Antibiotiques inhalés pour le traitement des pneumonies à BGN résistants?

Controverse: POUR

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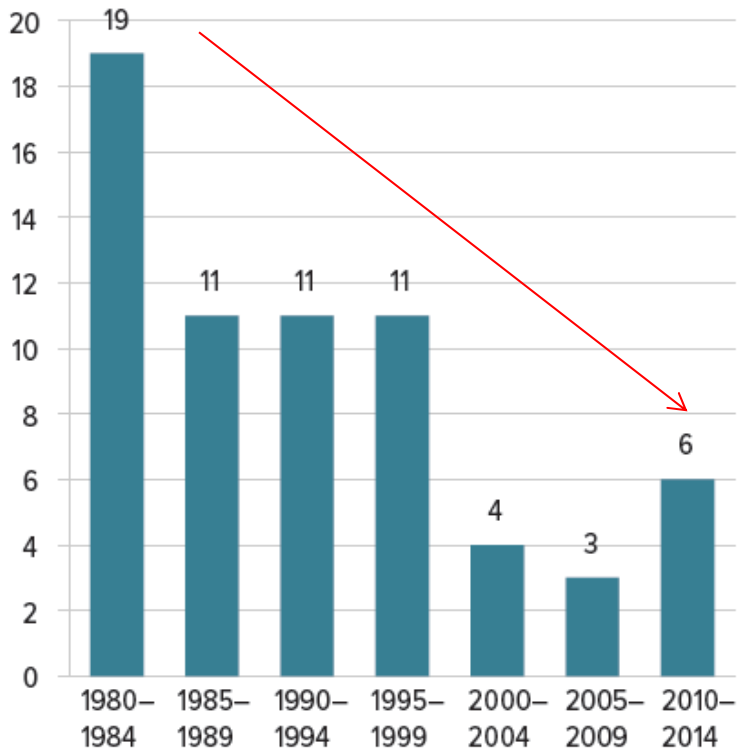
Avons-nous vraiment besoin d'antibiotiques inhalés?

Figure 1 Developing Antibiotic Resistance: A Timeline of Key Events[5]

ANTIBIOTIC RESISTANCE IDENTIFIED		ANTIBIOTIC INTRODUCED
Penicillin-R *Staphylococcus*	1940	
	1943	Penicillin
	1950	Tetracycline
	1953	Erythromycin
Tetracycline-R *Shigella*	1959	
	1960	Methicillin
Methicillin-R *Staphylococcus*	1962	
Penicillin-R pneumococcus	1965	
Erythromycin-R *Streptococcus*	1968	
	1967	Gentamicin
	1972	Vancomycin
Gentamicin-R *Enterococcus*	1979	
	1985	Imipenem and ceftazidime
Ceftazidime-R Enterobacteriaceae	1987	
Vancomycin-R *Enterococcus*	1988	
Levofloxacin-R pneumococcus	1996	1996 Levofloxacin
Imipenem-R Enterobacteriaceae	1998	
XDR tuberculosis	2000	2000 Linezolid
Linezolid-R *Staphylococcus*	2001	
Vancomycin-R *Staphylococcus*	2002	
PDR-*Acinetobacter* and *Pseudomonas*	2004/5	2003 Daptomycin
Ceftriaxone-R *Neisseria gonorrhoeae*	2009	
PDR-Enterobacteriaceae		2010 Ceftaroline
Ceftaroline-R *Staphylococcus*	2011	
	2016	
	2017	

PDR = pan-drug-resistant; R = resistant; XDR = extensively drug-resistant

The number of new antibiotics developped decreased steadily



Ceftolozane/tazobactam
Ceftazidime-Avibactam

Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections: Clinical Effectiveness and Evolution of Resistance

Haidar et al, Clinical Infectious Diseases 2017

Ceftolozane-tazobactam resistance induced in vivo during the treatment of MDR *Pseudomonas aeruginosa pneumonia*.

Plant et al, Expert Review of Anti-infective Thrapy, 2018

Table 1. Antibiogram of *P. aeruginosa* isolates.

	Susceptibility [MIC (mg/L)]		
	First isolate (1 January 2017)	Second isolate (5 January 2017)	Third isolate (5 February 2017)
Amikacin	≤0.5 (S)	≤0.5 (S)	8 (S)
Gentamicin	≤0.125 (S)	≤0.125 (S)	4 (S)
Tobramycin	≤0.125 (S)	≤0.125 (S)	1 (S)
Aztreonam	32 (R)	32 (R)	32 (R)
Ceftazidime	8 (S)	16 (R)	64 (R)
Imipenem	32 (R)	32 (R)	4 (S)
Meropenem	16 (R)	>32 (R)	32 (R)
Piperacillin-tazobactam	16 (S)	64 (R)	32 (R)
Carbenicillin	512 (R)	256 (R)	512 (R)
Ceftolozane-tazobactam	0.5 (S)	0.5 (S)	>16 (R)
Colistin	1 (S)	1 (S)	1 (S)
Ciprofloxacin	>8 (R)	>8 (R)	>8 (R)

In patients with severes sepsis, the antibiotic pharmacokinetics is modified:

Amikacin IV: 25-30 mg/kg

Cmax

Taccone et al, Crit Care 2010

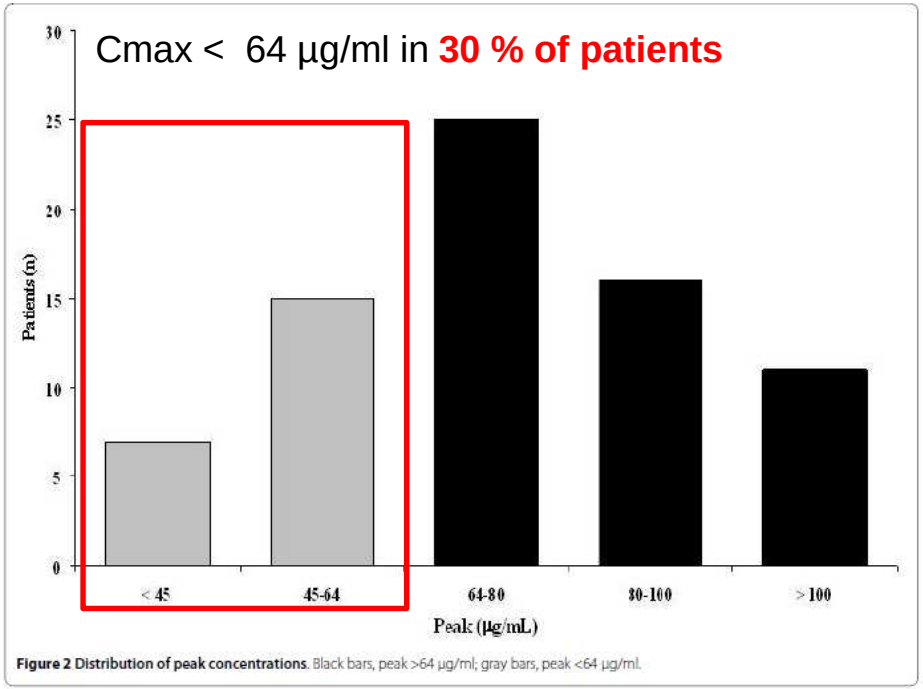
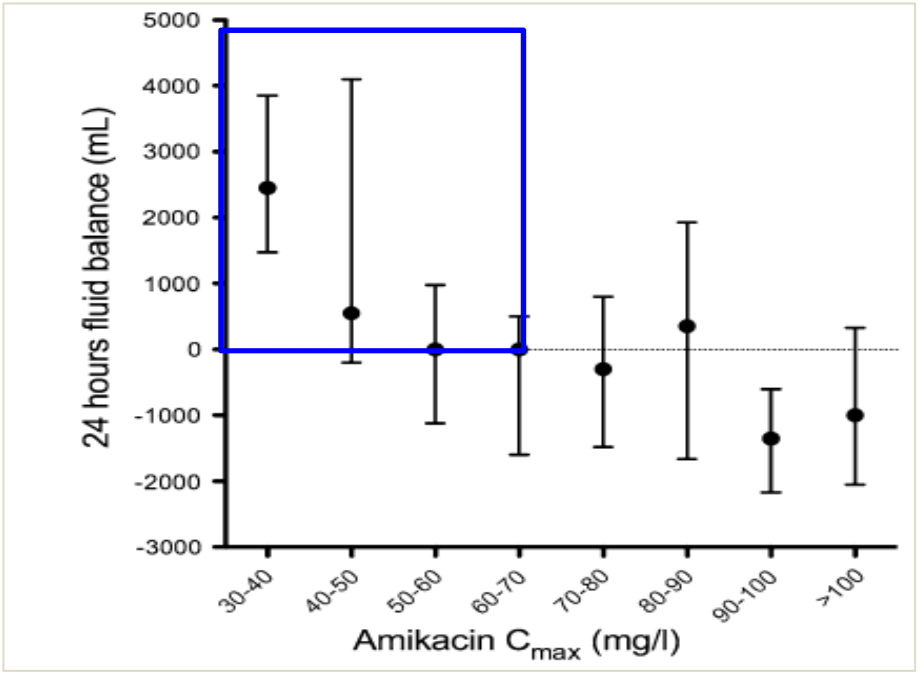


Figure 2 Distribution of peak concentrations. Black bars, peak >64 µg/ml; gray bars, peak <64 µg/ml.

Montmollin et al, Intensive Care Med 2014

Fluid balance



Les antibiotiques inhalés traitent-ils la pneumonie?

VAP caused by *P aeruginosa* susceptible to β-lactams

Aerosol group: Ceftazidime /3H (120 mg/kg) **AMK 1 x/j (25 mg/kg)**	**IV group: Ceftazidime IV (90 mg/kg)** **AMK 1 x/j (15 mg/kg)**

Table 3 Antibiotic treatment efficiency.

Phase II trial, n = 40

	Aerosol n=20	Intravenous n=20	p Value
Cure of *P aeruginosa* VAP at day 9 (n, %)	14 (70)	11 (55)	0.33
Day 9 : Positive BAL≥10^4 or miniBAL≥10^3 (n)	3	6	
Persisting *P aeruginosa* VAP at day 9 (n, %)	3 (15%)	6 (30%)	0.26
VAP caused by superinfection at 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 at day 28, n (%)	2(10%)	1(5%)	0.55

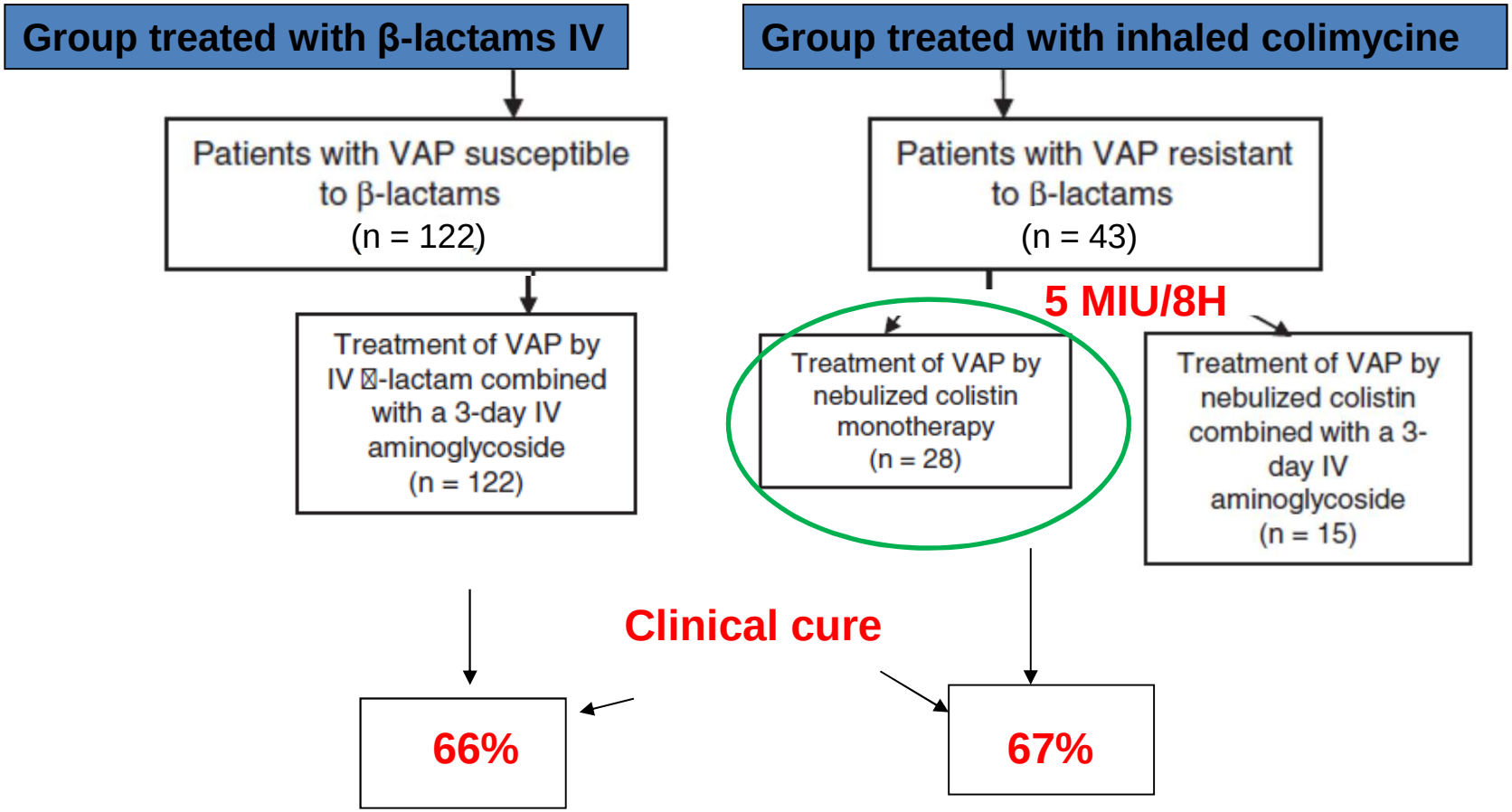
Vibrating mesh nebulizer: continous delivery

Lu et al, AJRCCM 2011

Efficacy of High-dose Nebulized Colistin in Ventilator-associated Pneumonia Caused by Multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

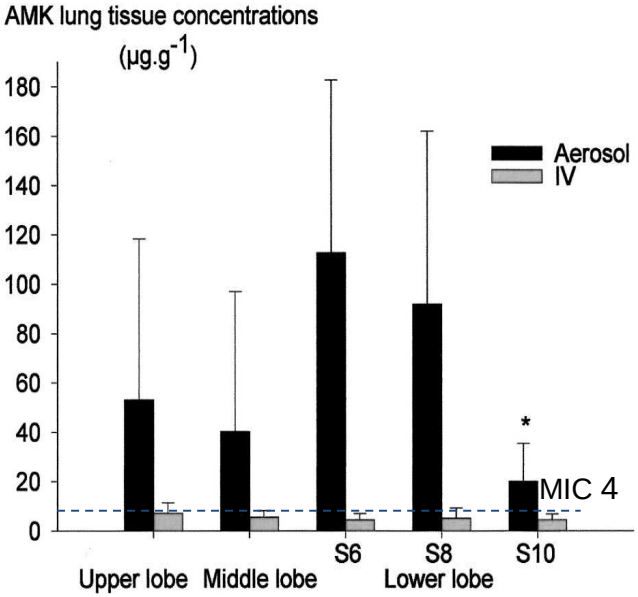
Lu et al, Anesthesiology, 2012

Non inferiority study

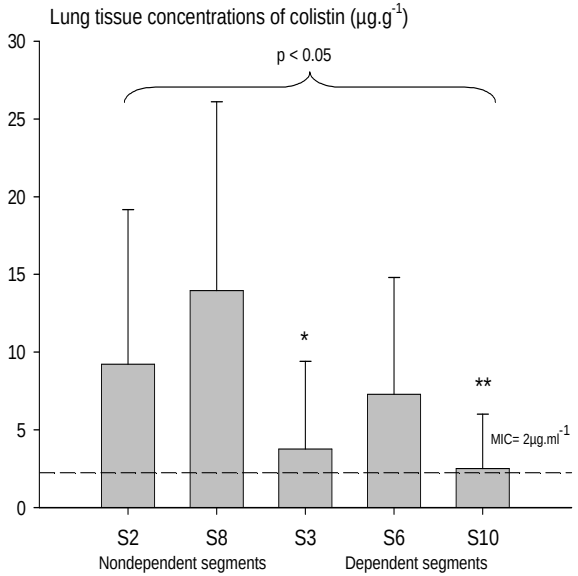


Quels bénéfices nous apportent les antibiotiques inhalés?

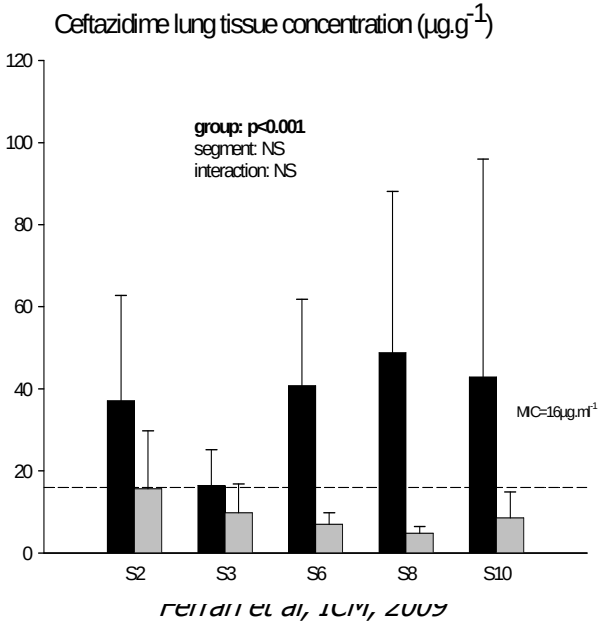
Increased lung tissue concentrations



Goldstein et al, AJRCCM 2000



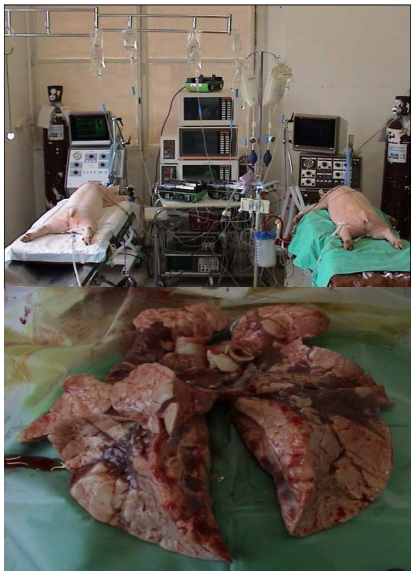
Lu et al, Intensive Care Med, 2010



Ferrari et al, ICM, 2009

Increased bacterial killing effect

Antibiotic	Pathogen	Sterilized lung segments (%)		
		Aerosol	IV	Control
Amikacin	*E coli* MIC 4	71%	24%	16%
Ceftazidime	*PA* MIC 16	83%	30%	10%
Colimycin	*PA* MIC 2	67%	28%	12%



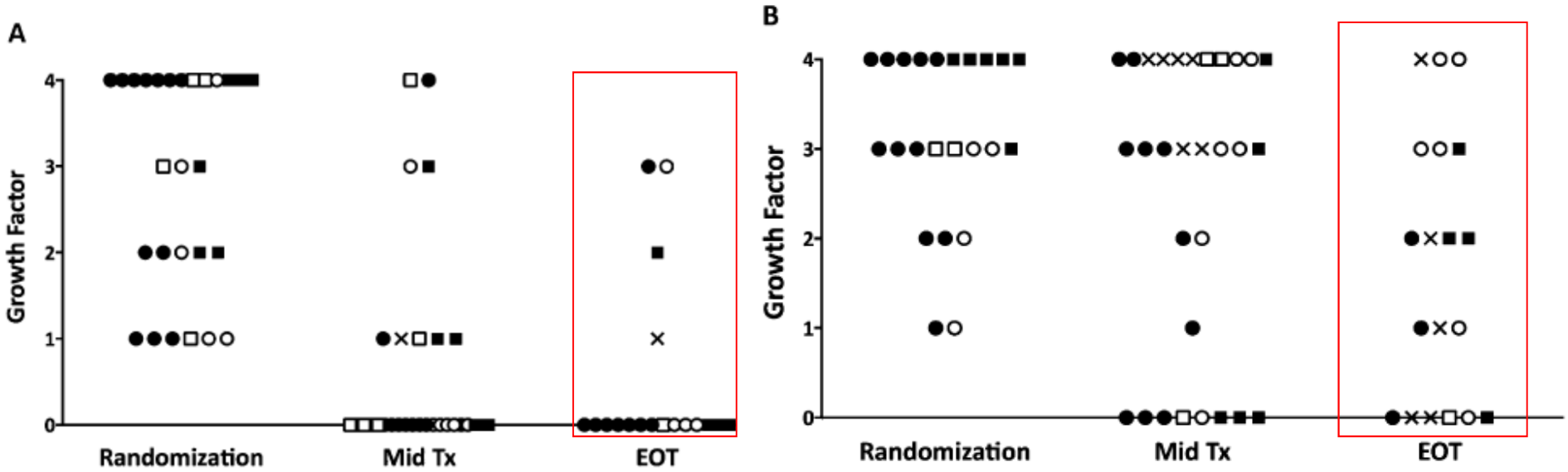
Reduction of Bacterial Resistance with Inhaled Antibiotics in the Intensive Care Unit

Lucy B. Palmer and Gerald C. Smaldone

Am J Respir Crit Care med 2014

VAT or VAP patients

Inhaled antibiotic:: Vanco, genta or amikacin + antibiotic IV

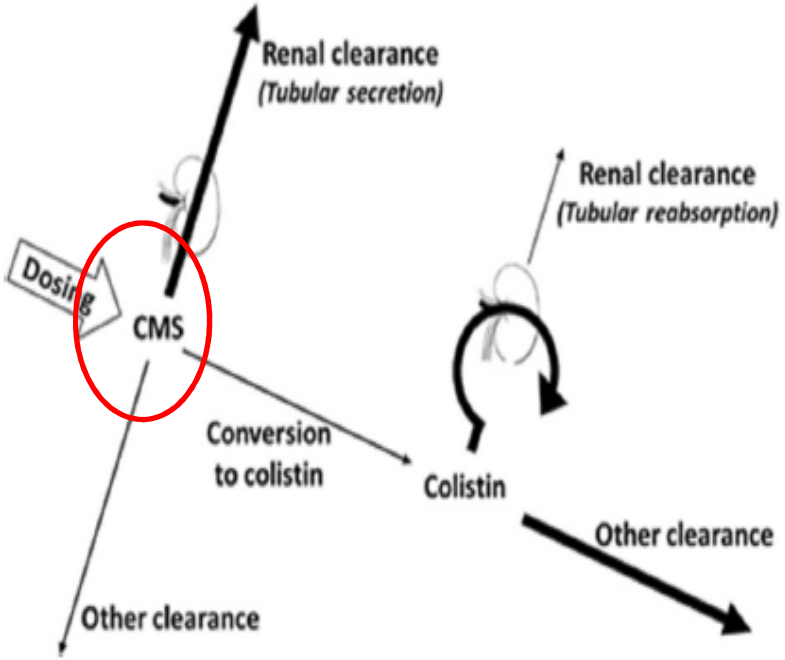


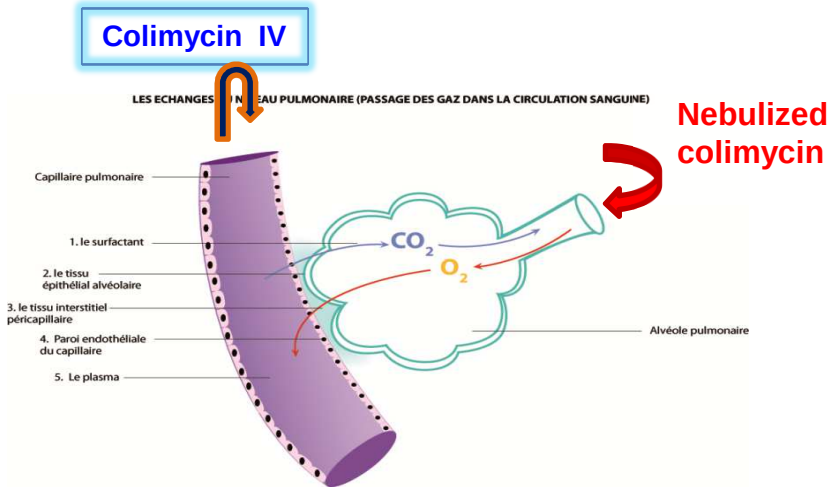
Aerosol group (n = 24)

Placebo group (n = 23)

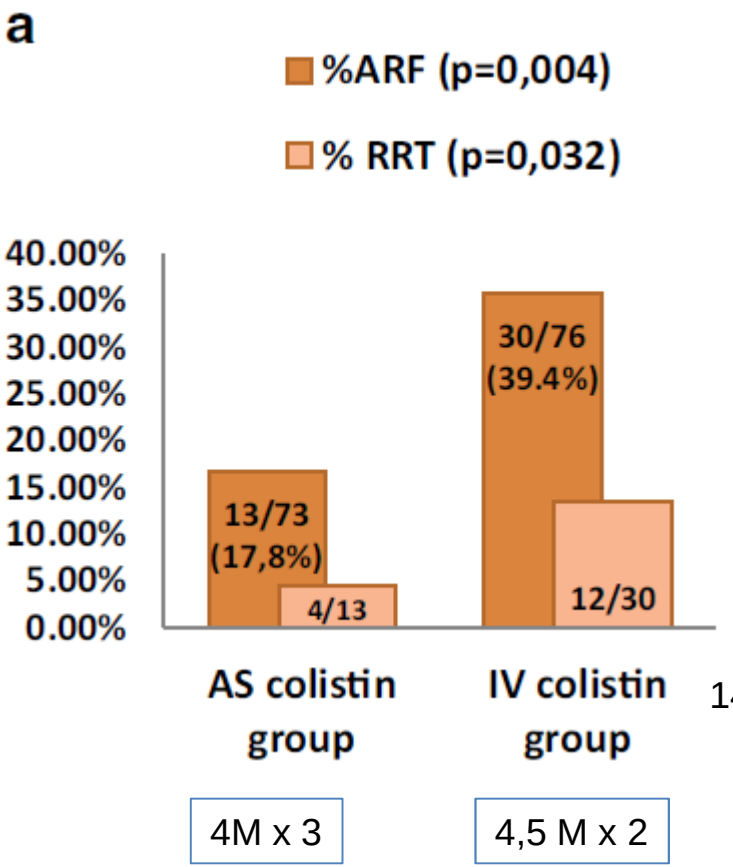
Filled symbols: resistant organisms
X: newly resistant organisms on treatment

Reduced renal toxicity with nebulized Colimycin (CMS)





Dose dependent-renal toxicity



Abdellatif et al, Ann Intensive Care 2016

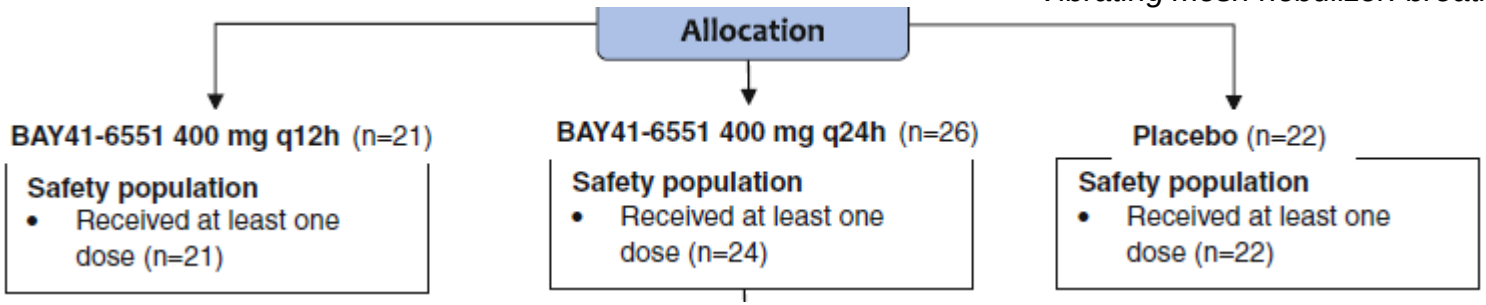
Michael S. Niederman
Jean Chastre
Kevin Corkery
James B. Fink
Charles-Edouard Luyt
Miguel Sánchez García

BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia

Niederman, ICM 2015

Multicenter randomized, placebo-controlled double-blind phase II study
(combined therapy, IV + inhaled amikacin 7-14 days)

Vibrating mesh nebulizer: breath-synchronized



Tracheal aspirate amikacin Cmax > 6400 (25 x256) µg/mL and AUC/MIC (256) >100 at day 1 (256 µg/mL: highest amikacin MIC for *P aeruginosa and Acinetobacter*)

	50%	17%	
Clinical cure rate	94%	75%	88%

Included all VAP caused by susceptible to GNB and response to IV treatment

-P aeruginosas 45%
-E coli 26%
-Klebsiella spp 18%
-Acinetobacter 13%

Phase III study…

A randomized trial of the amikacin fosfomycin inhalation system for the adjunctive therapyof Gram-negative ventilator-associated pneumonia: IASIS Trial. *Kollef et al, Chest 2016*

Standard of care IV + AFIS (amk300mg+120mg fosfomycin) par inhalation x2/J for 10 days

- 143 patients were randomized, 71 to AFIS, 72 to placebo.
- Already received IV antibiotic for several days
- Jet nebulizer and humidity maintained
- MDR bacteria 50%, XDR bacteria 22% including resistant to colistin
- Susceptibility to amikacin alone or to fosfomycin or to both not reported

.

Primary endpoint: No difference in CPIS change from baseline between treatment groups and placebo

- Mortality and clinical cure at Day 14 was not significant (P=0.68).
- The AFIS group had significantly fewer positive tracheal cultures on Days 3 and 7 compared to placebo

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.

+ 6 méta-analyses négatives

Rello et al, Clin Microbiol Infect 2017

…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)…

…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.

Etude COLIVAP

PHRC National 2013

Efficacy of nebulized versus intravenous Colimycin for treating ventilator-associated pneumonia caused by Gram-negative multidrug-resistant bacteria: a prospective, multicenter, randomized and double-blind study

Investigateur Coordinateur: Dr Qin Lu

Après 3 ans de préparation et 1 an d'inclusion (7 patients inclus pour 196 patients attendus), l'étude est arrêtée à la demande du promoteur pour:

-faute de patients éligibles

-2 EIG déclarés

-financement insuffisant

Faut-il attendre des études positives pour prescrire des antibiotiques inhalés?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 24, 2018 VOL. 378 NO. 21

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

A. Combes, D. Hajage, G. Capellier, A. Demoule, S. Lavoué, C. Guervilly, D. Da Silva, L. Zafrani, P. Tirot, B. Veber, E. Maury, B. Levy, Y. Cohen, C. Richard, P. Kalfon, L. Bouadma, H. Mehdaoui, G. Beduneau, G. Lebreton, L. Brochard, N.D. Ferguson, E. Fan, A.S. Slutsky, D. Brodie, and A. Mercat, for the EOLIA Trial Group, REVA, and ECMONet*

Pas de différence de mortalité à 60 jours

Global survey in 2014 on nebulization of antimicrobial agents in mechanically ventilated patients: a call for international guidelines *Sole-Lleonart et al. Clin Microbiol Infect 2016*

Characteristic	Asia (n = 37)		Europe (n = 32)		Australasia, North America and Latin America (n = 18)		Total (n = 87)	
	Global, n (%)	Neb alone, n (%)	Global, n (%)	Neb alone, n (%)	Global, n (%)	Neb alone, n (%)	Global, n (%)	Neb alone, n (%)
VAP treatment	32 (86.4)	7 (18.9)	16 (50)	1 (9.3)	10 (55.5)	0 (0)	58 (66.6)	8 (9.1)
VAT treatment	31 (83.7)	9 (24.3)	19 (59.3)	9 (28.1)	6 (33.3)	2 (11.1)	56 (64.3)	20 (22.9)

Position Paper

Nebulization of antimicrobial agents in mechanically ventilated adults in 2017: an international cross-sectional survey *Alves et al. Eur J Clin Microbiol Infect Dis, 2018*

261 centers (177 from europe): 73% reported using aerosolized antibiotics

Characteristic	Asia (N = 44), n (%)[a]	Europe (N = 177), n (%)[a]	America (N = 40), n (%)[a]	Total (N = 261), n (%)[a]
VAP treatment	33 (75)	134 (75.7)	27 (67.5)	194 (74.3)
VAT treatment	13 (29.5)	93 (52.5)	23 (57.5)	129 (49.4)

CONCLUSIONS

- Nous avons besoin d'antibiotiques inhalés pour traiter des PAVM à BGN résistants
- Bénéfices potentiels démontrés
- Les antibiotiques concentrations-dépendants restent les choix pour traiter des bactéries à BGN résistants par inhalation
- Les études multicentriques visant à démontrer l'efficacité d'antibiotiques inhalés sont difficiles à réaliser
- Il ne faut plus attendre des études positives pour prescrire des antibiotiques inhalés
- Continuer des études, investir dans la technologie et la formation à la technique de nébulisation