup>2</sup>=90%; very low quality of evidence). The overall quality of the evidence is low due to the very serious imprecision and serious indirectness of the results.

#### Recommendation

We suggest avoiding the use of nebulized antibiotics added to conventional IV antibiotic therapy for the treatment of patients with VAT in clinical practice.

Weak recommendation. Low quality of evidence.

#### Rationale for the Recommendation

The panel concluded that owing to significance heterogeneity, small sample sizes and inconsistent effects, the available evidence quality was low. Therefore, the only potential benefit of adding nebulized antibiotics to the systemic therapy would be a decrease in the emergence of resistant strains, which should still be confirmed with a period of follow-up of the patients greater than 28 days after commencing therapy.

1.2. Substitution Administration Strategy:- In mechanically ventilated patients with VAT, should nebulized antibiotics be used, as compared to the use of conventional IV antibiotic therapy, to improve clinical outcome?

#### Summary of the Evidence

No evidence was found regarding the use of nebulized antibiotics for the treatment of VAT in invasively mechanically ventilated patients, as a sole therapy, in comparison to the use of conventional IV antibiotic therapy.

#### Recommendation

We recommend avoiding the use of nebulized antibiotics as a single therapy, instead of conventional IV antibiotic therapy, for the treatment of patients with VAT in clinical practice.

Strong recommendation. No evidence available.

#### Rationale for the Recommendation

There is no available evidence for the use of nebulized antibiotics for the treatment of VAT as a sole therapy, instead of treatment with IV antibiotics. However, this absence of evidence leads the guideline panel to consider it consistent and responsible to not recommend nebulized antibiotics for the treatment of VAT.

#### Non-bacterial Respiratory Infections

1. In mechanically ventilated patients already receiving conventional antiviral therapy for a viral respiratory infection, should nebulized antivirals be used, in comparison to conventional antiviral therapy, to improve clinical outcome?

### Summary of the Evidence

No evidence was found regarding the use of nebulized antivirals for the treatment of viral respiratory infections in invasively mechanically ventilated patients. Some case series and reports exist regarding nebulization of zanamivir, which is not approved for nebulization. In fact, an FDA alert from October 2009 reported the death of a person affected with influenza, who had received zanamivir powder for inhalation through a nebulizer. According to the manufacturer, lactose sugar in the formulation increases the risk of obstruction of the circuit.

### Recommendation

We recommend avoiding the use of nebulized antivirals for the treatment of patients with a viral respiratory infection in clinical practice.

Strong recommendation. No evidence available.

### Rationale for the Recommendation

Due to the lack of available evidence, no recommendation should be made on the use of nebulized antivirals for the treatment of viral respiratory infections. However, this absence of evidence leads the panel to consider it consistent and responsible to recommend avoiding nebulization of antivirals in clinical practice.

2. In mechanically ventilated patients already receiving conventional antifungal therapy for a fungal respiratory infection, should nebulized antifungals be used, in comparison to conventional antifungal therapy, to improve clinical outcome?

### Summary of the Evidence

No evidence was found regarding the use of nebulized antifungals for the treatment of fungal respiratory infections in invasively mechanically ventilated patients. Only one case series [21] reported experience with nebulization of Amphotericin B Lipid Complex (ABLC) to 32 immunosuppressed oncological patients as adjunctive treatment to systemic antifungals. Only 8 of these patients were under mechanical ventilation. Mild respiratory complications (without specifying if they occurred to the patients under mechanical ventilation), were reported.

### Recommendation

We recommend avoiding the use of nebulized antifungals for the treatment of patients with a fungal respiratory infection in clinical practice.

Strong recommendation. No evidence available.

### Rationale for the Recommendation

Due to the lack of available evidence, no recommendation should be made on the use of nebulized antifungals for the treatment of fungal respiratory infections. However, this absence of evidence leads the guideline panel to consider it consistent and responsible to recommend the avoidance of their use in clinical practice

#### FUTURE RESEARCH PRIORITIES

Critical analysis of the existing literature regarding nebulization of antibiotics in invasively mechanically ventilated patients identified an important gap in the knowledge about it. After evaluating the evidence, we concluded that no recommendations supporting the standard clinical use of nebulized antibiotics could be reached, mainly due to the lack of strength of the existing studies and to the risk of severe adverse events, especially respiratory complications.

In addition, important gaps exist in terms of the dosages and devices used, with further experimental PK/PD studies required. Even more, some widely-variable clinical practices and technical aspects of the nebulization process are based on a rationale yet to be justified. Specific studies are also required in both the neonatal and pediatric populations. Future research is urgently needed to address this lack of data and generate a higher quality of evidence.

#### Experimental research priorities

##### Devices

Experimental in vivo studies comparing the lung parenchyma delivery between the different types of nebulizers should be performed in order to establish their optimal indications. At present, there is a single available in vivo experimental study comparing lung deposition of antibiotic particles delivered through ultrasonic and vibrating mesh nebulizers [22]. Positioning of the devices in the circuit should be particularly evaluated, as well as the potential benefit of breath-enhanced jet nebulizers synchronizing nebulization with inspiration.

##### Anti-infective drugs

A limited number of PK/PD experimental in vivo studies have been published on nebulized amikacin, ceftazidime and colistin [22-29]. Some important issues such as the potential benefit of combining IV administration and nebulization of the same antibiotic have not been assessed and should be an important area of future research. The possibility of nebulizing vancomycin to treat VAP caused by methicillin-resistant *Staphylococcus aureus* requires future experimental PK/PD in vivo studies before clinical use. The same type of experiments should also be performed to assess the potential benefit of nebulizing anti-viral and anti-fungal medication (specifically formulated for nebulization). Although they are technically complicated, such studies evaluating the optimal dosage regimens of various anti-infective agents are recommended to ensure optimal clinical use.

## Clinical research priorities

### Study design

As demonstrated in our meta-analysis [7], very limited RCT data is available, and the sample size of the current studies is too small. Results from various observational studies suggest that nebulized antibiotics may be effective for the treatment of respiratory infections. However, even the highest quality observational studies are never able to take into account all possible confounders, as they might be unknown or difficult to measure [30], especially with a retrospective approach. Thus, RCTs are urgently needed to increase the current level of evidence of the efficacy and safety of nebulized antibiotics. Even more, in the coming years it is imperative to have more data on the drugs, dosage regimens and optimal durations of the therapy, its indications and appropriate administration strategy, and whether combinations of antibiotics may offer additional advantages.

The panel acknowledges that a significant source of heterogeneity amongst the published studies in the area relates to inconsistencies in clinical definitions for diagnosis of the infection and of its resolution. Lack of gold standard for both VAT and VAP definitions (with great variability in VAT) require to consider both diagnoses, with microbiology and tests of cure specific to the therapy for each respiratory infection. Further studies using standardized definitions, as well as pre-defined clinically meaningful outcomes such as mechanical ventilation duration, and measurement of the effects on bacterial burden are required. Resolution of fever and hypoxemia in VAP is early (median within 72h) whereas pre-defined assessment at 8 or 15 days ignore potential meaningful differences between two strategies of therapy. Thus, for the particular outcome of resolution of the infection, the panel would recommend evaluating the “time to clinical resolution”, instead of the existence of a clinical resolution at a pre-defined point, to identify potential advantages of nebulization in VAP caused by MDR organisms.

Currently, there are ongoing phase III clinical trials (e.g., NCT01969799, NCT01799993) regarding aerosolized antimicrobials using novel integrated delivery technologies, such as Amikacin inhale, BAY41-6551 (NKTR-061) or PARI GMBH (Stamburg, Germany) [31]. Whether they will add value to the current delivery systems remains unknown. Detailed information on ongoing trials is shown in Table 2.

An urgent need of randomized clinical trials under the substitution administration strategy for treatment of pneumonia due to MDR pathogens exists and the panel identify this subset as a priority in research.

### Safety evaluation

Safety is an overriding concern regarding nebulization of antibiotics. Even though evidence seems to suggest that they are less harmful than IV antibiotics regarding the occurrence of nephrotoxicity, the existence of a higher risk of respiratory complications is an important concern, particularly as this risk seems to increase when they are administered to patients with severe hypoxemia. These are

patients most likely to receive nebulized antibiotics due to the severity of their infection. Standards to prevent use of agents that are not proven and ensure patients' safety should be similar to those for systemic administration. Specific safety evaluations and standardized administration techniques [5] are needed to properly establish their limitations and should be an integral part of future RCTs.

#### Nebulized colistin

A high priority should be given to RCTs comparing the treatment efficacy of systemic administration and nebulization of high doses of colistin in VAP (and VAT) caused by MDR Gram-negative pathogens. The rationale for combining IV and nebulized colistin to treat VAP is debatable, although it is a widely used clinical practice in spite of safety concerns. IV colistin has a slow and limited pulmonary diffusion but has a significant renal toxicity. Nebulized colistin has a limited systemic diffusion, which provides the possibility of achieving high lung tissue concentrations without systemic toxicity [32, 23, 33]. Combination of both routes of administration likely results in a higher risk of renal toxicity without increasing significantly lung tissue concentration, although the distribution of nebulized throughout different segments of the lung remains unclear.

#### Nebulized aminoglycosides

PK/PD experimental and clinical studies clearly demonstrate a very limited diffusion of IV aminoglycosides into the lung parenchyma [34-38]. Two RCTs have demonstrated that the addition of IV aminoglycosides to cephalosporins does not increase the recovery rate of HAP [39, 40]. Three meta-analyses have recommended avoidance of the use of IV aminoglycosides to treat HAP and VAP [41-43]. In contrast, PK/PD experimental studies have reported high lung tissue concentrations of nebulized amikacin [24, 25] and suggested potential synergy when associated with fosfomycin [44]. Therefore, RCTs comparing the treatment efficacy of the IV administration and the nebulization of high doses aminoglycosides in VAP (and VAT) caused by susceptible Gram-negative bacteria is a second-line research priority. Similar to colistin, the PK/PD rationale for combining both administration routes is weak. Intravenous amikacin has a limited pulmonary diffusion and has a significant systemic renal toxicity. On the other hand, nebulized amikacin rapidly diffuses into the systemic circulation, potentially exposing the patient to systemic toxicity [24, 25, 32] with plasma concentration monitoring advised. Combining both routes of administration likely results in an increased risk of renal toxicity and does not appear as a safe practice.

#### Other antibiotics

Most research in mechanically ventilated patients has been conducted with aminoglycosides and colistin. Ceftazidime has been used in a few studies [13]. The panel suggest the need to address research using other antibiotics, such as ceftazidime/avibactam or other cephalosporins.

#### Emergence of resistance

This is a key observation that is incompletely elucidated and is a vital research priority in the area. Emergence of resistance cannot be assessed only based in samples of patients already receiving antimicrobials and requires long-term follow-up, after completion of nebulization. Additionally,

further information is required on the impact of nebulized antibiotic therapy on the lung and airway microbiome, not just MDR pathogen emergence. There is emerging evidence that indicates that changes in the innate microbiome increase the likelihood of future infections, including in ventilated patients. However, it is unknown how quickly the damage is incurred to the microbiota and how long does it lasts. It is also unclear whether nebulized therapy is beneficial or whether it increases damage to the airway microbiota. While there is little data addressing this, it is recommended as an important future research direction.

#### Regulatory and clinical issues.

There are significant challenges in demonstrating superiority in clinical registration trials for new antibiotics whose main activity is likely to be against MDR pathogens. These include the patient population under study, the end-points to be studied and the choice of comparator. The most widely accepted outcome measure is resolution of infection, usually expressed as “Test of Cure”. This may be a microbiological evaluation or a clinical evaluation of patient improvement based on the clinician’s opinion or scores. “Time to resolution” is a recommended outcome variable because there is little room for improvement to demonstrate superiority using conventional regulator end-points.

To address the increasing threat of MDR pathogens and provide incentive for greater investment in antibiotic development, regulators have recognised the importance of pathogen-based studies. Whilst these remain operationally challenging to recruit for, they do offer an opportunity to better study aerosolized antibiotics in a population where it is most likely to have the greatest utility, and therefore, value.

Unfortunately, no information was available on costs. Pharmaco-economic studies, adapted to regional differences, should be performed to assess the cost-effectiveness of these strategies. At the reimbursement approval stage, some degree of cost/benefit, or cost-effectiveness assessment is considered at a national or regional level by health technology assessment agencies.

#### CONCLUSIONS.

Nebulisation of antibiotics in mechanically ventilated adults with respiratory infections is a practice that is increasingly used, despite a lack of standardization and limited evidence on the associated efficacy and safety [2-3]. Based on a prior systematic review and meta-analysis [7], this ESCMID panel does not support the use of nebulization of antibiotics in any of the scenarios assessed because the available evidence is weak and heterogeneous (and in some scenarios entirely absent). Further research to achieve high-quality evidence is urgently needed.

Given that aerosolization of antibiotics is an active area of research, and the literature is emerging [45-47], the meta-analysis should be updated periodically. Thus, these recommendations may change in the future as new study data becomes available.

#### COMPETING INTERESTS

J Rello has received research grants and consulting fees from Bayer and Genentech. JA Roberts has received consulting fees from Infectopharm, Astellas and MSD and research grants from MSD and Cardeas Pharma. J Chastre has received honoraria for lecture or advisory board from Bayer, Pfizer,

Basilea, Astra-Zeneca, Cubist-MSD, Kenta-Aridis and Medimmune. LB Palmer has received research grants from Nektar Therapeutics and consulting fees from Bayer. LB Palmer holds patents for the endobronchial delivery of antibiotics in ventilated patients through the Research Foundation of Stony Brook. CE Luyt has received honoraria for lecture or advisory board from Bayer, MSD, ThermoFisher Brahms, Astellas. The rest of authors declare that they have no competing interests.

#### Contributors

All authors contributed to the planning, scope, content, and critical review of the manuscript. The preparation of designated sections and literature search was done by CS, JJR, JRe. CS was responsible for the systematic review, meta-analysis and GRADE methodology. The final draft was written by CS and JRe. All authors read and approved the final version of the manuscript.

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**LIST OF ABBREVIATIONS**

CF	cystic fibrosis
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESGCIP	ESCMID Group for Infections in Critically Ill Patients
VAT	Ventilator-associated tracheobronchitis
VAP	Ventilator-associated pneumonia
HAP	Hospital-acquired pneumonia
MDR	Multidrug-resistant
IV	Intravenous
RCT	Randomized-controlled trials
RR	Risk ratio
OR	Odds ratio
RD	Risk difference
MD	Mean difference
CI	Confidence interval

**Appendix 1. List of pre-defined evaluated outcomes***Efficacy Outcomes:*

- Clinical resolution (yes/no; after 8 days of treatment) if one or more of the following occurred:
  - Removal of vital support (ventilation, vassopressors)
  - Improvement of daily organ failure score
  - Improvement of PaO<sub>2</sub>/FiO<sub>2</sub> ratio
  - Inflammatory parameters decrease (C-reactive protein and/or procalcitonin)
- 30-day mortality (yes/no)
- Duration of mechanical ventilation (days)
- Duration of ICU stay (days)
- Occurrence of superinfection (yes/no)
- Emergence of resistant strains (yes/no)

*Safety Outcomes:*

- Systemic toxicity (yes/no; especially nephrotoxicity)
- Cardiorespiratory complications (yes/no; including hypoxemia, cough, bronchoconstriction, lung injury or acute respiratory distress syndrome, problems with the nebulisation system such as obstruction of the expiratory filter; arrhythmias, cardiorespiratory arrest).

**Appendix 2. List of terms of the search strategy.**

- #1 "Aerosols" [Mesh]
- #2 "Nebulizers and Vaporizers" [Mesh]
- #3 nebul\*[tiab]
- #4 aerosol\*[tiab]
- #5 vaporiz\*[tiab]
- #6 inhal\*[tiab]
- #7 pulmonary delivery\*[tiab]
- #8 atomiz\*[tiab]
- #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
- #10 "Anti-Bacterial Agents" [Mesh]
- #11 antimicrobial\*[tiab]
- #12 antibacterial\*[tiab]
- #13 anti-bacterial\*[tiab]
- #14 antibiotic\*[tiab]
- #15 bacterio\*[tiab]
- #16 antiviral\*[tiab]
- #17 antifungal\*[tiab]
- #18 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
- #19 "Pneumonia, Ventilator-Associated" [Mesh]
- #20 ventilator associated pneumonia\*[tiab]
- #21 vap[tiab]
- #22 nosocomial pneumonia\*[tiab]
- #23 Hospital-acquired pneumonia\*[tiab]
- #24 hap[tiab]
- #25 respiratory tract\*[tiab]
- #26 ventilator associated tracheobronchitis\*[tiab]
- #27 vat[tiab]
- #28 viral respiratory infection\*[tiab]

- #29 fungal respiratory infection\*[tiab]
- #30 ventilat\*[tiab]
- #31 intubat\*[tiab]
- #32 lung infect\*[tiab]
- #33 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
- #34 #9 AND #18 AND #33
- #35 colistin\*[ti]
- #36 polymyxin\*[ti]
- #37 amikacin\*[ti]
- #38 gentamicin\*[ti]
- #39 tobramycin\*[ti]
- #40 aminoglycoside\*[ti]
- #41 ciprofloxacin\*[ti]
- #42 ribavirin\*[ti]
- #43 zanamivir\*[ti]
- #44 oseltamivir\*[ti]
- #45 amphotericin\*[ti]
- #46 pentamidin\*[ti]
- #47 caspofungin\*[ti]
- #48 fluconazole\*[ti]
- #49 posaconazole\*[ti]
- #50 voriconazole\*[ti]
- #51 vancomycin\*[ti]
- #52 meropenem[ti]
- #53 ertapenem[ti]
- #54 imipenem\*[ti]
- #55 doripenem\*[ti]
- #56 #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55

#57 #18 OR #56

#58 #9 AND #33 AND #57

#59 #34 OR #58

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**Table 1. Different strategies considered regarding the administration of nebulized antibiotics**

Strategy	Intervention	Comparison
Adjunctive	First-line IV antibiotics + IV colistin / aminoglycosides + Nebulised colistin / aminoglycosides	First-line IV antibiotics + IV colistin / aminoglycosides
Substitution	First-line IV antibiotics + Nebulised colistin / aminoglycosides	First-line IV antibiotics + IV colistin / aminoglycosides

**Table 2- Nebulized Antibiotics Ongoing Clinical Trials.**Sources: [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)

Accessed December 1st, 2016.

Title – Reference	Sponsors - collaborators	Intervention	Comparator	Primary outcome	Secondary outcome	Investigator
Nebulized and intravenous colistin in ventilator associated-pneumonia (COLIVAP) - NCT02906722	Assistance publique - Hôpitaux de Paris, France	QD, BID, TID nebulized colimycin (performed by vibrating plate nebulizer – aeroneb® solo) + intravenous placebo. <b>Four million International Units of colistimethate diluted in six ml of NaCl 0.9% solution are administered every eight hour.</b>	Nebulized placebo (performed by vibrating plate nebulizer – aeroneb® solo) + intravenous colimycin QD, BID, TID (according to renal function). <b>A loading dose of six million international units (IU) of colistimethate sodium followed by maintenance dose of two million IU diluted in 50 ml of NaCl 0.9% solution, every eight hour is administered.</b>	Clinical cure of VAP caused by Gram-negative multidrug resistant <b>bacteria (Pseudomonas aeruginosa resistive to aminoglycosides, cephalosporins, carbapenems and Acinetobacter baumannii resistive to carbapenems).</b>	Microbiological cure rate, VAP recurrence rate, lung superinfection rate, mortality, duration of mechanical ventilation, length of ICU stay, renal function during colimycin administration, side effects resulting from colimycin nebulization, side effects resulting from colimycin intravenous administration, colistin plasma concentrations	Quin Lu, Jean-Jacques Rouby
Effect of additional nebulized amikacin in ventilator-associated pneumonia caused by Gram negative bacteria - NCT02574130	Thammasat university, Thailand	Nebulized amikacin (400 mg BID for 10 days) plus intravenous antibiotic(s)	Nebulized placebo plus intravenous antibiotic(s)	Cure rate	The reduction of pathogens (quantitative sputum culture), mortality rate, duration of mechanical ventilation, duration of ICU stay, duration of hospitalization, safety of intervention drug (any adverse effect).	Pitchayapa Ruchiwit, Apichart Kanitsap
Therapy of ventilator-associated tracheobronchitis caused by Gram negative bacteria with nebulized colistin - NCT02619786	Mahidol University, Thailand	Inhaled colistin 75 mg mixed with normal saline up to 4 ml every 12 hours at least 5 days	None	Number of patients with cure, improved, failure or death	Number of patients with eradication, persistence or superinfection; number of patients with grade 3 - 5 adverse events that are related to study drug (NCI CTCAE version 3.0), grade 3 - 5 adverse events related to study drug focus on neurology and bronchospasm.	Adhiratha Boonyasiri

Title	Sponsors - collaborators	Intervention	Comparator	Primary outcome	Second
Amikacine nébulisée à forte dose. Pharmacocinétique dans la pneumonie associée à la ventilation mécanique D'ARTAGNAN 3 - 2008-000248-15	Association pour la promotion de la réanimation médicale à Tours, France	Nebulized Amikacin 60 – 100 mg/kg	Intravenous Amikacin 20 mg/kg	Dose of nebulized amikacin that allows to measure serum amikacin concentrations close to but inferior to those measured after standard intravenous amikacin infusion	To evaluate nebulized amikacin concentrations in tracheal aspirates after nebulization. To evaluate the benefit of nebulized amikacin compared to intravenous amikacin. To measure the absorption of nebulized amikacin.
A Double-Blind, Placebo-Controlled, Parallel Group Phase 2 Dose-Ranging Study of Nebulized Amikacin Delivered Via the Pulmonary Drug Delivery System (PDDS) in Patients With Ventilator-Associated Pneumonia Due to Gram-Negative Organisms - 2005-000060-16	Aerogen, Inc. USA.	Amikacin sulfate 125 mg/ml Inhalation	Placebo	Proportion of patients in each arm who achieve a Cmax for amikacin in tracheal aspirates that is $\geq 25X$ the reference MIC for hospital-acquired organisms, and an AUC(0-24h)/MIC $\geq 100X$ on Day 1	To assess the tolerability and safety of nebulized amikacin. To evaluate the pharmacokinetics of nebulized amikacin. To evaluate the efficacy of nebulized amikacin compared to intravenous amikacin. To measure the absorption of nebulized amikacin.