Antibiotiques inhalés pour le traitement des pneumonies à BGN résistants?

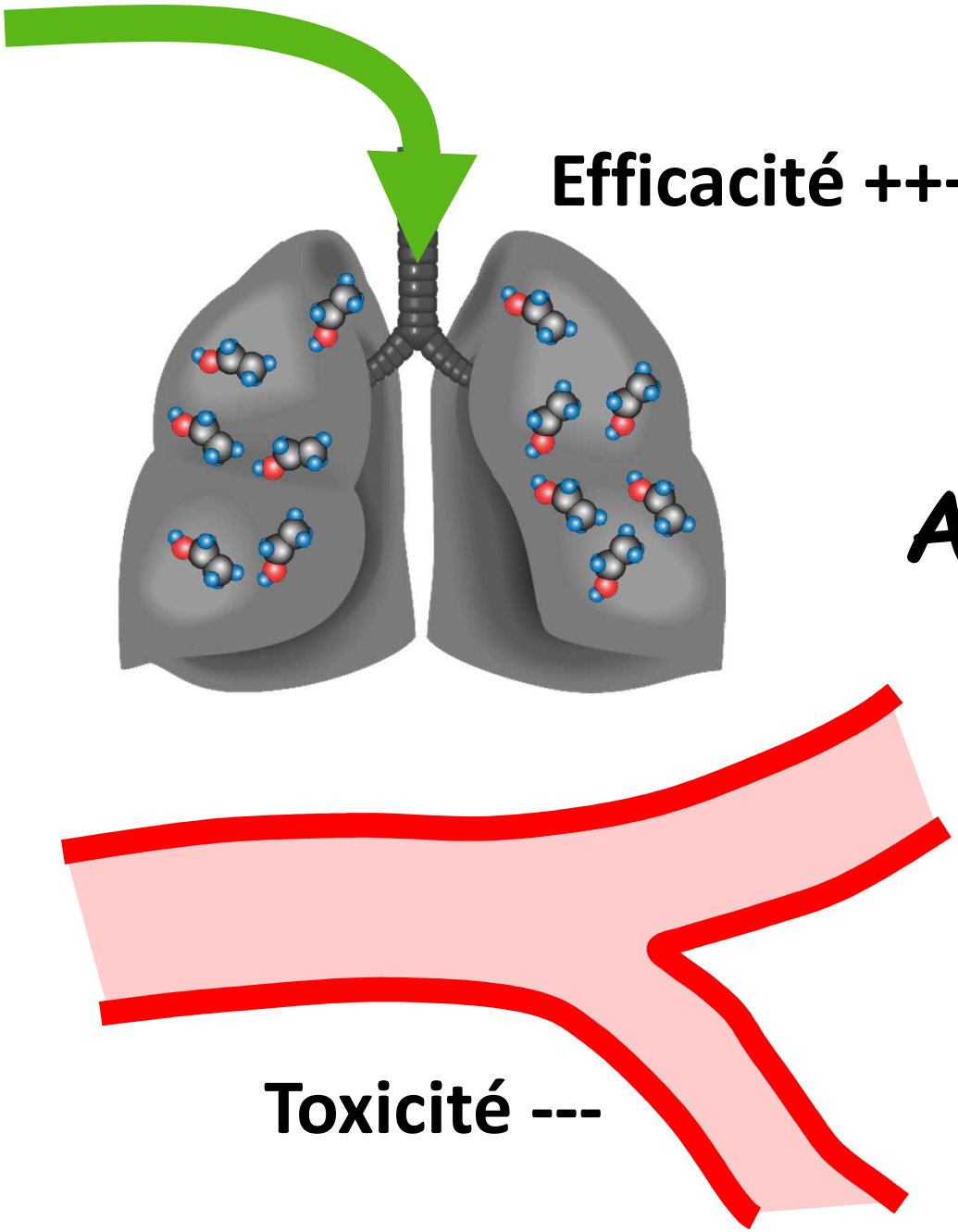
CONTRE

REANIMATION
MEDECINE INTENSIVE
TOURS

Stephan EHRMANN

Liens d’intérêt

- **Aerogen, Galway, Irlande**
- Baxter, Deerfield, Etats-Unis
- Fisher & Paykel, Auckland, Nouvelle Zélande
- **La Diffusion Technique Française, Saint-Etienne**
- **Penn-Century Inc., Wyndmoor, Etats-Unis**
- **Bayer Pharma AG, Berlin, Allemagne**
- Hamilton medical, Bonaduz, Suisse



Aérosolthérapie

Historique

Archives of Disease in Childhood, 1970, **45**, 605.

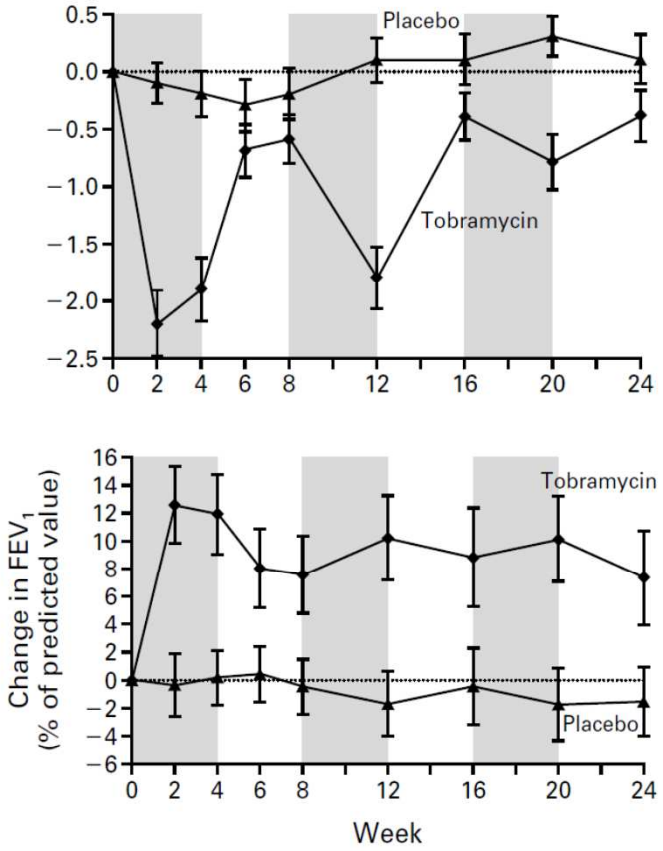
Aerosol Therapy in Cystic Fibrosis

THE LANCET, NOVEMBER 21, 1981

AEROSOL CARBENICILLIN AND GENTAMICIN TREATMENT OF PSEUDOMONAS AERUGINOSA INFECTION IN PATIENTS WITH CYSTIC FIBROSIS

MARGARET E. HODSON A. R. L. PENKETH
J. C. BATTEN

Cardiothoracic Institute and Brompton Hospital, Fulham Road, London SW3 6HP



BW Ramsey, N Engl J Med 1999

AMM : Tobramycine, Colistine, Aztreonam

Mauvais concept

Compliqué

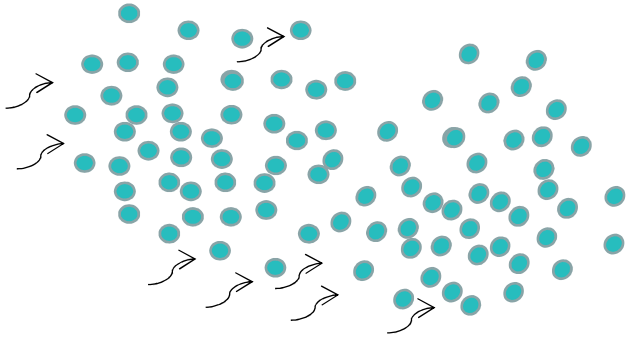
Aucune maitrise

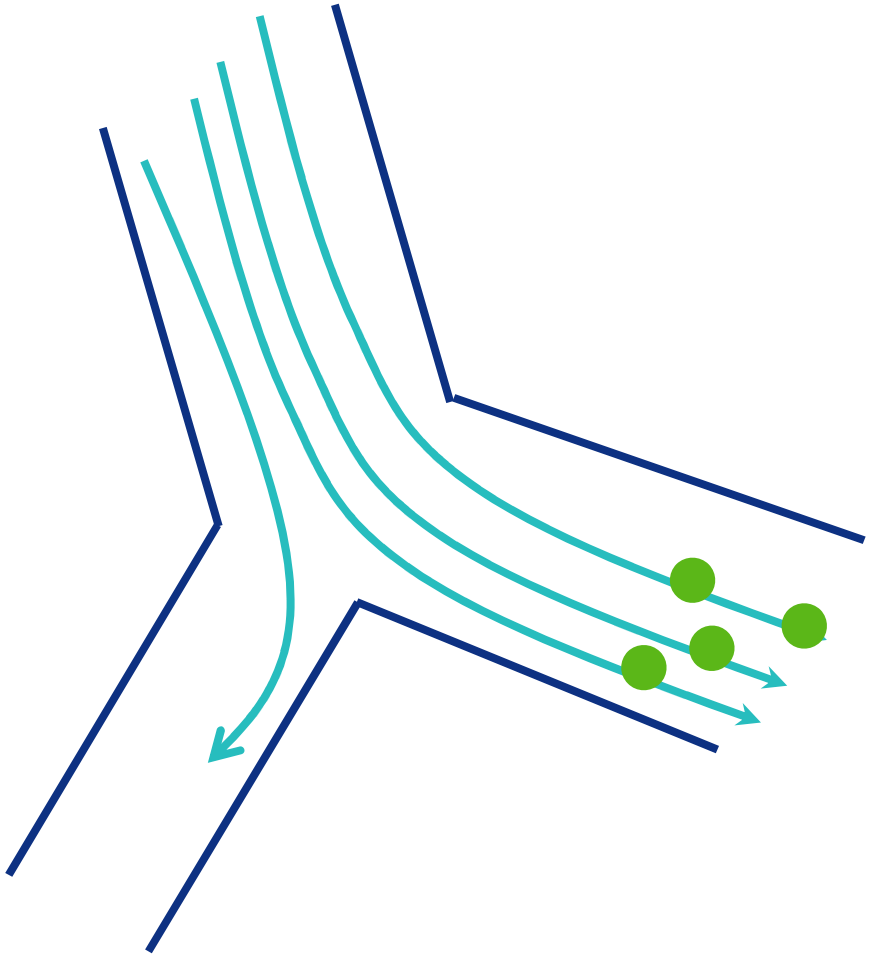
Effets secondaires graves

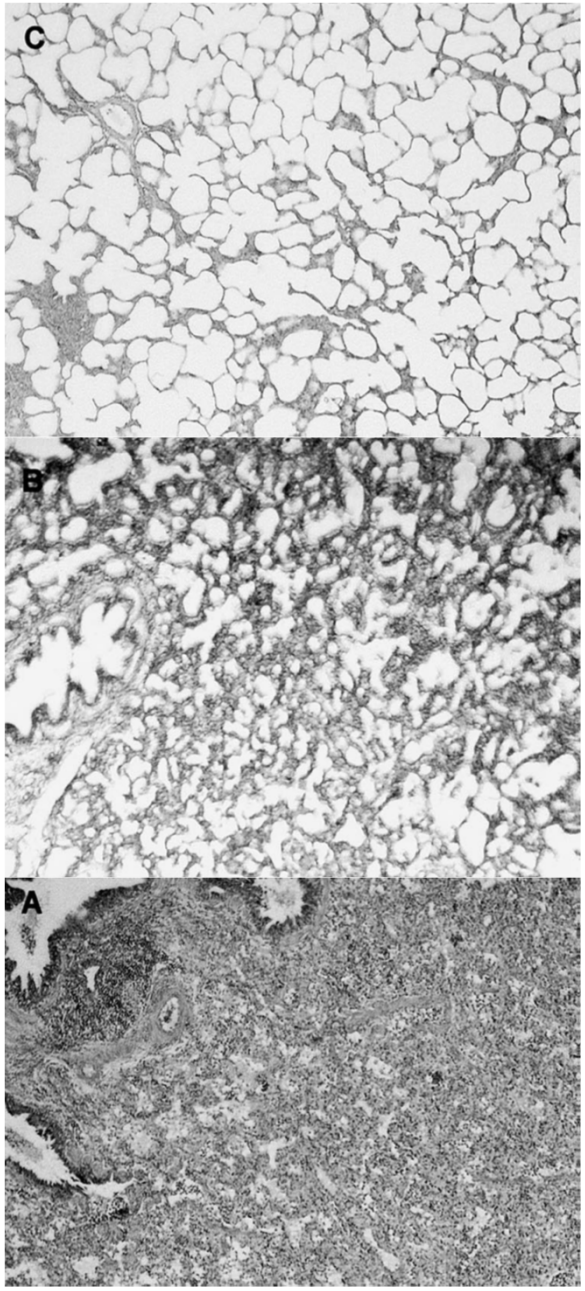
Toxique

Etudes cliniques négatives

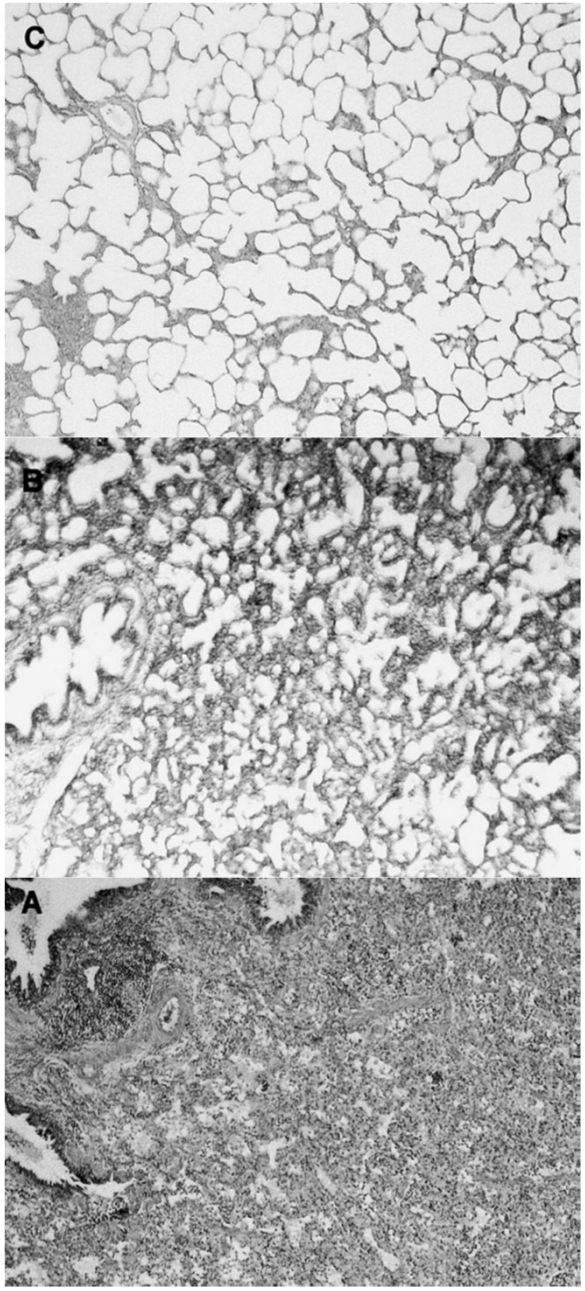
Aérosol

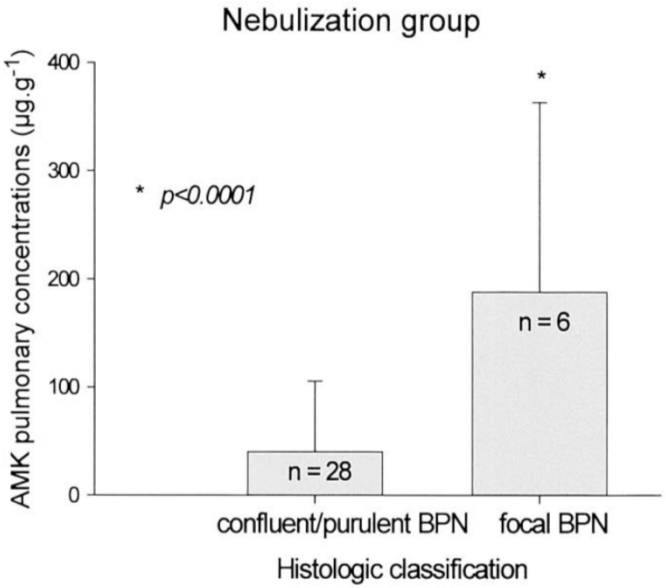




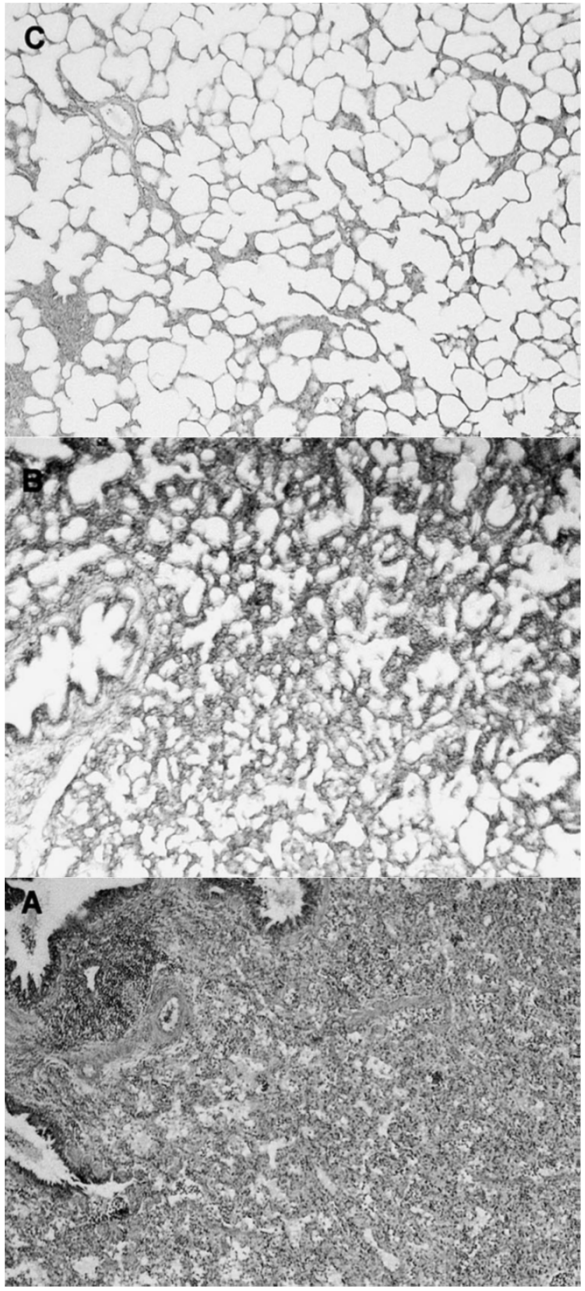


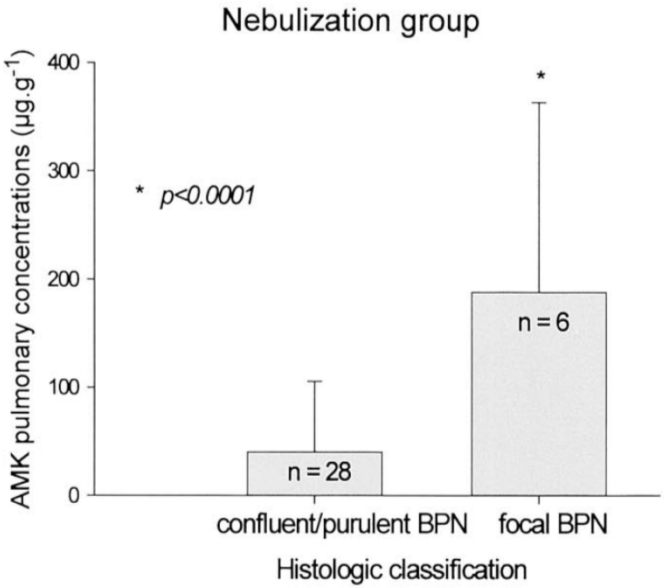
M Elman, Anesthesiology 2002

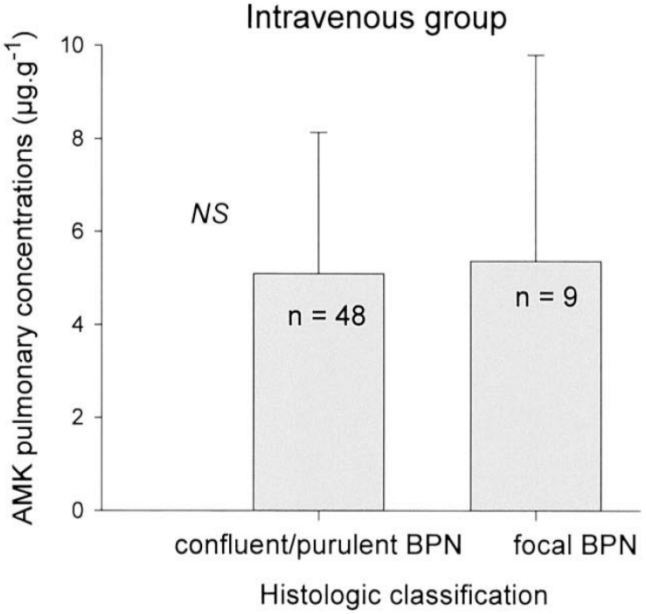




M Elman, Anesthesiology 2002







M Elman, Anesthesiology 2002

Mauvaise idée

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

Annals of Intensive Care

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]

Practical constraints to optimizing nebulized antibiotic delivery during mechanical ventilation

Medical orders

Physician _____ Date _____

Dosages	Ventilation before aerosol	Ventilation during aerosol	Sedation during aerosol
☐ **Ceftazidime** _____ mg every 3 h Diluted in _____ ml ☐ **Amikacin** _____ $mg.day^{-1}$ Diluted in _____ ml	☐ Mode _____ ☐ RR _____/min ☐ I/E ratio _____ ☐ Plateau _____% ☐ TV_____ml ☐ FiO_2 = _____ %	☐ VC ; TV= 8 $ml.kg^{-1}$ ☐ RR =12.min^{-1} ☐ I/E ratio = 50% ☐ Plateau 20% ☐ constant flow ☐ FiO_2 = _____ %	☐ propofol _____$mg.h^{-1}$ (if patient desynchronized with the ventilator)

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	☐	☐	☐	☐

Lu Q, Am J Respir Crit Care Med 2012

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	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	☐	☐	☐	☐
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Lu Q, Am J Respir Crit Care Med 2012

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	Stop propofol	☐	☐	☐	☐

Lu Q, Am J Respir Crit Care Med 2012

C’est compliqué

Sécrétions trachéales

Parameter	Day 1		Day 3	
	BAY41-6551 400 mg q12h	BAY41-6551 400 mg q24h	BAY41-6551 400 mg q12h	BAY41-6551 400 mg q24h
PK-evaluable PK population, *n*	14	20	14	20
T_{max} (h), median (range)	0.25 (0.3–8.0)	1.00 (0.3–4.1)	0.25 (0.3–4.1)	0.25 (0.3–2.1)
C_{max} (μg/mL), mean (CV %)	11,903 (99)	6,083 (58)	16,212 (85)	6,893 (95)
$AUC_{0–12h}$ (μg h/mL), mean (CV %)	24,034 (52)	20,101 (58)	39,484 (88)	17,332 (93)
$AUC_{0–24h}$ (μg h/mL), mean (CV %)*	41,991 (60)	25,284 (77)	61,908 (51)	25,216 (85)
PK-evaluable efficacy population, *n*	12	18	12	18
Patients with $C_{max} \geq 6{,}400$ μg/mL and $AUC_{0–24h}/256 \geq 100$, % (90% CI)*	50.0 (24.5–75.5)	16.7 (4.7–37.7)	Not reported	Not reported

MS Niederman, Intensive Care Med 2012

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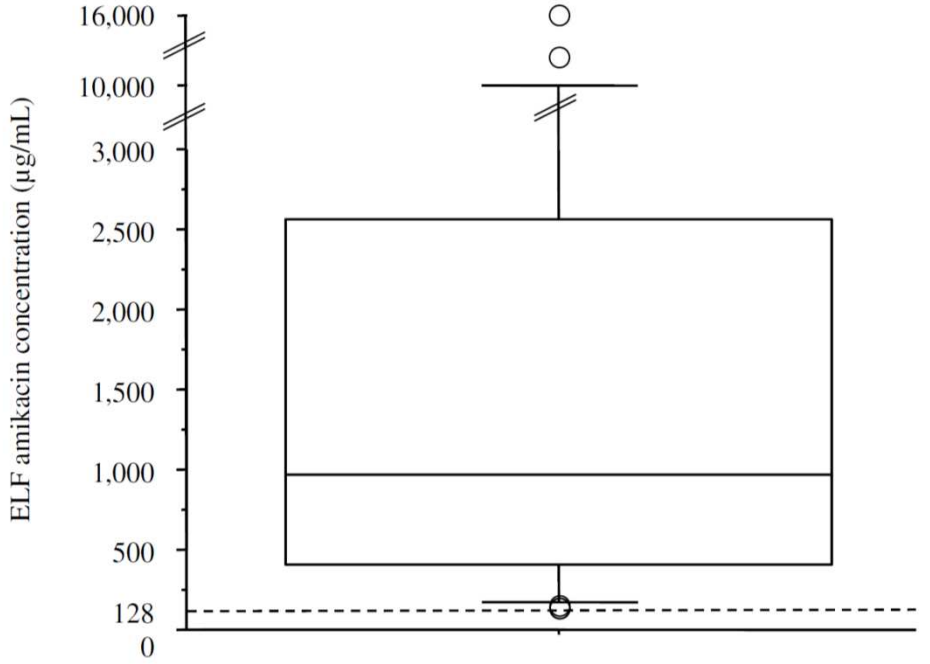
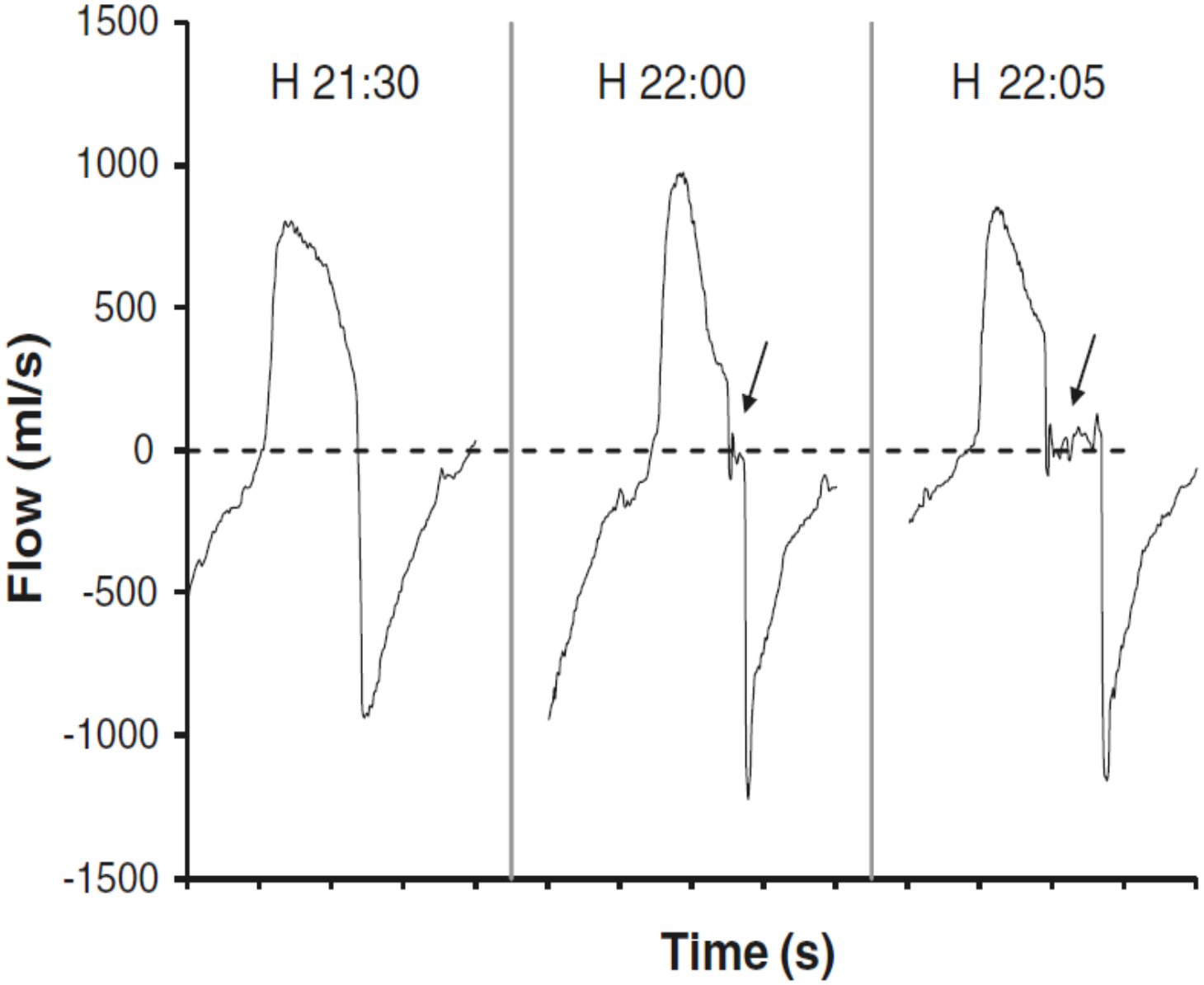
Epithelial lining fluid

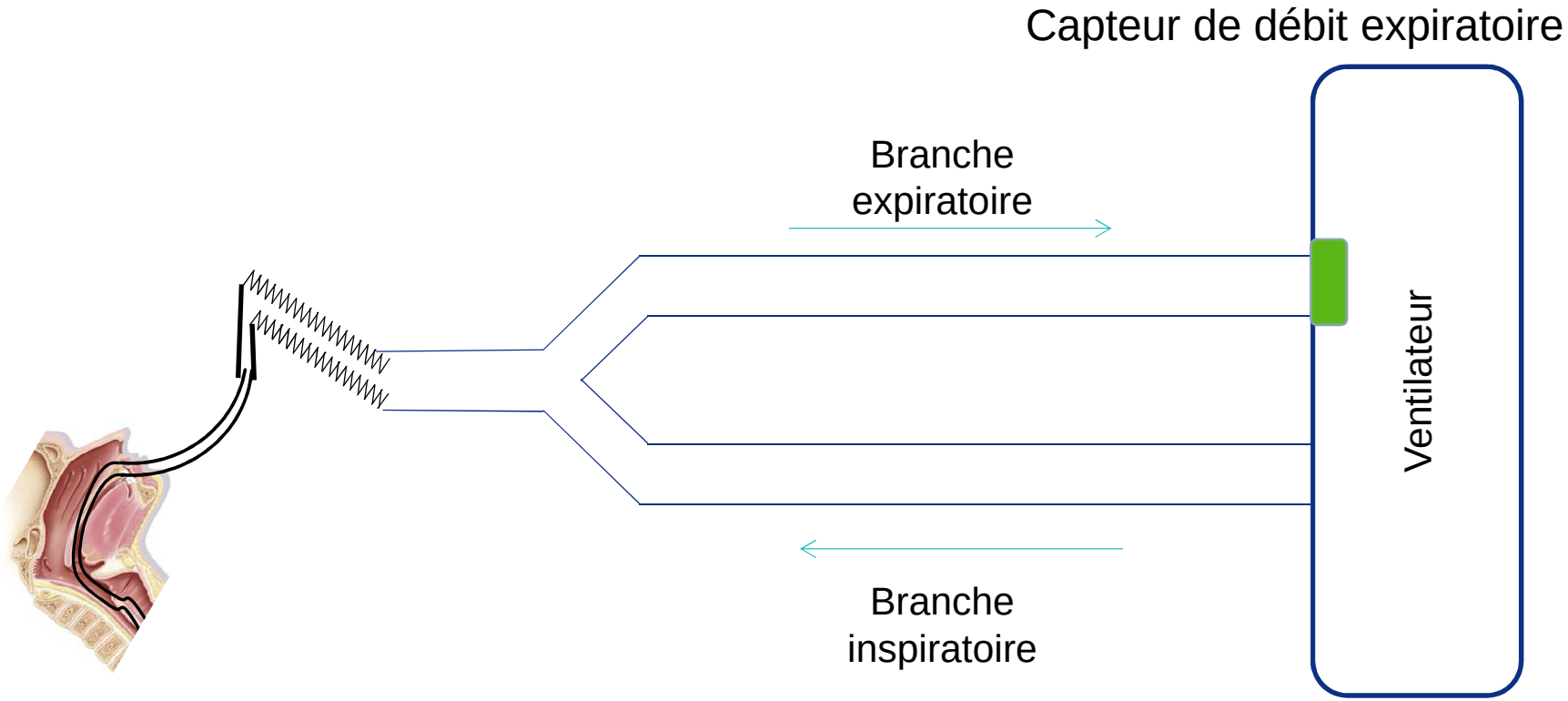


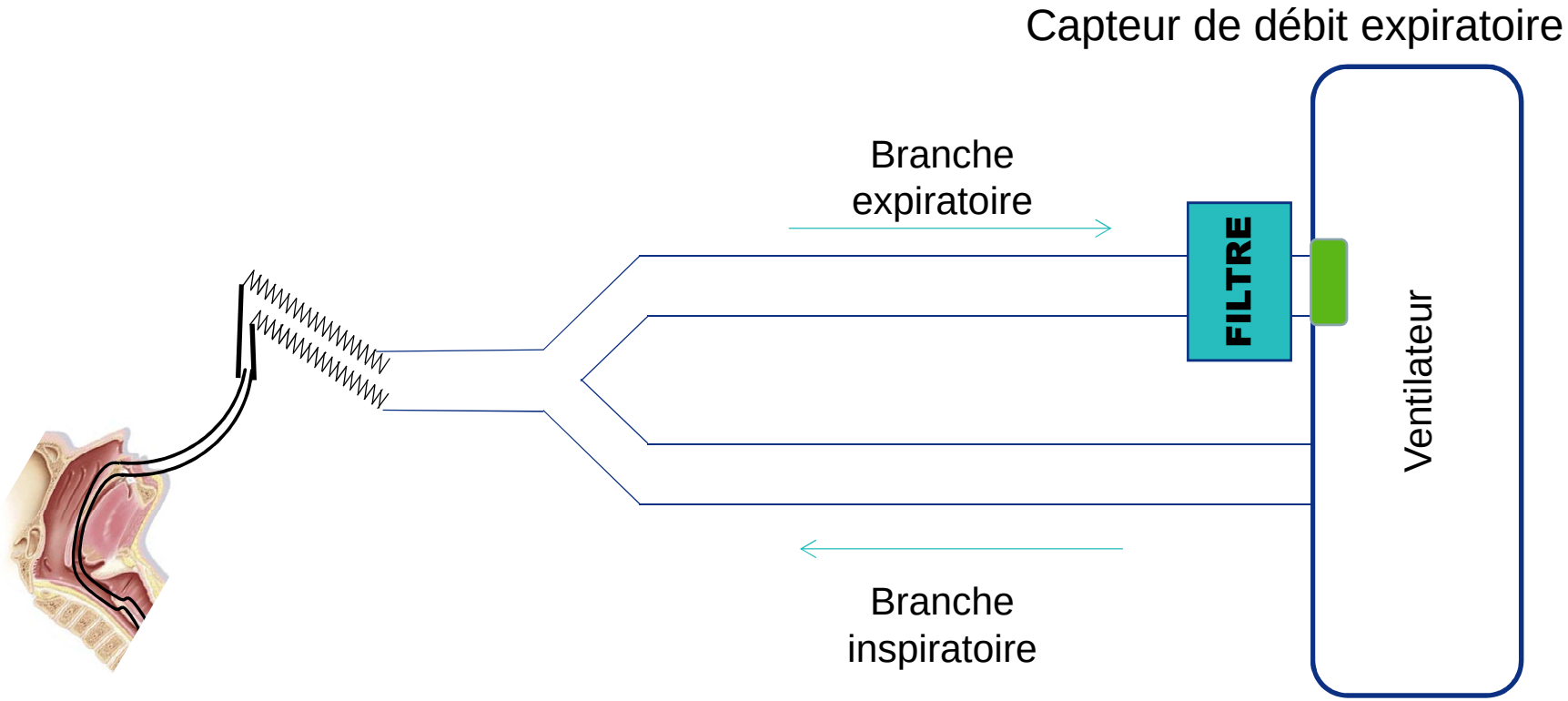
CE Luyt, Crit Care 2009

Une technique non maitrisée



F Mojoli, Intensive Care Med 2012


Capteur de débit expiratoire
Branche
expiratoire
Ventilateur
Branche
inspiratoire


Capteur de débit expiratoire
Branche
expiratoire
FILTRE
Ventilateur
Branche
inspiratoire

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

RATIONALE:
In experimental pneumonia, nebulization of antibiotics provides high lung tissue concentrations and rapid bacterial killing.
OBJECTIVES:
To assess the efficacy and safety of nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by Pseudomonas aeruginosa.
METHODS:
Forty patients with ventilator-associated pneumonia caused by Pseudomonas aeruginosa were included in a randomized comparative phase II trial. Twenty patients infected with susceptible or intermediate strains received nebulized ceftazidime (15 mg·kg(-1)·3 h(-1)) and amikacin (25 mg·kg(-1)·d(-1)). Seventeen patients infected with susceptible strains received intravenous ceftazidime (90 mg·kg(-1)·d(-1), continuous administration) and amikacin (15 mg·kg(-1)·d(-1)). In three patients infected with intermediate strains, amikacin was replaced by ciprofloxacin (400 mg·12 h(-1)).
MEASUREMENTS AND MAIN RESULTS:
After 8 days of antibiotic administration, aerosol and intravenous groups were similar in terms of successful treatment (70 vs. 55%), treatment failure (15 vs. 30%), and superinfection with other microorganisms (15 vs. 15%). Antibiotic-induced changes in lung aeration, determined by computed tomography, were not different between groups (increase in gas volume, 159 ± 460 vs. 251 ± 583 ml; decrease in tissue volume, -58 [-77, 25] vs. -89 [-139, 5] ml). Acquisition of per-treatment antibiotic resistance was observed exclusively in the intravenous group. In the aerosol group, four patients infected with intermediate strains were successfully treated. Nebulization induced an obstruction of the expiratory filter in three patients. The obstruction caused cardiac arrest in one patient, who fully recovered after brief cardiopulmonary resuscitation.
CONCLUSIONS:
Nebulization and intravenous infusion of ceftazidime and amikacin provide similar efficiency for treating ventilator-associated pneumonia caused by Pseudomonas aeruginosa. Nebulization is efficient against intermediate strains and may prevent per-treatment acquisition of antibiotic resistance.

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2,5% d'arrêt cardiaques

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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 $\geqslant 10^4$ 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

Q Lu, Am J Respir Crit Care Med 2011

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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

Q Lu, Am J Respir Crit Care Med 2011

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*

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TABLE 2. ANTIBIOTIC TREATMENT EFFICIENCY

+ 11 jours de ventilation (+61%)
(+ 6 jours de ventilation post randomisation +75%)
+ 9 jours en réanimation (+31%)
(+ 8 jours en réanimation post randomisation +50%)

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
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Medical orders

Physician _____ Date _____

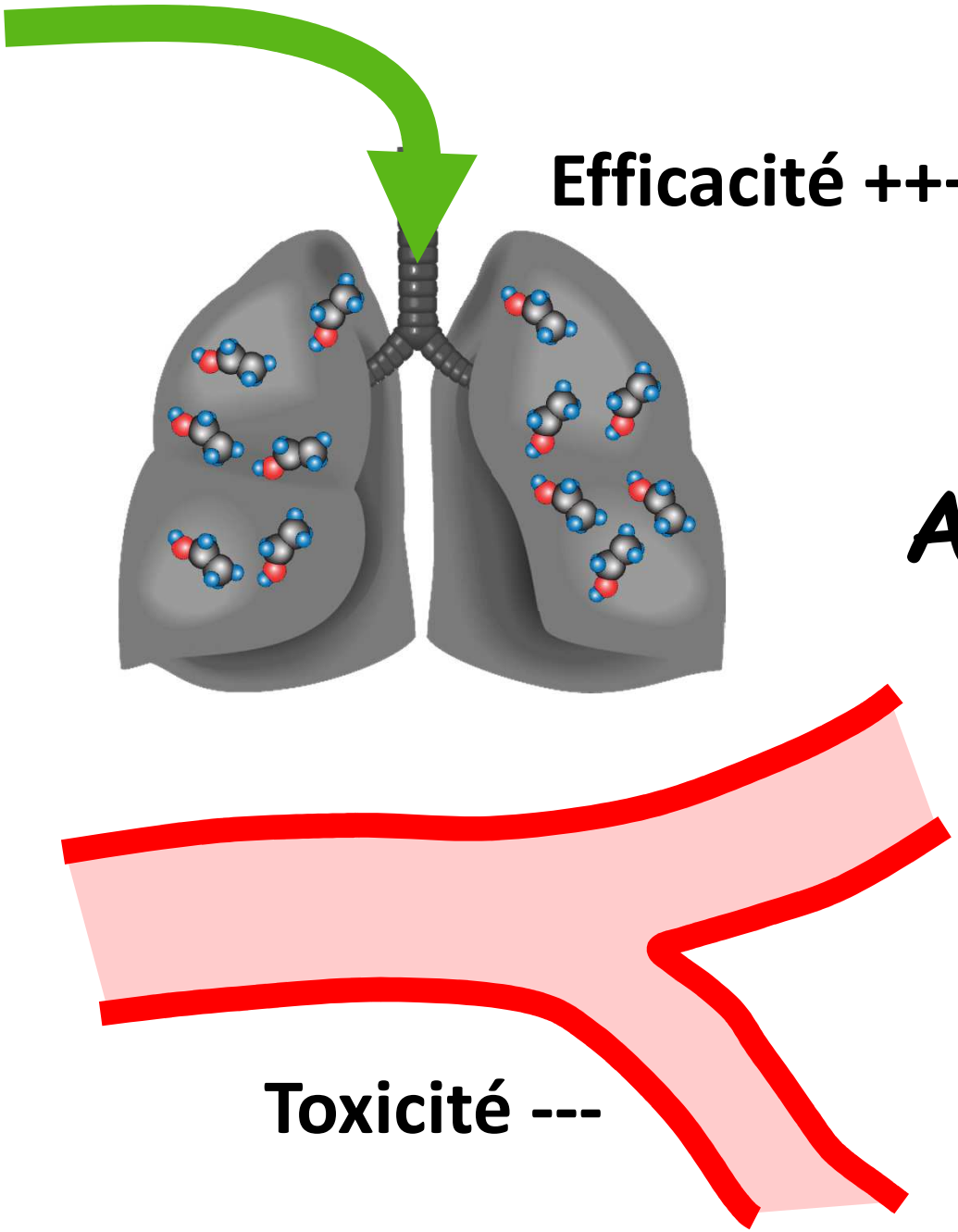
Dosages	Ventilation before aerosol	Ventilation during aerosol	Sedation during aerosol
☐ **Ceftazidime** _____ mg every 3 h Diluted in _____ ml ☐ **Amikacin** _____ $mg.day^{-1}$ Diluted in _____ ml	☐ Mode _____ ☐ RR _____/min ☐ I/E ratio _____ ☐ Plateau _____% ☐ TV_____ml ☐ FiO_2 = _____ %	☐ VC ; TV= 8 $ml.kg^{-1}$ ☐ RR =12.min^{-1} ☐ I/E ratio [illegible]0% ☐ Pl[illegible]au 20% ☐ constant flow ☐ FiO_2 = _____ %	☐ propofol _____$mg.h^{-1}$ (if patient desynchronized with the ventilator)

Checklist form

Nurse _____ Date _____

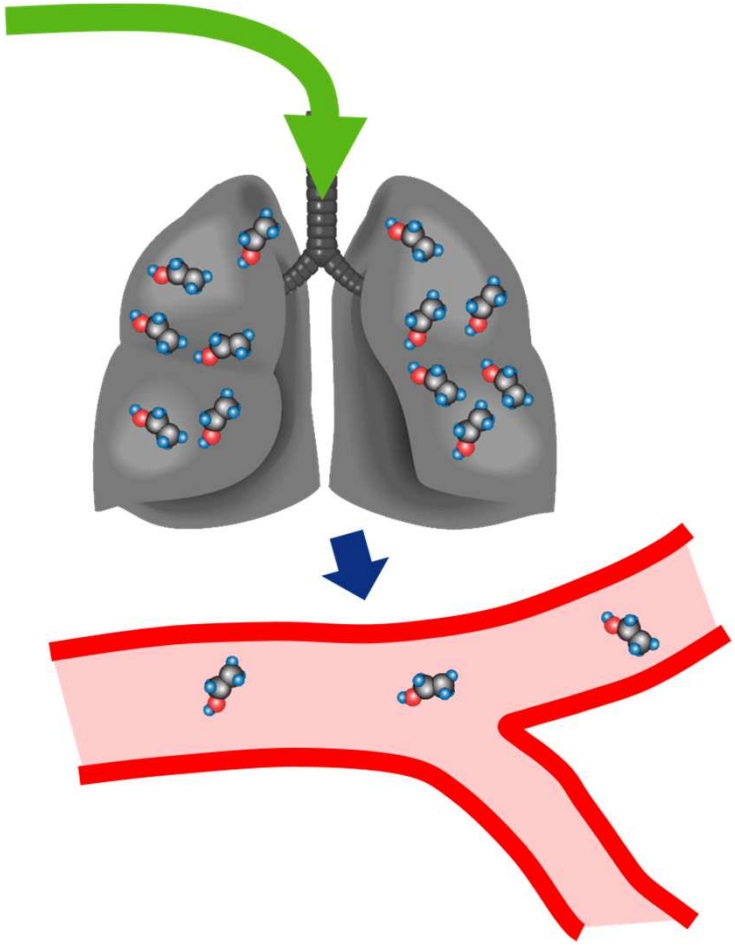
		__ h __ min ☐Cefta/AMK	__ h __ min ☐ Cefta/AMK	__ h __ min ☐Cefta/AMK	[illegible] h __ min ☐Cefta/AMK
Before aerosol	Removal of moisture exchanger	☐	☐	☐	☐
	Removal of connecting tube	☐	☐	☐	☐
	Nebulizer inserted 10 cm before Y piece	☐	☐	☐	☐
	Connection of expiratory filter positioned between expiratory 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	☐	☐	☐	☐

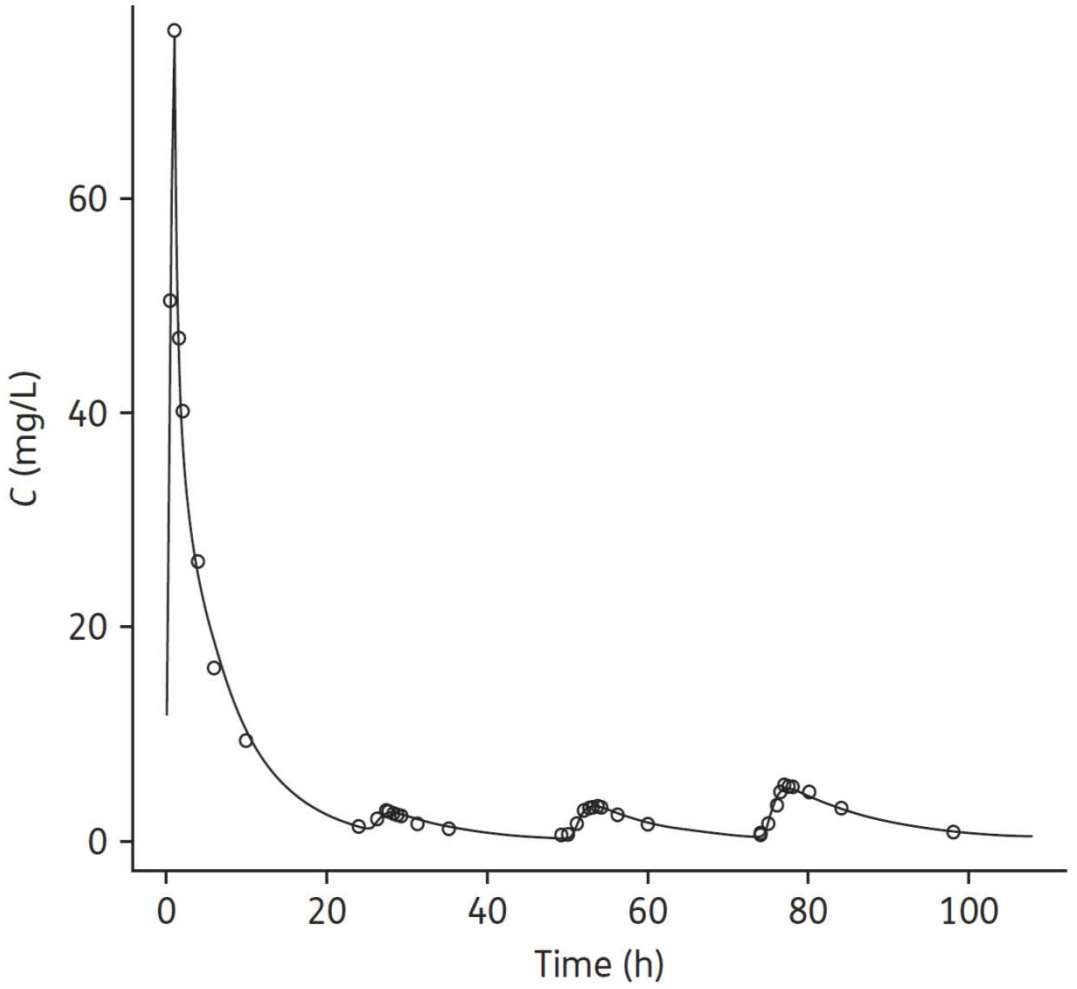
Lu Q, Am J Respir Crit Care Med 2012



Aérosolthérapie

Passage systémique





A Petitcollin, J Antimicrob Chemother 2016

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

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

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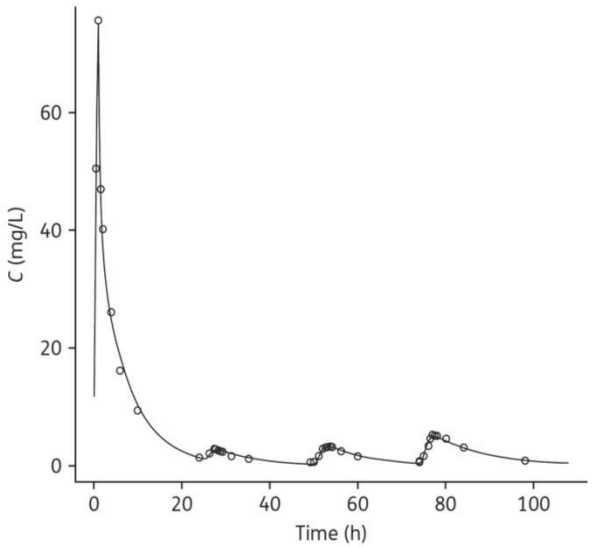

A Petitcollin, J Antimicrob Chemother 2016

Mauvais concept

Compliqué

Technique non maitrisée

Effets secondaires graves

Toxicité potentielle

CHEST

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

IASIS Trial

N=143

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 Koura, MD; Epaminondas Zakynthinos, MD; George Dimopoulos, MD; Antonio Torres, MD; Wayne Danker, MD; and A. Bruce Montgomery, MD

TABLE 2] Gram-Negative Bacteria Identified at Baseline in More Than One Patient

Organism	AFIS Group (n = 71)	Placebo Group (n = 71)	Carbapenem Resistant	Colistin Resistant
Acinetobacter baumannii	16	13	27 (93)	27 (93)
Pseudomonas aeruginosa	18	13	16 (52)	5[a] (16)
Enterobacteriaceae	36	26	4 (6)	20 (32)
Enterobacter aerogenes	2	2	...	...
Enterobacter cloacae	6	5	...	2 (18)
Escherichia coli	7	6	...	...
Klebsiella oxytoca	1	2	...	...
Klebsiella pneumonia	10	5	4 (27)	2 (13)
Proteus mirabilis	3	3	...	6 (100)
Serratia marcescens	7	3	...	10 (100)
Stenotrophomonas maltophilia	3	1	4 (100)	1 (25)

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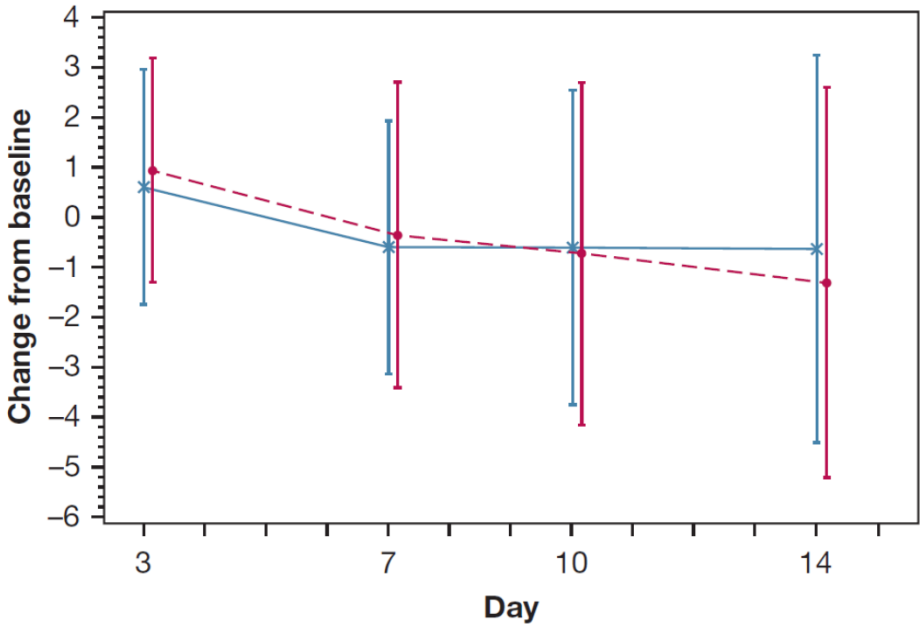
Evolution score CPIS



Critères secondaires NEGATIFS :

- Guérison à J14
- VFD
- Mortalité

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

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

ClinicalTrials.gov Identifier: NCT01799993

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

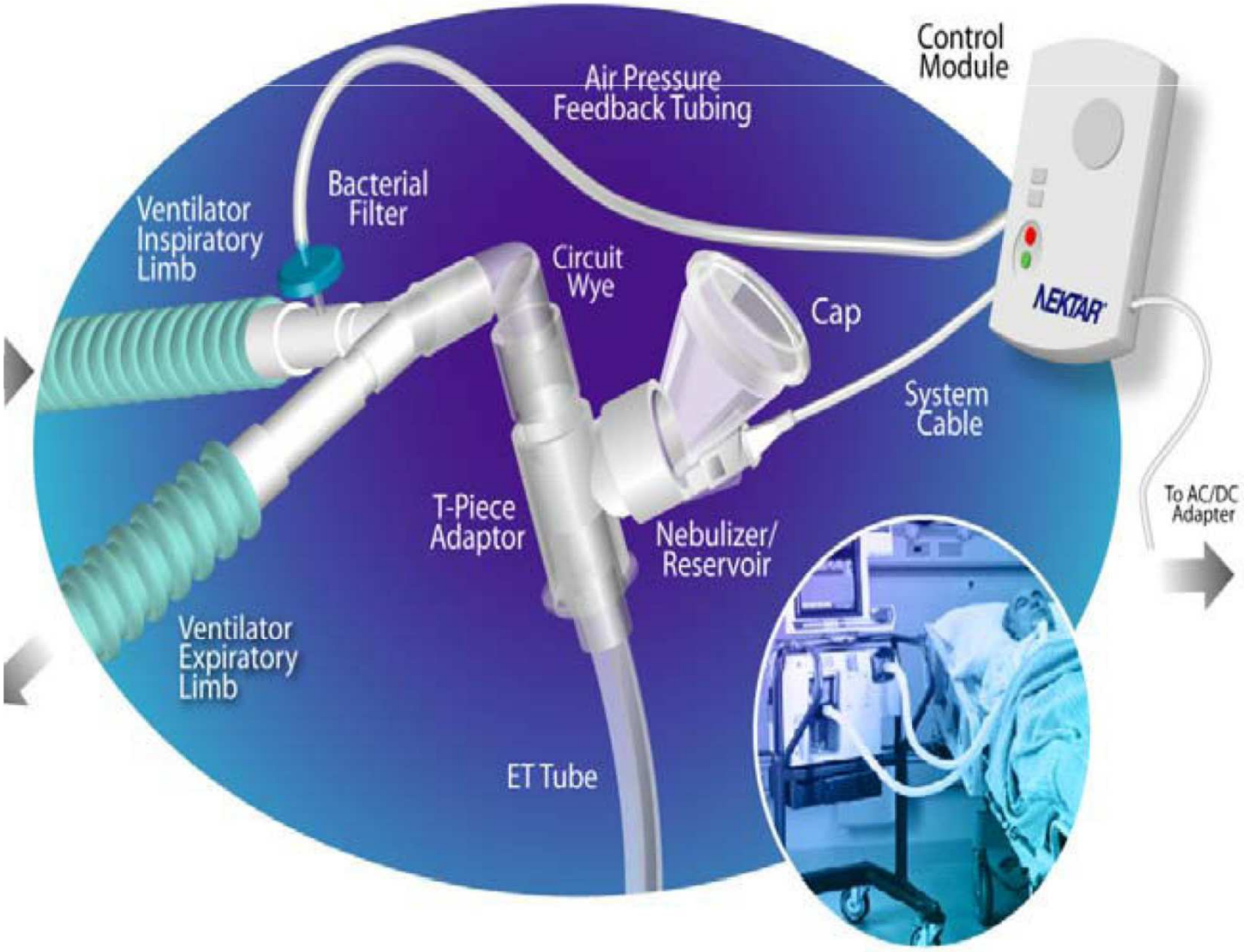
Sponsor:
Bayer

Collaborator:
Nektar Therapeutics

Information provided by (Responsible Party):
Bayer

Study 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

Tamis vibrant synchronisé :



CE Luyt, 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

Mauvais concept

Compliqué

Technique non maitrisée

Effets secondaires graves

Toxicité potentielle

Etudes cliniques négatives


BAYER
PRIMAIR

BAYER + MONSANTO = A TOXIC MIX

NEONICOTINOIDS
causes mass death
of pollinators

GLYPHOSATE
kills biodiversity and
harms human health

#BAYSANTO

CONTRE

REANIMATION
MEDECINE INTENSIVE
TOURS

Merci pour votre attention,

stephanEHRMANN@gmail.com