Prise en charge des pneumopathies nosocomiales: Antibiothérapie inhalée Versus IV en réanimation: Controverse?

Pr Nozha Brahmi- Pr Ag Hassen Ben Ghezala.

Centre Mahmoud Yaacoub d'assistance médicale urgente de Tunis.

Samedi 02 Décembre 2023

Remerciements Pr S Ehrmann

ATR
الجمعية التونسية لطب الانعاش
ASSOCIATION TUNISIENNE DE REANIMATION

FMT
Faculté de Médecine de Tunis

UTM
جامعة تونس المنار
UNIVERSITÉ DE TUNIS EL MANAR

CONFLICT OF INTEREST DISCLOSURE.

I have No conflict of Interest to report in relation to this Presentation.

AVANTAGES THÉORIQUES

- Apport d'une grande quantité de médicaments au niveau du site d'action délivrés directement dans les poumons.

- Faible exposition systémique aux effets secondaires de celui-ci.

S. Ehrmann et al. Réanimation (2012) 21:42-54

S. Ehrmann et al. NEJM 2023, ESICM 2023

- **Voie d'administration séduisante des antibiotiques…**
- **Il n'y a pas de controverse…**
- **Traitement de choix** PAVM en réanimation.
- **Curatif et préventif:** Etudes expérimentales et cliniques.
- Sur tous les plans: **Histoire, Présent et Futur…**

PLAN

- Introduction- Historique.
- Rationnel d'utilisation- Etudes expérimentales.
- Mécanisme d'action d'un ATB inhalé.
- Moyens d'administration.
- Résultats cliniques.
- Perspectives et nouveautés.

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Attributable mortality up to 13%

Lengths of ventilation
Lengths of stay

Cost

- *Melsen WG, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis 2013*
- *Muscedere JG, et al. Mortality, attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and hospital-acquired pneumonia. Clin Infect Dis 2010*
- *Koulenti D, et al. Ventilator-associated tracheobronchitis: to treat or not to treat? Antibiotics (Basel) 2020*
- *Restrepo MI, et al. Economic burden of ventilator-associated pneumonia based on total resource utilization. Infect Control Hosp Epidemiol 2010*
- *Kollef MH, et al. Economic impact of ventilator-associated pneumonia in a large matched cohort. Infect Control Hosp Epidemiol 2012*
- *Zimlichman E, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med 2013*

INTRODUCTION

- Incidence annuelle : 15-37%. Mortalité attribuable: 13-60%.
- Pathologie en Augmentation en Tunisie :

Etude Noso-réa 1: 2017 Tunisie	Etude Noso-réa 2: 2022 Tunisie (16 Services)
Prévalence : 25%.	**Prévalence: 41.6% (33-49%).** PAVM (55%) +++
1- Pseudomonas Aeruginosa. 2- Acinetobacter Baumanii. 3-Enterobacteries: Klebsiella Pneumoniae BLSE	1-Emergence de Klebsiella Pneumoniae BMR (Post-Covid-19). 2-Acinetobacter Baumanii (ABRI) 3-Pseudomonas Aeruginosa.

Johnstone J et al. Definitions, rates and associated mortality of ICU-acquired pneumonia. J Crit Care 2023.

Melsen WG et al. Attributable mortality of ventilator-associated pneumonia. Lancet Infect Dis 2013.

Jamoussi A. et al. The prevalence of healthcare-associated infection in medical intensive care units in Tunisia. La Tunisie Med 2018.

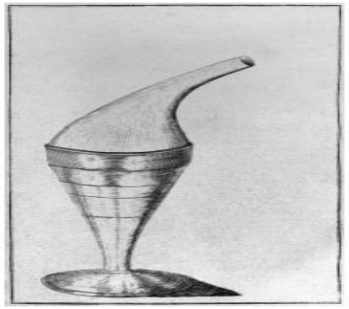
Jamoussi A et al. Annals of Intensive Care 2023, 13 (Suppl 1):FC-0233

Medical History, 2010, **54**: 171–194

"Divine Stramonium":
The Rise and Fall of Smoking for Asthma

MARK JACKSON*

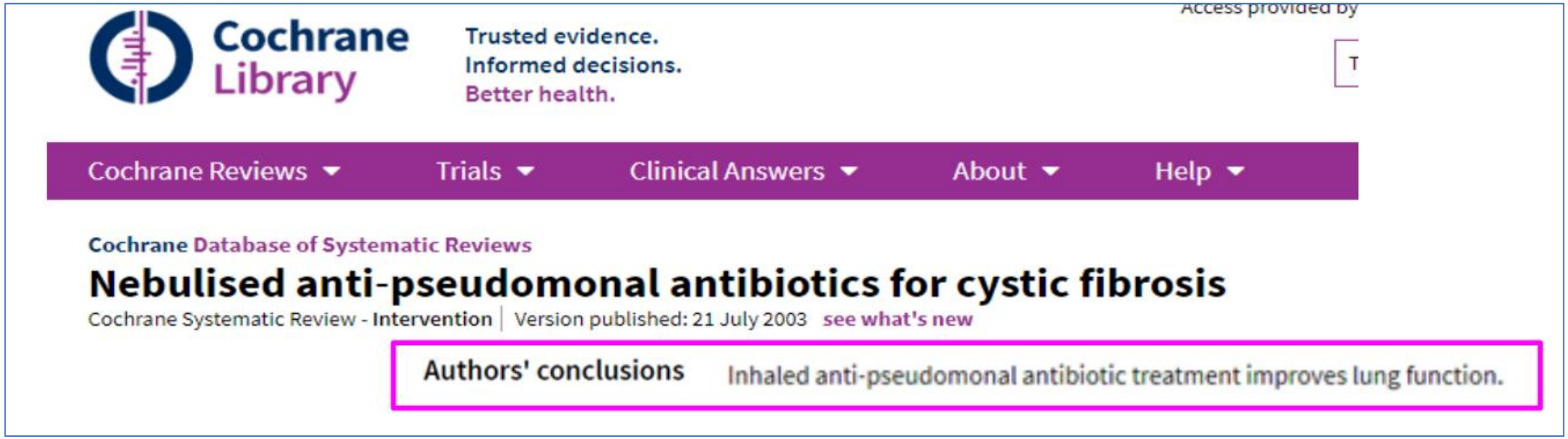
HISTOIRE



- **Avant le 19ème siècle**, Indiens Amérique du Nord (Datura pour traiter Asthme).
- **En 1945:** Domaine médical anti infectieux: micro aérosols de pénicilline dans les suppurations bronchopulmonaires.
- **Années 1950 :** Nébuliseurs à ultrasons (1 à 3 MHz), grâce à un champ électrique alternatif.
- **En 1990-2000,** la nébulisation ayant fait ses preuves dans la fibrose kystique.

J-F DESSANGES, A History of Nebulization. JOURNAL OF AEROSOL MEDICINE;2001

HISTOIRE RECENTE



Cochrane Library

Trusted evidence.
Informed decisions.
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Cochrane Reviews | Trials | Clinical Answers | About | Help

Cochrane Database of Systematic Reviews

Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Cochrane Systematic Review - Intervention | Version published: 21 July 2003 see what's new

Authors' conclusions Inhaled anti-pseudomonal antibiotic treatment improves lung function.

Treatment Group

Inhaled (synonymous with nebulised or aerosolised) antibiotics with activity against *P. aeruginosa.*

Antibiotics included were aminoglycosides (gentamicin, tobramycin, amikacin), colomycin (colistin), penicillins and cephalosporins with usual activity against *P. aeruginosa.*

Antibiotics to be given for one month or more.

All doses and methods of inhalation were included.

Trials in which an antibiotic was tested at two or more doses and trials in which two inhaled anti-pseudomonal antibiotics were compared were also selected.

Place importante dans la mucoviscidose en curatif…

Mais aussi Aztreonam, Lévofloxacine liposomale, Ciprofloxacine Vancomycine…

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RATIONNEL

- Livraison directe et rapide…
- Concentrations locales élevées (CMI très élevées 80-100 fois)…
- Moins d'effets secondaires systémiques (Insuffisance rénale, Diarrhée Clostridium Difficilae)…
- Diminution des risques de résistance…
- Raccourcir la durée des ATB systémiques…

Palmer LB, AJRCCM 2014

LA VOIE IV A SES LIMITES…

- Faibles concentrations de la **Tobramycine IV** dans l'épithélium tissulaire pulmonaire après injection IV de 7–10 mg/kg.
- En injectant en IV 25–30 mg/kg d'**Amikacine IV** les doses cibles tissulaires dans le parenchyme pulmonaire sont rarement atteintes.
- Plusieurs études pour la **Colimycine** IV ont montré une faible diffusion pulmonaire de cet ATB par voie IV

Carcas AJ et al. Tobramycin penetration into epithelial lining fluid of patients with pneumonia. Clin Pharmacol Ther 1999.

De Montmollin E et al. Predictors of insufficient amikacin peak concentration in critically ill patients receiving a 25 mg/kg total body weight regimen. Intensive Care Med. 2014.

Taccone *et al. Critical Care* 2010, **14**:R53
http://ccforum.com/content/14/2/R53

CRITICAL CARE

RESEARCH Open Access

Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock

Fabio Silvio Taccone[1], Pierre-François Laterre[2], Herbert Spapen[3], Thierry Dugernier[4], Isabelle Delattre[5], Brice Layeux[6], Daniel De Backer[1], Xavier Wittebole[2], Pierre Wallemacq[5], Jean-Louis Vincent[1] and Frédérique Jacobs*[6]

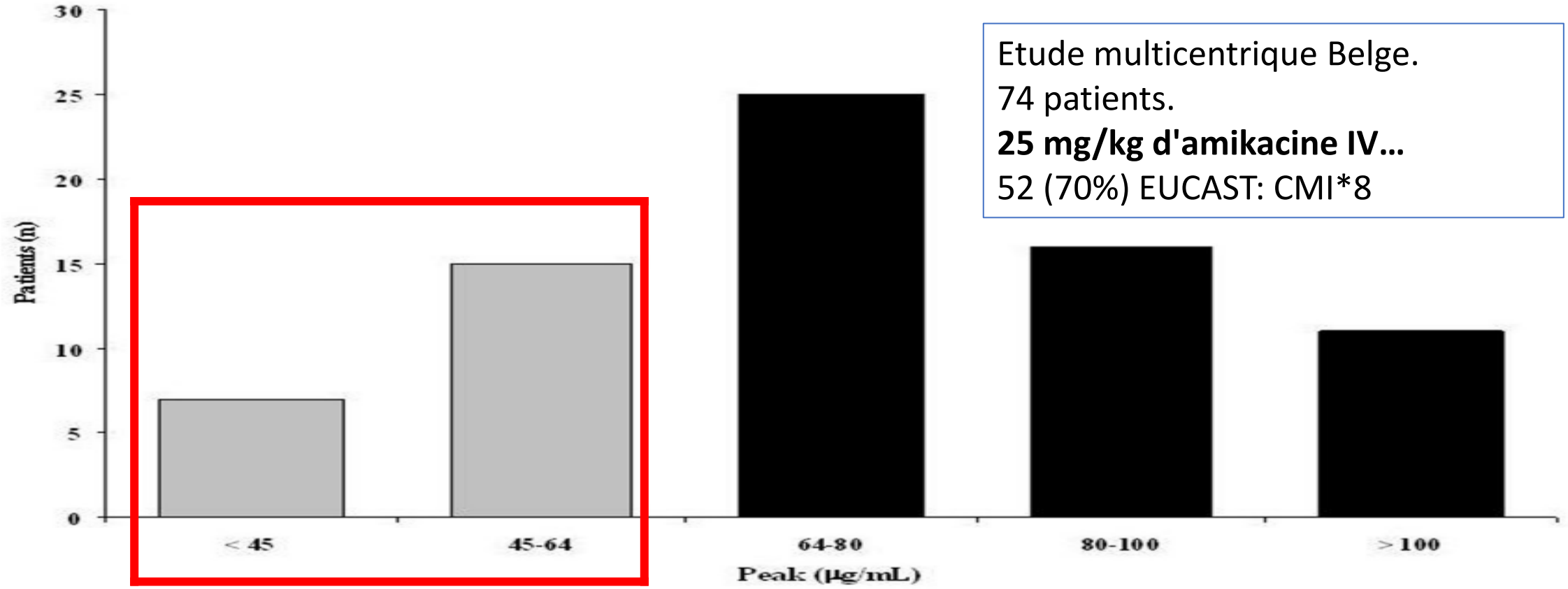


Figure 2 Distribution of peak concentrations. Black bars, peak >64 µg/ml; gray bars, peak <64 µg/ml.

Etude multicentrique Belge.
74 patients.
25 mg/kg d'amikacine IV…
52 (70%) EUCAST: CMI*8

CHEST

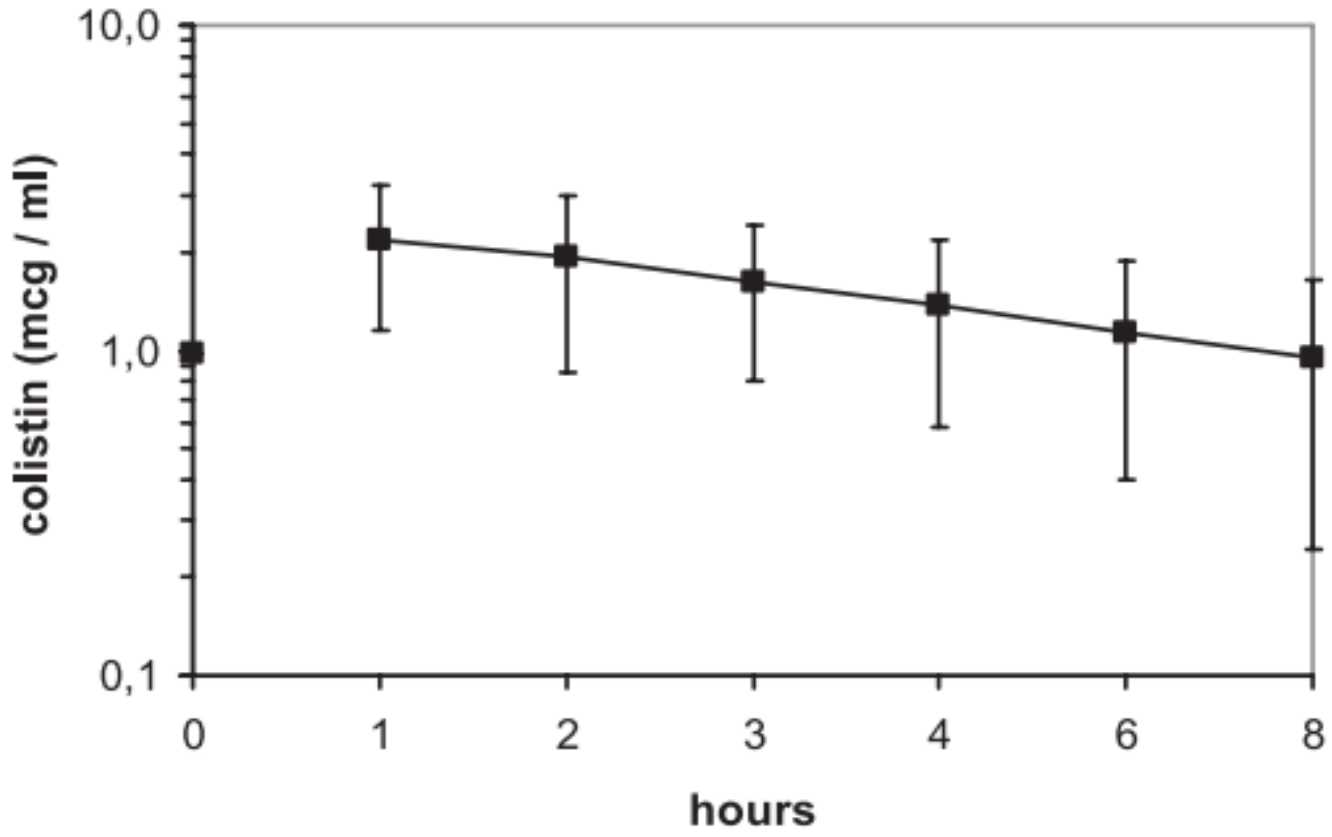
Official publication of the American College of Chest Physicians

CHEST ONLINE

Steady-State Pharmacokinetics and BAL Concentration of Colistin in Critically Ill Patients After IV Colistin Methanesulfonate Administration

Roberto Imberti, Maria Cusato, Paola Villani, Livio Carnevale, Giorgio A. Iotti, Martin Langer and Mario Regazzi

Chest 2010;138;1333-1339; Prepublished online June 17, 2010;
DOI 10.1378/chest.10-0463



To the best of our knowledge, colistin has never been measured in BAL. Two hours after the start of CMS infusion, colistin was undetectable in BAL but was present at a relevant concentration in the BAL of a patient who received CMS by aerosol, used as internal control (0.48 µg/mL).

- Colistine IV 2 Millions Unités * 2 /J IV
- **Concentration dans le LBA à H2: ZERO!**

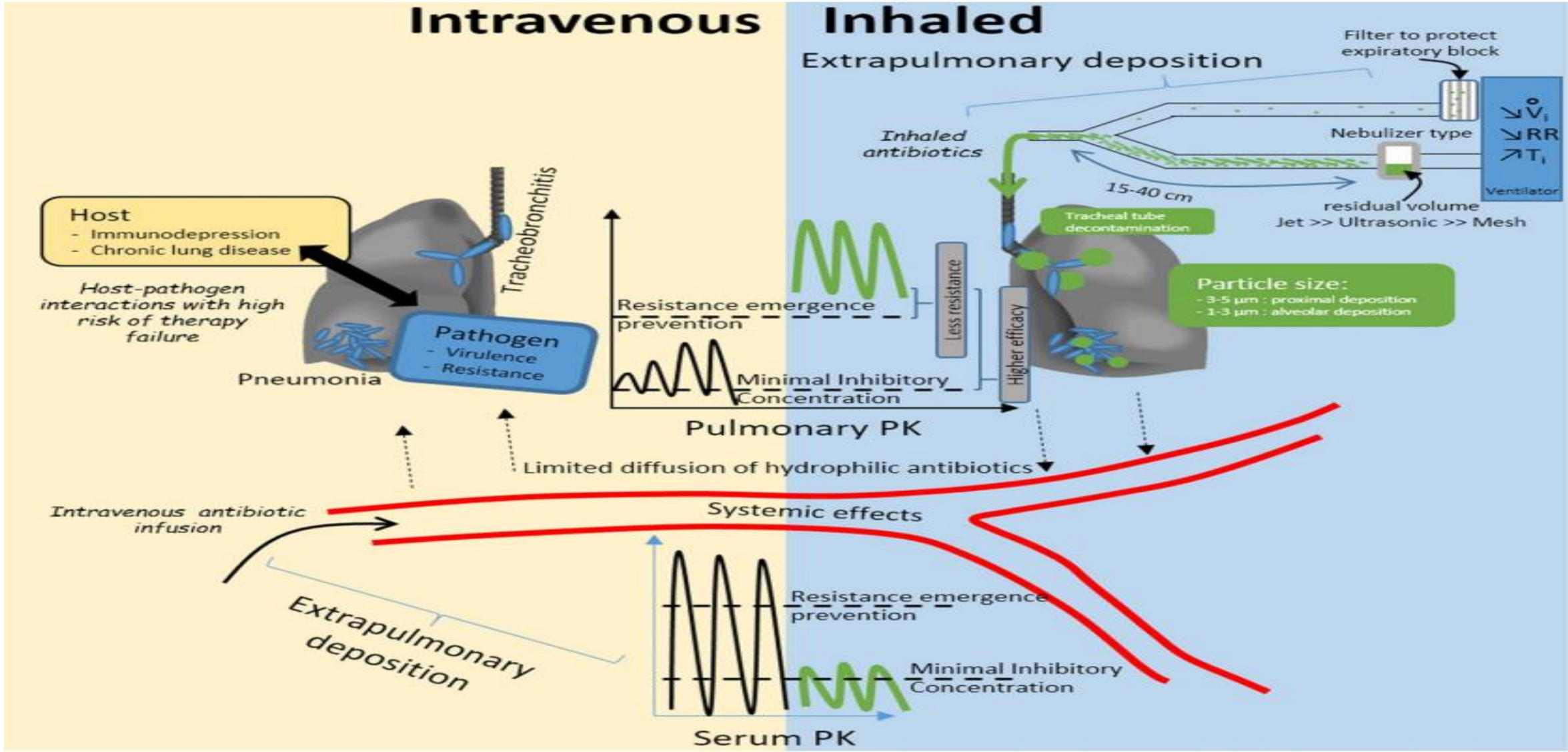
REVIEW Open Access

Nebulized antibiotics in mechanically ventilated patients: a challenge for translational research from technology to clinical care

Stephan Ehrmann[1,2*], Jean Chastre[3], Patrice Diot[2,4] and Qin Lu[5]

Ehrmann *et al. Ann. Intensive Care (2017) 7:78*
DOI 10.1186/s13613-017-0301-6

Annals of Intensive Care



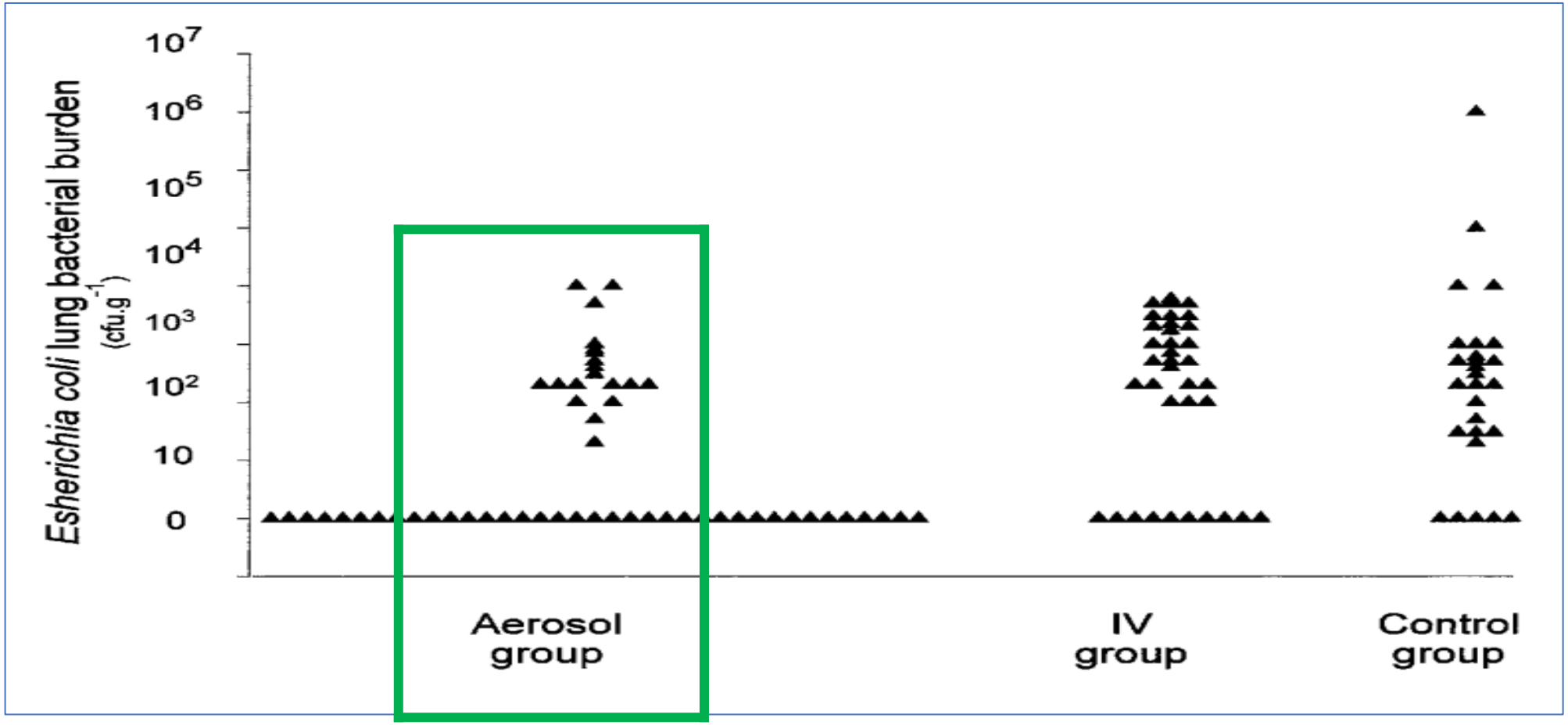
LA VOIE INHALEE A FAIT SES PREUVES DANS LES ETUDES EXPERIMENTALES…

Lung Deposition and Efficiency of Nebulized Amikacin during *Escherichia coli* Pneumonia in Ventilated Piglets

Ivan Goldstein, Frederic Wallet, Armelle Nicolas-Robin, Fabio Ferrari, Charles-Hugo Marquette, Jean-Jacques Rouby, and the Experimental Intensive Care Unit Study Group

Réanimation Chirurgicale Pierre Viars, Department of Anesthesiology, Pitié-Salpêtrière Hospital, University of Paris VI, Paris; and Department of Bacteriology, DHURE and INSERM U 416, University of Medicine, Lille, France

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 166 2002

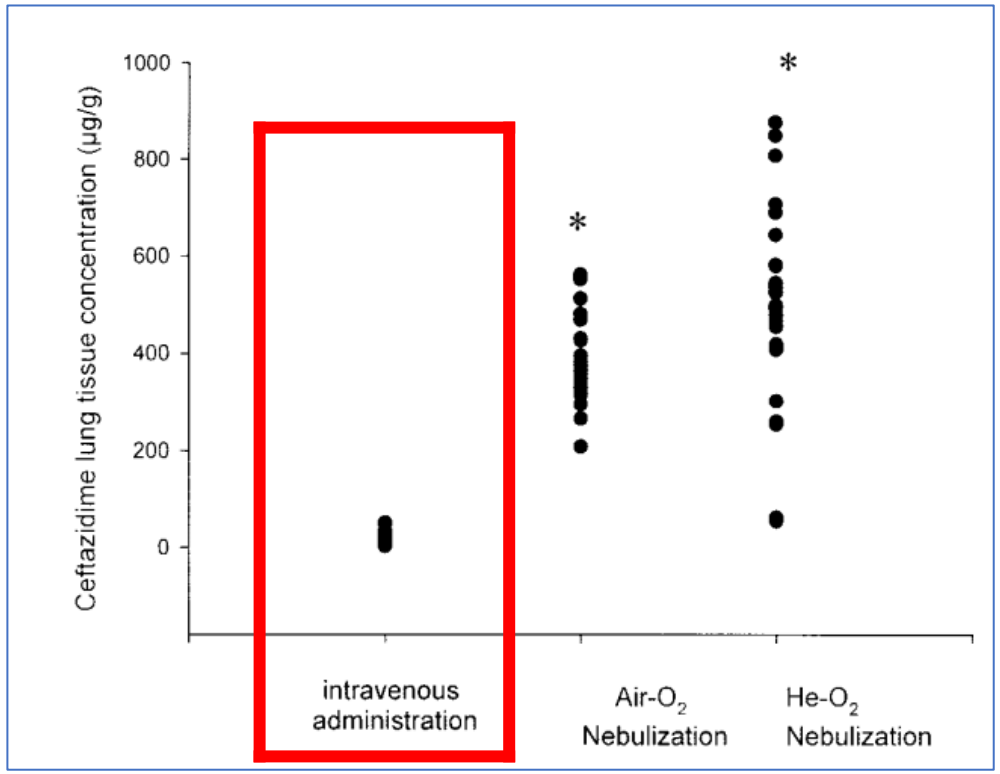


Anesthesiology 2005; 102:995–1000
© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

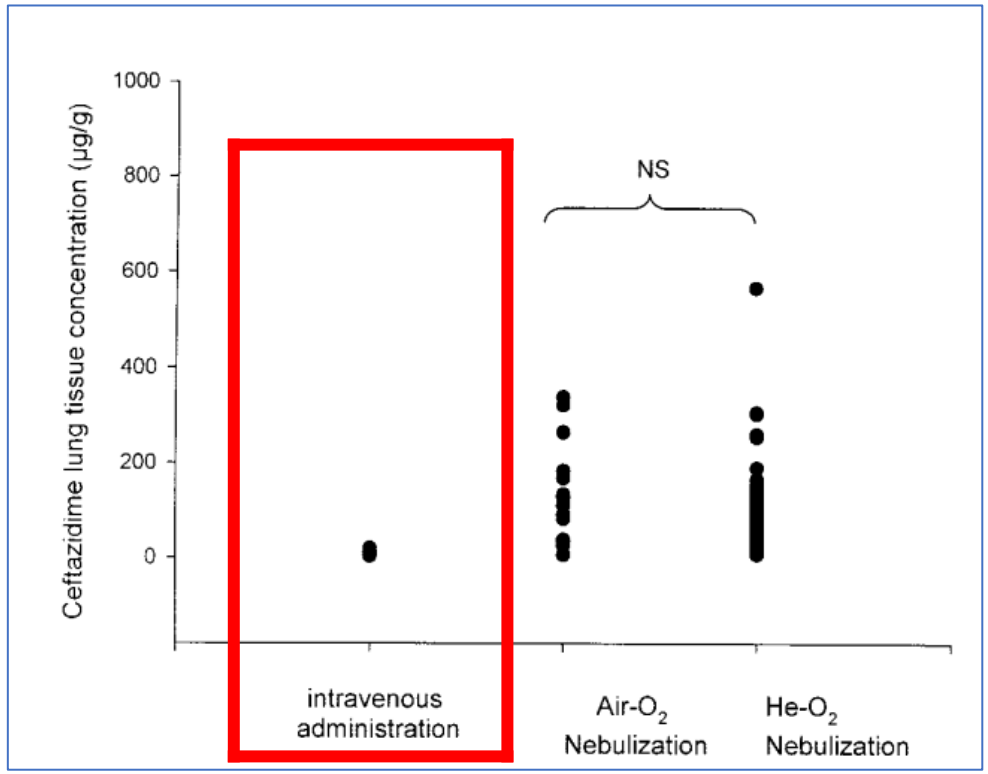
Intravenous versus *Nebulized Ceftazidime in Ventilated Piglets with and without Experimental Bronchopneumonia*

Comparative Effects of Helium and Nitrogen

Marc Tonnellier, M.D.,‡ Fabio Ferrari, M.D.,† Ivan Goldstein, M.D., Ph.D.,‡ Alfonso Sartorius, M.D.,§ Charles-Hugo Marquette, M.D., Ph.D.,‖ Jean-Jacques Rouby, M.D., Ph.D.#



Poumons sains



Avec Pneumonie

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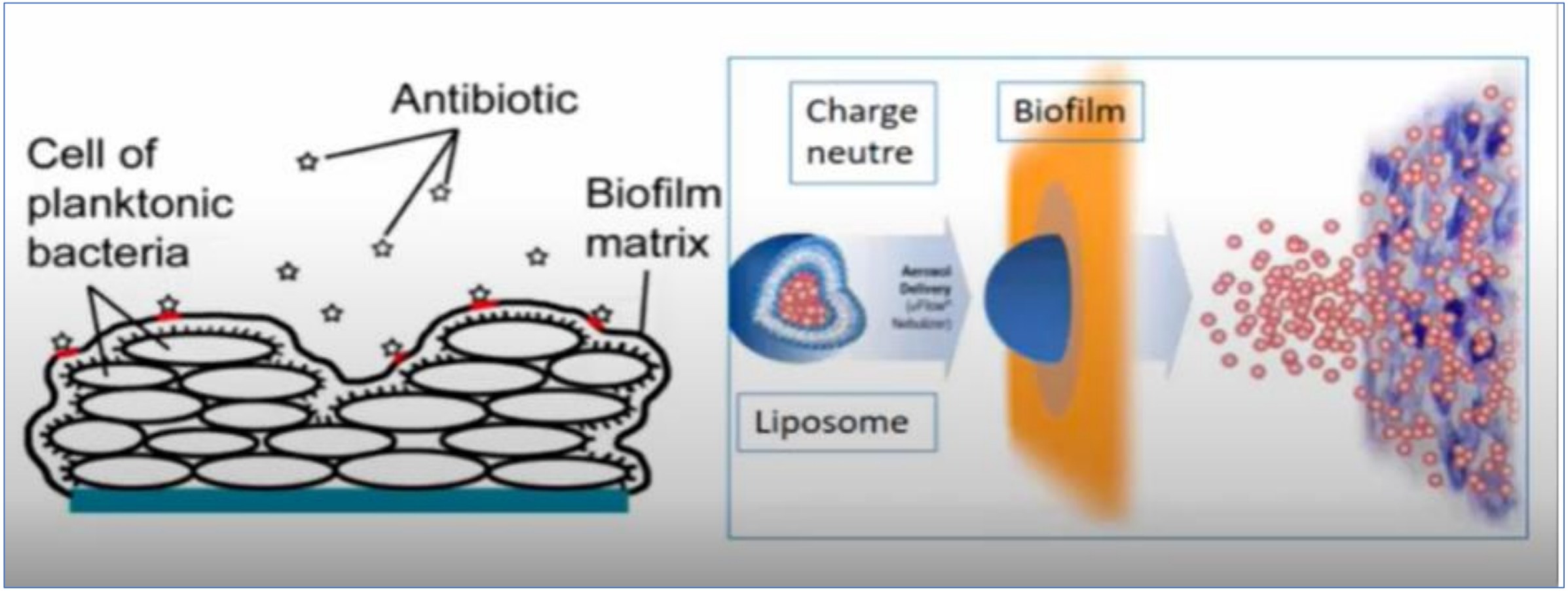
MÉCANISME D'ACTION

10 à 35% du produit inhalé atteint les poumons (3 à 5 µm)
Biofilm: Pénétration plus difficile.
Formes liposomales+++

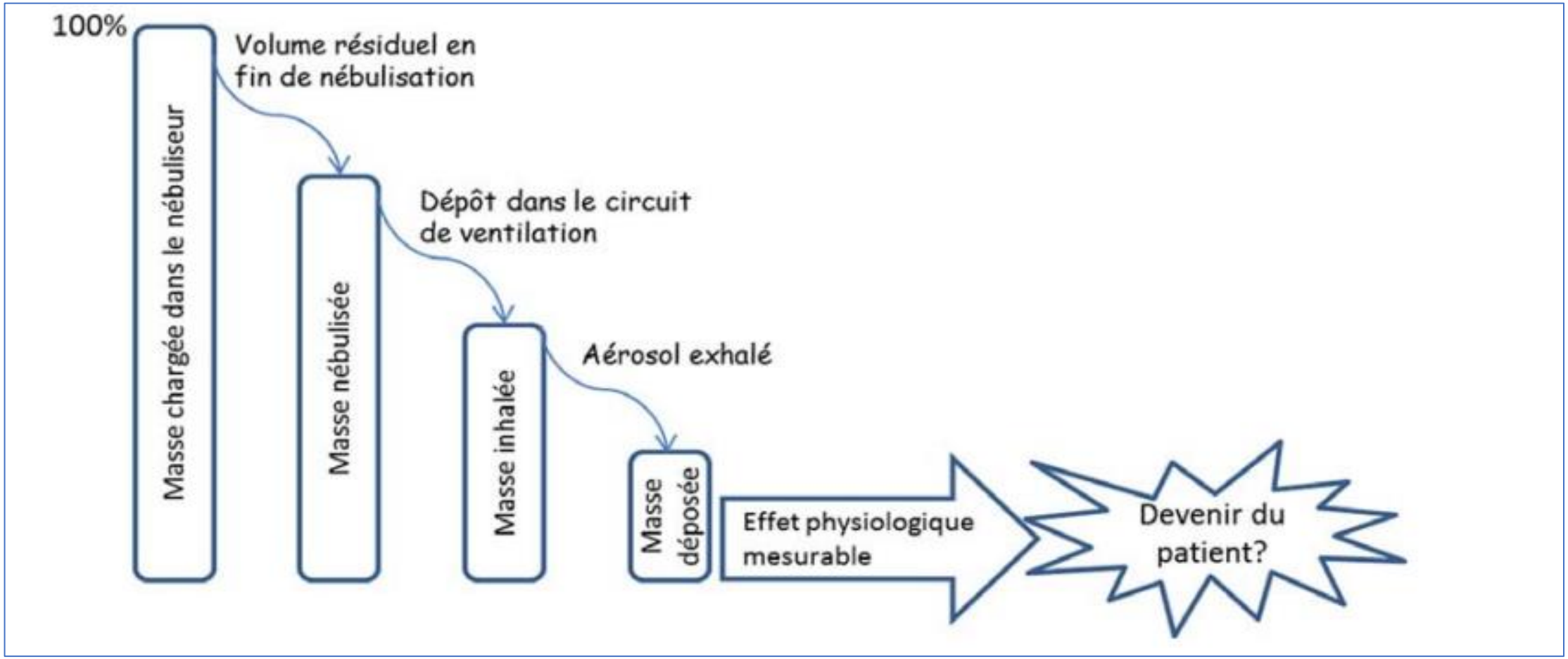


Li et al Annals of Intensive Care 2023

RENDEMENT

Rendement (masse déposée/masse placée dans le nébuliseur) < 5 % VM

Etudes récentes : rendements > à 20-60 % dans certains cas.



Ehrmann et al. Ann. Intensive Care (2017) 7:78

LISTE DES ATB: BACTÉRICIDES+++

Aucune recommandation par rapport au choix.

L'antibiothérapie inhalée utilise surtout des ATB bactéricides :

- Colistine 1 Million UI * 2…
- Tobramycine 300 mg* 2…

Préparation pour inhalation

- Amikacine 500 mg *2
- Gentamicine 80 mg * 2
- Céfotaxime 250mg * 2
- Ceftazidime 500 mg * 4

Konstan Pediatr Pulmonol 2013 Schuster Thorax 2013 AJRCCM 2013, ERJ 2014(44)

Elborn Clinical therapeutics 2016 BTS Guidelines Thorax 2010

Cochrane Database Systematic reviews 2012, 2017

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ATM 2021

Review Article on Medical Aerosol in Acute and Critical Care

Inhaled antibiotics during mechanical ventilation—why it will work

Maxime Desgrouas[1,2,3], Stephan Ehrmann[1,3]

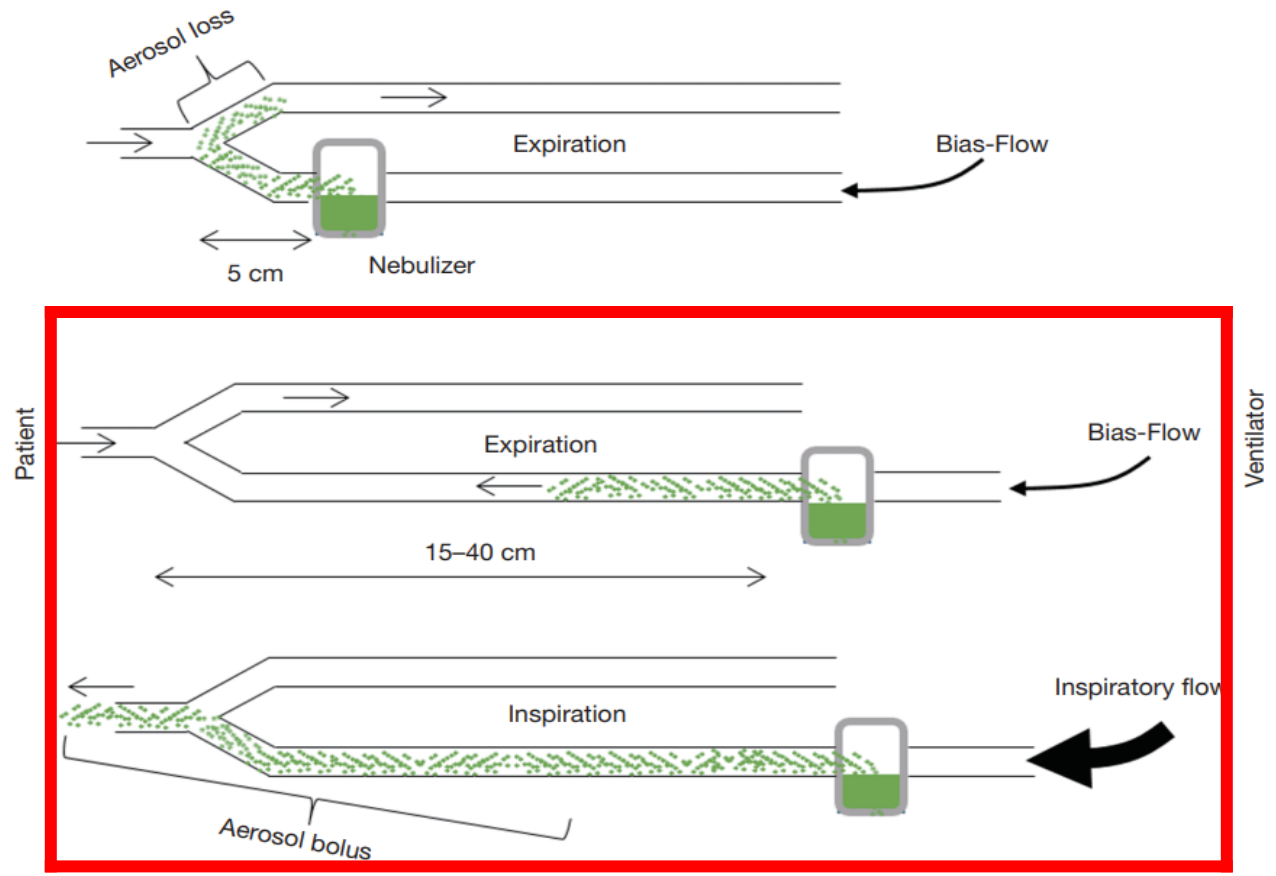


Figure 1 Influence of the nebulizer position on aerosol loss during expiration. With permission (19).

Position optimale: 15-40 cm sur la branche inspiratoire…

- ❑ **Baisser FR**
- ❑ **Augmenter Temps insp.**
- ❑ **Diminuer débit insp.**

Humidification : baisse de la dose délivrée

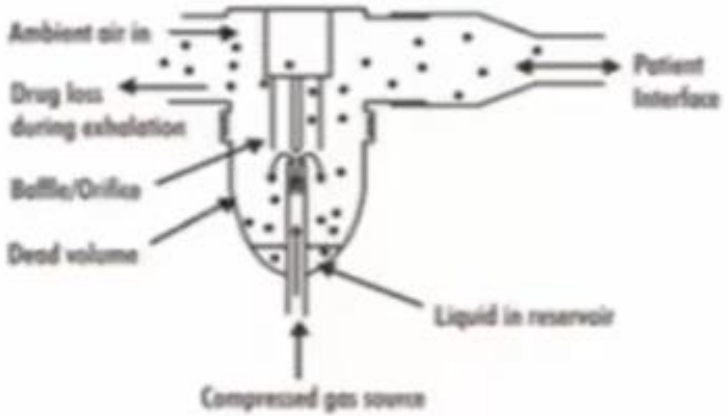
Ann Transl Med 2021;9(7):598 | http://dx.doi.org/10.21037/atm-20-3686

DIFFÉRENTS TYPES DE NÉBULISEURS

Tamis vibrant> Pneumatique

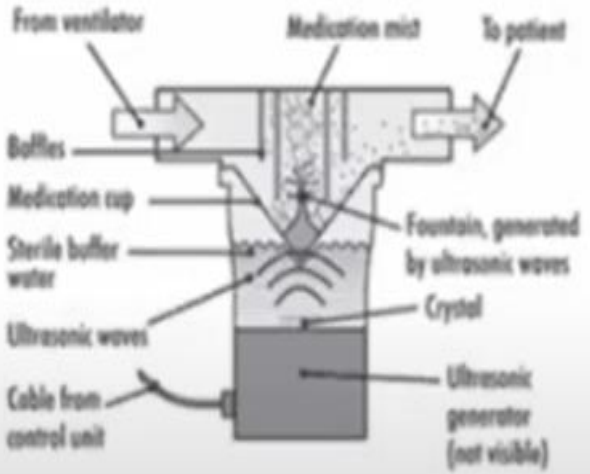
Pneumatiques

Figure 1: Functioning of Pneumatic Jet Nebulizer



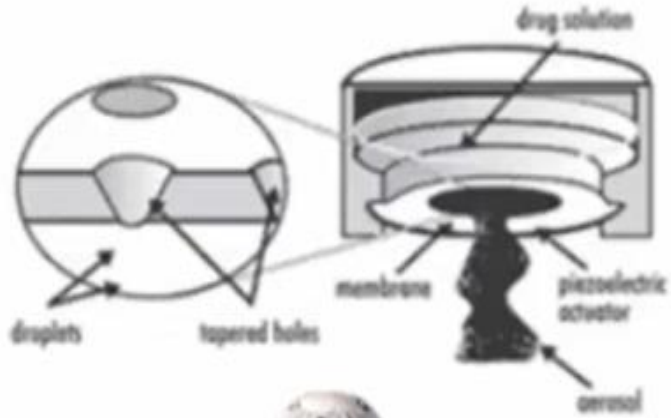
Ultrasoniques

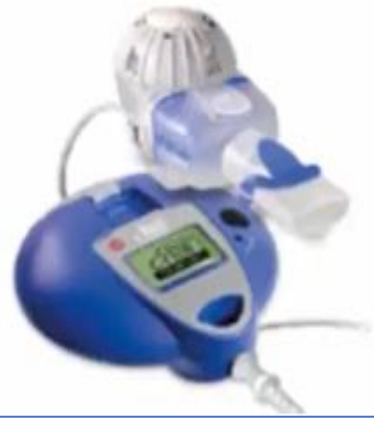
Figure 3: The Ultrasonic Nebulizer



À tamis vibrant

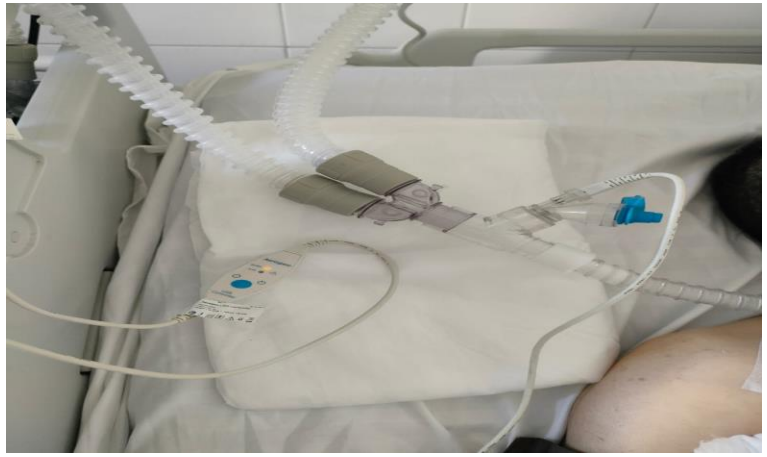
Figure 2: Principles of Mesh Nebulizer

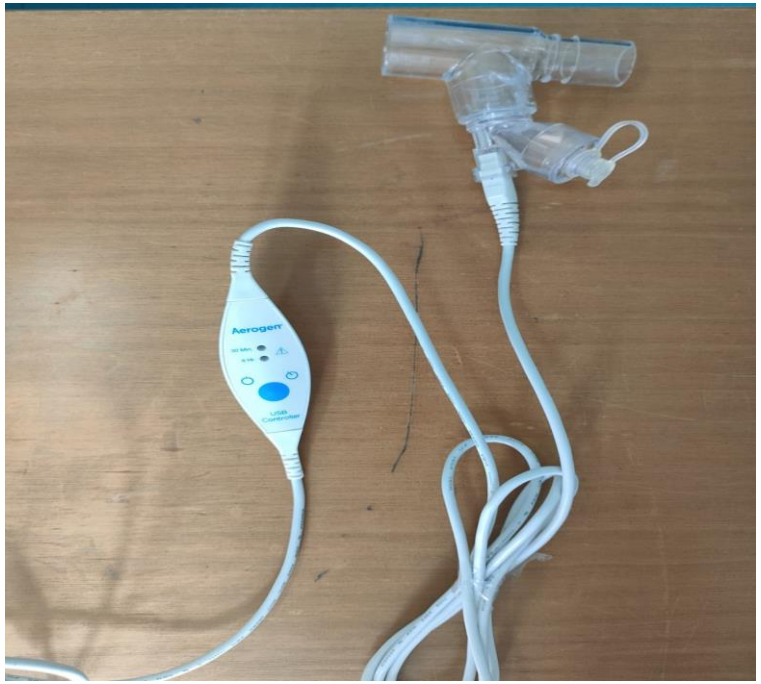




Contraintes Humidification

Tobramycine, Colimycine+++





Nébuliseurs à tamis vibrant disponibles en Tunisie !

Nébuliseurs Ultrasoniques vibrant disponibles en Tunisie !

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- Mécanisme d'action d'un ATB inhalé.
- Caractéristiques d'un ATB inhalé idéal.
- Moyens d'administration.
- **Résultats cliniques.**
- Perspectives et nouveautés.

ORIGINAL ARTICLE

Reduction of Bacterial Resistance with Inhaled Antibiotics in the Intensive Care Unit

Lucy B. Palmer and Gerald C. Smaldone

Pulmonary, Critical Care and Sleep Division, Department of Medicine, State University of New York at Stony Brook, Stony Brook, New York

American Journal of Respiratory and Critical Care Medicine Volume 189 Number 10 | May 15 2014

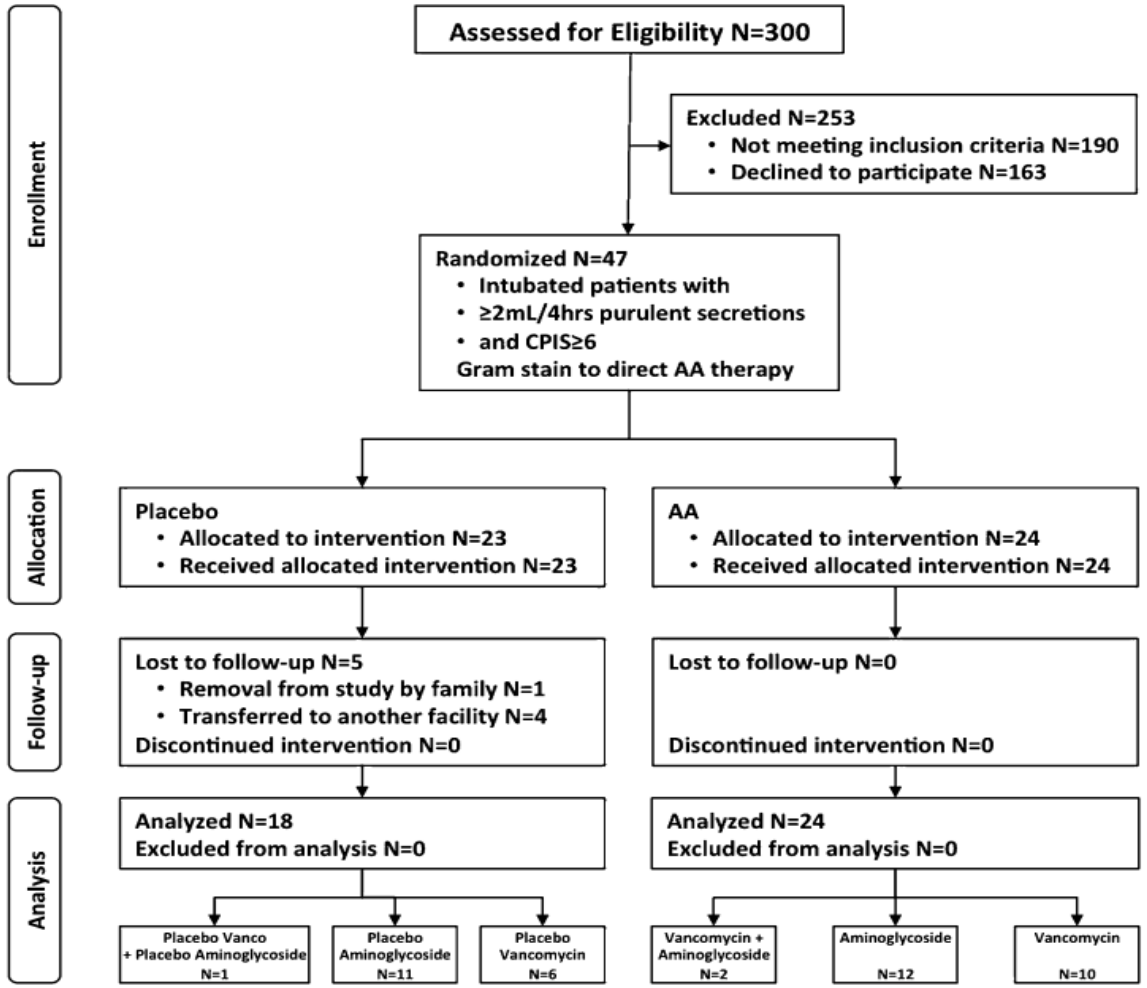

Table 2: Bacterial Isolates from Tracheal Aspirates at Randomization

	AA	Placebo
Gram-positive bacteria		
Methicillin-sensitive *Staphylococcus aureus*	3	2
Methicillin-resistant *Staphylococcus aureus*	5	7
Streptococcus agalactiae	1	0
Gram-negative bacteria		
Pseudomonas sp.	1	2
MDR* *Pseudomonas aeruginosa*	6	3
Acinetobacter sp.	0	1
MDR* *Acinetobacter* sp.	8	3
Enterobacter sp.	0	1
MDR* *Enterobacter* sp.	1	0
Escherichia coli	1	0
Klebsiella pneumoniae	1	2
Citrobacter freundii	0	1
Stenotrophomonas maltophilia	0	1

Definition of abbreviations: AA = aerosolized antibiotics; MDR = multidrug resistant.
Details are shown in Table 3, serial cultures in Figure 2.
*MDR gram-negative defined as resistance to ceftazidime or amikacin/gentamicin.

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American Journal of Respiratory and Critical Care Medicine Volume 189 Number 10 | May 15 2014

	Aerosolized Antibiotics	Placebo	*P* Value*
No. of randomization organisms eradicated†	96% (26/27)	9% (2/23)	<0.0001
No. of patients with eradication of resistant organisms	88% (14/16)	9% (1/11)	<0.0001

*Fisher exact test.
†Resistant and nonresistant organisms.

- **Etude contrôlée randomisée en double aveugle monocentrique.**
- **Eradication bactérienne sans augmentation des résistances.**
- **Diminution du recours aux ATB IV additionnels.**
- **Pas d'effets sur la mortalité.**

ORIGINAL ARTICLE

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Lucy B. Palmer and Gerald C. Smaldone

Pulmonary, Critical Care and Sleep Division, Department of Medicine, State University of New York at Stony Brook, Stony Brook, New York

American Journal of Respiratory and Critical Care Medicine Volume 189 Number 10 | May 15 2014

	Patients with New Resistance during Treatment	Patients	Aerosolized Treatment	Systemic Treatment	Organism
AA (n = 16)	2 (13%)	1	Gentamicin	Piperacillin/tazobactam	VRE
		2	Vancomycin	Cefepime	*Enterobacter* sp.
Placebo (n = 11)	6 (55%)	1	Placebo	Imipenem	PA
		2	Placebo	Imipenem	PA
		3	Placebo	Cefepime, meropenem, vancomycin	*Acinetobacter* sp.
		4	Placebo	Cefepime, gentamicin	PA
		5	Placebo	Vancomycin, piperacillin/tazobactam	*Klebsiella pneumoniae*, MRSA
		6	Placebo	Meropenem, vancomycin	*Enterobacter* sp.
P value*	0.03				

Definition of abbreviations: AA = aerosolized antibiotics; MRSA = methicillin-resistant *staphylococcus aureus*; PA = *Pseudomonas aeruginosa*; VRE = vancomycin-resistant enterococcus.
Data from patients with serial cultures throughout the study.
*Fisher exact test.

Abdellatif *et al. Ann. Intensive Care (2016) 6:26*
DOI 10.1186/s13613-016-0127-7

Annals of Intensive Care

RESEARCH Open Access

Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial

Sami Abdellatif, Ahlem Trifi*, Foued Daly, Khaoula Mahjoub, Rochdi Nasri and Salah Ben Lakhal

Etude prospective randomisée en simple aveugle. N=149 patients.
Colistine aérosol 4 Millions UI * 3 versus Colistine IV 9 MUI puis 4.5*2/24 heures.
+ Imipenème 1g*3/ jour pour les 2 groupes.

Critère de jugement principal: Guérison de la PAVM J14

Critères de jugement secondaires: Incidence Insuffisance rénale aigüe.

Abdellatif et al. Ann. Intensive Care (2016) 6:26
DOI 10.1186/s13613-016-0127-7

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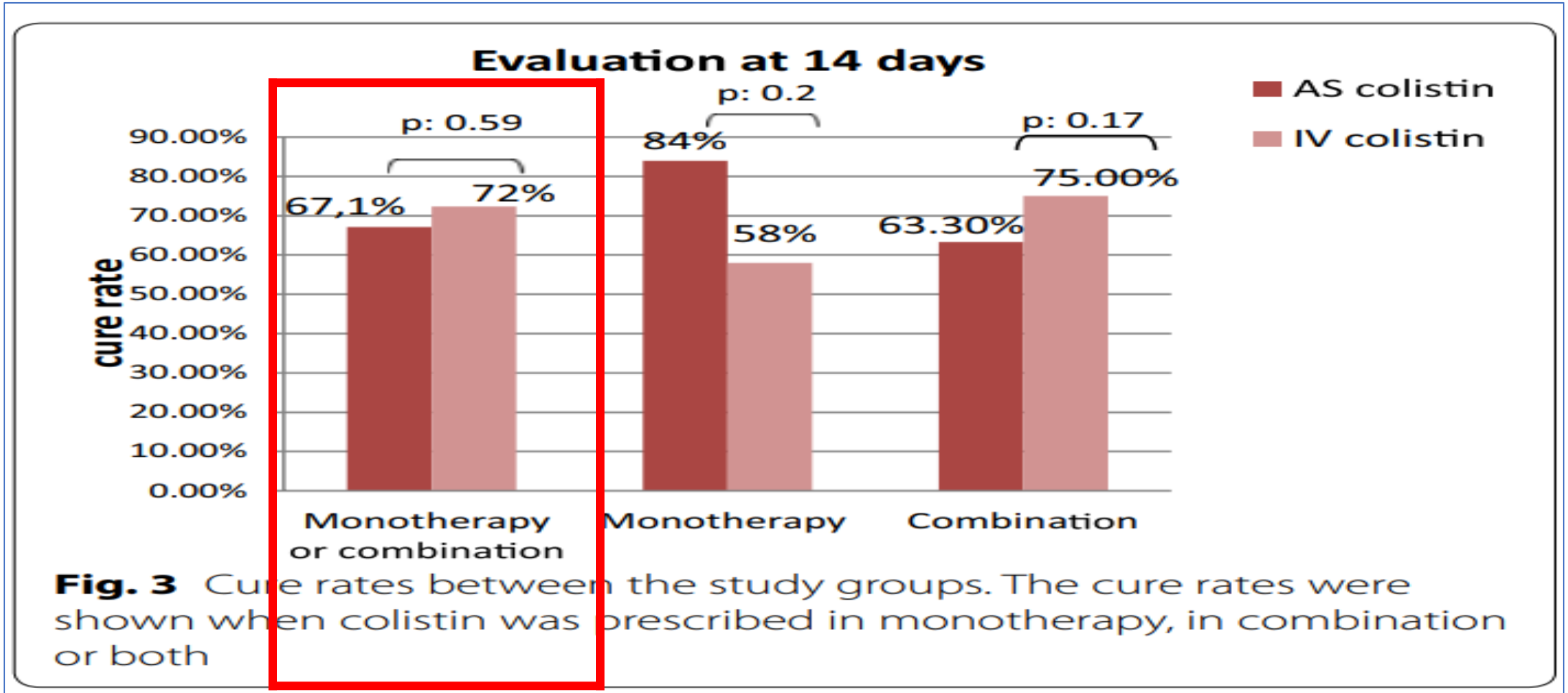

Fig. 3 Cure rates between the study groups. The cure rates were shown when colistin was prescribed in monotherapy, in combination or both

Abdellatif et al. Ann. Intensive Care (2016) 6:26
DOI 10.1186/s13613-016-0127-7

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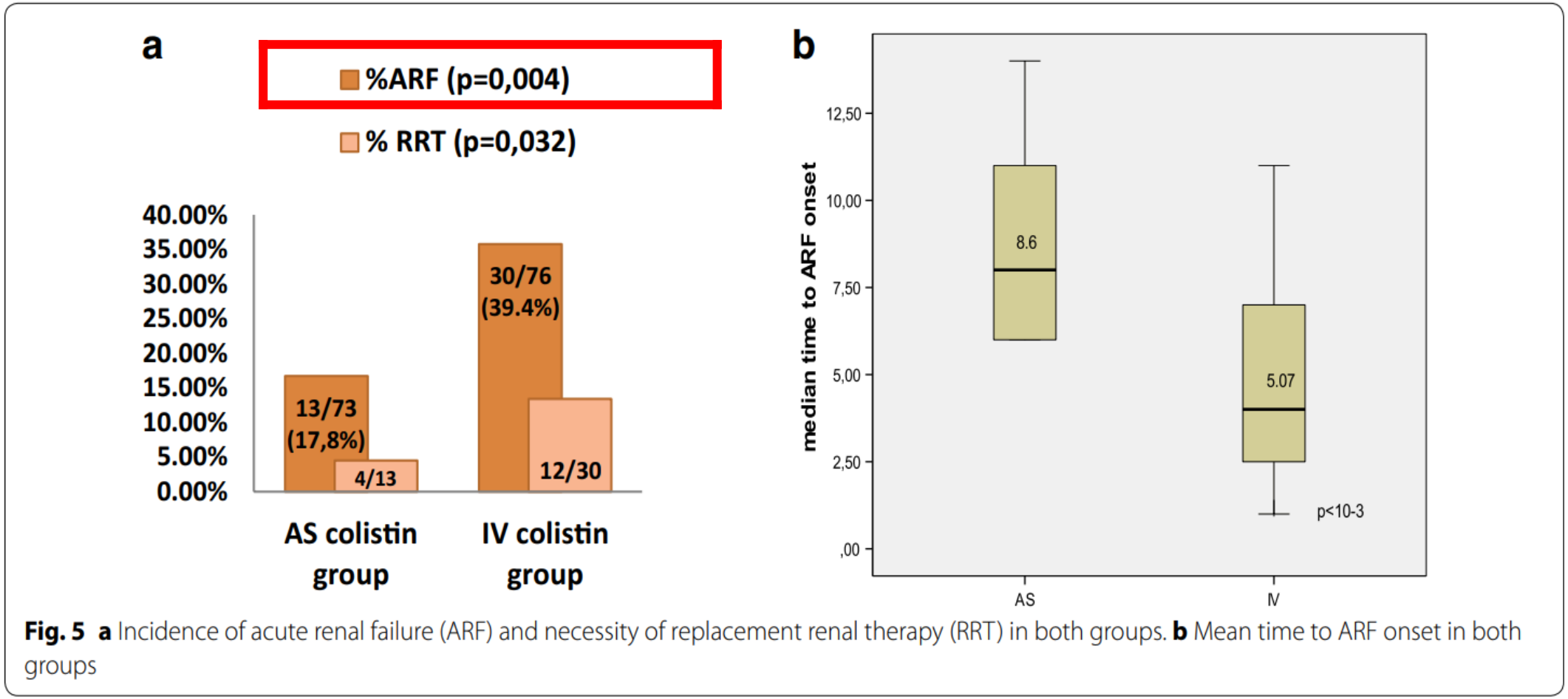

Fig. 5 **a** Incidence of acute renal failure (ARF) and necessity of replacement renal therapy (RRT) in both groups. **b** Mean time to ARF onset in both groups

Nebulized Ceftazidime and Amikacin in Ventilator-associated Pneumonia Caused by *Pseudomonas aeruginosa*

Qin Lu[1], Jianxin Yang[2], Zhihai Liu[2], Claudia Gutierrez[3], Guy Aymard[4], Jean-Jacques Rouby[1], and the Nebulized Antibiotics Study Group*

[1]Multidisciplinary Intensive Care Unit Pierre Viars, Department of Anesthesiology and Critical Care Medicine, La Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France; [2]Department of Emergency Medicine, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [3]Department of Anesthesiology, Faculty of Medicine, Federal University of Rio Grande do Sul, Hospital das Clinicas de Porto Alegre, Porto Alegre, Brazil; and [4]Department of Pharmacology, La Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France

Ceftazidime 15 mg/Kg + Amikacine 25 mg/Kg Neb.
Vs
Ceftazidime 90 mg/Kg + Amikacine 15 mg/kg IV.

Am J Respir Crit Care Med Vol 184. pp 106–115, 2011
Originally Published in Press as DOI: 10.1164/rccm.201011-1894OC on April 7, 2011
Internet address: www.atsjournals.org

	Aerosol ($n = 20$)	Intravenous ($n = 20$)	*P* Value
Cure of *P. aeruginosa* VAP on Day 9, n (%)	14 (70)	11 (55)	0.33
Day 9: Positive BAL $\geqslant 10^4$ cfu·ml^{-1} or mini-BAL $\geqslant 10^3$ cfu·ml^{-1}, n	3	6	
Persisting *P. aeruginosa* VAP on Day 9, n (%)	3 (15)	6 (30)	0.26
VAP caused by superinfection on Day 9, n (%)	3 (15)	3 (15)	NS
Recurrence of *P. aeruginosa* VAP, n	3	1	NS
Recurrence of VAP caused by superinfection, n	2	0	NS
Duration of MV, median (IQR)	29 (22–38)	18 (13–31)	0.13
Duration of MV after inclusion, median (IQR)	14 (7–22)	8 (6–12)	0.18
Length of stay in ICU, median (IQR)	38 (29–55)	29 (18–44)	0.08
Length of stay in ICU after inclusion, median (IQR)	24 (18–48)	16 (11–23)	0.08
Mortality on Day 28, n (%)	2 (10)	1 (5)	0.55

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journal homepage: www.journals.elsevier.com/journal-of-critical-care

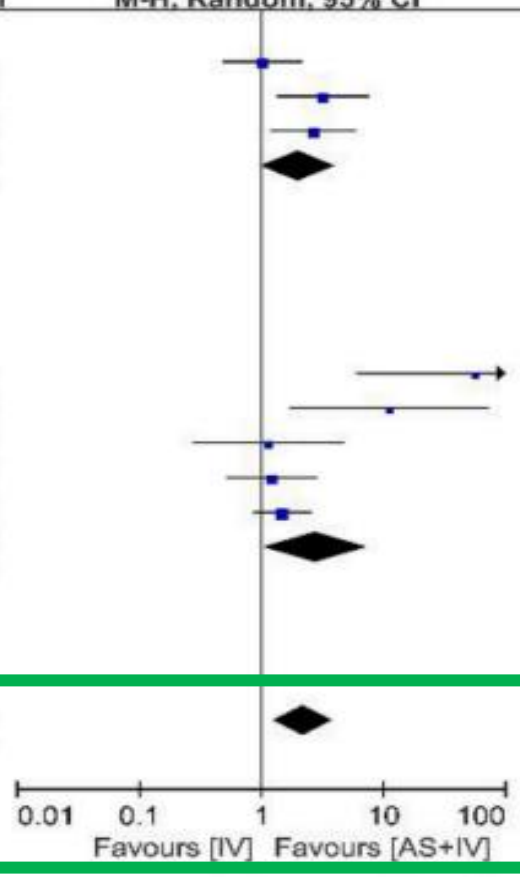
Nebulized colistin as the adjunctive treatment for ventilator-associated pneumonia: A systematic review and meta-analysis

Xiaoyu Zhang, MM [a,b,c], Xuanxuan Cui, MM [a,b,c], Mengke Jiang, MM [a,b,c], Shanshan Huang, MM [a,b,c], Min Yang, MD [a,b,c,*]

Réponse Clinique.
Réponse Microbiologique.

(B)

Study or Subgroup	AS+IV Events	Total	IV Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 RCT						
Abdellatif 2016	55	73	57	76	16.1%	1.02 [0.48, 2.14]
Nassar 2018	41	52	27	50	14.6%	3.18 [1.33, 7.56]
Rattanaumpawan 2010	31	51	18	49	15.3%	2.67 [1.19, 5.99]
Subtotal (95% CI)		**176**		**175**	**46.1%**	**2.00 [0.98, 4.09]**
Total events	127		102			
Heterogeneity: Tau² = 0.23; Chi² = 4.72, df = 2 (P = 0.09); I² = 58%						
Test for overall effect: Z = 1.90 (P = 0.06)						
1.2.2 Observational study						
Alikiaie 2018	15	20	1	20	5.0%	57.00 [6.00, 541.47]
Bogovic 2014	5	8	3	23	6.5%	11.11 [1.70, 72.56]
Kalin 2012	22	29	11	15	9.3%	1.14 [0.27, 4.76]
Kofteridis 2010	19	43	17	43	14.8%	1.21 [0.51, 2.86]
Tumbarello 2013	52	104	42	104	18.4%	1.48 [0.85, 2.56]
Subtotal (95% CI)		**204**		**205**	**53.9%**	**2.81 [1.03, 7.63]**
Total events	113		74			
Heterogeneity: Tau² = 0.83; Chi² = 14.60, df = 4 (P = 0.006); I² = 73%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Total (95% CI)		**380**		**380**	**100.0%**	**2.21 [1.25, 3.92]**
Total events	240		176			
Heterogeneity: Tau² = 0.39; Chi² = 19.32, df = 7 (P = 0.007); I² = 64%						
Test for overall effect: Z = 2.72 (P = 0.006)						



PLAN

- Introduction- Historique.
- Rationnel d'utilisation- Etudes expérimentales.
- Mécanisme d'action d'un ATB inhalé.
- Moyens d'administration.
- Résultats cliniques.
- **Perspectives et nouveautés.**

THE LANCET
Infectious Diseases

Volume 20, Issue 3, March 2020, Pages 330-340

ESSAI INHALE 1 + 2

Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial

Prof Michael S Niederman, MD • Jeff Alder, PhD • Prof Matteo Bassetti, MD • Francis Boateng, PhD • Prof Bin Cao, MD • Kevin Corkery, BSc • et al. Show all authors

Published: December 19, 2019 • DOI: https://doi.org/10.1016/S1473-3099(19)30574-2 •

Check for updates

Etude multicentrique internationale randomisée double aveugle.
25 Pays, 725 Patients.
400 mg Amikacine inhalée /12 heures Versus Placebo pendant 10 jours.
Critère de jugement principal: Survie à J 28.
Pas de différence de survie.
Mais….La moitié des souches n'étaient pas des BMR…

Patients

19 ICUs in France

Inclusion

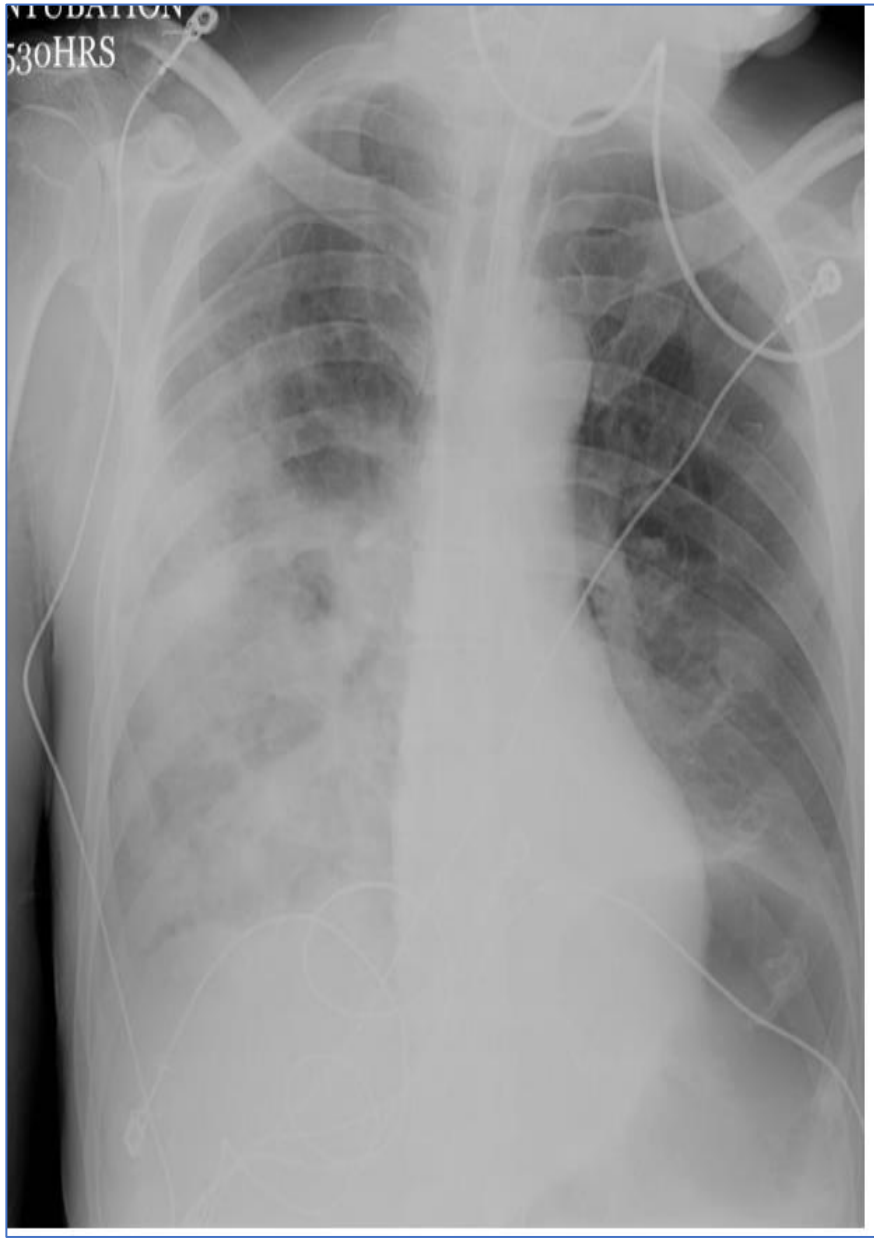
- Adult patients
- >72h of invasive mechanical ventilation

Non-Inclusion

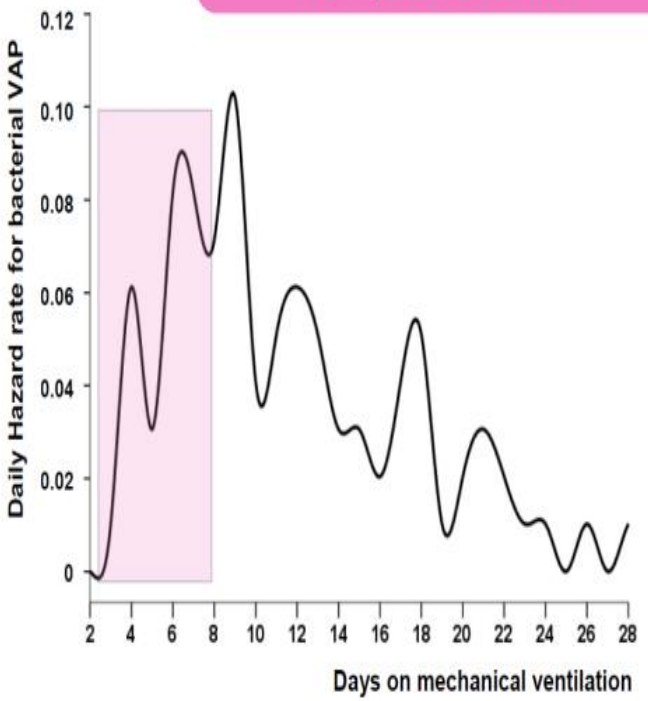
- >96h of invasive mechanical ventilation
- Suspected or confirmed VAP
- Severe acute kidney injury without RRT
- Chronic kidney disease (GFR < 30 mL/min)
- Tracheostomy
- Scheduled extubation within the next 24h
- Systemic aminoglycoside therapy

With Permission Pr S Ehrmann

ESICM LIVES 2023 MILAN



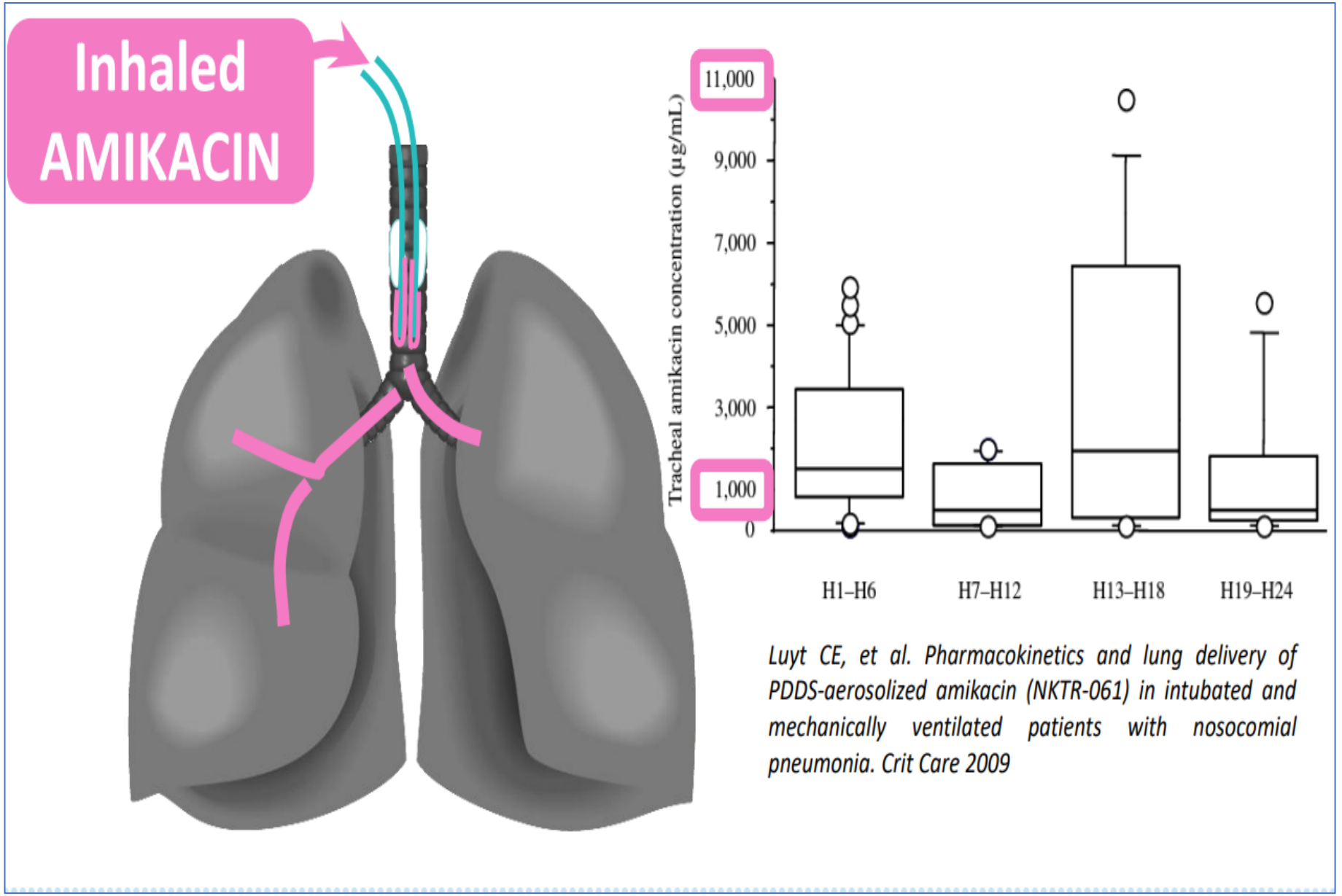
Window of opportunity for prevention



Forel JM, et al. Ventilator-associated pneumonia and ICU mortality in severe ARDS patients ventilated according to a lung-protective strategy. Crit Care 2012

With Permission Pr S Ehrmann

ESICM LIVES 2023
MILAN

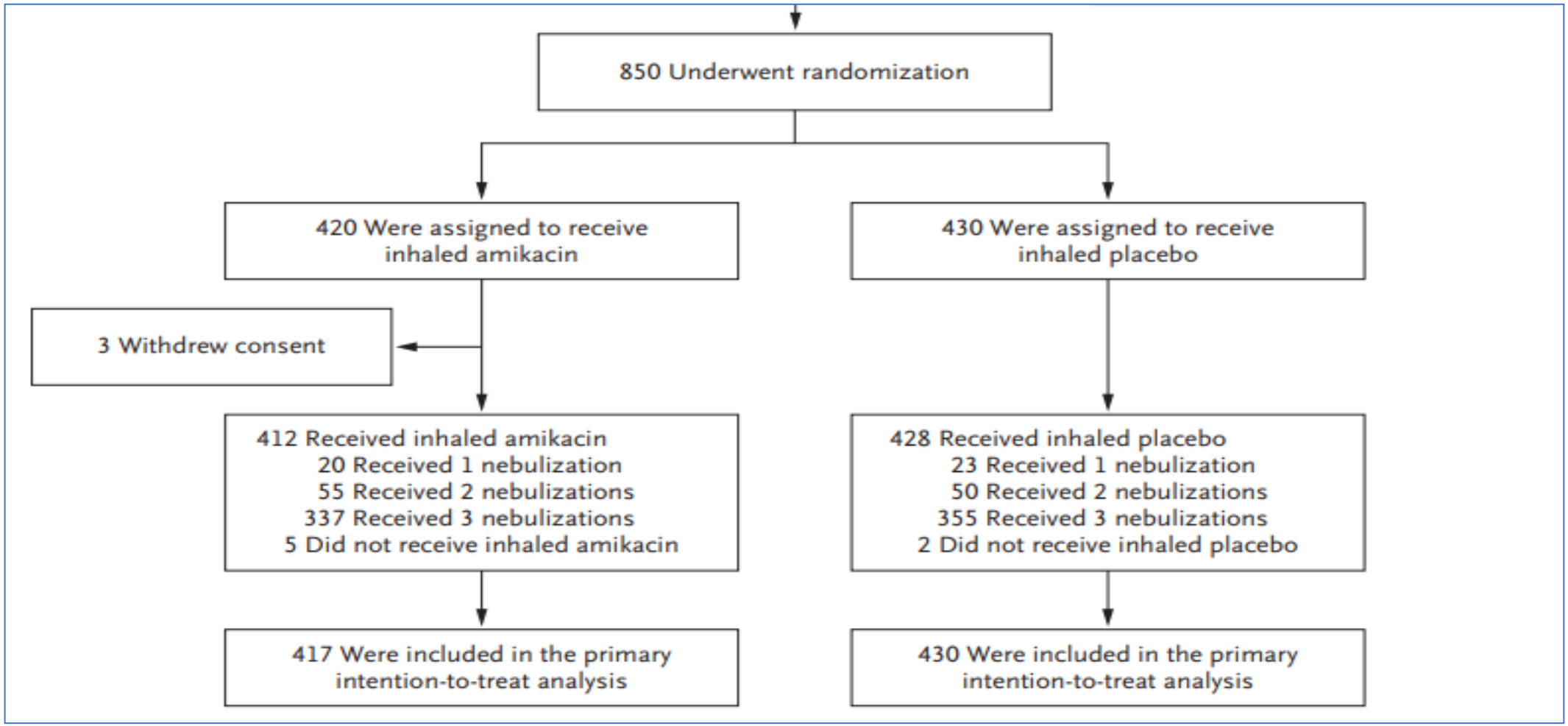


Luyt CE, et al. Pharmacokinetics and lung delivery of PDDS-aerosolized amikacin (NKTR-061) in intubated and mechanically ventilated patients with nosocomial pneumonia. Crit Care 2009

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia



The NEW ENGLAND JOURNAL of MEDICINE

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Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia

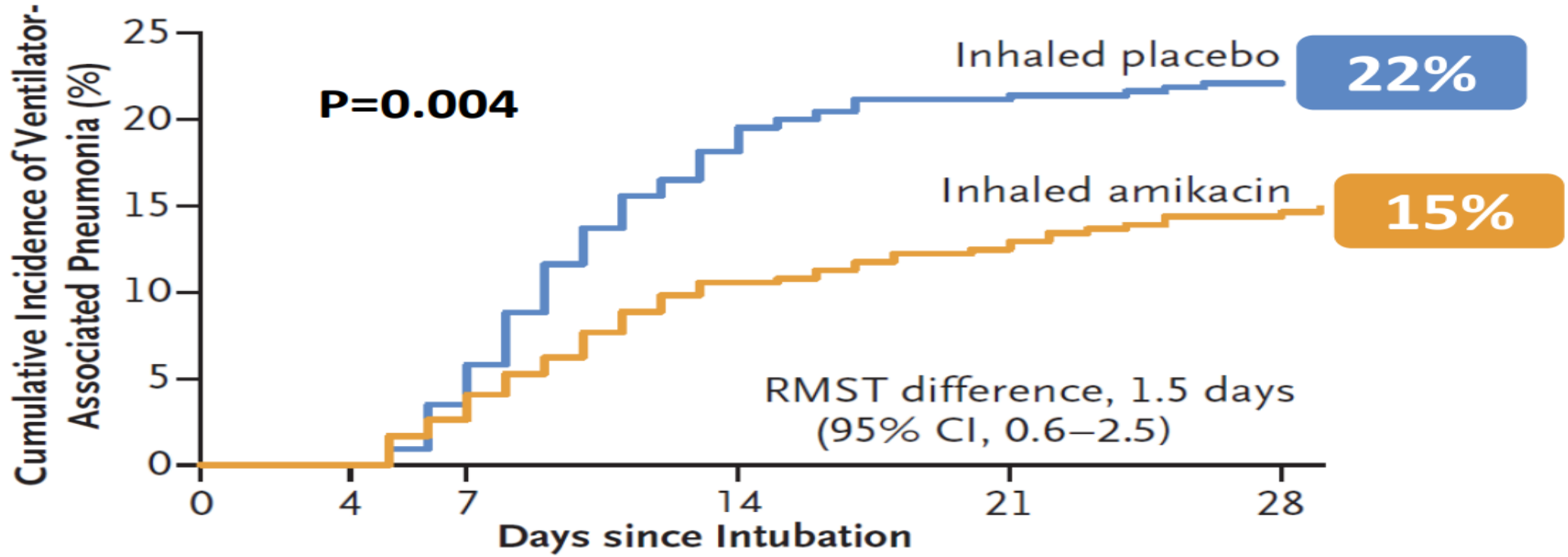
Patients

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Amikacin Group (N=417)	Placebo Group (N=430)
Age — yr	62y	61y
Sex		
Female	32%	36%
Male	282 (68)	273 (63)
Body-mass index†	29±7	29±8
Serum creatinine — mg per dl	1.2±1.1	1.1±1.0
Type of admission — no. (%)		
Scheduled surgery	14%	13%
Unscheduled surgery or trauma		
Medical	86%	87%
Charlson Comorbidity Index score‡	4±3	4±2
Simplified Acute Physiology Score II§	52	
Sequential Organ Failure Assessment score¶	8±4	8±4
Invasive mechanical ventilation before randomization — days	3.5d	
Systemic antibiotic therapy at randomization — no. (%)	78%	77%

Table 2. Outcomes.*

Outcome	Amikacin Group (N=417)	Placebo Group (N=430)	Hazard Ratio, Rate Ratio, or Difference (95% CI)	P Value
Primary outcome				
A first VAP episode from randomization to day 28 — no. (%)	62 (15)	95 (22)	1.5 (0.6 to 2.5)†	0.004



RMST: restricted mean survival time to VAP (adjusted for competing risk of extubation and death)

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Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia

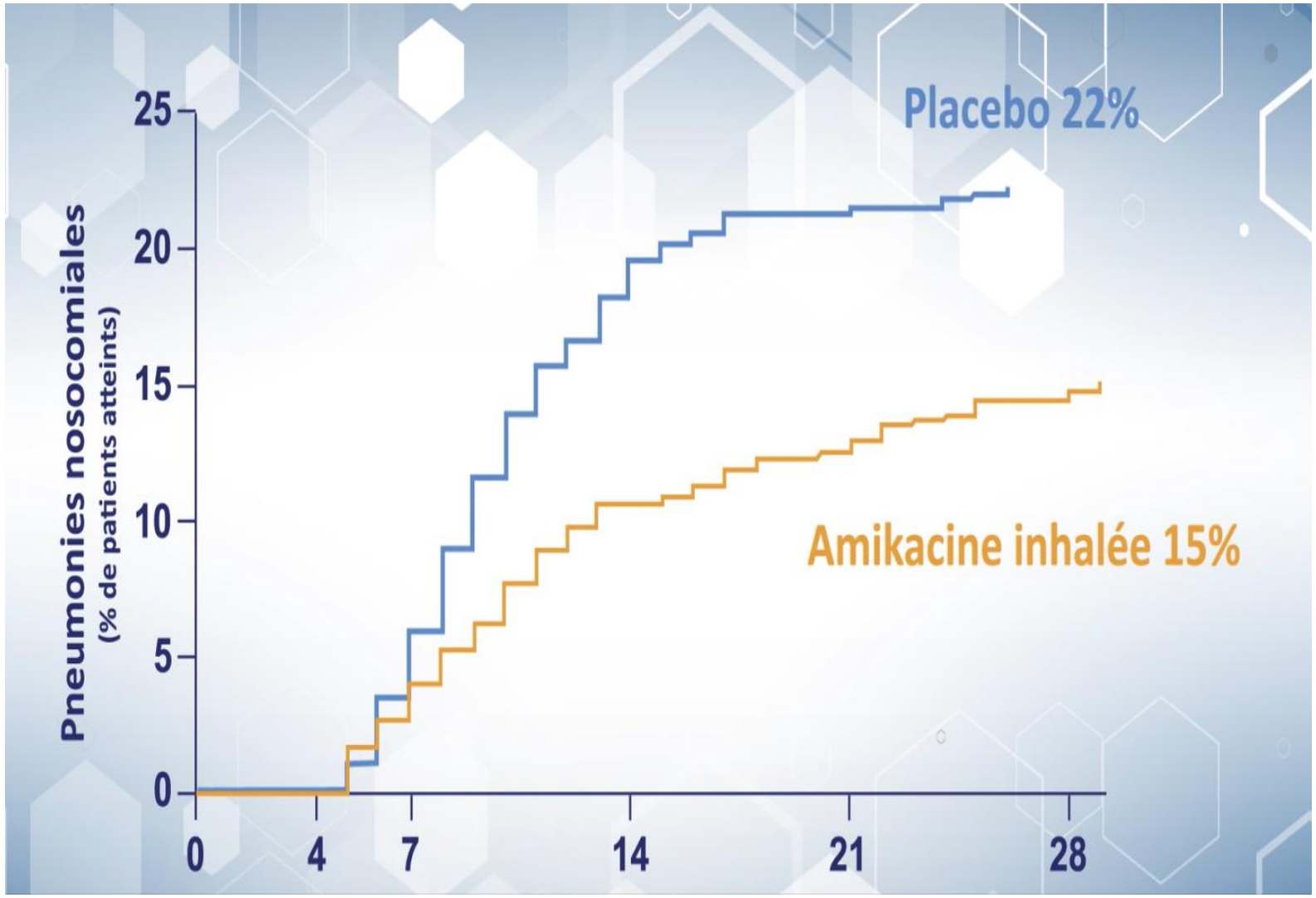
Median length of stay in days (IQR)				
ICU	12 (9 to 20)	13 (9 to 19)	−1 (−3 to 1)‖	
Hospital	27 (17 to 45)	27 (18 to 43)	0 (−3 to 4)‖	
Deaths — no. (%)				
ICU	99 (24)	112 (26)	0.89 (0.68 to 1.17)‡	
Hospital	123 (29)	136 (32)	0.91 (0.71 to 1.16)‡	
Safety outcomes				
Any serious adverse event — no. (%)	15 (4)	15 (3)		>0.99
Respiratory tract–disorders event — no. (%)	9 (2)	7 (2)		0.62
Serious adverse effect — no. (%)**	7 (2)	4 (1)		0.38
Respiratory tract effect — no. (%)	7 (2)	3 (1)		0.22
Acute kidney injury occurrence from randomization to day 28 — no./total no. (%)	11/294 (4)	24/309 (8)		0.03
Isolation on routine bacteriological samples of bacteria with acquired resistance to amikacin — no. (%)††	41 (10)	41 (10)		0.91
Acquired rectal carriage of resistant bacteria from randomization to ICU discharge — no. (%)				
Extended-spectrum beta-lactamase enterobacterales	16 (4)	9 (2)		0.16
High-level cephalosporinase-producing enterobacterales	11 (3)	8 (2)		0.49
Vancomycin-resistant enterococcus species	1 (<1)	0		>0.99

With Permission Pr S Ehrmann

Hot topics session:

7% Absolute reduction.

32% Relative Reduction.



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Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia

Conclusion:

Chez les patients intubés ventilés en réanimation pendant plus de 72 heures, un traitement préventif par amikacine inhalée pendant 03 jours réduit le risque de développer une PAVM pendant les prochains 28 jours.

Antibiotic consumption	19 (5)	42 (10)	0.46 (0.27 to 0.78)‡
Days with administration of at least one antibiotic — no. per 1000 patient-days of ICU stay	570	589	0.97 (0.89 to 1.01)
Antibiotic-days — no. per 1000 patient-days of ICU stay¶	887	968	0.92 (0.81 to 1.03)

Guidelines?

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

Antoni Torres, Michael S. Niederman, Jean Chastre, Santiago Ewig, Patricia Fernandez-Vandellos, Hakan Hanberger, Marin Kollef, Gianluigi Li Bassi, Carlos M. Luna, Ignacio Martin-Loeches, J. Artur Paiva, Robert C. Read, David Rigau, Jean François Timsit, Tobias Welte, Richard Wunderink

European Respiratory Journal 2017 50: 1700582; **DOI:** 10.1183/13993003.00582-2017

Pas de Place jusqu'en 2018-2019…!!!
Au cas par cas pour les BMR…

ELSEVIER

Clinical Microbiology and Infection 23 (2017) 629–639

Clinical Microbiology and Infection

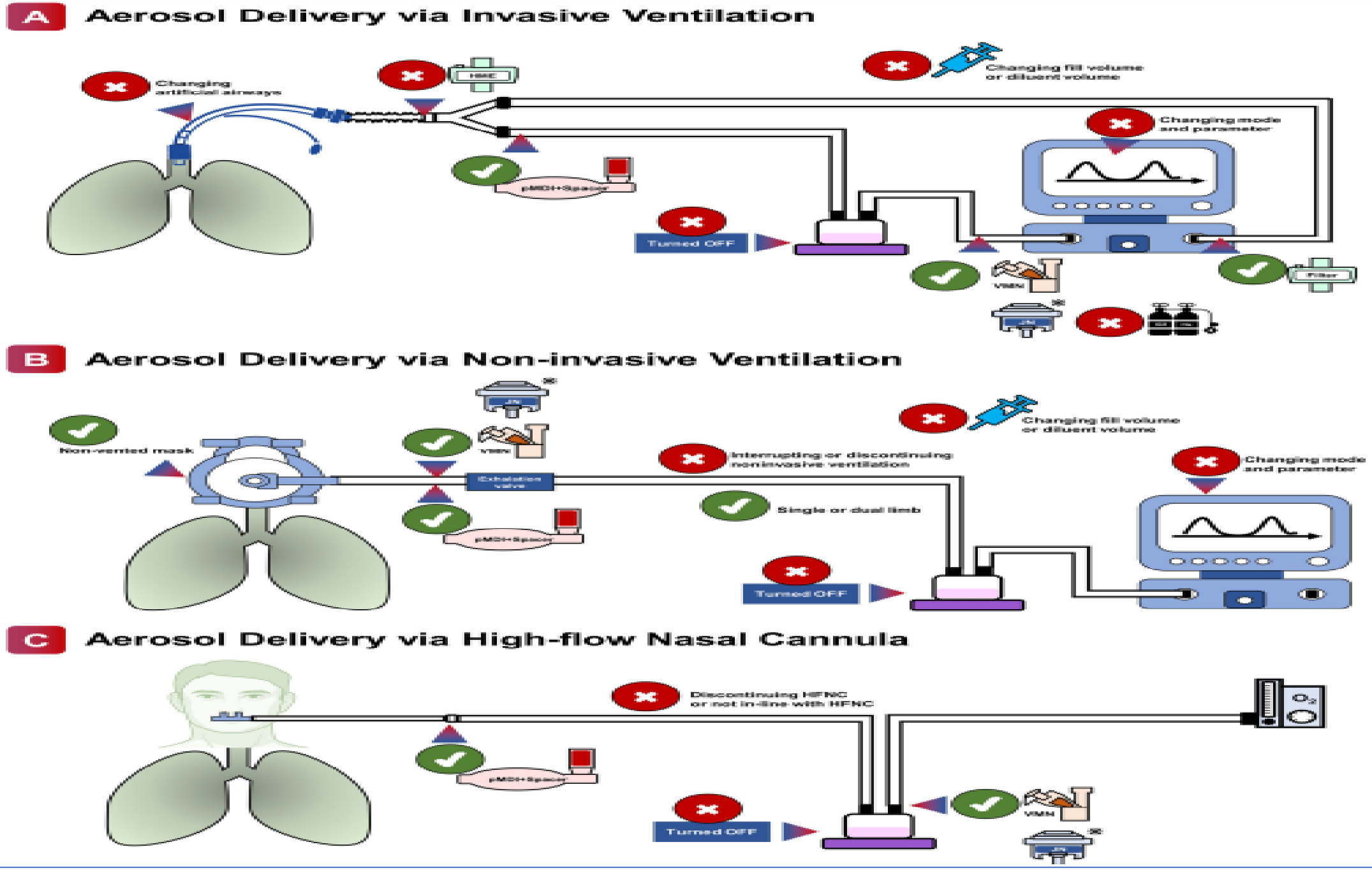
journal homepage: www.clinicalmicrobiologyandinfection.com

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

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]


A
Aerosol Delivery via Invasive Ventilation
Changing artificial airways
HMEC
pMDI+Spacer
Changing fill volume or diluent volume
Changing mode and parameter
Turned OFF
VMN
Filter
B
Aerosol Delivery via Non-invasive Ventilation
Non-vented mask
VMN
Exhalation valve
pMDI+Spacer
Changing fill volume or diluent volume
Interrupting or discontinuing noninvasive ventilation
Changing mode and parameter
Single or dual limb
Turned OFF
C
Aerosol Delivery via High-flow Nasal Cannula
Discontinuing HFNC or not in-line with HFNC
pMDI+Spacer
Turned OFF
VMN

Take Home Messages

- La recherche évolue sur les ATB inhalées…
- L'antibiothérapie inhalée est indiquée dans la prise en charge thérapeutique curative et préventive des PAVM (AMIKINHAL) en réa...
- L'Amikacine, la Colistine et la Ceftazidime sont les plus étudiées avec des résultats favorables : PAVM à BGN MR (Acinetobacter RI, Pseudomonas…)
- Plusieurs questions restent posées:

Quel protocole?

Quelle dose optimale?

Est-ce applicable dans les règles sur notre population

(Formation Personnel, moyens…)

Merci pour votre Attention