PRISE EN CHARGE DES PNEUMOPATHIES NOSOCOMIALES :

ANTIBIOTIQUES PAR VOIE INHALÉE !

Pr Ag AYACHI JIHENE

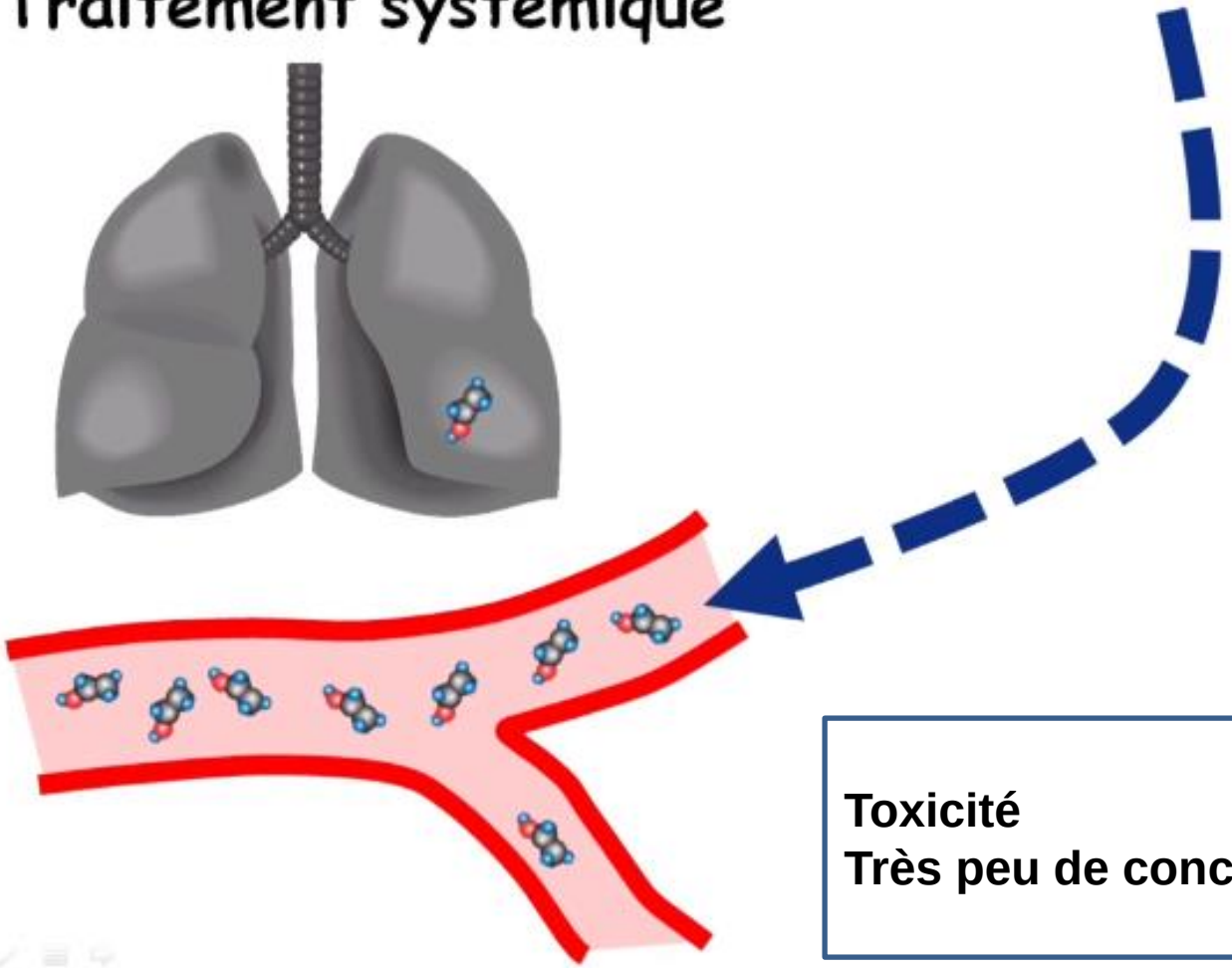
Service de Réanimation Médicale

CHU Ibn El Jazzar Kairouan

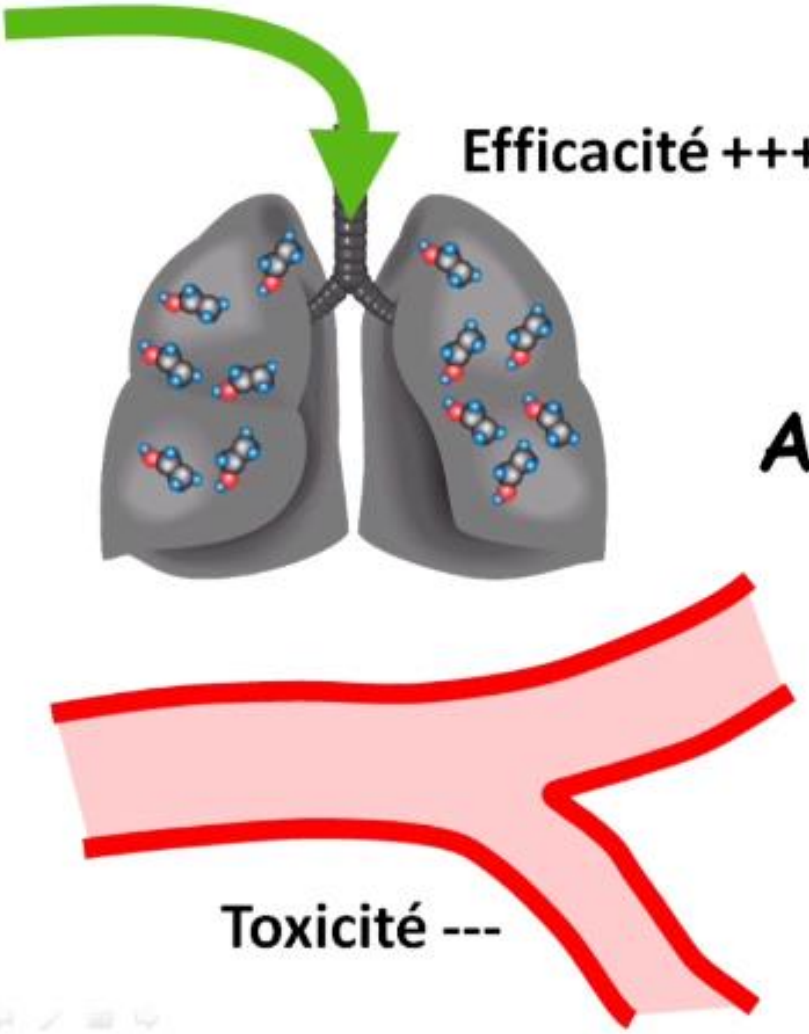
ATR Décembre 2023

RATIONNEL

Traitement systémique

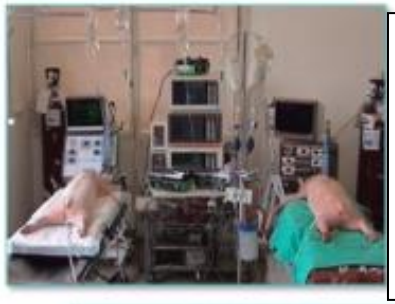


Toxicité
Très peu de concentration pulmonaire



Aérosolthérapie

Etudes expérimentales animales

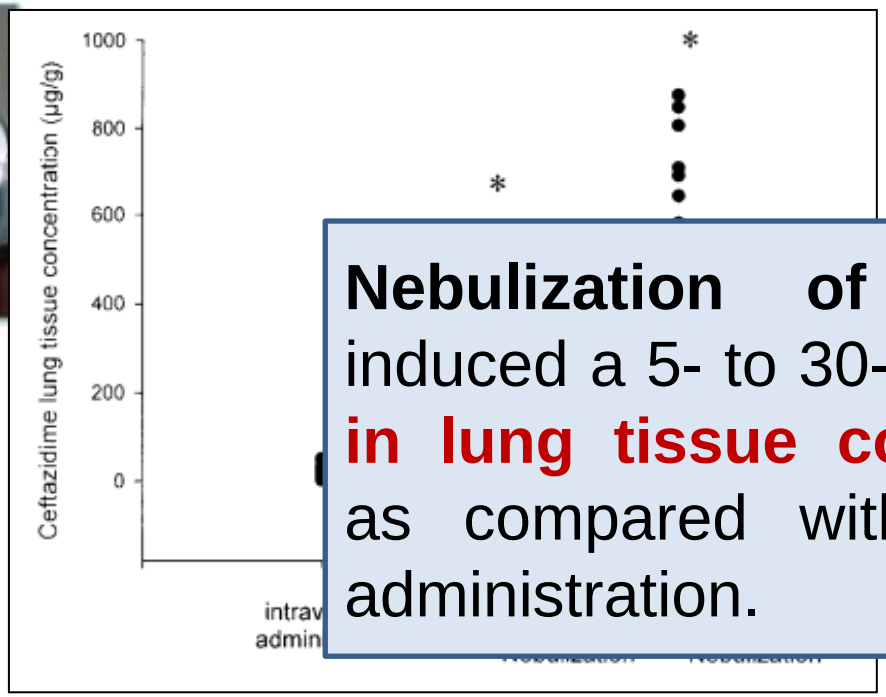


Anesthesiology 2005; 102:995–1000
© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

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

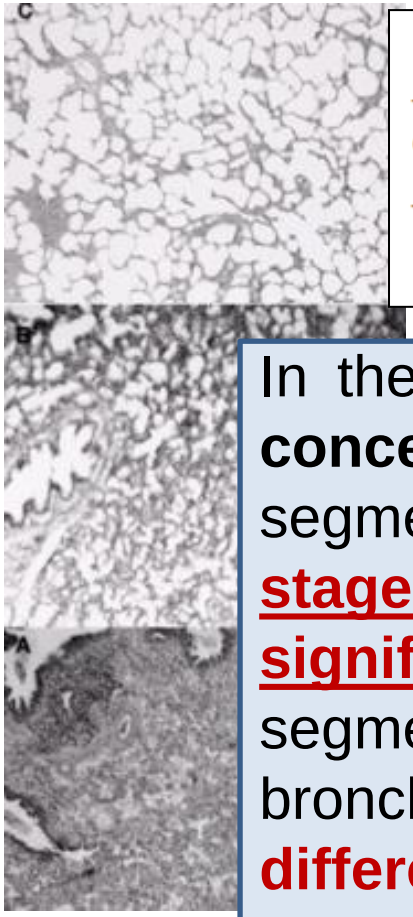
Comparative Effects of Helium and Nitrogen

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.#



Nebulization of ceftazidime induced a 5- to 30- fold **increase in lung tissue concentrations** as compared with intravenous administration.

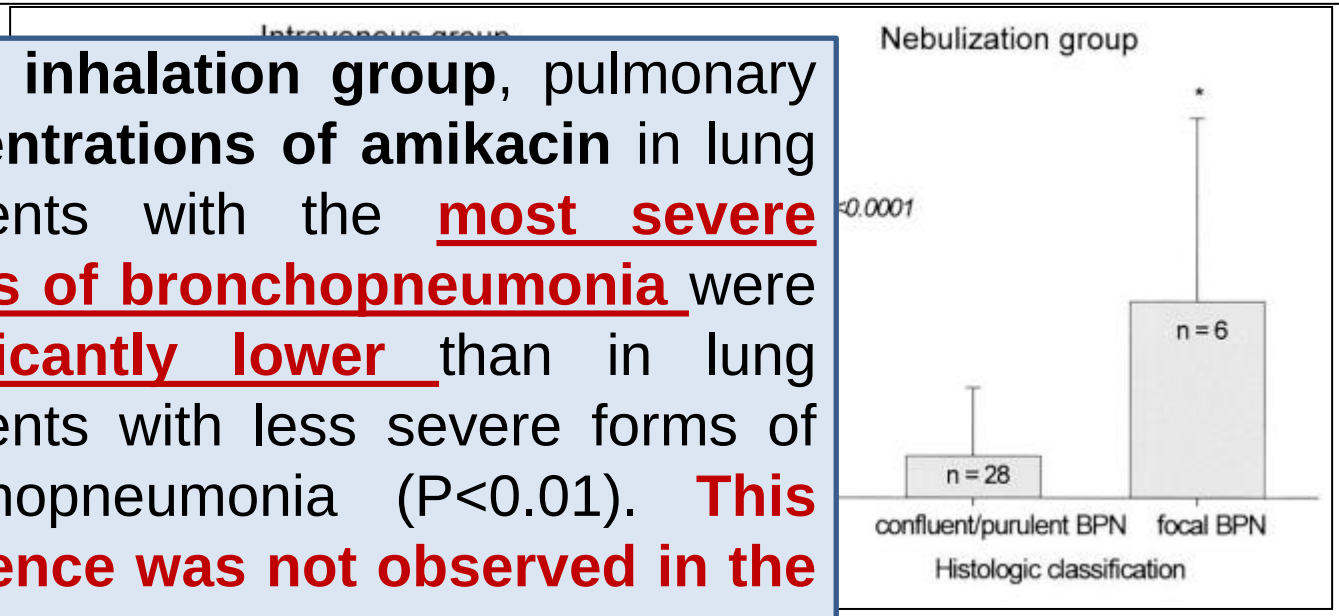
Etudes expérimentales animales



Anesthesiology 2002; 97:199–206
© 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Influence of Lung Aeration on Pulmonary Concentrations of Nebulized and Intravenous Amikacin in Ventilated Piglets with Severe Bronchopneumonia

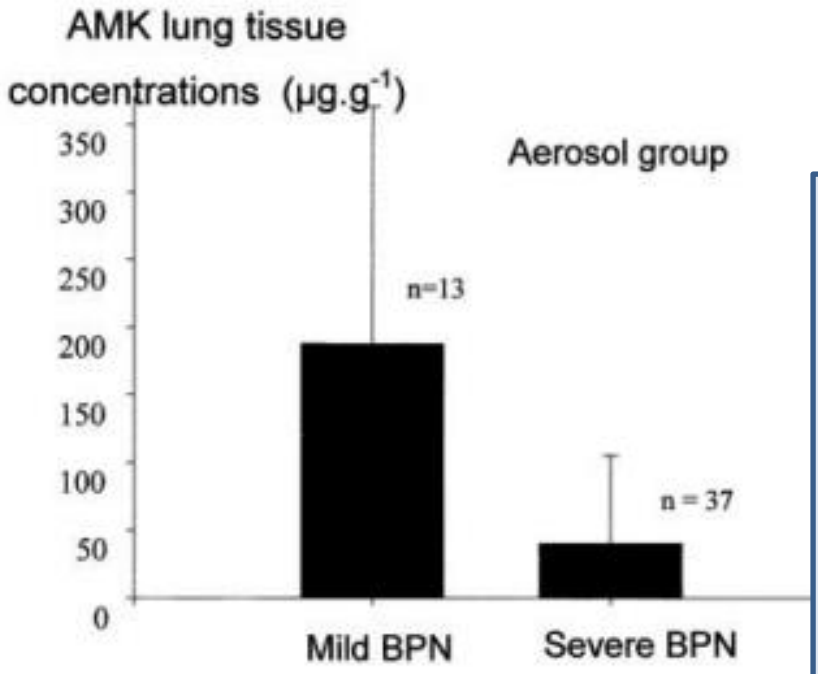
Marilia Elman, M.D., Ivan Goldstein, M.D.,† Charles-Hugo Marquette, M.D., Ph.D.,‡ Fréderic Wallet, M.D.,§ Gilles Lenaour, Ph.D.,‖ Jean-Jacques Rouby, M.D., Ph.D.,# the Experimental ICU Study Group***

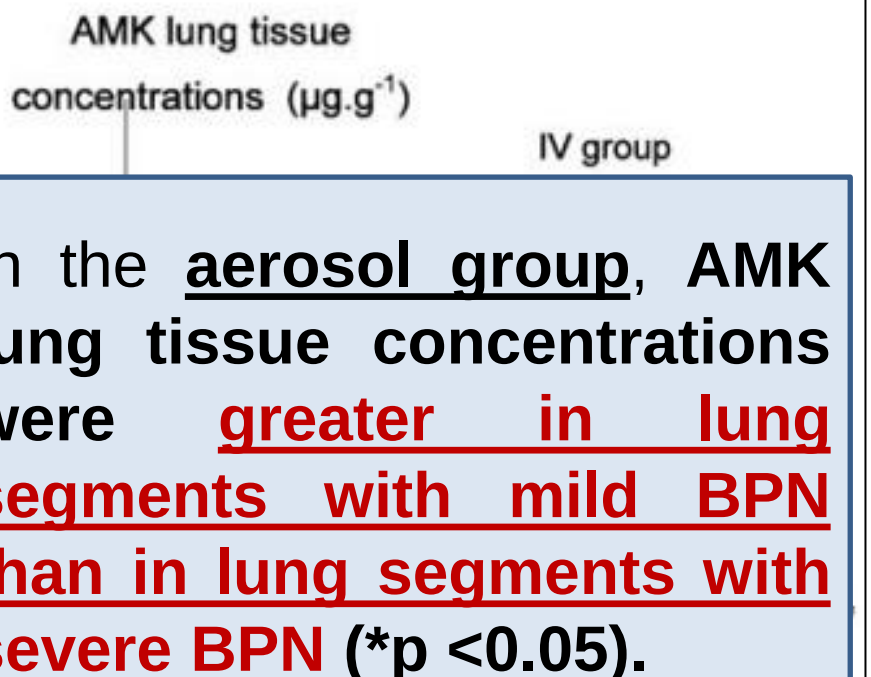


In the **inhalation group**, pulmonary **concentrations of amikacin** in lung segments with the **most severe stages of bronchopneumonia** were **significantly lower** than in lung segments with less severe forms of bronchopneumonia (P<0.01). **This difference was not observed in the intravenous group.**

Etudes expérimentales animales

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



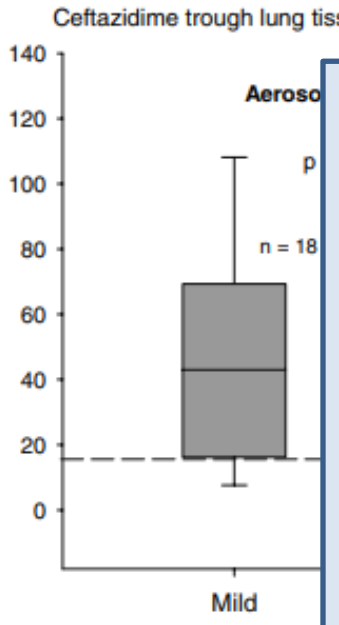


In the **aerosol group**, **AMK lung tissue concentrations were greater in lung segments with mild BPN than in lung segments with severe BPN (*p <0.05).**

Etudes expérimentales animales

Intensive Care Med (2009) 35:1792–1800
DOI 10.1007/s00134-009-1605-2

EXPERIMENTAL



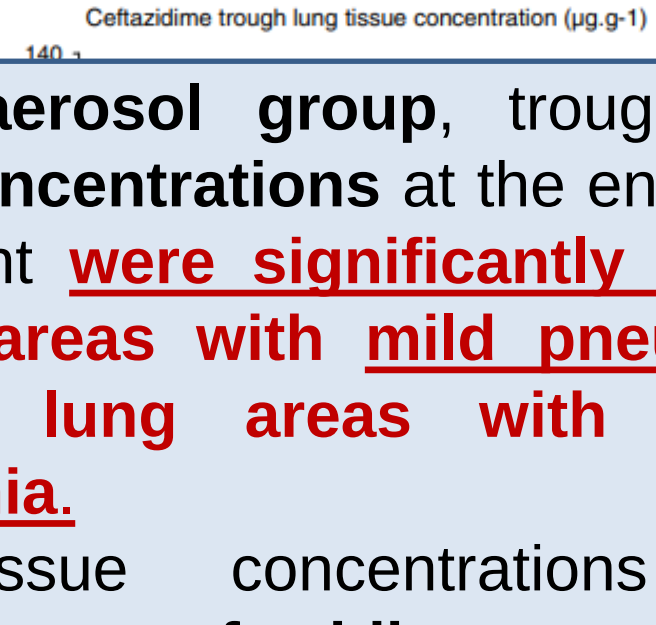


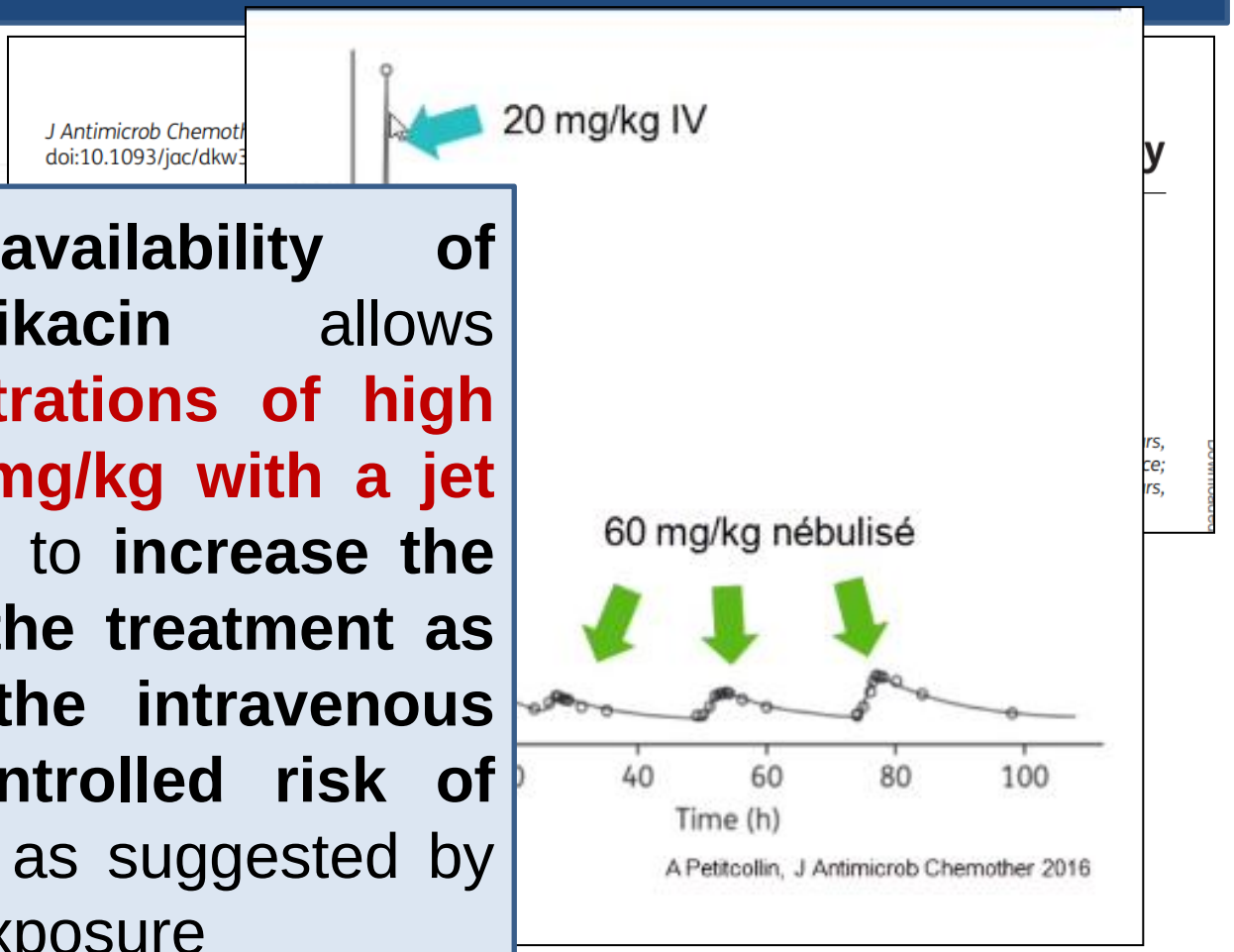
Fig. 3 Ceftazidime trough lung tissue con
the histological severity of pneumonia in
boxes, left panel) and continuous intravenou
right panel) groups. *Dashed lines* represe
concentration (MIC) of inoculated *Pseudo*

In the aerosol group, trough **lung tissue concentrations** at the end of the experiment **were significantly greater in lung areas with mild pneumonia than in lung areas with severe pneumonia.**

Lung tissue concentrations after **intravenous ceftazidime were not influenced by the histological grade of pneumonia.**

Passage systémique

The low bioavailability of nebulized amikacin allows **multiple administrations of high doses up to 60 mg/kg with a jet nebulizer** in order to **increase the success rate of the treatment as compared with the intravenous** route, with a **controlled risk of systemic toxicity** as suggested by the low systemic exposure



Passage systémique

REVIEW ARTICLE

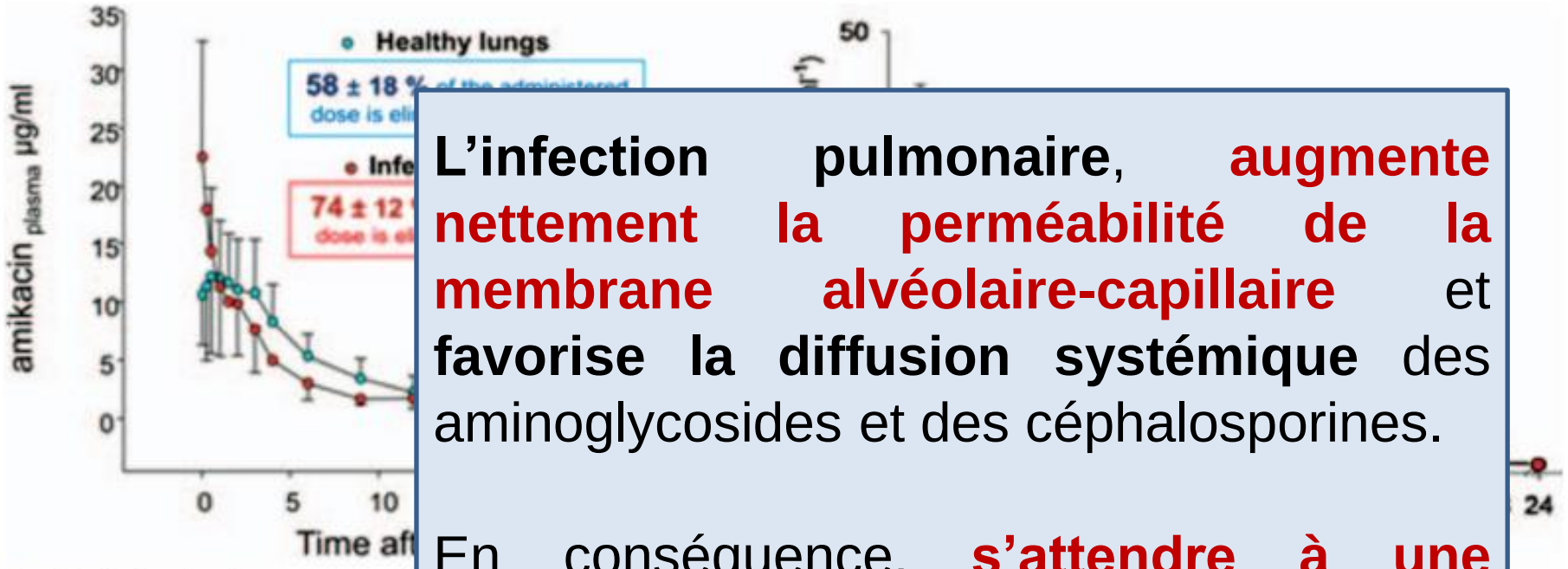


Fig. 11. Amikacin plasma concent
(*blue circle*) or inoculation *Escher*
dose of amikacin (15 mg/kg) in ve
Ref. 28. Reprinted with permissio

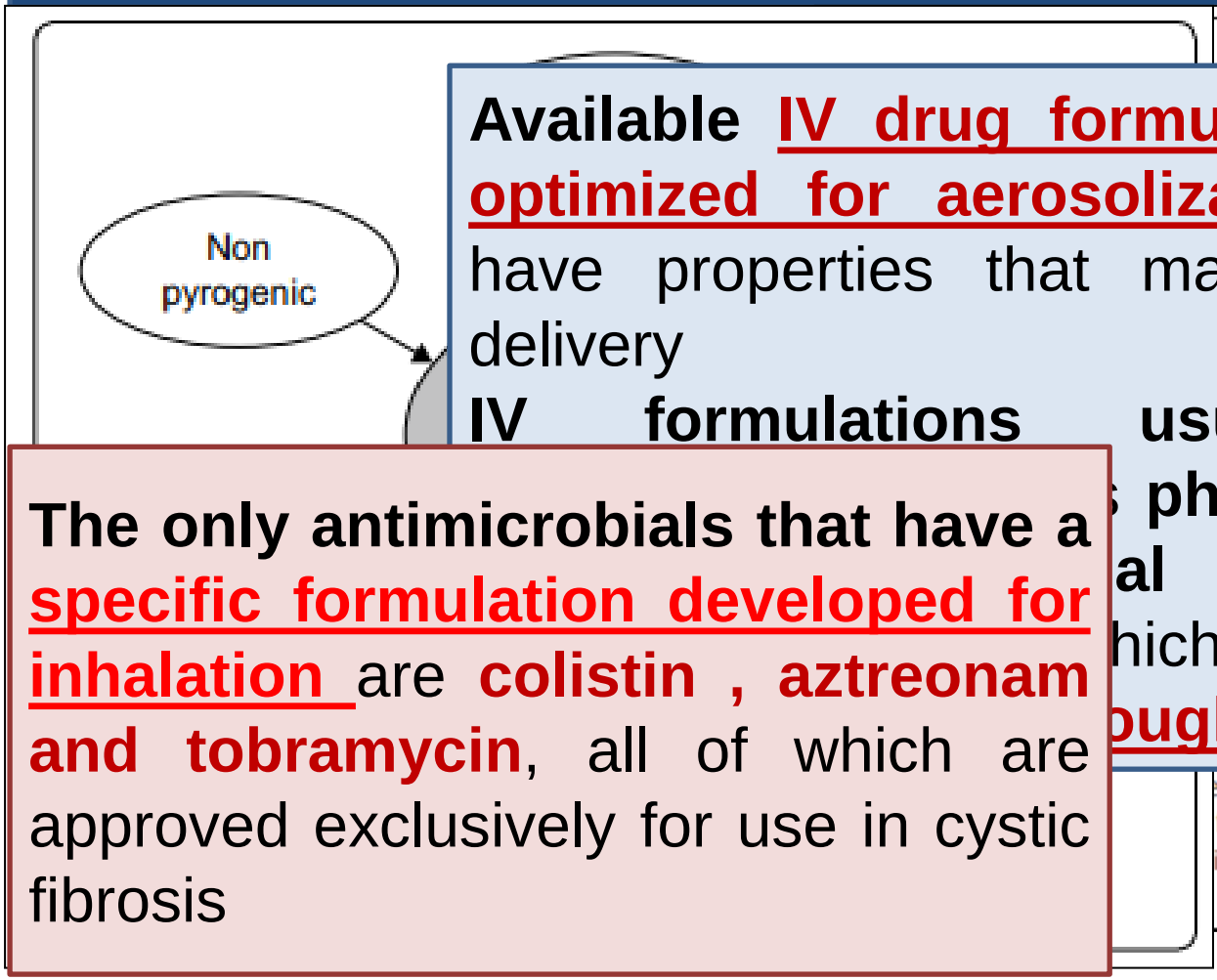
ungs
nous
From

L'infection pulmonaire, **augmente nettement la perméabilité de la membrane alvéolaire-capillaire** et **favorise la diffusion systémique** des aminoglycosides et des céphalosporines.

En conséquence, **s'attendre à une toxicité systémique moindre pour ces antibiotiques en utilisant la voie nébbulisée est probablement injustifié**.

Quelles modalités ?

Dépôt de l'aérosol



Available <u>IV drug formulations are not optimized for aerosolization</u> and often have properties that may impede drug delivery

IV formulations usually contain phenols and many **al osmolarity** hich **<u>can increase oughing</u>**

size for deposition throughout the
from Ref. [70]. Figure reproduced with
is copyrighted material is Mary Ann

The only antimicrobials that have a <u>specific formulation developed for inhalation</u> are **colistin , aztreonam and tobramycin**, all of which are approved exclusively for use in cystic fibrosis

Générateur d'aérosol

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Consensus statement

Key considerations on nebulization of antimicrobial agents to mechanically ventilated patients

J. Rello [1,*,9], J.J. Rouby [3,9], C. Sole-Lleonart [5], J. Chastre [4], S. Blot [6], C.E. Luyt [4], J. Riera [2], M.C. Vos [7], A. Monsel [3], J. Dhanani [8], J.A. Roberts [8]

Générateur d'aérosol

PNEUMATIQUE

+ AVANTAGES

- Jetable
- Simple

− INCONVENIENTS

- Débit de gaz
- Bruit
- Volume résiduel ++

ULTRA-SONIQUE

- Pas de débit de gaz
- Volume résiduel –
- Silencieux

- Décontamination
- Température

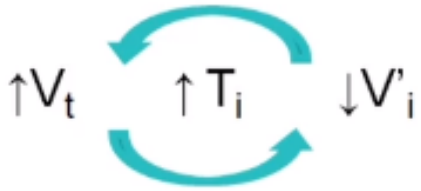
TAMIS VIBRANT

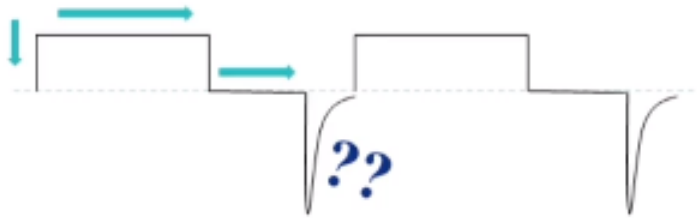
- Pas de débit de gaz
- Volume résiduel - -
- Silencieux
- Jetable

- Solutions visqueuses

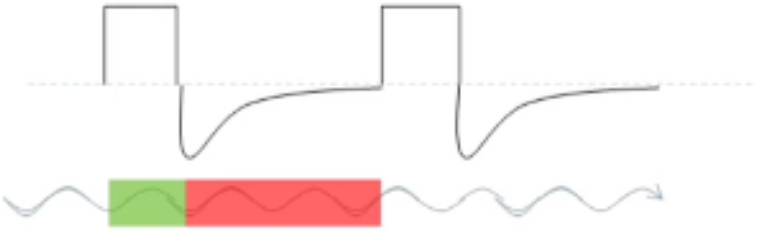
Réglage du ventilateur

"Deep, large, slow breath…"

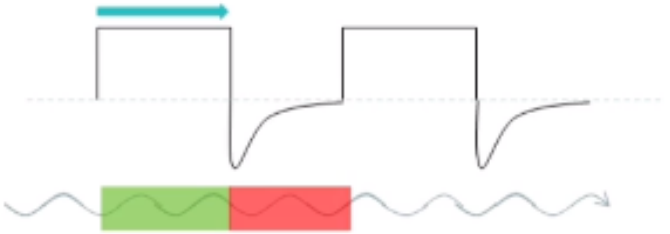




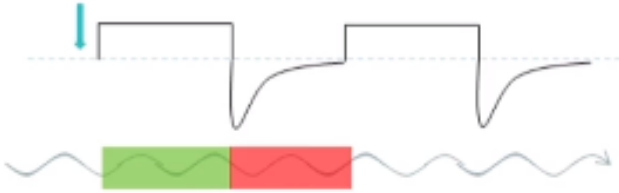
Ventilation du patient obstructif?
Sédation?



Nébulisation continue



Nébulisation continue

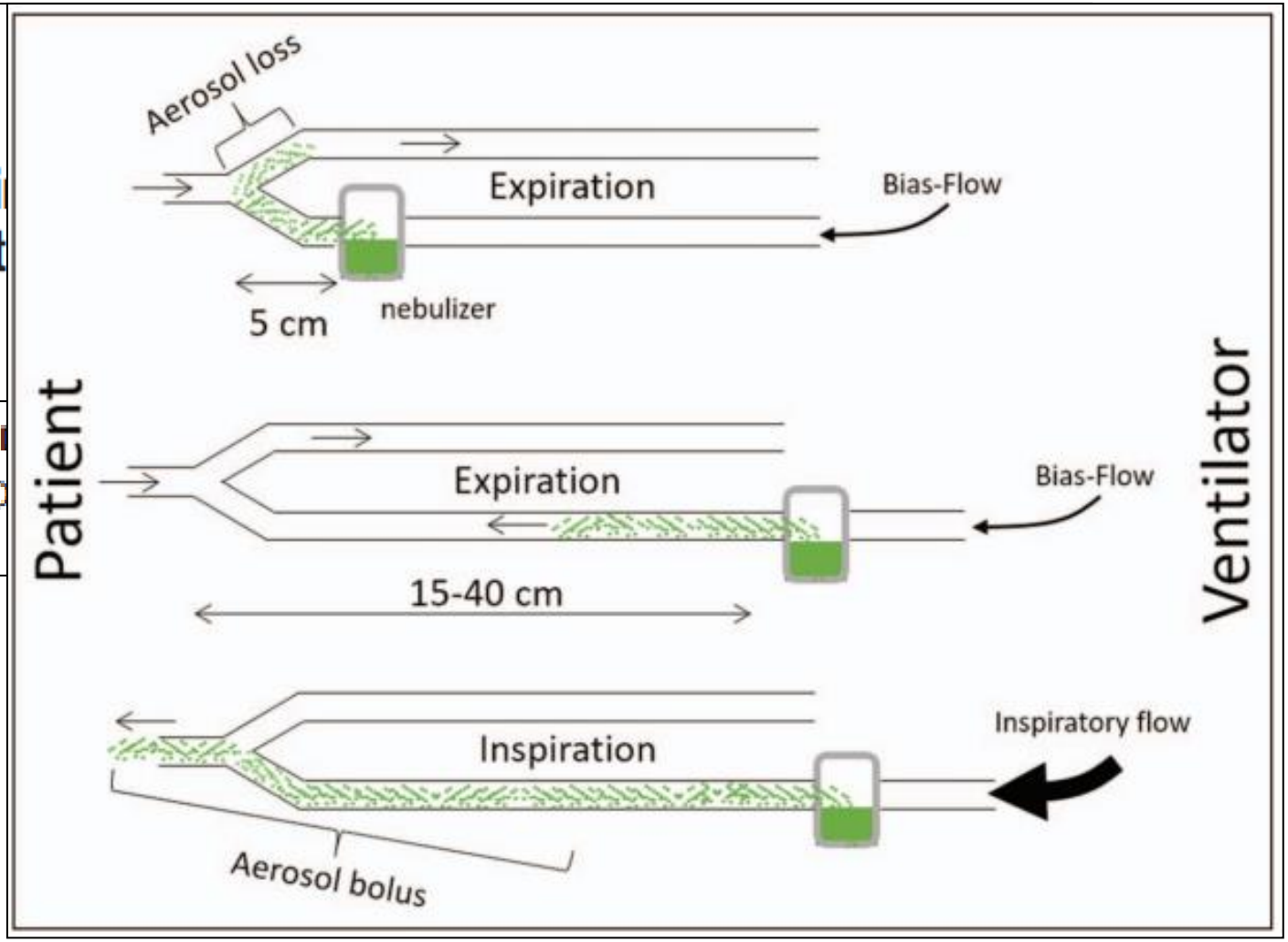


Nébulisation continue

Position du nébuliseur

REVIEW

Curr Opin Infect
DOI:10.1097/QCO



Filtre

Intensive Care Med (2013) 39:535–536
DOI 10.1007/s00134-012-2778-7

CORRESPONDENCE

The importance of protecting the mechanical ventilator during colistin methanesulfonate nebulization

Francesco Mojoli
Giorgio Antonio Iotti
Roberto Imberti
Antonio Braschi

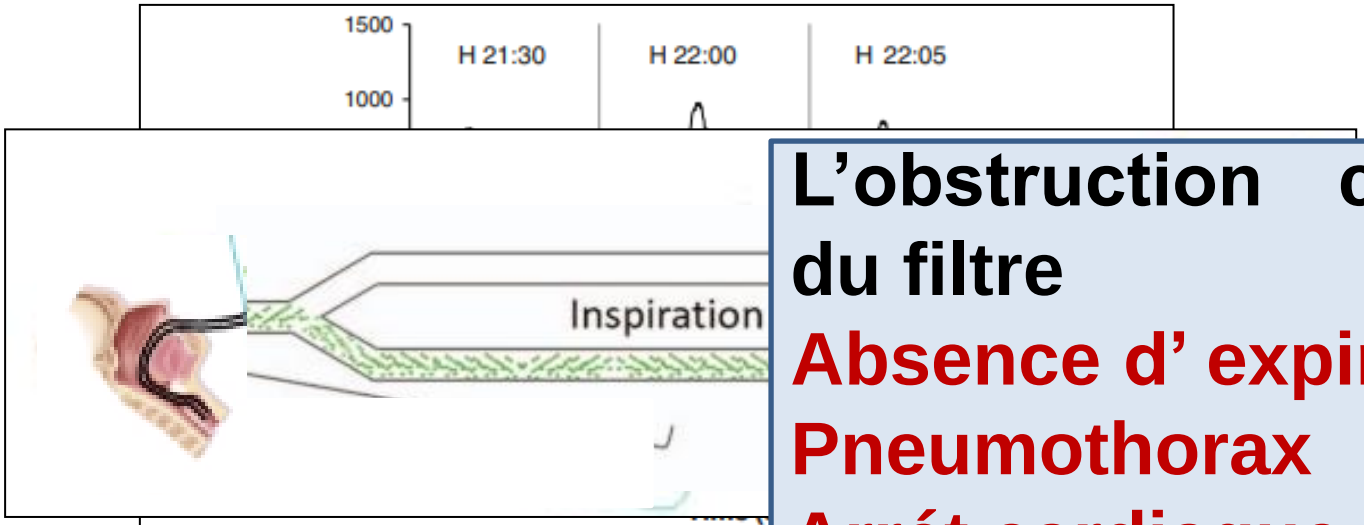


Fig. 1 Airways flow tracings during pressure-support
rapidly progressive expiratory valve malfunction after

L'obstruction complète du filtre

Absence d' expiration

Pneumothorax

Arrét cardiaque

ire

Quelle place dans le traitement curatif des PAVM ?

Efficacité microbiologique / clinique

Nebulized Ceftazidime and Amikacin in Ventilator-associated Pneumonia Caused

TABLE 2. ANTIBIOTIC TREATMENT EFFICIENCY

	Aerosol ($n = 20$)	Intravenous ($n = 20$)	P Value
C	14 (70)	11 (55)	0.33
D	3	6	
P	3 (15)	6 (30)	0.26
V			
R			
R			
D			
D			
L			
L			
Mortality on Day 28, n (%)			

Nebulization and intravenous infusion of ceftazidime and amikacin provide **similar efficiency** for treating **ver** **associated pneumonia c** **by Pseudomonas aerugin**

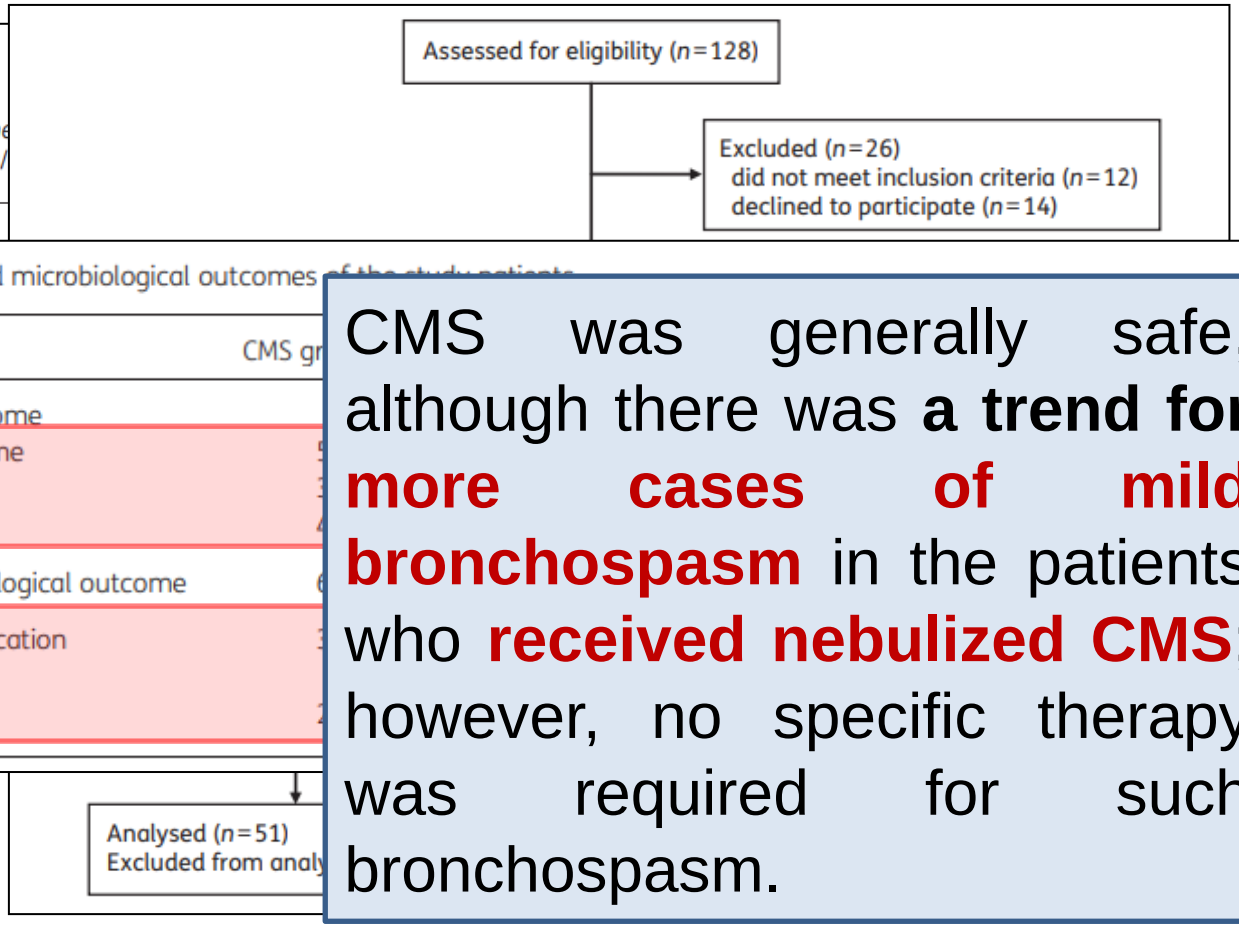
Nebulization induced an **obstruction of the expiratory filter in three patients**. The obstruction caused **cardiac arrest**

day; 15 mg.kg^{-1} each

aerosol of 25 mg.kg^{-1}

(strain)

Efficacité microbiologique / clinique



J Antimicrob Che
doi:10.1093/jac/

Table 2. Clinical and microbiological outcomes of the study patients

	CMS gr	(95% CI)	*P* value
28 day clinical outcome			
favourable outcome	5	6–1.40)	0.84
death due to VAP	3	5–1.76)	0.80
overall mortality	4	7–1.68)	0.81
Favourable microbiological outcome	6	3–2.37)	0.03
Incidence of complication	3	8–2.42)	0.44
bronchospasm		5–33.19)	0.36
renal impairment	2	6–2.29)	0.82

CMS was generally safe, although there was **a trend for more cases of mild bronchospasm** in the patients who **received nebulized CMS**; however, no specific therapy was required for such bronchospasm.

Table 2. Clinical and Bacteriological Outcomes, Mortality, and Adverse Events in Both Treatment Groups

Outcome	No. (%) of patients: IV colistin group (n = 43)	No. (%) of patients: AS-IV colistin group (n = 43)	P
Clinical outcome			
Clinical cure	14 (32.5)	23 (54)	.05
Clinical improvement			
Clinical failure			
Recurrence			
Bacteriological outcome[a]			
Eradication			
Persistent			
Recurrence			
Colonization			
Mortality			
All-cause			
VAP-related	11 (26)	7 (16)	.289
Adverse events			
Nephrotoxicity	8 (19)	8 (19)	>.99
Neurotoxicity	0	0	

NOTE. AS, aerosolized; IV, intravenous; VAP, ventilator-associated pneumonia

[a] Bacteriological outcome was evaluated in 34 patients in the IV colistin group and in 42 patients in the AS-IV colistin group.

In multivariate analysis **No statistically significant better clinical cure rate was observed in association with AS-IV colistin treatment** (odds ratio, 2.375; 95% confidence interval, 0.901–6.258; P=0.80).

Efficacité microbiologique / clinique

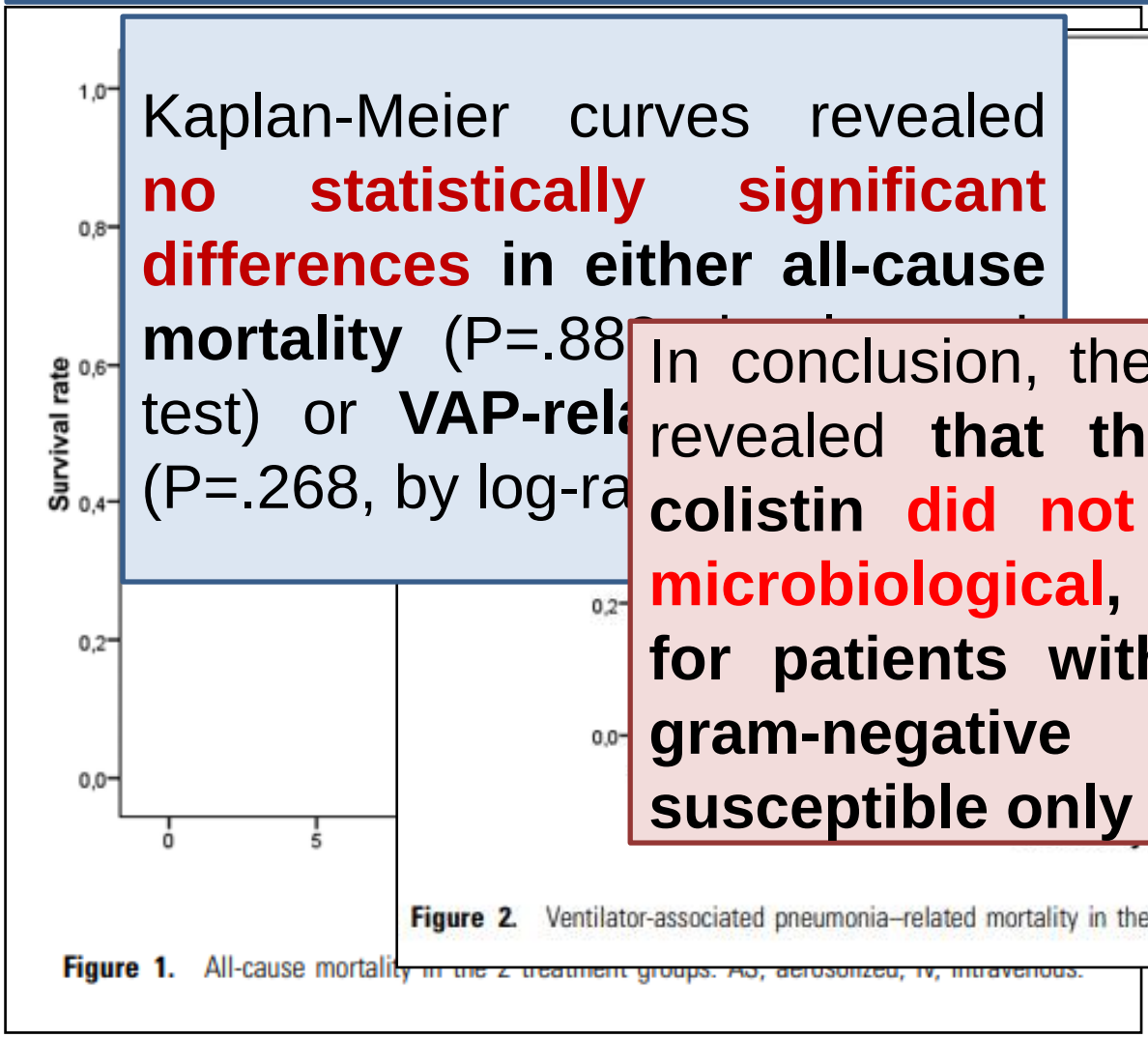


Figure 1. All-cause mortality in the 2 treatment groups. AS, aerosolized; IV, intravenous.

Kaplan-Meier curves revealed **no statistically significant differences in either all-cause mortality** (P=.88 test) or **VAP-rela** (P=.268, by log-ra

Figure 2. Ventilator-associated pneumonia–related mortality in the 2 treatment groups. AS, aerosolized; IV, intravenous.

In conclusion, the present study has revealed **that the addition of AS colistin did not add any clinical, microbiological, or survival benefit for patients with VAP caused by gram-negative MDR pathogens susceptible only to colistin**

Efficacité microbiologique / clinique

Change from baseline

Table 3. Secondary Efficacy and Microbiological Endpoints

Secondary Efficacy Endpoint	AFIS (N=71)	Placebo (N=71)	Difference Between Groups (95%CI)	P value
Hierarchical composite endpoint of mortality and time to clinical cure[a,b]				
Mortality first	10	10		
Clinical cure	15	18		
Hierarchical composite endpoi ventilator-free days[b]				
Mortality first				
Ventilator free days				
Days free of mechanical venti (mean(SD))			5)	0.02
Days of IV antibiotics (mean(S			5)	0.13
Number of ICU days (Day 1 to 28) (mean(SD))	28.9 (12.4)	26.2 (15.6)	2.7 (-2.0,7.4)	0.09
Mortality (Day 1 to 28)(%)	17 (24)	12 (17)	7 (-6,20)	0.32
Clinical relapse rates[c](%)	10 (14)	14 (20)	-6 (-18,7)	0.37
Tracheal culture at Day 3 postive for Gram-negative bacteria*(%)	19 (27)	40 (56)*	-29 (-44,-13)	<0.001
Tracheal culture at Day 7 postive for Gram-negative bacteria**(%)	12 (17)	29 (41) **	-24 (-37,-9)	0.002

Critères secondaires négatifs :
Guérison J14
VFD
Mortalité

Effic

	Amikacin Inhale group	Placebo group
Primary endpoint*		
Survival at days 28–32		

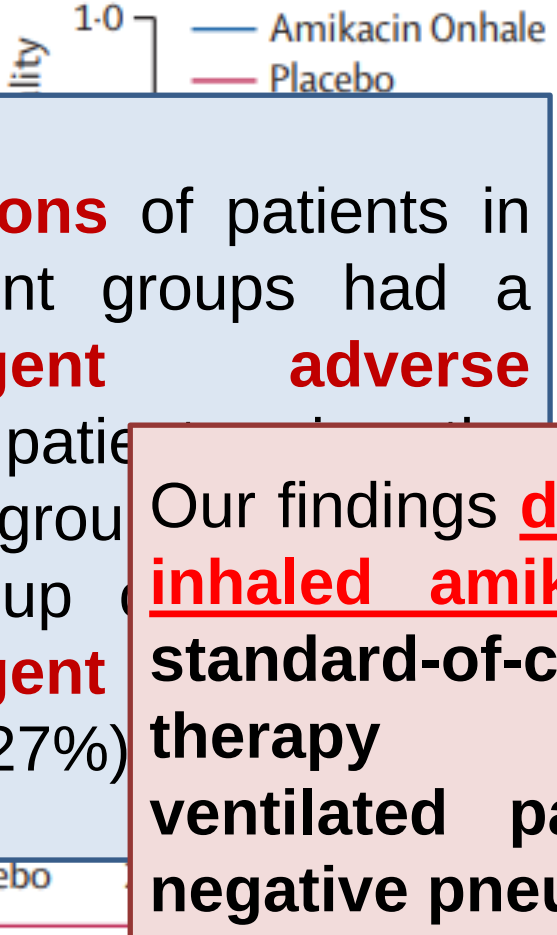


Figure 2: Cumulative all-cause mortality over time

Table 2: Primary and secondary outcomes in the efficacy population

Similar proportions of patients in the two treatment groups had a **treatment-emergent adverse event** (84%) patie
Amikacin Inhale grou
the placebo group
treatment-emergent event (29%) vs (27%)

Our findings **do not support use of inhaled amikacin adjunctive to standard-of-care intravenous therapy in mechanically ventilated patients with Gram-negative pneumonia.**

Efficacité microbiologique / clinique

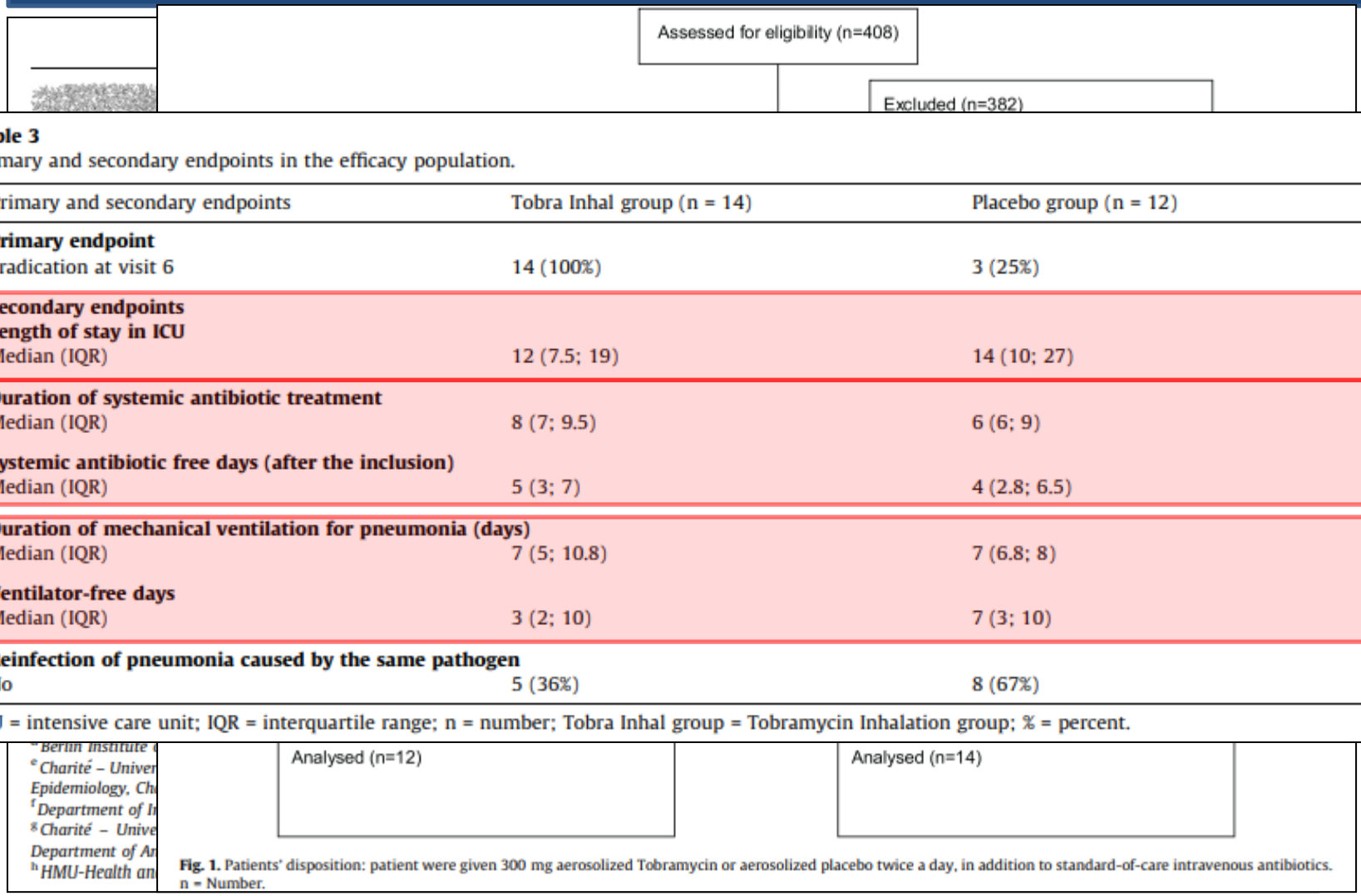


Fig. 1. Patients' disposition: patient were given 300 mg aerosolized Tobramycin or aerosolized placebo twice a day, in addition to standard-of-care intravenous antibiotics. n = Number.

Table 3
Primary and secondary endpoints in the efficacy population.

Primary and secondary endpoints	Tobra Inhal group (n = 14)	Placebo group (n = 12)	*p*-Value
Primary endpoint			
Eradication at visit 6	14 (100%)	3 (25%)	<0.001
Secondary endpoints			
Length of stay in ICU			
Median (IQR)	12 (7.5; 19)	14 (10; 27)	0.465
Duration of systemic antibiotic treatment			
Median (IQR)	8 (7; 9.5)	6 (6; 9)	0.324
Systemic antibiotic free days (after the inclusion)			
Median (IQR)	5 (3; 7)	4 (2.8; 6.5)	0.712
Duration of mechanical ventilation for pneumonia (days)			
Median (IQR)	7 (5; 10.8)	7 (6.8; 8)	0.812
Ventilator-free days			
Median (IQR)	3 (2; 10)	7 (3; 10)	0.624
Reinfection of pneumonia caused by the same pathogen			
No	5 (36%)	8 (67%)	NA

ICU = intensive care unit; IQR = interquartile range; n = number; Tobra Inhal group = Tobramycin Inhalation group; % = percent.

Efficacité microbiologique / clinique

Russell *et al. BMC Pulmonary Medicine* (2016) 16:40
DOI 10.1186/s12890-016-0202-8

BMC Pulmonary Medicine

Table 1 Study Characteristics, Quality and Results, in Chronological Order

Author and year	Study Participants (age, in years)	Description of intervention	Study period	Length of follow up	Primary Outcome (successful treatment)	Results
Hallal, et al, 2007 [9]	*N* = 10 Age: 23–72 (Mean age: AA 52.6, IV 53.6)	Inhaled tobramycin or IV tobramycin AND IV β-lactam	7 months	28 days	Resolution of VAP	100 % of AA vs. 60 % of IV patients had clinical resolution of VAP. No p value reported.
Palmer et al, 2008 [12]	*N* = 4 Age: AA 6				e Control ial Infection f ventilator- onia (VAP) nary PIS)	AA group had reduced signs of respiratory infection [Centers for Disease Control National Nosocomial Infection Survey and VAP (73.6 % to 35.7 % vs. placebo: 75 % to 78.6 %) and reduction in clinical pulmonary infection score (−1.42 vs. placebo: + 0.04), (both p ≤ .05).
Rattanaumpawan et al, 2010 [14]	*N* = 1 AA 7				utcome	Favorable clinical outcome was 51.0 % in the AA group and 53.1 % in the placebo group ($p = 0.84$). Significant increase in favorable microbiological outcome in AA vs. placebo group (60.9 vs. 38.2 %; $p = 0.03$)
Lu et al, 2011 [10]	*N* = 40 patients Ages 43–77 (Mean age: AA 58, IV 60)	Nebulized ceftazidime and amikacin OR IV ceftazidime and amikacin/ciprofloxacin.	36 month	28 days	Successful treatment	AA and IV groups performed similar in terms of successful treatment (70 vs. 55 %; $p = 0.33$).
Niederman et al, 2012 [11]	*N* = 69 (Mean age: AA q12h 56.1, AA q24h 62.8, or placebo 62.0)	Inhaled amikacin (BAY41-6551) q12h, q24h, or placebo q12h for 7–14 days, plus standard IV antibiotics	13 months	31 days	Clinical cure (secondary study outcome)	Clinical cure achieved in 93.8 % (AA q12h), 75 % (AA q24h) and 87.5 % (placebo; $p = 0.467$).
Palmer et al, 2014 [13]	*N* = 43 (Mean age AA 57.5, placebo 60.6)	AA or saline placebo AND systemic antibiotics (per treating MD) was given for 14 days or until extubation	Does not state	14 days	Clinical Pulmonary Infection Score (CPIS)	CPIS score in AA significantly reduced when compared to placebo (Mean ± SE AA: 9.3 ± 2.7 to 5.3 ± 2.6 vs. placebo: 8.0 ± 23 to 8.6 ± 2.10; $p = 0.0008$)

This systematic review **found insufficient evidence for the use of inhaled antibiotic therapy as primary or adjuvant treatment of VAP or VAT.**

Efficacité microbiologique / clinique

Intensive Care Med (2020) 46:888–906
https://doi.org/10.1007/s00134-020-05980-0

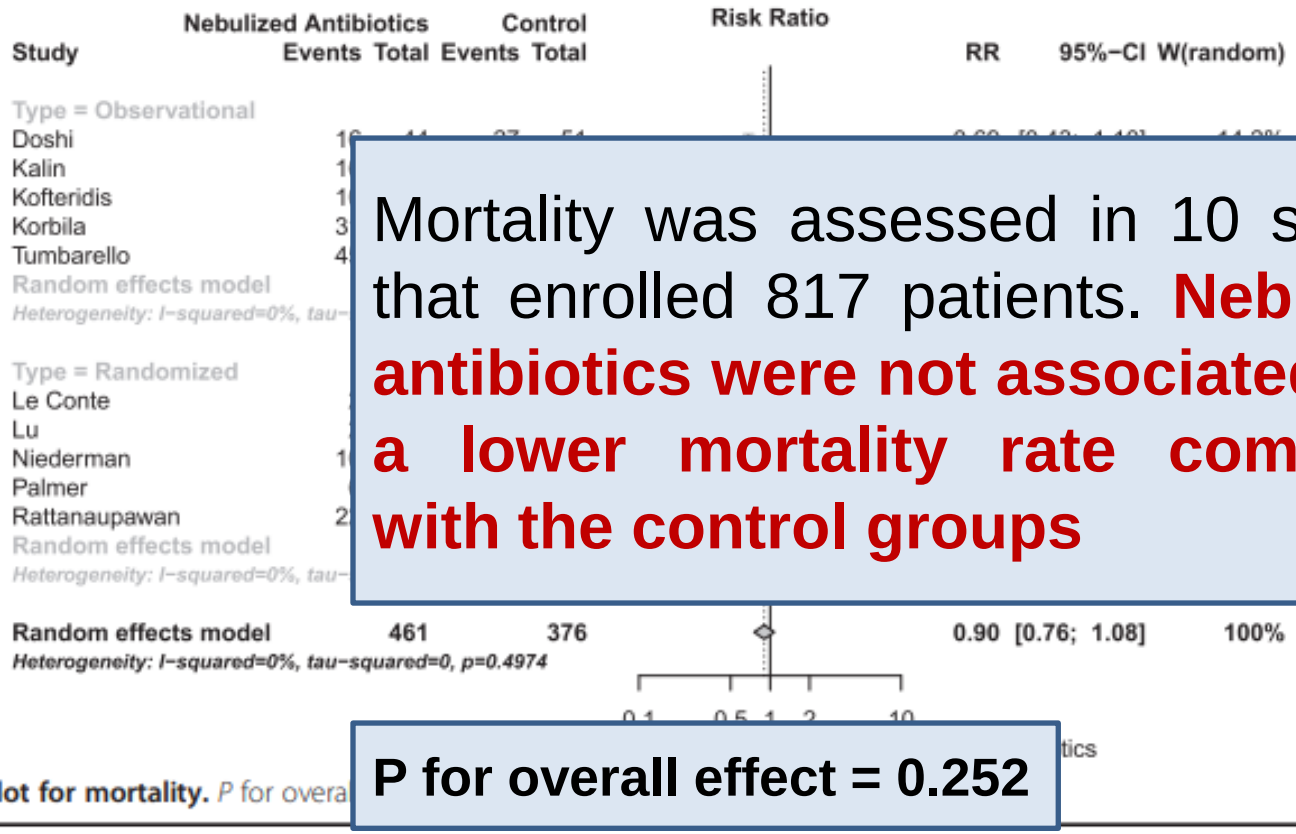
NARRATIVE REVIEW

Ventilat
narrativ

Laurent Papa

of mechanical ventilation [148, 149]. The use of nebulised antibiotics as an adjunctive treatment (i.e., in addition to effective intravenous therapy) is also not recommended; two recent randomized-controlled trials failed to demonstrate superiority of nebulised antibiotics (amikacin alone or combined with fosfomycin) over placebo in patients with VAP due to "traditional pathogens" [150, 151]. The use of nebulised antibiotics should therefore be restricted to patients with VAP to XDR-Gram-negative pathogens susceptible only to colistin or aminoglycosides

Efficacité microbiologique / clinique



Mortality was assessed in 10 studies that enrolled 817 patients. **Nebulized antibiotics were not associated with a lower mortality rate compared with the control groups**

P for overall effect = 0.252

Figure 6 Forest plot for mortality. *P* for overa

Table 1

Study design and patient characteristics in the included studies

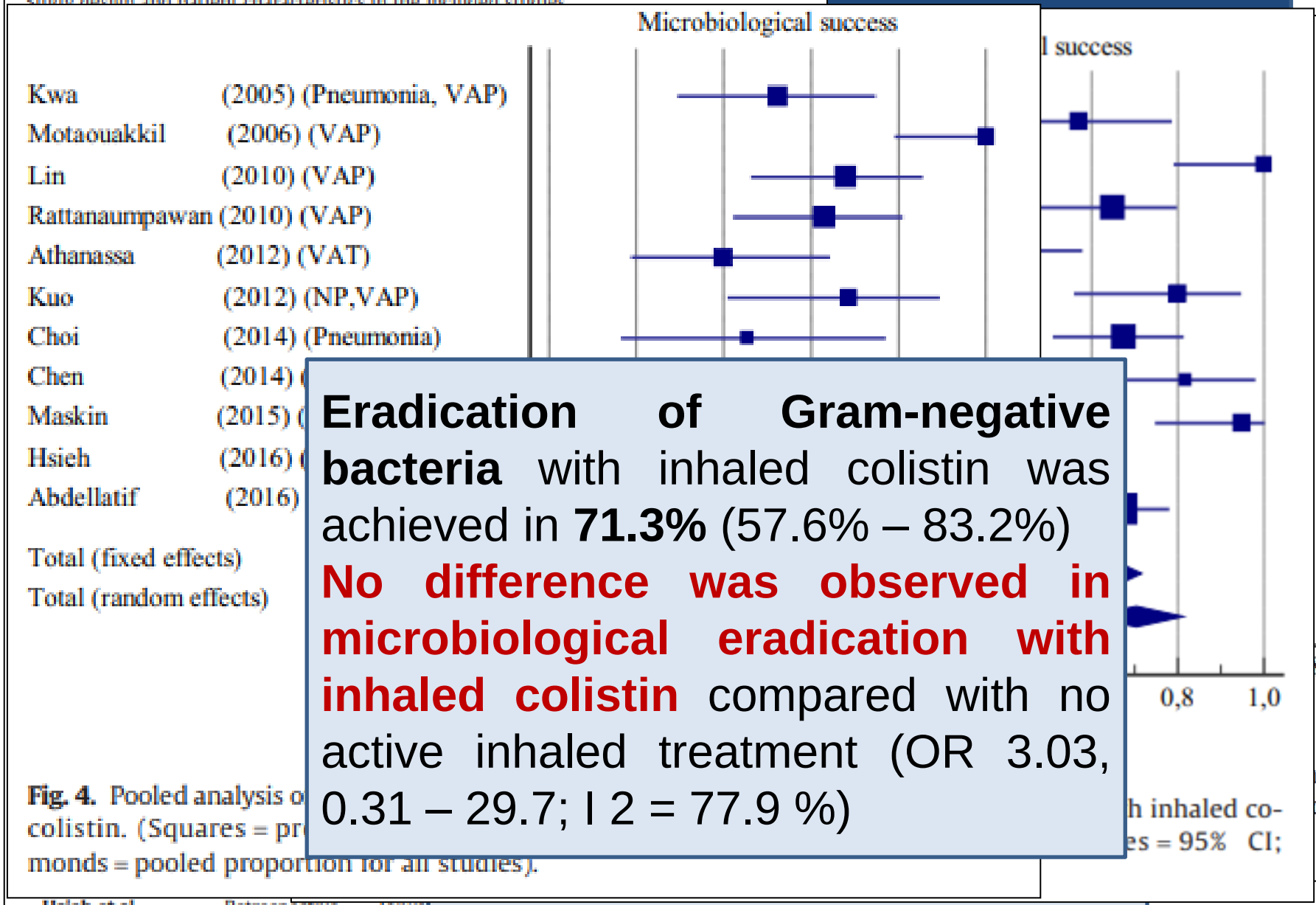


Fig. 4. Pooled analysis o
colistin. (Squares = pr
monds = pooled proportion for all studies).

h inhaled co-
es = 95% CI;

Eradication of Gram-negative bacteria with inhaled colistin was achieved in **71.3%** (57.6% – 83.2%)

No difference was observed in microbiological eradication with inhaled colistin compared with no active inhaled treatment (OR 3.03, 0.31 – 29.7; I 2 = 77.9 %)

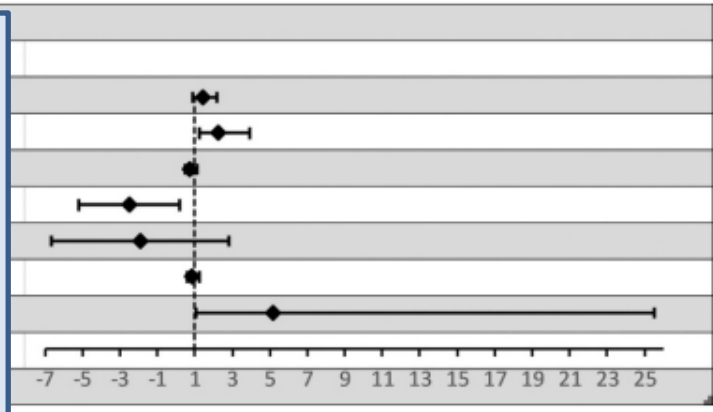
Hsieh et al., 2016 [22]	Retrospective cohort	Taiwa	

0.31 – 3.88; I2 = 68.2%).

Efficacité microbiologique / clinique

The **overall <u>mortality, nephrotoxicity, length of MV, and ICU stay</u> did not differ between the two groups**.

Bronchospasm occurred more common in NC group with **statistical significance** (OR, 5.19; 25.52; **p = 0.04**)



while in **3 RC** **statistically sign** 95% CI, 0.98–4.09

Subtotal
Total eve
Heteroge
Test for
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Heterogeneity: Tau² = 0.39; Chi² = 19.32, df = 7 (P
Test for overall effect: Z = 2.72 (P = 0.006)
Test for subgroup differences: Chi² = 0.29, df = 1 (

In conclusion, based on the present evidence, **administration of NC cannot improve the clinical response** but increases microbiological eradication with a **higher risk of bronchospasm** compared to the systemic antibiotic group

Quelle place dans la prévention des PAVM ?

Effic

ORIGINAL ARTIC
RESPIRATORY IN

Nebulis
pneumo

Marios Karvou
Apostolos Tria
Efthimia Petir

Affiliations: [1]Critic
[2]Microbiology Labo

Eur Respi

TABLE 2 Outcomes of participants in the two arms of the study[#]

TABLE 3 MDR and colistin-resistant isolates in blood and TBA in the Col and NS groups during the study period[#]

	Overall	Col group	NS group	p-value
Overall isolates	194 (100)	97 (100)	97 (100)	
Total TBA isolates	130 (67)	60 (61.9)	70 (72.2)	0.17
Total blood isolates	64 (33)	37 (38.1)	27 (27.8)	0.17
MDR TBA isolates	79 (40.7)	30 (30.9)	49 (50.5)	0.01
Airway colonisation cases	48 (24.7)	20 (20.6)	28 (28.9)	0.24
VAT or VAP cases	31 (16)	10 (10.3)	21 (21.6)	0.05
Gram-positive TBA isolates	7 (3.6)	3 (3.1)	4 (4.1)	1.0
Gram-				0.01
MDR blo				0.74
Gram-				0.28
Gram-				1.0
Colistin-				0.39
Airway				0.33
VAT or				0.78
Gram-				0.75
Gram-				1.0
Colistin-				0.48
Gram-				0.28
Gram-negative isolates				1.0

All data are presented as n (%). MDR: multidrug-resistant; TBA: tracheobronchial aspirate; Col group: colistin group; NS group: normal saline group; VAT: ventilator-associated tracheobronchitis; VAP: ventilator-associated pneumonia. [#]: polymicrobial cases containing Gram-negative microbes were included in the Gram-negative group.

Tracheostomy	76 (45.2)	43 (51.2)	33 (39.3)	0.16

Our findings suggest that **nebulised colistin had no significant effect on VAP incidence**.

En pratique ?

Les recommandations ?

Recommandations

ROLE OF INHALED ANTIBIOTIC THERAPY

XIX. Which A
Due to *Acine*
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XX. Which Antibiotic Should Be Used to Treat Patients With HAP/VAP Due to Carbapenem-Resistant Pathogens?

Recommendation

1. In patients with HAP/VAP caused by a carbapenem-resistant pathogen that is sensitive only to polymyxins, we recommend intravenous polymyxins (colistin or polymyxin B) *(strong recommendation, moderate-quality evidence)*, and we suggest adjunctive inhaled colistin *(weak recommendation, low-quality evidence)*.

Values and Preferences: These recommendations place a high value on achieving clinical cure and survival; they place a lower value on burden and cost.

infecting organism is or is not multidrug resistant (MDR).

Recommandations

Clinical Microbiology and Infection 23 (2017) 629–639

Nebulization 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 previous 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. Hence, these recommendations may change in the future as new study data become available.

Recommandations

SFAR

srlf
SOCIÉTÉ DE RÉANIMATION DE LANGUE FRANÇAISE

Recommandations formalisées d'experts

PNEUMONIES ASSOCIÉES AUX SOINS DE RÉANIMATION

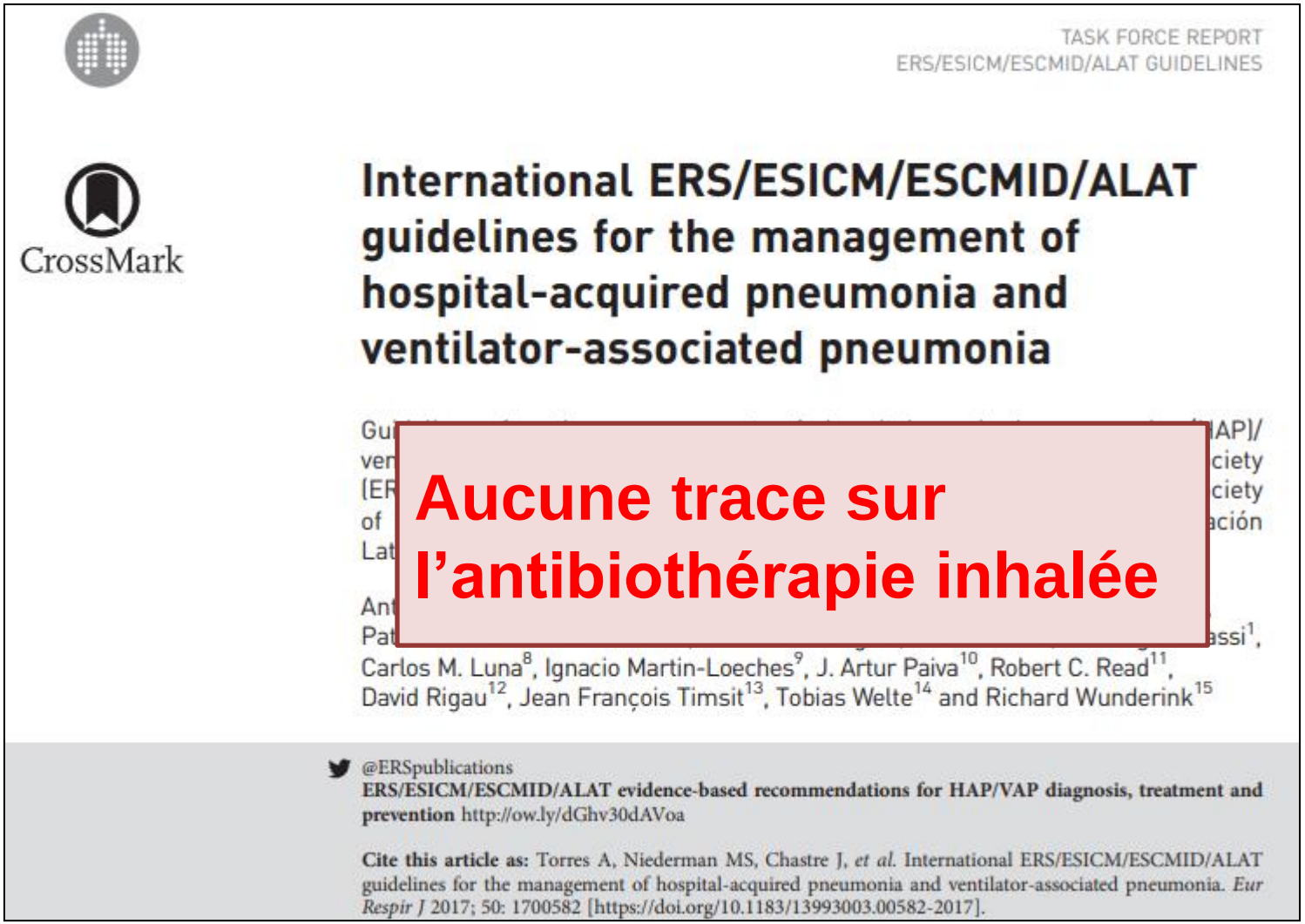
RFE commune SFAR – SRLF
Société Française d'Anesthésie et de Réanimation

R3.6 –Dans le cadre des pneumonies documentées à bacilles à Gram négatif multirésistants, définis comme sensibles à la colimycine et/ou aux aminosides et lorsqu'aucun autre antibiotique n'est efficace, il faut probablement administrer la colimycine (colistiméthate sodique) et/ou un aminoside par voie nébulisée.

GRADE 2+, ACCORD FORT

HEALTHCARE ASSOCIATED PNEUMONIA IN INTENSIVE CARE UNIT

Recommandations



TASK FORCE REPORT
ERS/ESICM/ESCMID/ALAT GUIDELINES

CrossMark

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

Aucune trace sur l'antibiothérapie inhalée

Carlos M. Luna[8], Ignacio Martin-Loeches[9], J. Artur Paiva[10], Robert C. Read[11], David Rigau[12], Jean François Timsit[13], Tobias Welte[14] and Richard Wunderink[15]

@ERSpublications
ERS/ESICM/ESCMID/ALAT evidence-based recommendations for HAP/VAP diagnosis, treatment and prevention http://ow.ly/dGhv30dAVoa

Cite this article as: Torres A, Niederman MS, Chastre J, *et al.* International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. *Eur Respir J* 2017; 50: 1700582 [https://doi.org/10.1183/13993003.00582-2017].

Conclusion

Très peu de preuves en faveur de l'utilisation d'antibiotiques nébulisés dans le traitement des PAVM

Meilleure concentration pulmonaire Pneumonies graves??!

Risque de toxicité et effets indésirables graves

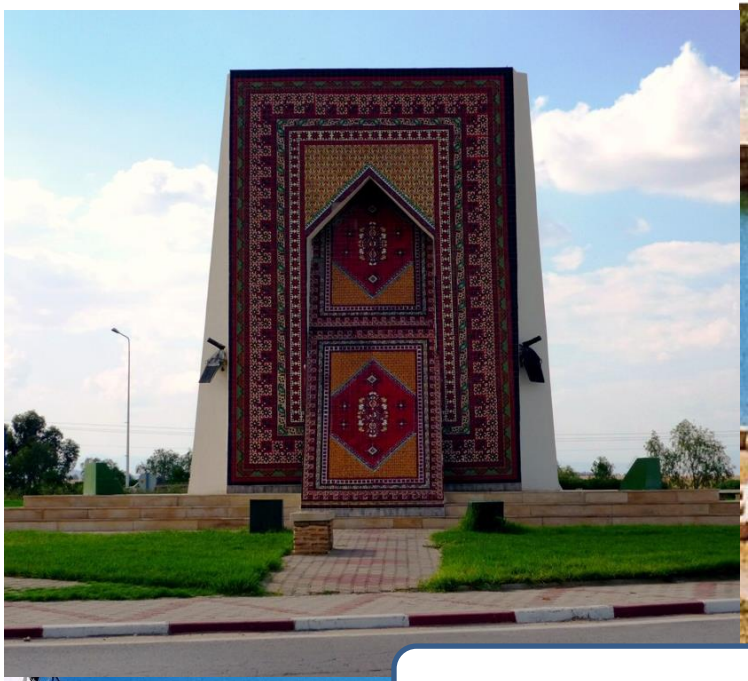
Absence de gain :
éradication microbiologique, efficacité clinique et mortalité

Conclusion

Absence de recommandations formelles indiquant l'utilisation des aérosols d'antibiotiques
(Il faut probablement… we suggest….)

Intérêt probable :
PAVM à BMR en dernier recours devant des difficultés thérapeutique malgré un traitement systémique bien conduit

Le débat reste ouvert…
Résultats contradictoires….



Merci pour votre attention