Antibiotiques inhalés

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Liens d'intérêt

- **Conseil scientifique / financement recherche ou congrès**
  - Gilead
  - Astellas
  - Coreviome
  - Mylan
  - Pfizer

Au menu

- Principes
- Etudes cliniques
- Recommandations
- En pratique

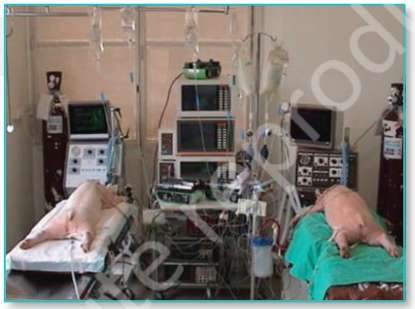
Principes des ATB inhalés

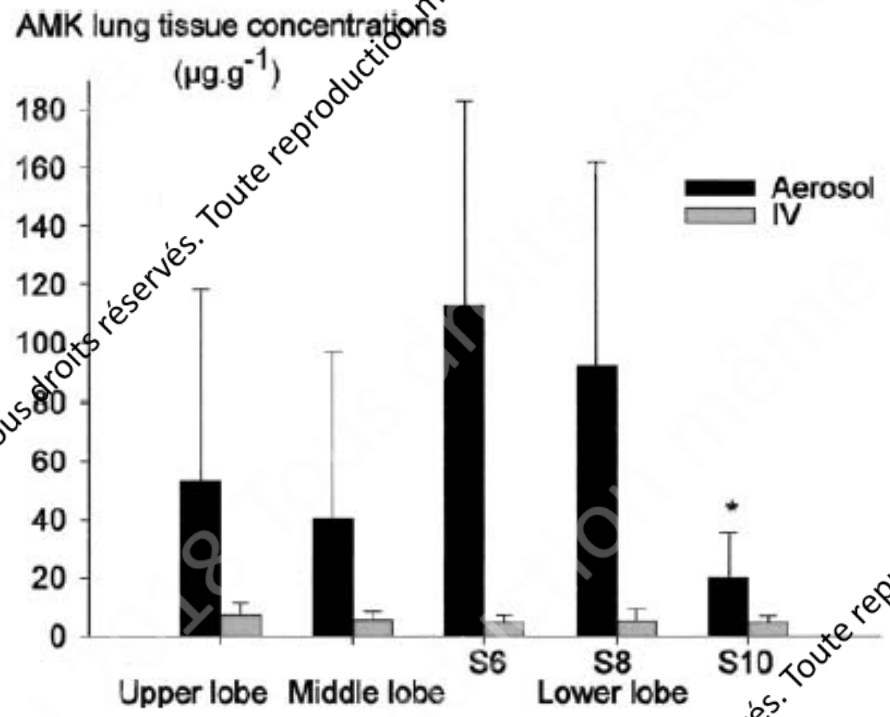
- **Concentrations locales + élevées** (parenchyme/alvéoles)
- **Concentrations systémiques + basses**
- **Idéal pour:**
  - **molécules toxiques par voie systémique**
  - **diffusion intra-pulmonaire médiocre**
  - **situations complexes (PAVM à bactéries XDR)**

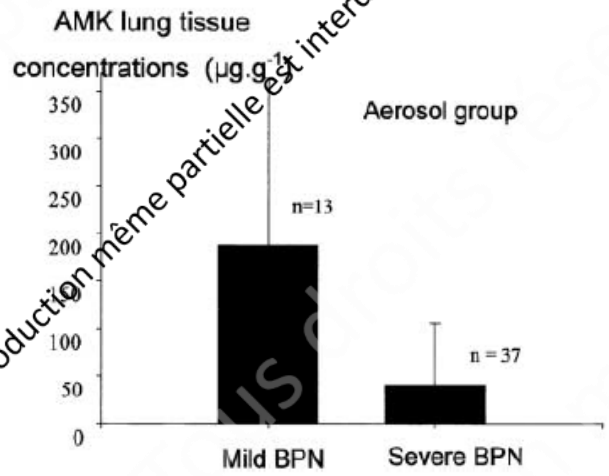
Colimycine / Aminosides

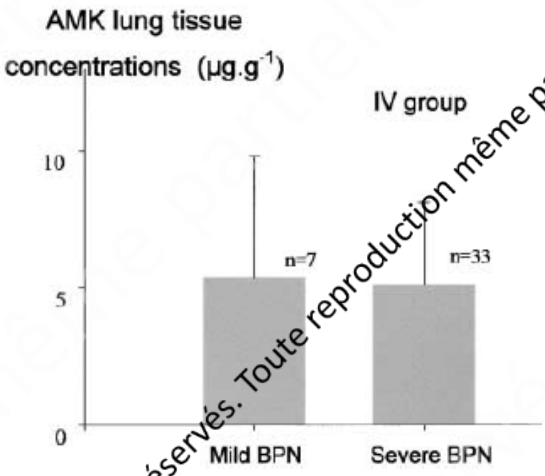
Lung Deposition and Efficiency of Nebulized Amikacin during *Escherichia coli* Pneumonia in Ventilated Piglets

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









Concentrations pulmonaires AMK 30 X supérieures avec aérosols

- 3 fois moins élevées dans lobes moyen et sup.
- 3 fois moins élevées si pneumopathie modérée

Goldstein I et al. Am J Respir Crit Care Med 2002

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

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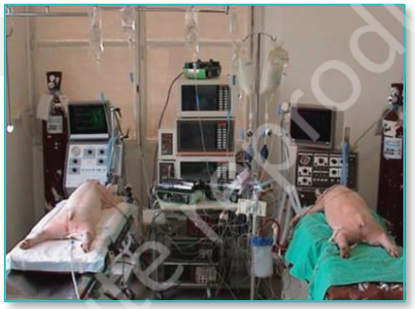
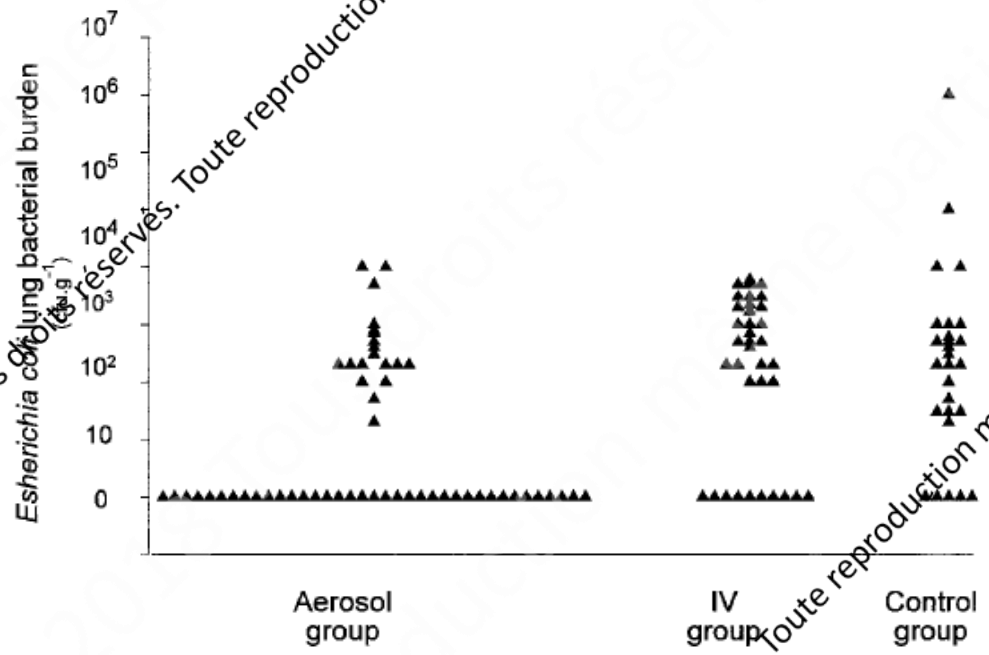


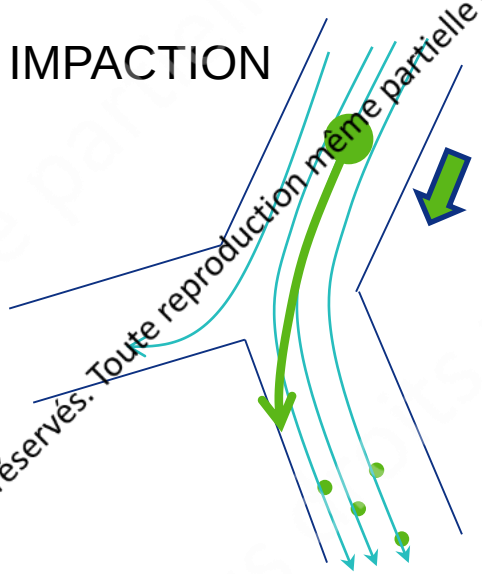


- Aérosols **+ efficaces** sur critères microbios (PAVM *E. coli, CMI AMK=4*)
- Concentrations plasmatiques basses => **faible toxicité systémique**

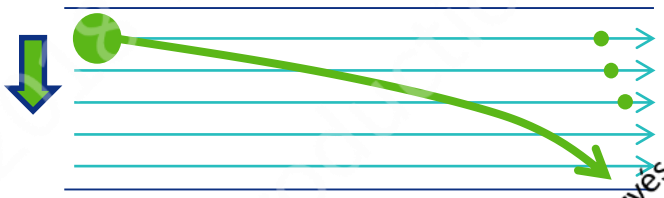
Goldstein I et al. Am J Respir Crit Care Med 2002

Mais c'est compliqué…

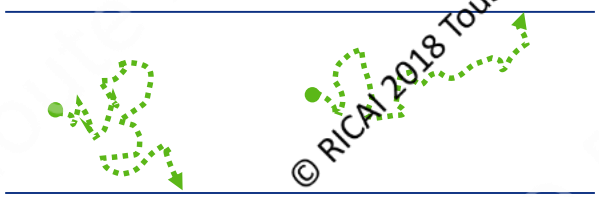
IMPACTION

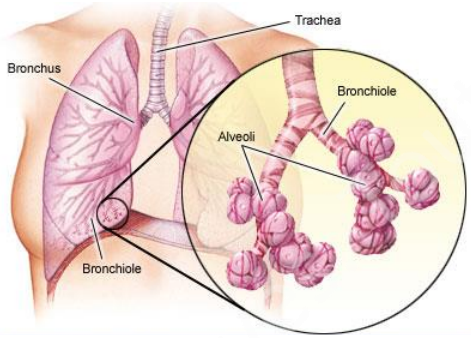


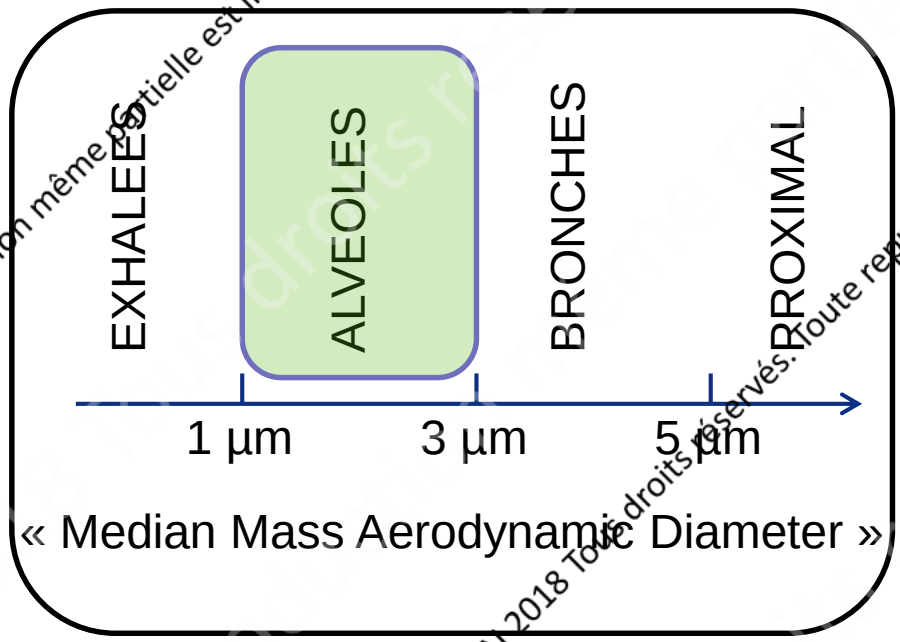
SEDIMENTATION



DIFFUSION

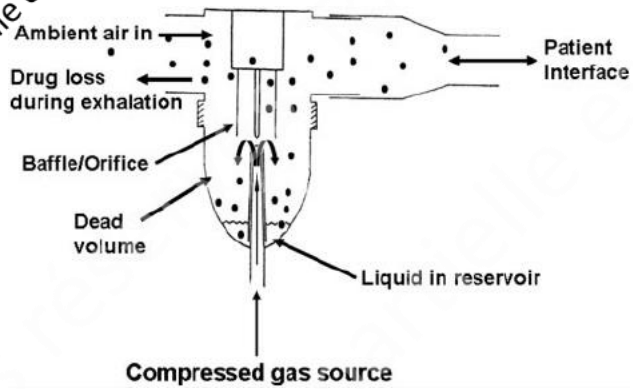






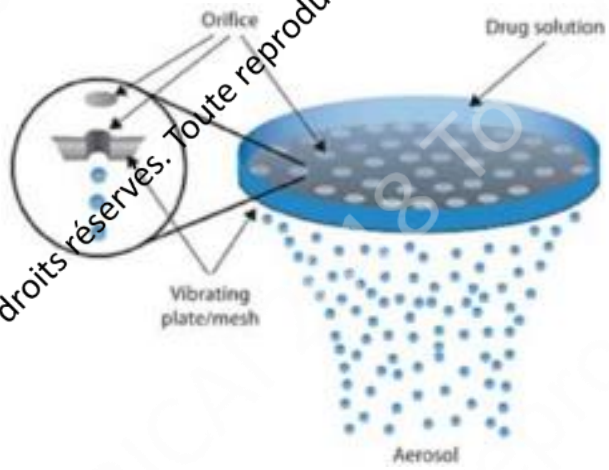
Générateurs d'aérosols

PNEUMATIQUE

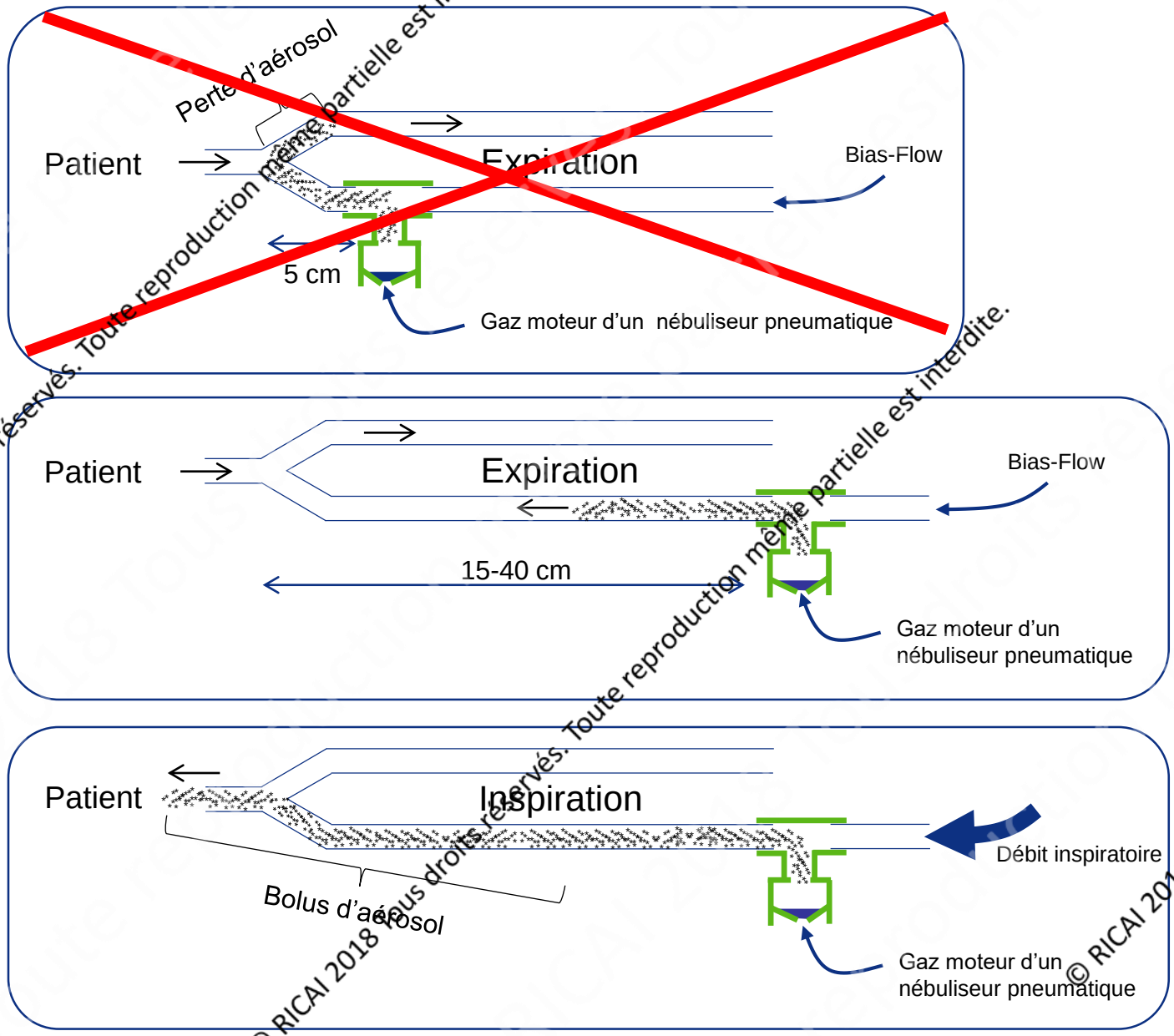


ULTRA-SONIQUE

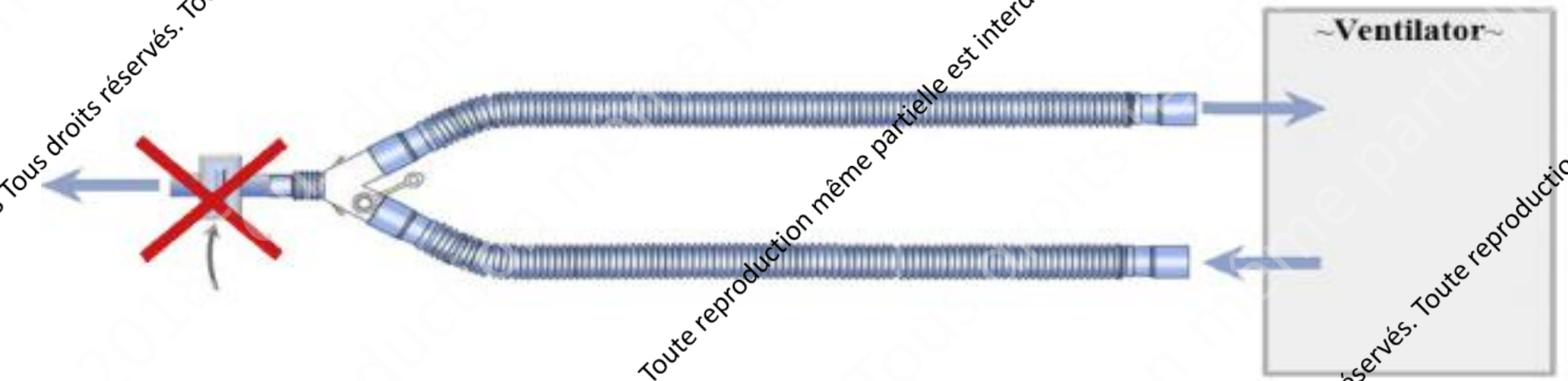
TAMIS VIBRANT



Position du nébuliseur



Position du filtre



Consensus statement

Key considerations on nebulization of antimicrobial agents to mechanically ventilated patients

J. Rello [1,*,9], J.J. Rouby [2,9], 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]

Optimal ventilator modes and settings during the period of nebulization

Characteristic	Description
Ventilator mode	• Volume-controlled mode. • Constant inspiratory flow.
Ideal ventilator parameters	• Tidal volume 8 mL/kg. • Respiratory frequency 12–25 breaths per minute. • Inspiratory to expiratory (I:E) ratio ≤50%. • End-inspiratory pause of 20% of duty cycle. • Positive end expiratory pressure 5–10 cm H_2O.
Important considerations	• Avoid sharp angles and rough inner surfaces in ventilator's circuit. • Avoid asynchronies and triggering. • Increase level of sedation if necessary. • Remove heat and moisture exchanger during procedure (and replace immediately afterwards). • Stop heat humidifiers during nebulization. • Change expiratory filter after each nebulization (expired particles are collected there and can cause obstruction).

Rello J et al. Clin Microbiol Infect 2017

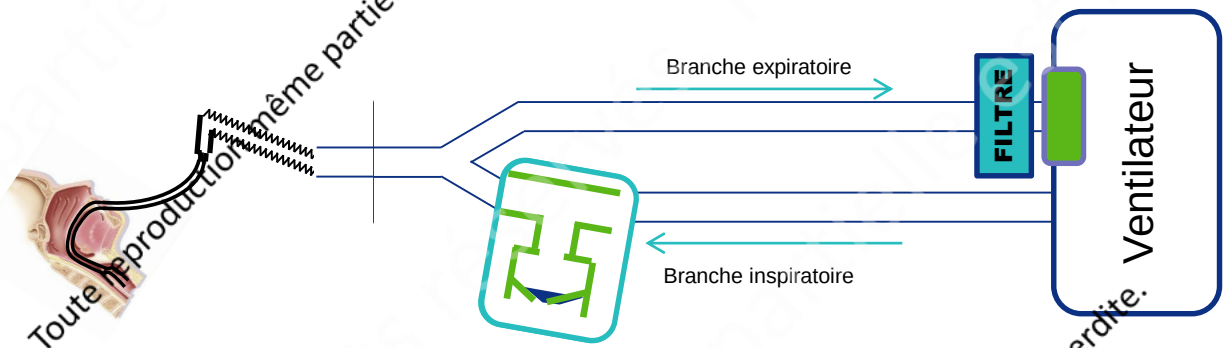
Checklist form

Nurse _____ Date _____

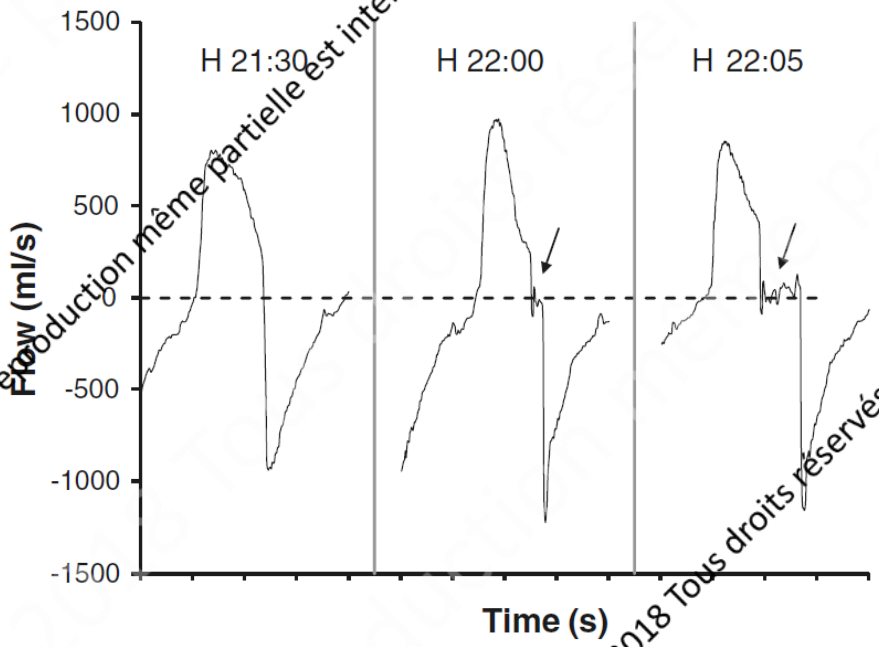
		__ h __ min ☐Cefta/AMK	__ h __ min ☐ Cefta/AMK	__ h __ min ☐Cefta/AMK	__ h __ min ☐Cefta/AMK
Before aerosol	Removal of moisture exchanger	☐	☐	☐	☐
	Removal of connecting tube	☐	☐	☐	☐
	Nebulizer inserted 10 cm before Y piece	☐	☐	☐	☐
	Connection of expiratory filter positioned between expiratory circuit and ventilator	☐	☐	☐	☐
	Ventilator settings (see medical order)	☐	☐	☐	☐
	Patient desynchronized with the ventilator : start propofol	☐	☐	☐	☐
After aerosol	Connection of moisture exchanger	☐	☐	☐	☐
	Reinsertion of connecting tube	☐	☐	☐	☐
	Removal of nebulizer	☐	☐	☐	☐
	Removal of expiratory filter	☐	☐	☐	☐
	Initial ventilator settings (see medical order)	☐	☐	☐	☐
	Stop propofol	☐	☐	☐	☐

Liu Q et al. Am J Respir Crit Care Med 2011

Et potentiellement dangereux !



Capteur de débit expiratoire



Mojoli F et al. Intensive Care Med 2013

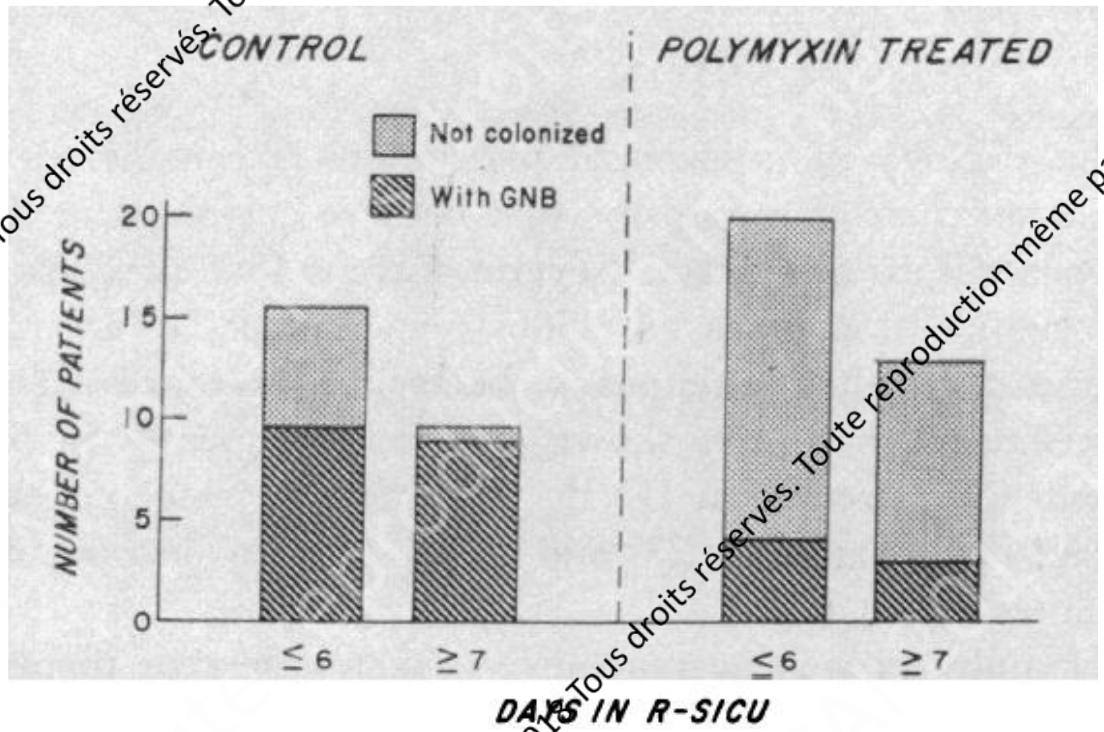
Obstruction du filtre / pneumothorax / arrêt cardiaque

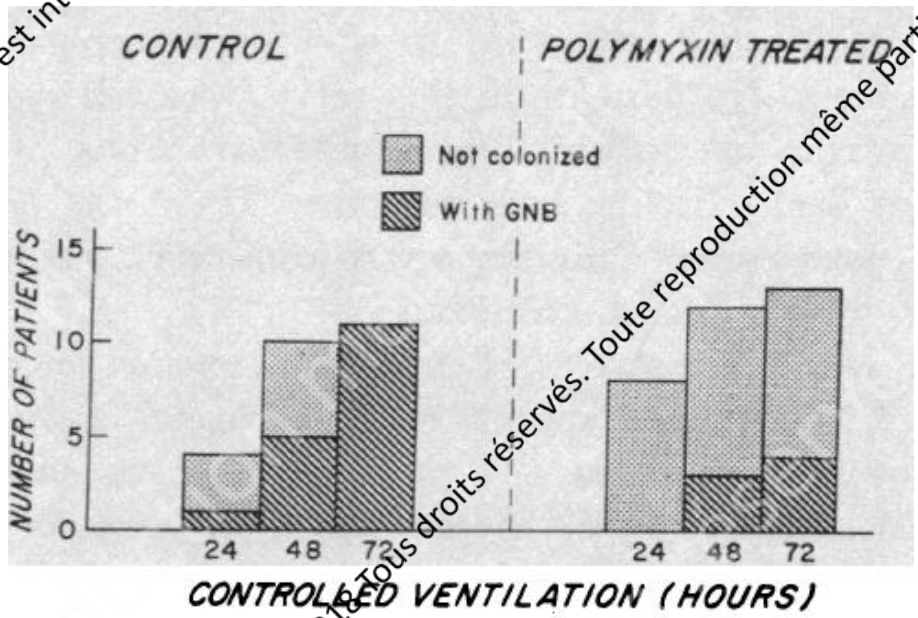
Etudes cliniques

1. prévention

Prevention of Gram-Negative Bacillary Pneumonia Using Aerosol Polymyxin as Prophylaxis. I. EFFECT ON THE COLONIZATION PATTERN OF THE UPPER RESPIRATORY TRACT OF SERIOUSLY ILL PATIENTS

Spray manuel, 6 vaporisations/j, oropharynx + tube



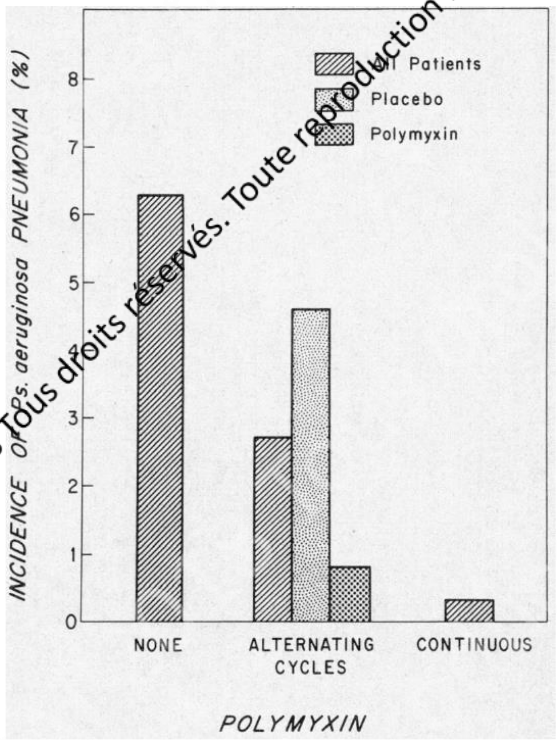


Greenfield S et al. J Clin Invest 1973

AEROSOL POLYMYXIN AND PNEUMONIA IN SERIOUSLY ILL PATIENTS

T. W. FEELEY, M.D., G. C. DU MOULIN, M.S., J. HEDLEY-WHYTE, M.D., L. S. BUSHNELL, M.D., J. P. GILBERT, PH.D., AND D. S. FEINGOLD, M.D.

=> Baisse d'incidence des PAVM, mais augmentation de la létalité et des résistances



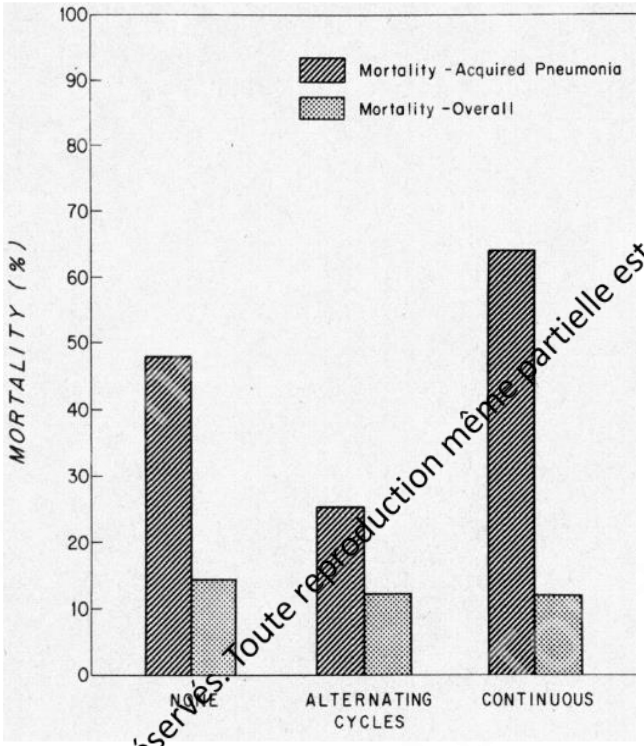


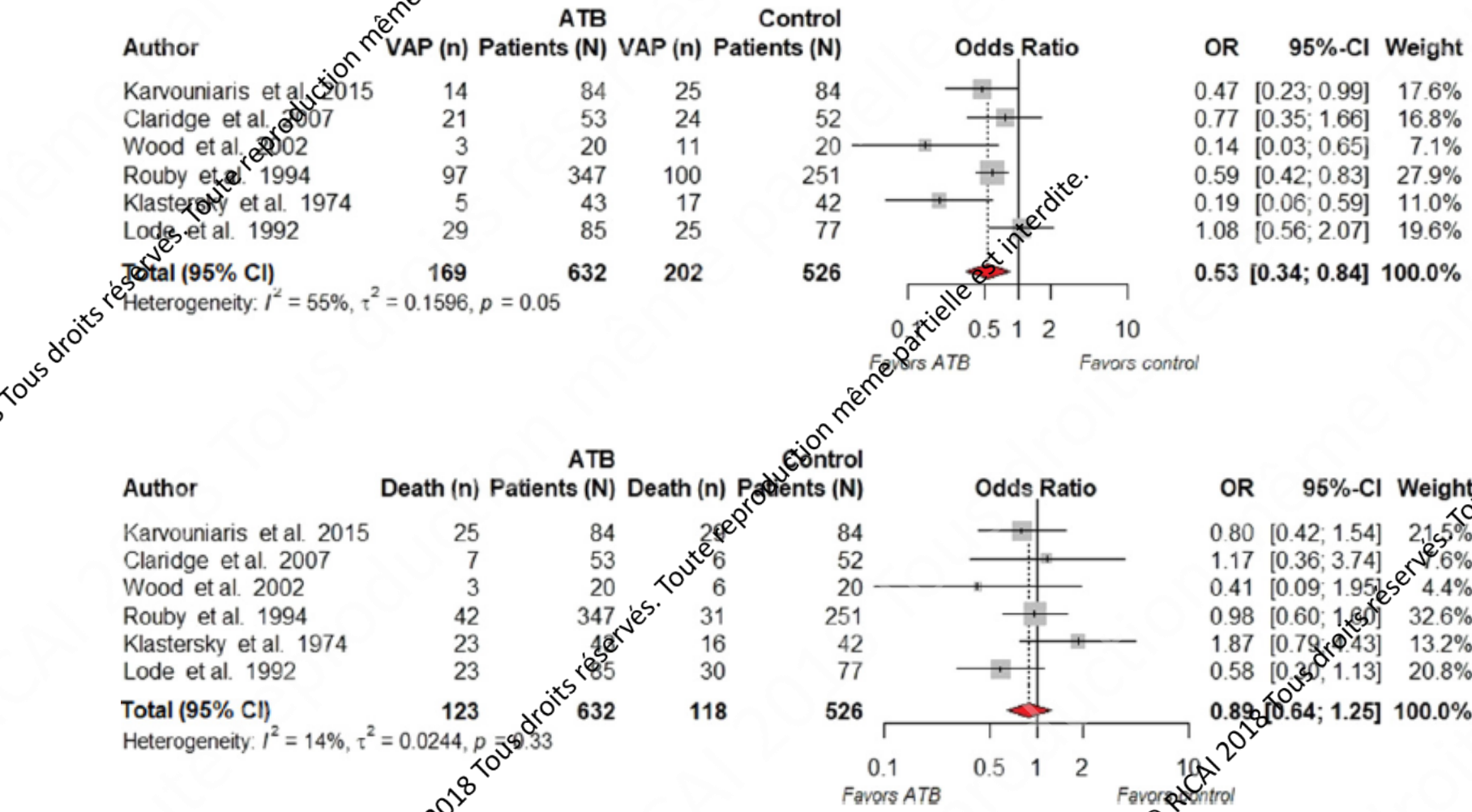
Table 2. Organisms Causing Pneumonia during Polymyxin Prophylaxis.

ORGANISM	POLYMYXIN SENSITIVITY*	NO. OF CASES	NO. OF DEATHS
Ps aeruginosa	S	1	1
Proteus species	R	3	2
Ps cepacia	R	2	2
Ps maltophilia	R	2	0
Serratia species	R	2	0
Flavobacterium species	R	1	1
Str faecalis	R	1	1
Total		11	7

« Continuous use of aerosol polymyxin appears to be a dangerous form of therapy »

Feeley TW et al. N Engl J Med 1975

Effect of antibiotics administered via the respiratory tract in the prevention of ventilator-associated pneumonia: A systematic review and meta-analysis



Povoa FCC et al. J Crit Care 2018

Etudes cliniques - résumé

1. Prévention

- Efficace sur la prévention des PAVM
- Sans bénéfice clinique
- Emergence de résistances

Etudes cliniques

2. Traitement curatif substitutif

(à la place de traitement i.v.)

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

- CAZ + AMK i.v. vs. CAZ + AMK en aérosols (8/j pour CAZ !)

TABLE 2. ANTIBIOTIC TREATMENT EFFICIENCY

	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 $\geq 10^4$ cfu·ml^{-1} or mini-BAL $\geq 10^3$ 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 (13–32)	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

Liu Q et al. Am J Respir Crit Care Med 2011

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

- CAZ + AMK i.v. vs. CAZ + AMK en aérosols (8/j pour CAZ !)

TABLE 3. MICROBIOLOGICAL RESPONSE TO TREATMENT AND ANTIBIOTIC SUSCEPTIBILITY OF *PSEUDOMONAS AERUGINOSA* IN EACH GROUP OF PATIENTS

	Baseline	Day 3	Day 5	Day 7	Day 9
Aerosol Group					
BAL, n	20	17	16	12	12
BAL *P. aeruginosa* + *P. aeruginosa* susceptibility, n	20	1	0	2	5*
CAZ–AMK					
S–S	16	1		2	5
S–I†	1				
I‡–S	2				
I§–I†	1				
Intravenous Group					
BAL, n	20	16	15	10	11
BAL *P. aeruginosa* + *P. aeruginosa* susceptibility, n	20	8	8	5	6
CAZ–AMK					
S–S	17	6	5	1	3
S–I	3	2		1	
I–S				2	1
R–S			2	1	1
R–I					1

Liu Q et al. Am J Respir Crit Care Med 2011

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

- CAZ + AMK i.v. vs. CAZ + AMK en aérosols (8/j pour CAZ !)

TABLE 4. AMIKACIN AND CEFTAZIDIME PLASMA CONCENTRATIONS MEASURED ON DAYS 3 AND 4

	Aerosol	Intravenous	*P* Value
Ceftazidime			
Daily dose, mg·kg^{-1}	76*	90	
C_{peak}, mg·L^{-1}	12.1 ± 8.4		
C_{trough}, mg·L^{-1}	8.1 (6.0–12.4)	32.2 ± 9	<0.001
Amikacin			
Daily dose, mg·kg^{-1}	15.7*	15.0	
C_{peak}, mg·L^{-1}	8.9 (5–11)	45.1 (33–58)	<0.001
C_{trough}, mg·L^{-1}	2.4 (1.7-5.9)	3.3 (1.9–5.8)	0.742

Liu Q et al. Am J Respir Crit Care Med 2011

Etudes cliniques - résumé

2. Traitement curatif substitutif

(à la place de traitement i.v.)

- Efficacité identique
- Moindre risque de résistance locale
- Diffusion systémique moyenne

⇒ **Être sûr de l'absence de dissémination !**

Etudes cliniques

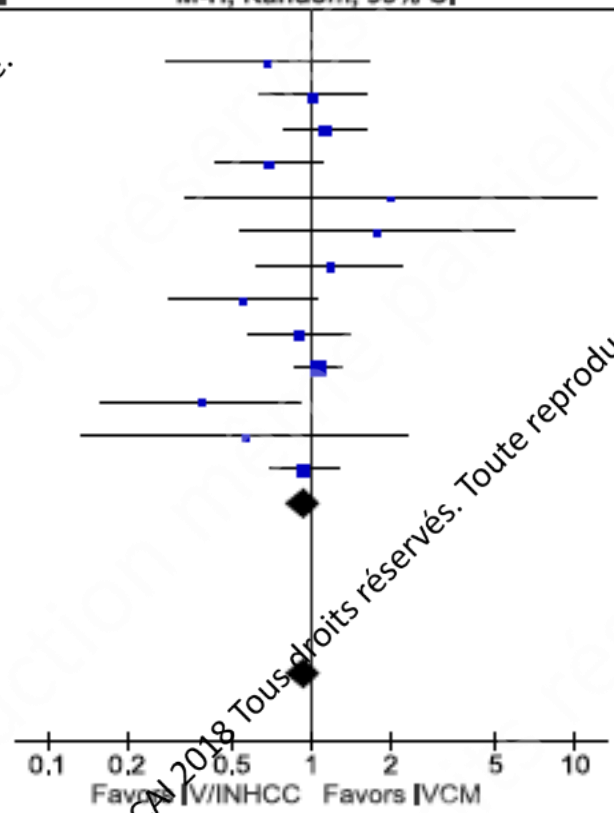
3. Traitement curatif adjuvant

(en complément de traitement i.v.)

Intravenous plus inhaled versus intravenous colistin monotherapy for lower respiratory tract infections: A systematic review and meta-analysis

Konstantinos Z. Vardakas [a,b], Andreas D. Mavroudis [c], Maria Georgiou [a], Matthew E. Falagas [a,b,d,*]

Study or Subgroup	Inhaled/Intravenous Events	Total	Intravenous Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 inhaled						
Amin et al. 2013	8	28	5	12	2.6%	0.69 [0.28, 1.67]
Bogovic et al. 2014	6	8	17	23	8.4%	1.01 [0.64, 1.62]
Demirdal et al 2016	23	43	38	80	12.7%	1.13 [0.78, 1.62]
Doshi et al 2013	16	44	27	51	8.4%	0.69 [0.43, 1.10]
Falagas et al. 2006	2	9	2	18	0.7%	2.00 [0.33, 11.97]
Garrapathy et al 2009	10	17	2	6	1.5%	1.76 [0.53, 5.86]
Kalin et al. 2012	16	29	7	15	5.0%	1.18 [0.63, 2.23]
Kofteridis et al 2010	10	43	18	43	4.8%	0.56 [0.29, 1.06]
Korbila et al 2010	31	78	19	43	9.6%	0.90 [0.58, 1.39]
Korkmaz et al. 2016	45	69	128	210	26.2%	1.07 [0.87, 1.31]
Naesens et al 2011	3	9	5	5	2.1%	0.38 [0.16, 0.92]
Perez-Pedrero et al. 2010	2	10	5	14	1.1%	0.56 [0.13, 2.33]
Tumbarello et al. 2013	45	104	48	104	16.4%	0.94 [0.69, 1.27]
Subtotal (95% CI)		**491**		**624**	**100.0%**	**0.94 [0.81, 1.08]**
Total events	217		321			
Heterogeneity: Tau² = 0.01; Chi² = 14.28, df = 12 (P = 0.28); I² = 16%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**491**		**624**	**100.0%**	**0.94 [0.81, 1.08]**
Total events	217		321			
Heterogeneity: Tau² = 0.01; Chi² = 14.28, df = 12 (P = 0.28); I² = 16%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Test for subgroup differences: Not applicable						



Vardakas KZ et al. J Infection 2018

Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults

A Systematic Review and Meta-analysis

Intérêt potentiel :

- Traitement adjuvant
- Bactéries multi-R

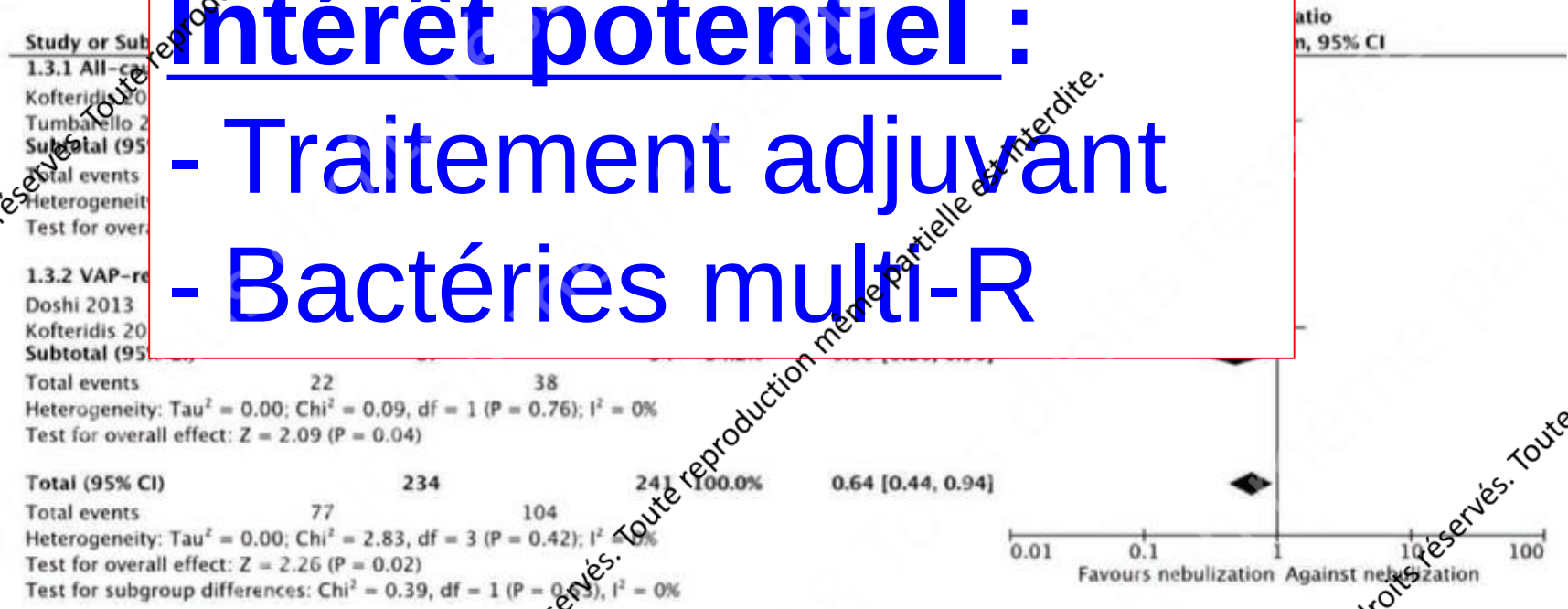


Fig. 5. Mortality of patients treated with nebulized antibiotics for ventilator-associated pneumonia (VAP) caused by resistant pathogens—adjunctive administration strategy. I = heterogeneity index; M–H = Mantel–Haenszel.

Solé-Lleonart et al. Anesthesiology 2017

Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults

A Systematic Review and Meta-analysis

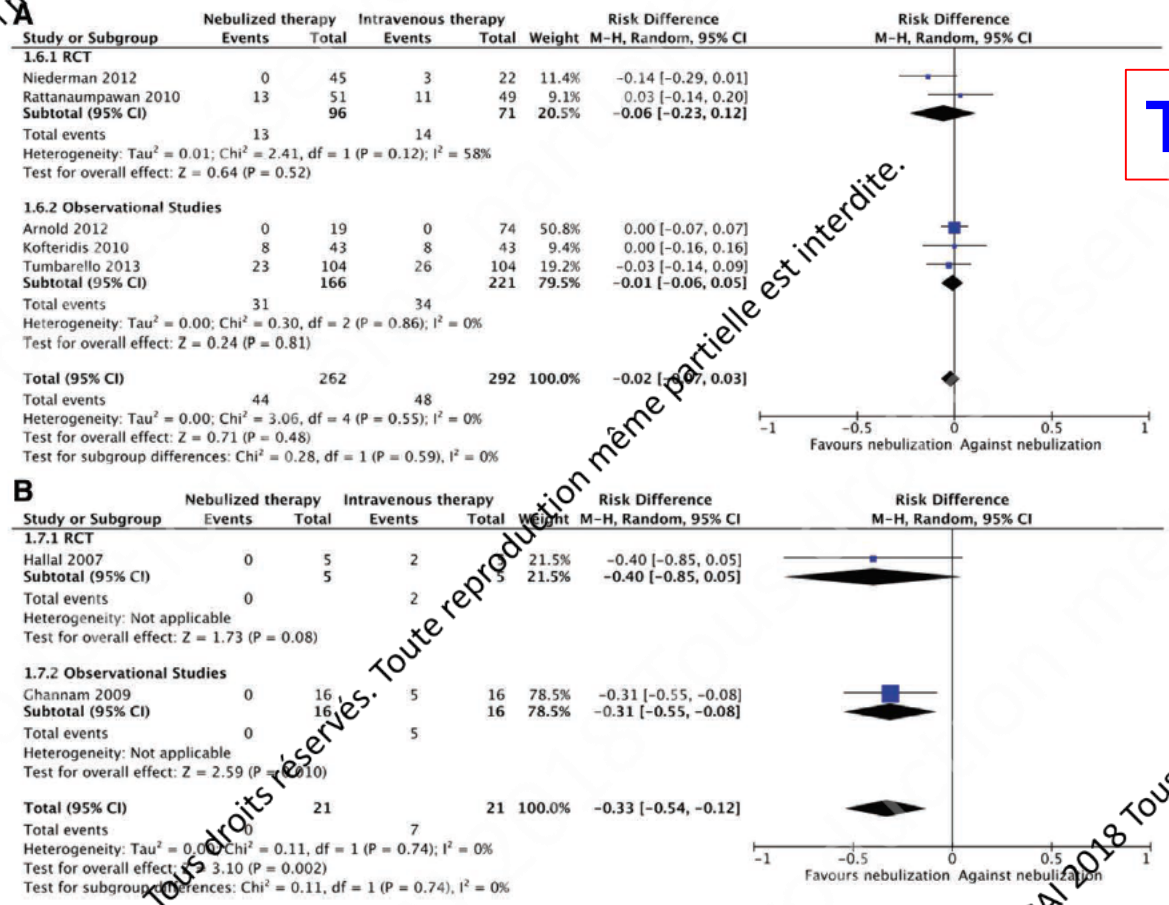


Fig. 7. Nephrotoxicity in patients treated with nebulized antibiotics for ventilator-associated pneumonia—(*A*) adjunctive administration strategy and (*B*) substitution administration strategy. I = heterogeneity index; M–H = Mantel–Haenszel; RCT = randomized controlled trial.

Toxicité rénale

adjuvant

substitutif

Solé-Lleonart et al. Anesthesiology 2017

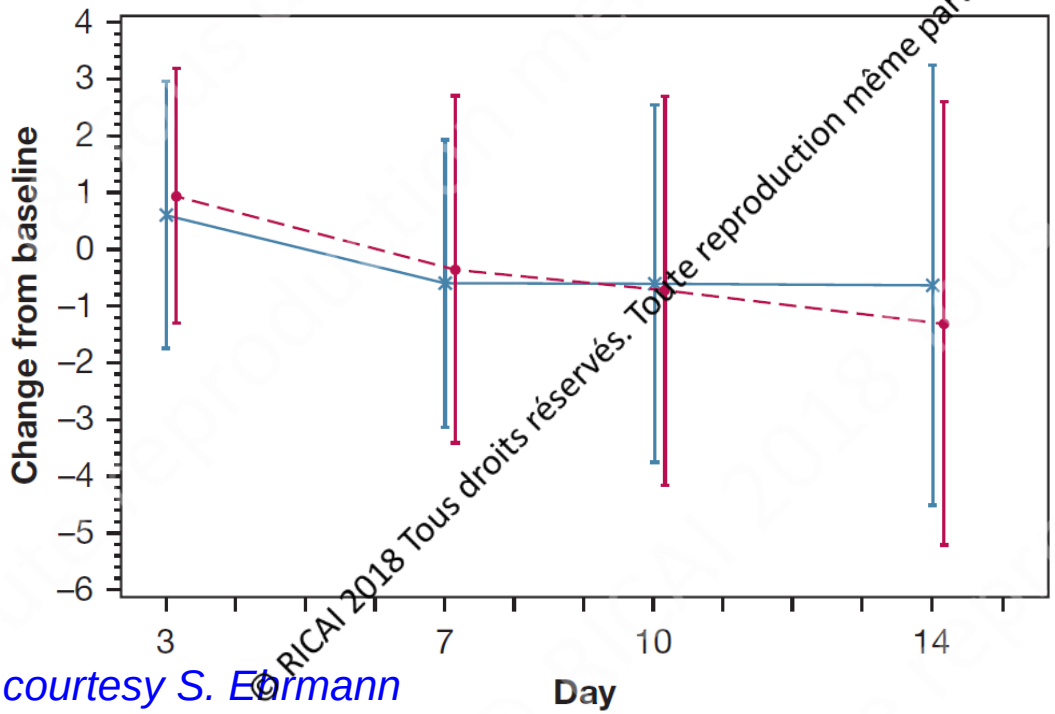
CHEST

A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia

IASIS Trial

Marin H. Kollef, MD; Jean-Damien Ricard, MD; Damien Roux, MD; Bruno Francois, MD; Eleni Ischaki, MD; Zsolt Rozgonyi, MD; Thierry Boulain, MD; Zsolt Ivanyi, MD; Gál János, MD; Denis Garot, MD; Firas Kouta, MD; Epaminondas Zakynthinos, MD; George Dimopoulos, MD; Antonio Torres, MD; Wayne Danker, MD; and A. Bruce Montgomery, MD

n=143



Critères secondaires, aucun bénéfice !

- Guérison à J14
- Durée ventilation
- Mortalité

Moins de culture positive de l'aspiration trachéale à J3 et J7 ?

Diapo: courtesy S. Ehrmann

Kollef MH et al. Chest 2017

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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Save this study

Inhaled Amikacin Solution BAY41-6551 as Adjunctive Therapy in the Treatment of Gram-Negative Pneumonia (INHALE 1)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT01799993

Recruitment Status: Completed
First Posted: February 27, 2013
Results First Posted: June 26, 2018
Last Update Posted: July 23, 2018

Sponsor:
Bayer

Collaborator:
Nektar Therapeutics

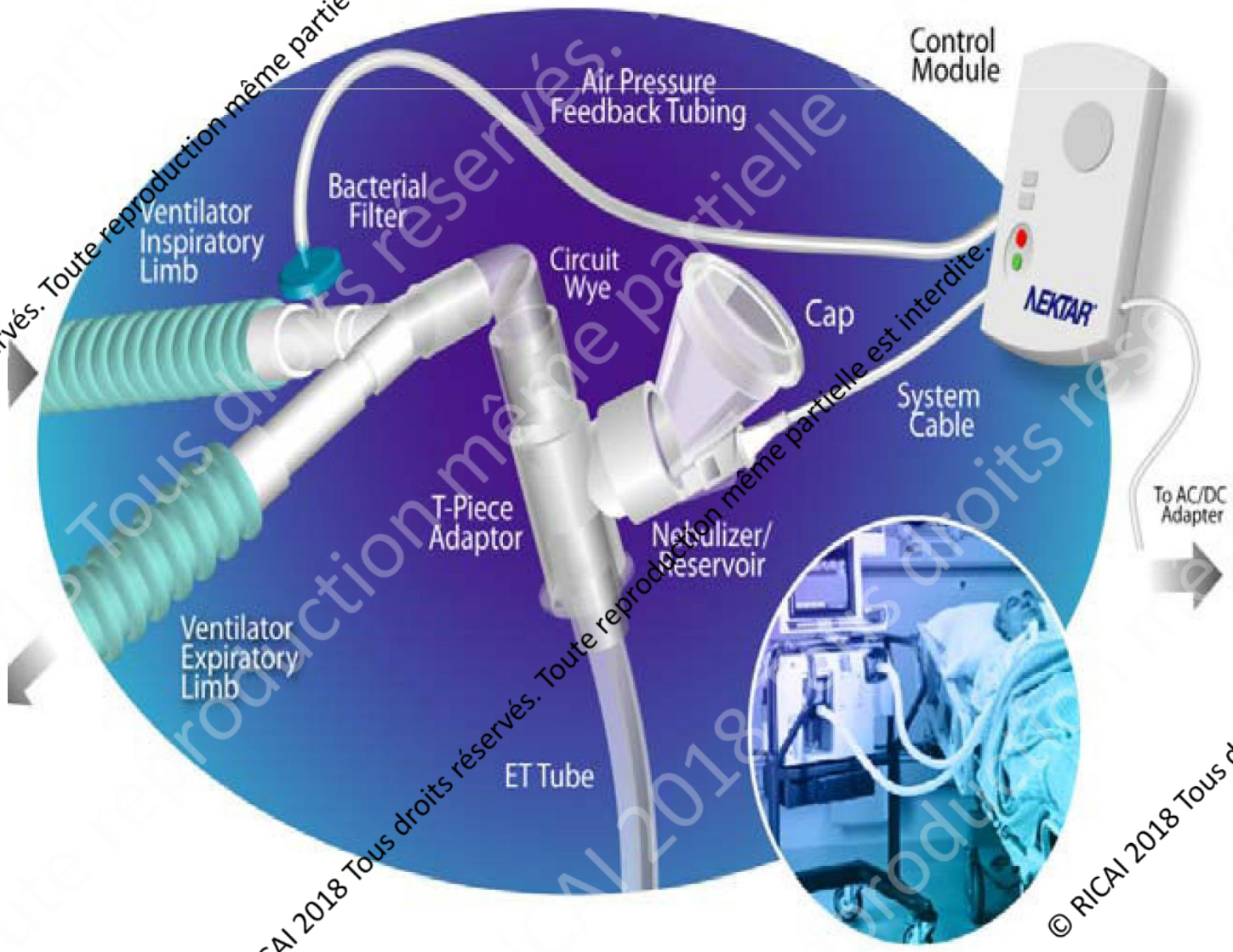
Information provided by (Responsible Party):
Bayer

Study Details | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Study Type:	Interventional
Study Design:	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor); Primary Purpose: Treatment
Condition:	Pneumonia, Bacterial
Interventions:	Drug: Amikacin Inhalation Solution (BAY41-6551) Drug: Aerosolized Placebo

n=725 patients

Diapo: courtesy S. Ehrmann



CE Luyt et al. Crit Care 2009

Reporting Groups

	Description
Amikacin Inhale (BAY41-6551)	Participants received 400 mg (3.2 mL) aerosolized Amikacin (BAY41-6551) solution every 12 hours via Pulmonary Drug Delivery System (PDDS) Clinical from Day 1 to Day 10.
Placebo	Participants received 3.2 mL aerosolized placebo solution every 12 hours via PDDS Clinical from Day 1 to Day 10.

Participant Flow: Overall Study

	Amikacin Inhale (BAY41-6551)	Placebo
STARTED	362	363
ITT Population	354	358
mITT Population	255	253

n=725 patients

Critère de jugement principal

Measured Values

	Amikacin Inhale (BAY41-6551)	Placebo
Participants Analyzed	255	253
Number of Participants Surviving Through LFU Visit [Units: Participants] Count of Participants		
Clinical Success (Survive)	191 74.9%	196 77.5%
Clinical Failure (Did not survive)	64 25.1%	57 22.5%

Statistical Analysis 1 for Number of Participants Surviving Through LFU Visit

Groups [1]	All groups
Statistical Test Type [2]	Superiority
Statistical Method [3]	Cochran-Mantel-Haenszel
P Value [4]	0.4263
Odds Ratio (OR) [5]	0.841
95% Confidence Interval	0.554 to 1.277

Aucun bénéfice !

Diapo: courtesy S. Ehrmann

Recommandations

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

XIV. Should Patients With VAP Due to Gram-Negative Bacilli Be Treated With a Combination of Inhaled and Systemic Antibiotics, or Systemic Antibiotics Alone?

Recommendation

1. For patients with VAP due to gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), we suggest both inhaled and systemic antibiotics, rather than systemic antibiotics alone *(weak recommendation, very low-quality evidence)*.

Kalil AC et al. Clin Infect Dis 2016

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

Conclusions

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.

Rello J et al. Clin Microbiol Infect 2017

Brief summary of French guidelines for the prevention, diagnosis and treatment of hospital-acquired pneumonia in ICU

R3.6 We suggest administering nebulised colimycine (sodium colistiméthate) and/or aminoglycosides in documented HAP due multidrug-resistant Gram-negative bacilli documented pneumonia established as sensitive to colimycin and/or aminoglycoside, when no other antibiotics can be used (based on the results of susceptibility testing) [136–152] (Grade 2+).

Leone M et al. Annals Intensive Care 2018

Pratiques (2017)

Nebulization of antimicrobial agents in mechanically ventilated adults in 2017: an international cross-sectional survey

- **Prescription ATB inhalés (n=261 ICU)**
  - **Jamais, 27%**
  - **Seulement sur documentation MDR/XDR, 64%**
  - **Prophylaxie, 8% (vs. 51% en 2014)**
- **Matériel nébulisation**
  - Pneumatique 50% / Ultra-sons 31% / **Tamis vibrant 14%**
  - **Changement filtre après chaque aérosol 18%**
- **ATB**
  - CMS 58%, colistine base 42%, amikacine 31%, tobramycine 25%

Alves J et al. Eur J Clin Microbiol Infect Dis 2018

Conclusions

Aerosol Therapy for Pneumonia in the Intensive Care Unit

Charles-Edouard Luyt, MD, PhD[a], Guillaume Hékimian, MD[a], Nicolas Bréchot, MD, PhD[a], Jean Chastre, MD[a,b,*]

les antibiotiques inhalés

Luyt CE et al. Clin Chest Med 2018 (décembre !)

Conclusions: les ATB inhalés

- Beau concept, mais **mise en œuvre très complexe**
  - Indications sélectionnées, équipes affutées
  - Matériel spécifique
  - Pas dénué de risques

- **Indications réfutées**
  - Prophylaxie
  - Substitution au traitement systémique

- **Indications valides, mais restreintes**
  - **Traitement adjuvant de PAVM XDR sans alternative satisfaisante**
  - Colimycine, amikacine, ou tobramycine

Remerciements +++ : Stephan Ehrmann, Tours