

Inhalační podání antibiotik v IM

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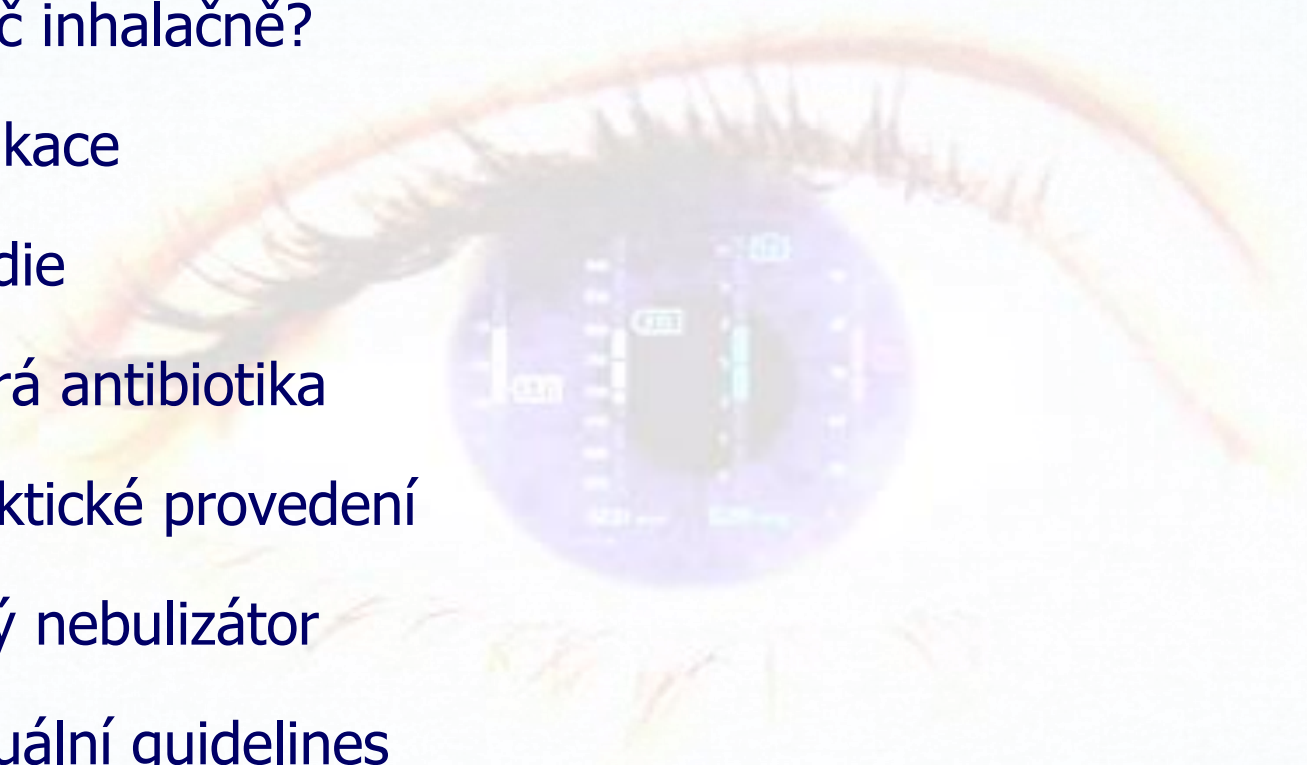
no conflict of interest

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přehled

1. proč inhalačně?
2. indikace
3. studie
4. která antibiotika
5. praktické provedení
6. jaký nebulizátor
7. aktuální guidelines



inhaled antibiotic
PK/PD profile

The **rationale** for using aerosolized antimicrobial therapy in mechanically ventilated patients with VAP or VAT is rooted in **achieving high concentrations** of unbound **drug** in the **lower respiratory tract**, surpassing the **MIC breakpoints** for commonly implicated pathogens while **minimizing systemic diffusion** to mitigate ecological and toxicological **side effects**.

in **three multicenter studies** focused on patients with **VAP**, aerosolization of 300–400mg of **amikacin** every 12 hours through a vibrating mesh nebulizer yielded median **concentrations in the epithelial lining fluid** (calculated on the basis of BAL concentration) or tracheal aspirates (concentration in the sputum) ranging from **976 mg/L to 16,212 mg/L**, surpassing **MIC breakpoints** by several orders of magnitude (e.g., 8mg/L for Enterobacterales and *A. baumannii*, 16 mg/L for *P. aeruginosa* and *S. aureus*).

Similarly, nebulization of colistimethate sodium, the prodrug of **colistin**, led to **concentrations fivefold higher** than MIC breakpoints in **aerated lung parenchyma** and around MIC breakpoints in areas of alveolar consolidation.



indikace



Healthcare-associated lower respiratory tract infection of increasing severity

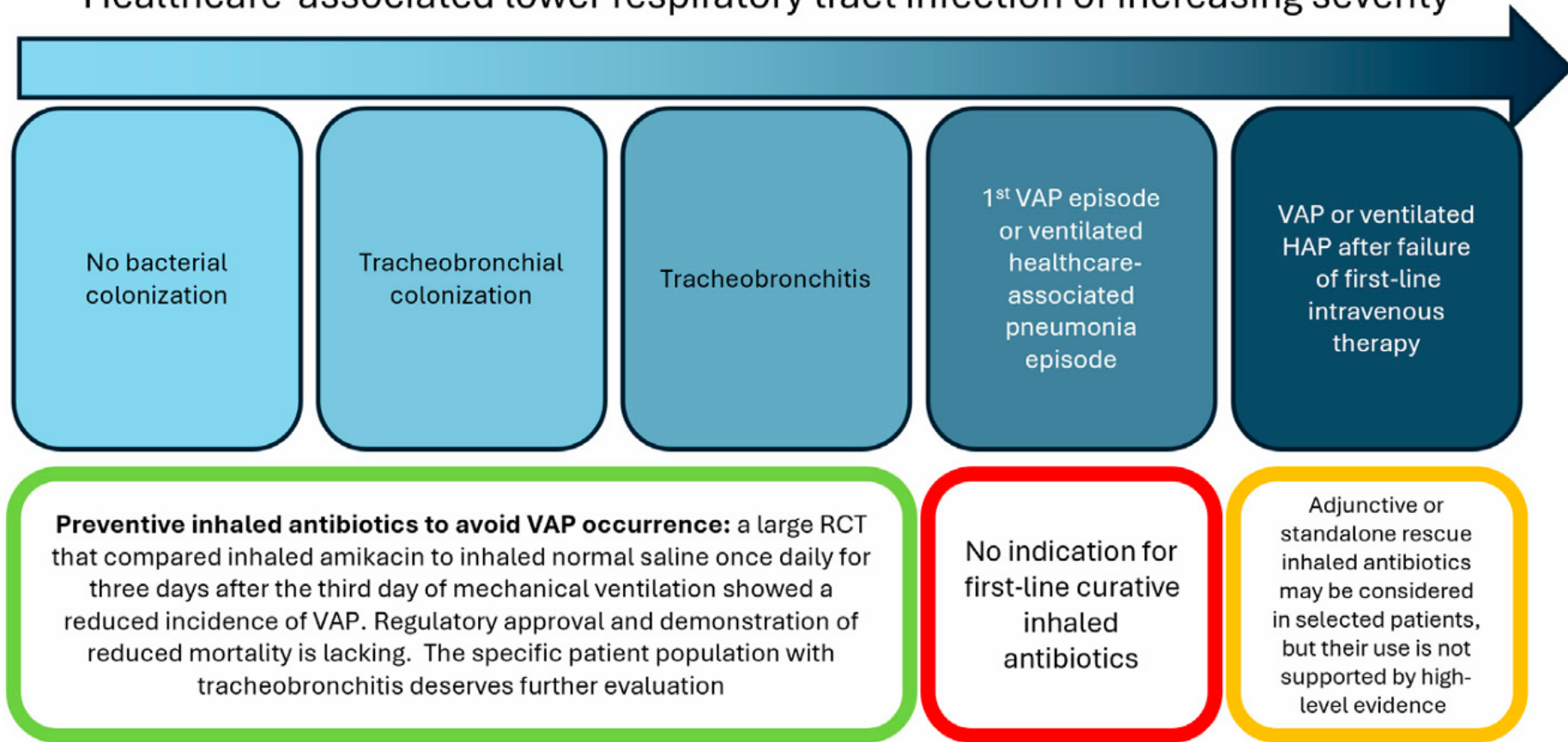


Figure 1. Framework for potential implementation of inhaled antibiotics in different clinical situations. HAP = hospital-acquired pneumonia; RCT = randomized controlled trial; VAP = ventilator-associated pneumonia.

inhaled antibiotics

a) **terapeuticky**

- *ventilator-associated pneumonia*
- *ICU-acquired pneumonia*
- *multidrug-resistant pneumonia*

b) **preventivně**

c) **pacienti s cystickou fibrózou**

d) **experimenty/studie**

Effects of prophylactic nebulized antibiotics on the prevention of ICU-acquired pneumonia: a systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the efficacy and safety of prophylactic nebulized antibiotics in preventing intensive care unit (ICU)-acquired pneumonia through a meta-analysis.

Methods: Randomized controlled trials (RCTs) investigating the potential reduction in the incidence of ICU-acquired pneumonia through prophylactic nebulized antibiotics were collected by searching the PubMed, Embase, and Cochrane Library databases from their inception to January 23, 2024. The primary endpoint was the incidence of ICU-acquired pneumonia, while the secondary endpoints included mortality, length of ICU stay, mechanical ventilation days, and nebulization-related side effects. Statistical analyses were performed using RevMan 5.3 and STATA 14.0 software.

Results: A total of six RCTs were included in the analysis, involving 1,287 patients (636 patients in the study group received prophylactic antibiotic therapy, including Polymyxin B, Tobramycin, Ceftazidime, Colistimethate sodium, and amikacin; 651 patients in the control group primarily received saline). The results indicated that prophylactic nebulized antibiotic therapy significantly reduced the incidence of ICU-acquired pneumonia compared to that in the control group (odds ratio (OR) = 0.57, 95% confidence interval (CI) [0.43–0.74], $P < 0.0001$). No significant difference was observed in the mortality rate between the treatment and control groups (OR = 0.86, 95% CI [0.68–1.10], $P = 0.24$). Prophylactic nebulized antibiotic therapy also did not significantly reduce the length of ICU stay (MD = 0.2 days; 95% CI [–0.81 to 1.20], $P = 0.70$) or the number of mechanical ventilation days (MD = 0.43 days; 95% CI [–0.47 to 1.33], $P = 0.35$). Additionally, there was no evidence that prophylactic nebulized antibiotic therapy contributed to the development of multiple drug-resistant (MDR) bacterial pneumonia or increased the incidence of associated side effects, such as airway spasms.

Conclusions: This meta-analysis suggests that ICU-acquired pneumonia can be prevented by prophylactic nebulized antibiotic therapy in critically ill patients without increasing the risk of MDR bacterial infections or airway spasms. However, the reduction in the incidence of ICU-acquired pneumonia did not result in significant improvements in mortality or length of ICU stay.



studie



Musíme podávat antibiotika vždy bolusově a intravenózně?

Jak a proč inhalačně?

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1. LÉKAŘSKÁ
FAKULTA
Univerzita Karlova

***která
antibiotika?***

inhaled antibiotics

ceftazidim

fosfomicin

colistin

aztreonam

amikacin

levofloxacin

gentamycin

tobramycin

....

on/off

label?

EU / US Manufacturer-Approved Inhaled Antibiotics

Antibiotic	Brand Name(s)	Approved Indication	Region
Tobramycin	TOBI®, <u>Bramitob®</u> , TOBI Podhaler®	Chronic <i>P. aeruginosa</i> lung infection in CF patients	EU, US
Colistin (Colistimethate sodium)	Colobreathe®, <u>Promixin®</u>	Chronic <i>P. aeruginosa</i> lung infection in CF patients	EU
Aztreonam lysine	Cayston®	Chronic <i>P. aeruginosa</i> lung infection in CF patients	EU, US
Levofloxacin	<u>Quinsair®</u> (EU)	Chronic <i>P. aeruginosa</i> lung infection in CF patients (adults)	EU (approved by EMA)
Amikacin liposome inhalation suspension (ALIS)	Arikayce®	Refractory nontuberculous mycobacterial (NTM) lung disease (esp. <i>Mycobacterium avium</i> complex)	US, EU (limited)

everything else is off-label

***jaký
nebulizátor?***

Table 1 Advantages and disadvantages of the three types of nebulizers

	Jet Nebulizer	Ultrasonic Nebulizer	Vibrating mesh Nebulizer
Advantages	• Low cost	• No interference with the ventilator • Silent	• Small residual volume • No interference with the ventilator • Small size • Silent • Closed reservoir
Disadvantages	• High residual volume • Need of compressed gas • Potential interference with the ventilator • Loud • Need to remove from circuit for cleaning and filling • Reservoir open to circuit	• Degradation of heat-sensitive drugs • Bulky • Need for decontamination • Reservoir open to circuit	• High concentrated viscous solution may reduce output rate • High cost

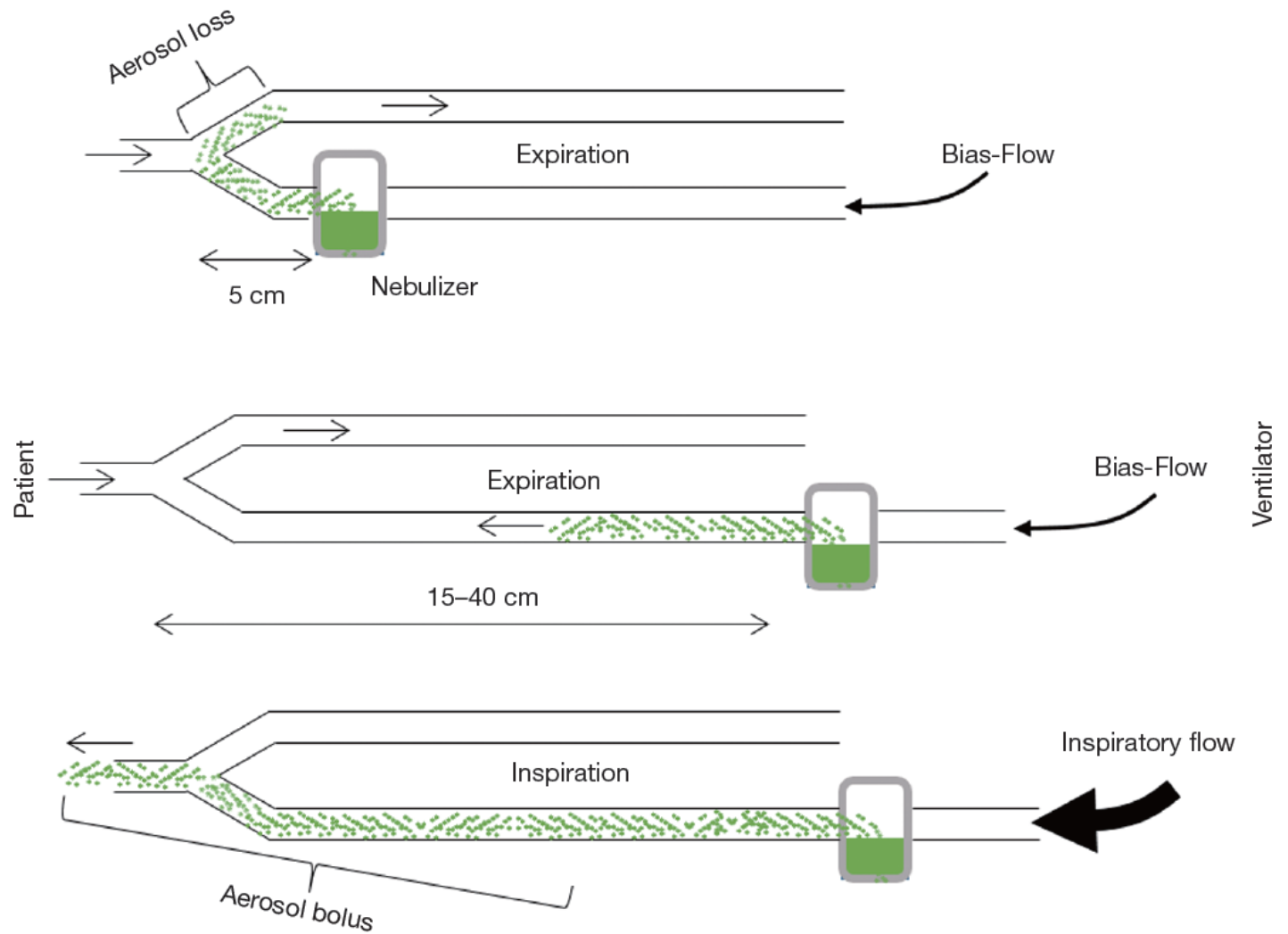


Figure 1 Influence of the nebulizer position on aerosol loss during expiration. With permission (19).

***praktické
provedení***

RESEARCH

Open Access



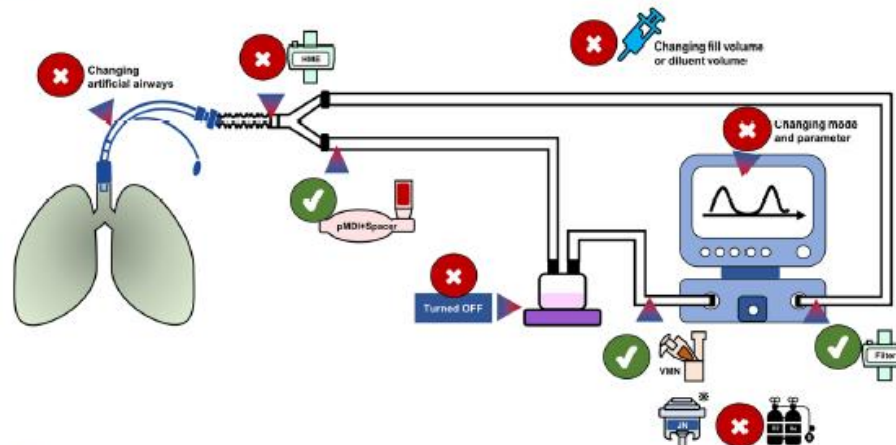
Aerosol therapy in adult critically ill patients: a consensus statement regarding aerosol administration strategies during various modes of respiratory support

Jie Li^{1*}, Kai Liu^{2†}, Shan Lyu^{3†}, Guoqiang Jing^{4†}, Bing Dai^{5†}, Rajiv Dhand⁶, Hui-Ling Lin⁷, Paolo Pelosi^{8,25^}, Ariel Berlinski⁹, Jordi Rello^{10,23,24}, Antoni Torres^{11,23}, Charles-Edouard Luyt¹², Jean-Bernard Michotte¹³, Qin Lu¹⁴, Gregory Reyckler^{15,21,22}, Laurent Vecellio¹⁶, Armèle Dornelas de Andrade¹⁷, Jean-Jacques Rouby¹⁸, James B. Fink^{1,19} and Stephan Ehrmann²⁰

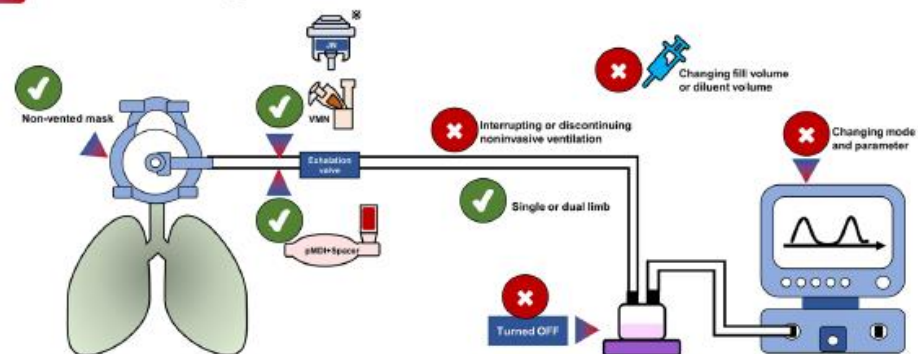
Results We present a comprehensive document with 20 statements, reviewing the evidence, efficacy, and safety of delivering inhaled agents to adults needing respiratory support, and providing guidance for healthcare workers. Most recommendations were based on in-vitro or experimental studies (low-level evidence), emphasizing the need for randomized clinical trials. The panel reached a consensus after 3 rounds anonymous questionnaires and 2 online meetings.

Conclusions We offer a multinational expert consensus that provides guidance on the optimal aerosol delivery techniques for patients receiving respiratory support in various real-world clinical scenarios.

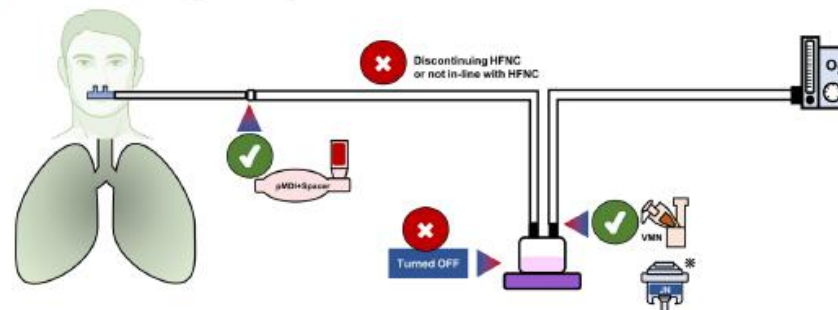
A Aerosol Delivery via Invasive Ventilation



B Aerosol Delivery via Non-invasive Ventilation



C Aerosol Delivery via High-flow Nasal Cannula

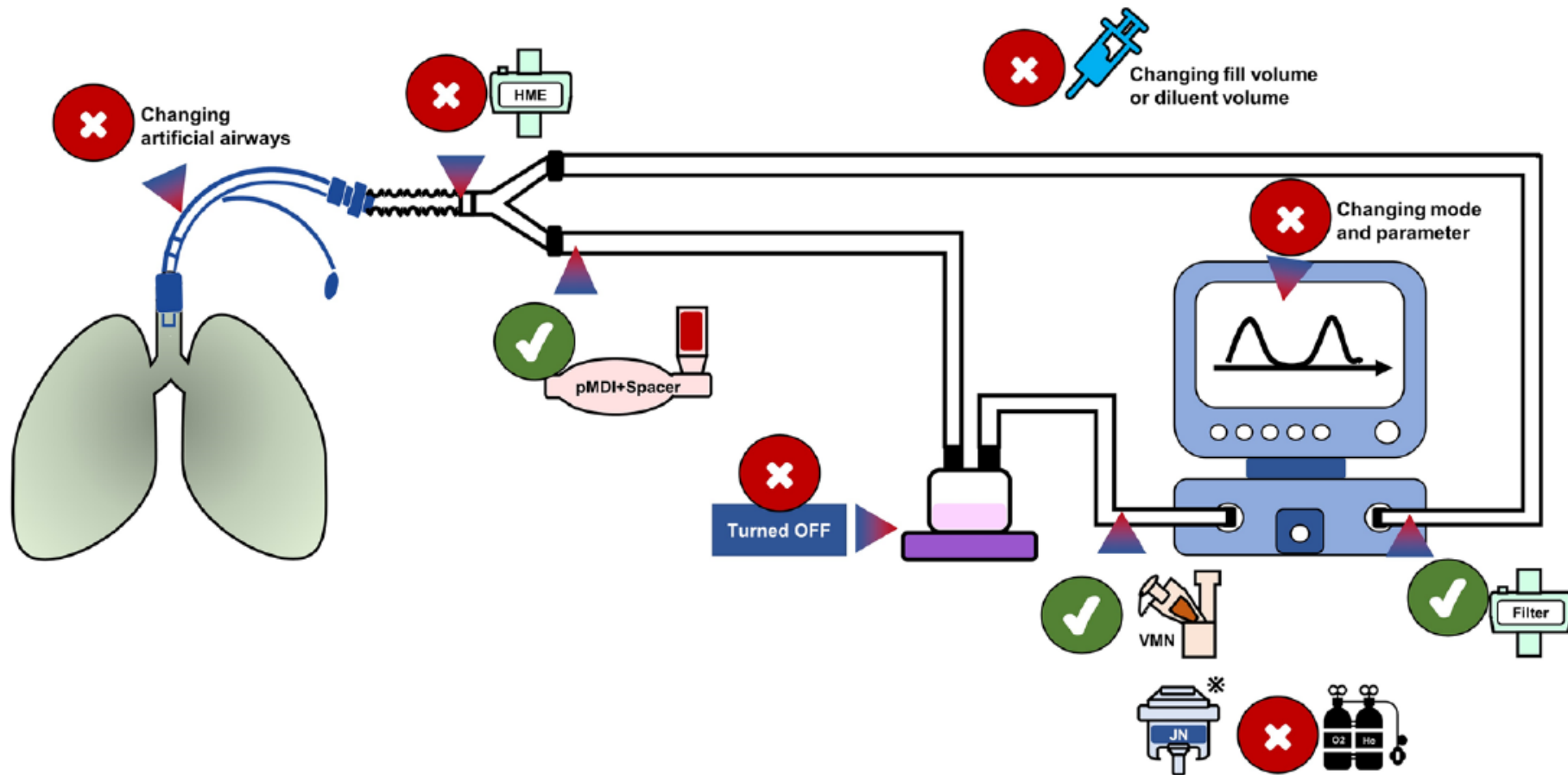


* in some in vitro experiments a continuous JN placed in those positions is less efficient than VMN for aerosol delivery.

Fig. 3 Graphic synopsis of recommendations on aerosol delivery via mechanical ventilation, noninvasive ventilation, and high-flow nasal cannula

A

Aerosol Delivery via Invasive Ventilation



***side
effects?***

- **bronchospasm**

- nephrotoxicity

- allergy

- ...

....incidence is low



dávkování?



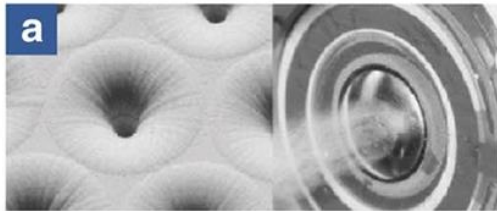
inhaled antibiotics

- **tobramycin** 300 mg á 8/12 h
- **amikacin** 300-400 mg á 8/12 h
- **colistin** 1-4 MIU á 8 h
- **fosfomycin** 80-120mg á 8/12 h
- **levofloxacin** 240 mg á 12 h

Nebulized amikacin and colistin for ventilator-associated pneumonia caused by MDR Gram bacteria

**Priority to mesh nebulizers
and specifically designed circuits**

Mass median aerodynamic diameter → **2 - 5 μ**
High lung deposition **20-30%** Easy to handle for nurses
Chamber deposition **< 5%**



Initial dose inserted into the nebuliser's chamber

Colistimethate 4 m IU diluted in 6 ml x3/24h

Mesh nebulizers → chamber residual volume **< 10%**
Jet nebulizers → chamber residual volume **> 40%**

Amikacin 40 mg/kg/24h diluted in 6 ml

Circuits deposit (inspiratory tubing + Y piece
+ endotracheal tube) around **30%**

Nebulization time $\leq$ 30 min - Specific ventilator settings to limit inspiratory inertial impaction

Volume control ventilation with constant inspiratory flow,
no patient's triggering. No asynchrony between the patient
and the ventilator (propofol if necessary)

Removal of heat and moisture exchangers, stop of heat humidifier
and addition of a filter on the expiratory limb

**TV 8 ml/kg, RF 12-15 bpm, I/E 1:2, end-inspiratory pause
20%, PEEP 5-10 cmH₂O**

Return to previous settings after nebulization
Change the expiratory filter



benefits ?





Review

Nebulized Antibiotics for Preventing and Treating Gram-Negative Respiratory Infections in Critically Ill Patients: An Overview of Reviews

Marios Karvouniaris ¹, Despoina Koulenti ^{2,3,*}, Konstantinos I. Bougioukas ⁴, Eirini Pagkalidou ^{5,6}, Elizabeth Paramythiotou ⁷ and Anna-Bettina Haidich ⁶

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Table 4. Evidence summary on nebulization treatment intervention vs. control.

	Amikacin vs. Control	Colistin vs. Control
	Significance Level/Certainty of Evidence	
Outcome		
Clinical response	Significant/Moderate	Non-significant/Low–very low
Microbiological eradication	Significant/Low	Significant/Low–very low
All-cause mortality	Non-significant/Moderate	Non-significant/Low–very low
Infection-associated mortality	Non-significant/Moderate	Non-significant/Very low
Mechanical ventilation duration	Non-significant/Very low	Non-significant/Very low *
Length of ICU stay	Non-significant/Low	Non-significant/Very low
Nephrotoxicity	Non-significant/Moderate	Non-significant/Very low
Bronchospasm	Significant/Moderate	Significant/Low

* The majority received colistin treatment while the rest aminoglycosides. Abbreviations: ICU, intensive care unit.



guidelines?



Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Andre C. Kalil,^{1,a} Mark L. Metersky,^{2,a} Michael Klompas,^{3,4} John Muscedere,⁵ Daniel A. Sweeney,⁶ Lucy B. Palmer,⁷ Lena M. Napolitano,⁸ Naomi P. O'Grady,⁹ John G. Bartlett,¹⁰ Jordi Carratalà,¹¹ Ali A. El Solh,¹² Santiago Ewig,¹³ Paul D. Fey,¹⁴ Thomas M. File Jr,¹⁵ Marcos I. Restrepo,¹⁶ Jason A. Roberts,^{17,18} Grant W. Waterer,¹⁹ Peggy Cruse,²⁰ Shandra L. Knight,²⁰ and Jan L. Brozek²¹

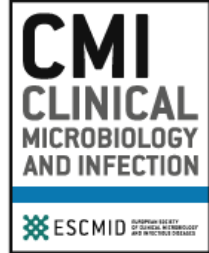
guidelines **recommended the adjunctive use** of inhaled antibiotics alongside systemic antibiotics for treating patients with VAP caused by bacteria susceptible only to antibiotics with limited efficacy via the systemic route, such as aminoglycosides and colistin



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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

position paper advising **against the use** of inhaled antibiotics alone or in combination with systemic antibiotics for VAP treatment, regardless of bacterial susceptibility

International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT)

Antoni Torres^{1,16}, Michael S. Niederman^{2,16}, Jean Chastre³, Santiago Ewig⁴, Patricia Fernandez-Vandellos⁵, Hakan Hanberger⁶, Marin Kollef⁷, Gianluigi Li Bassi¹, Carlos M. Luna⁸, Ignacio Martin-Loeches⁹, J. Artur Paiva¹⁰, Robert C. Read¹¹, David Rigau¹², Jean François Timsit¹³, Tobias Welte¹⁴ and Richard Wunderink¹⁵

International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT)

Recent European VAP guidelines **did not mention** inhaled antibiotic delivery.

None of the available guidelines **covers the potential use** of inhaled antibiotics **to prevent** lung infection or **to treat** lung colonization and VAT.

***the
others?***

- **bacteriophages**

(preclinical studies involving mechanically ventilated piglets with *P. aeruginosa* pneumonia)

- pathogen-directed **monoclonal antibodies**

- **immunomodulating peptides**

(improve the local pulmonary immune response)

- **flagellin** - *Toll-like receptor 5 agonist*

(enhances innate immunity, reduces inflammation, and decreases pneumonia severity)

-



budoucnost?



Table 3

Trials reported on clinicaltrials.gov investigating inhaled antibiotics for VAP.

NCT Number	Country	Title	Status	Enrolment	Drug Intervention
NCT02440828	Spain & Netherlands	Addition of Tobramycin Inhalation in the Treatment of Ventilator-Associated Pneumonia	Complete	80	Inhaled Tobramycin in addition to standard IV antibiotics for the treatment of VAP in adults
NCT06488794	Tunisia	Inhaled Colistin to Prevent Paediatric Ventilator-associated Pneumonia	Pending	100	Inhaled Colistin for the prevention of VAP in children
NCT03622450	Egypt	The Effect of Colistin Inhalation on Ventilator-Associated Pneumonia	Complete	40	Inhaled Colistin for the treatment of suspected MDR gram negative VAP in adults
NCT03921645	China	Use of Aerosol Combined With Intravenous Antibiotics for the Treatment of Multidrug Resistant GNB Pneumonia	Recruiting	60	Aerosol Amikacin combined with IV antibiotics for the treatment of MDR gram negative VAP in adults
NCT01025921	Greece	Tracheobronchitis Prevention Trial	Complete	84	Inhaled Colistin for the prevention of VAP in mechanically ventilated adults
NCT02478710	USA	Aerosolised Antibiotics in the Treatment of Ventilator Associated Pneumonia	Terminated	16	Aerosolised Tobramycin or Vancomycin in conjunction with IV antibiotics for the treatment of VAP in adults
NCT02515448	France	A Pharmacokinetic-pharmacodynamic Dose Comparison Study of 8 mg/kg of Inhaled or Parenteral Gentamicin in 12 Mechanically Ventilated Critically Ill Patients Treated for Ventilator-associated Pneumonia	Complete	12	Inhaled Gentamicin for the treatment of VAP in adults
NCT03149640	France	Study Comparing Inhaled Amikacin Versus Placebo to Prevent Ventilator-Associated Pneumonia	Complete	850	Inhaled Amikacin for the prevention of VAP in adults
NCT03749226	Spain	Nebulised Aztreonam for Prevention of Gram-Negative Ventilator-associated Pneumonia	Terminated	9	Nebulised Aztreonam Lysine for the prevention of gram-negative VAP in adults
NCT02683603	Tunisia	Effect of Aerosolised Colistin in Ventilator Associated Pneumonia	Complete	133	Aerosolised Colistin for the treatment of VAP in adults
NCT04208945	Greece	Nebulised Colistin for Gram Negative VAP Prevention.	Recruiting	152	Nebulised Colistin for the prevention of gram-negative VAP in adults
NCT01878643	USA	Reduction of Bacterial Resistance With Inhaled Antibiotics in the Intensive Care Unit	Complete	47	Inhaled Vancomycin or Gentamicin for the prevention of VAP in adults
NCT00645723	Spain	Intravenous Colistin Versus Intravenous Colistin Plus Nebulised Colistin in VAP Due MDR Acinetobacter Baumannii	Recruiting	67	Inhaled Colistin combined with IV Colistin for the treatment of Multi-resistant Acinetobacter Baumannii VAP in adults

NCT = clinicaltrials.gov identifier number; VAP = ventilator-associated pneumonia; MDR = multi-drug resistance; IV = intravenous.



...děkuji Vám za pozornost