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Guidelines

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

J. Rello [1, *, 15], C. Solé-Lleonart [2, *, 15], J.-J. Rouby [3], J. Chastre [4], S. Blot [5], G. Poulakou [6], C.-E. Luyt [3], J. Riera [7], L.B. Palmer [8], J.M. Pereira [9,10], T. Felton [11], J. Dhanani [12], M. Bassetti [13], T. Welte [14], J.A. Roberts [12]

[1] *CIBERES, Universitat Autonòma de Barcelona, European Study Group of Infections in Critically Ill Patients, Barcelona, Spain*
[2] *Service de Médecine Intensive Adulte, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland*
[3] *Multidisciplinary Intensive Care Unit, Department of Anesthesiology and Critical Care, La Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, University Pierre et Marie Curie of Paris 6, Paris, France*
[4] *Service de Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie of Paris, Paris, France*
[5] *Department of Internal Medicine, Faculty of Medicine & Health Science, Ghent University, Ghent, Belgium*
[6] *4th Department of Internal Medicine, Athens University School of Medicine, Attikon University General Hospital, Athens, Greece*
[7] *Clinical Research & Innovation in Pneumonia and Sepsis, Vall d'Hebron Institute of Research, CIBERES, Barcelona, Spain*
[8] *Pulmonary, Critical Care and Sleep Division, Department of Medicine, State University of New York at Stony Brook, Stony Brook, NY, USA*
[9] *Emergency and Intensive Care Department, Centro Hospitalar S. João EPE, Porto, Portugal*
[10] *Department of Medicine, Faculty of Medicine, University of Porto, Porto, Portugal*
[11] *Acute Intensive Care Unit, University Hospital of South Manchester, Manchester, United Kingdom*
[12] *Burns Trauma and Critical Care Research Centre and Centre for Translational Anti-infective Pharmacodynamics, The University of Queensland, Butterfield Street, Herston, Brisbane, Australia*
[13] *Infectious Diseases Division, Santa Maria Misericordia University Hospital, Udine, Italy*
[14] *German Centre for Lung Research (DZL), Department of Respiratory Medicine, Medizinische Hochschule, Hannover, Germany*

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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 when there is a 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 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 avoiding the 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 guidance for researchers in this field. In particular, the panel identified an urgent need for randomized clinical trials of nebulized

* Corresponding authors: J. Rello, Pg. Vall d'Hebron 129, AMI-14, 08035 Barcelona, Spain or C. Sole-Lleonart, Service de Médecine Intensive Adulte, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.
E-mail addresses: jrello@crips.es (J. Rello), pm.Nebat@gmail.com (C. Solé-Lleonart).
[15] J. Rello and C. Solé-Lleonart contributed equally as first author of the manuscript.

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antibiotic therapy as part of a substitution approach to treatment of pneumonia due to multidrug-resistant pathogens. **J. Rello, Clin Microbiol Infect 2017;23:629**

Introduction

The administration of nebulized antibiotics is formally approved by regulatory bodies for the management of patients with bronchiectasis or cystic fibrosis [1]. However, the clinical challenges posed by extremely- or pan-drug-resistant 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, anaesthesiologists, 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 previous 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 standardization of their delivery 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 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 CDC [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 <5 μm in 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):

(a) Adjunctive strategy: nebulized colistin or aminoglycosides administered to patients already receiving intravenous (IV) colistin or aminoglycosides, added to standard first-line IV

Table 1
Different strategies considered regarding the administration of nebulized antibiotics

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

Abbreviation: IV, intravenous.