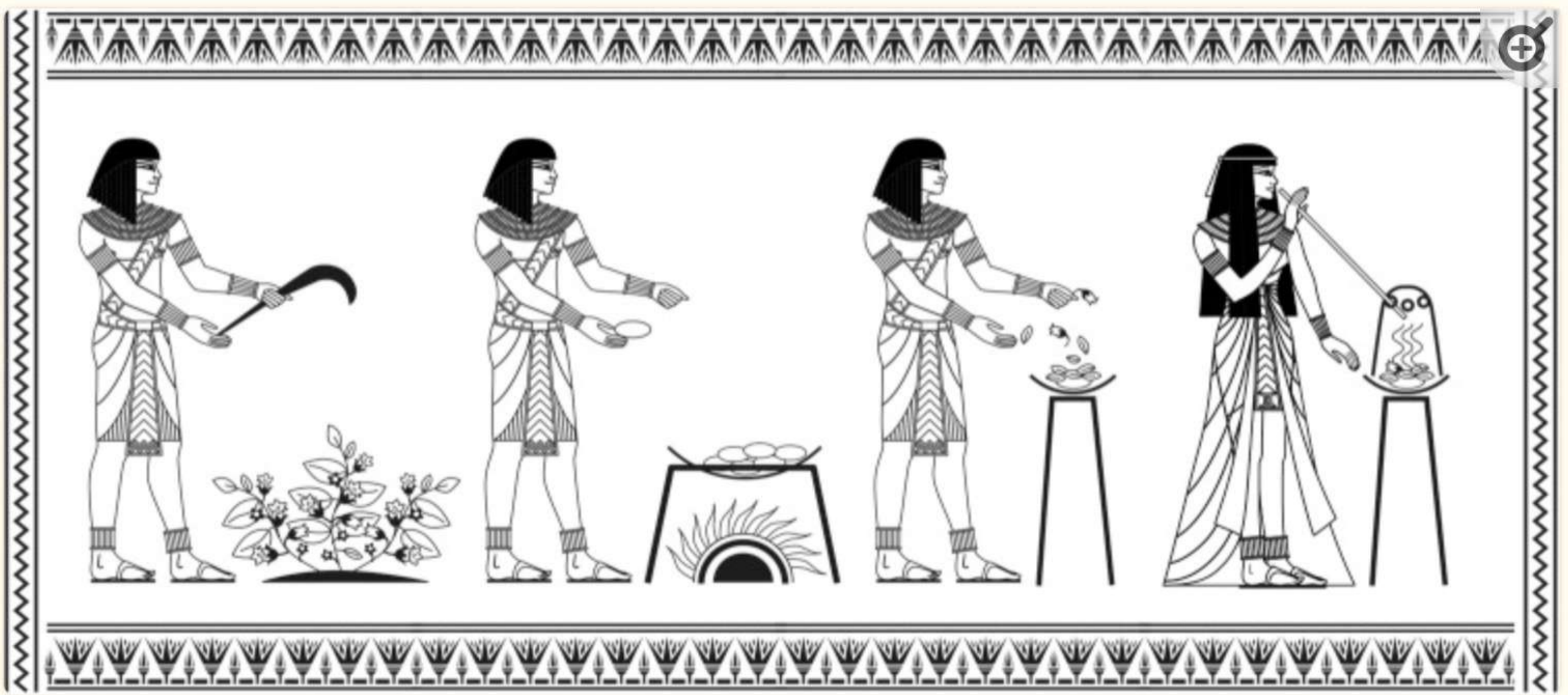
ANTIBIOTHÉRAPIE INHALÉE EN REANIMATION

AEROSOLS D'AMINOSIDE ET DE COLIMYCINE

VAN ASSCHE Cédric

DESAR 7e Semestre

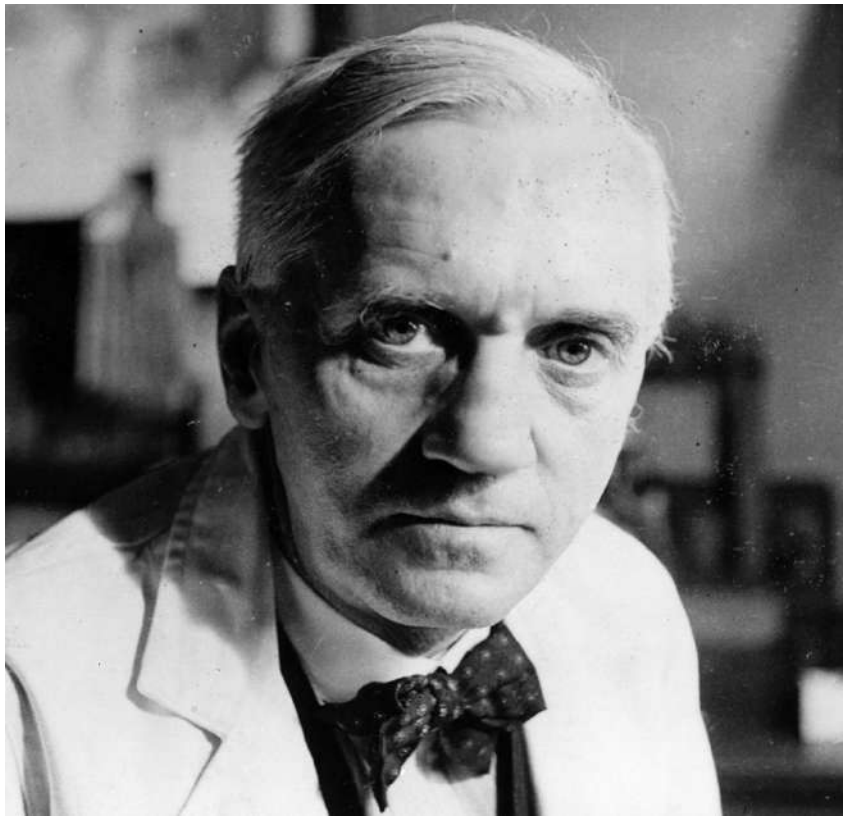
HISTOIRE



Stein, et al. *Journal of aerosol medicine and pulmonary drug delivery* (2017)

Histoire

- 1928: Pénicilline
- 1930s : Sulfamides
- Début 1940: Production de masse Pénicilline
- 1944: Streptomycine



Aug. 5, 1943

INHALATIONAL THERAPY IN THE TREATMENT OF SERIOUS RESPIRATORY DISEASE*

MAURICE S. SEGAL, M.D.†

BOSTON

Segal, M S. “Inhalation therapy in treatment of serious respiratory disease..” *NEJM* (1943)

Graeser, J B et al.. “Inhalation of Adrenalin for the Relief of Asthma.” *California and western medicine* (1935)

JULY 14, 1944

AEROSOLIZATION OF PENICILLIN SOLUTIONS[1]

VERNON BRYSON
BIOLOGICAL LABORATORY,
COLD SPRING HARBOR, N. Y.

EVA SANSOME
CARNEGIE INSTITUTION OF WASHINGTON,
COLD SPRING HARBOR

SIDNEY LASKIN
BIOLOGICAL LABORATORY,
COLD SPRING HARBOR

Bryson, V et al. "Aerosolization of penicillin solutions." *Science (*1944)

The New England
Journal of Medicine

Copyright, 1945, by the Massachusetts Medical Society

Volume 233 DECEMBER 20, 1945 Number 25

PENICILLIN AEROSOLIZATION IN THE TREATMENT OF SERIOUS RESPIRATORY INFECTIONS*

A Preliminary Report

MAURICE S. SEGAL, M.D.,† AND CLAIRE MACINTYRE RYDER, M.D.‡

BOSTON

Segal, M S, and C M Ryder. NEJM (1945)

Jan. 23, 1947

THE NEW ENGLAND JOURNAL OF MEDICINE

PENICILLIN INHALATION THERAPY*

MAURICE S. SEGAL, M.D.,† AND CLAIRE MACINTYRE RYDER, M.D.‡

BOSTON

SEGAL, et al "Penicillin inhalation therapy." *NEJM (*1947)

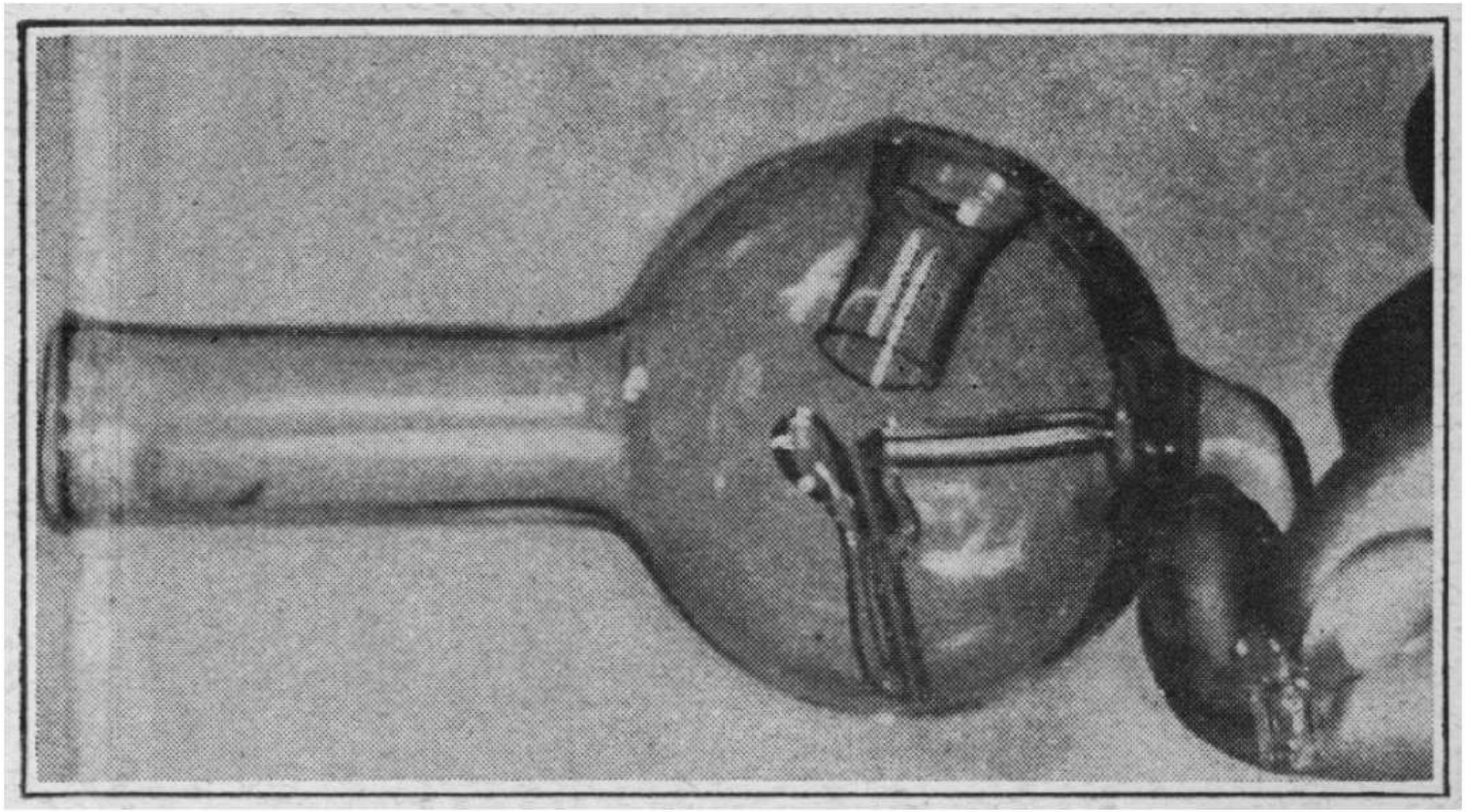
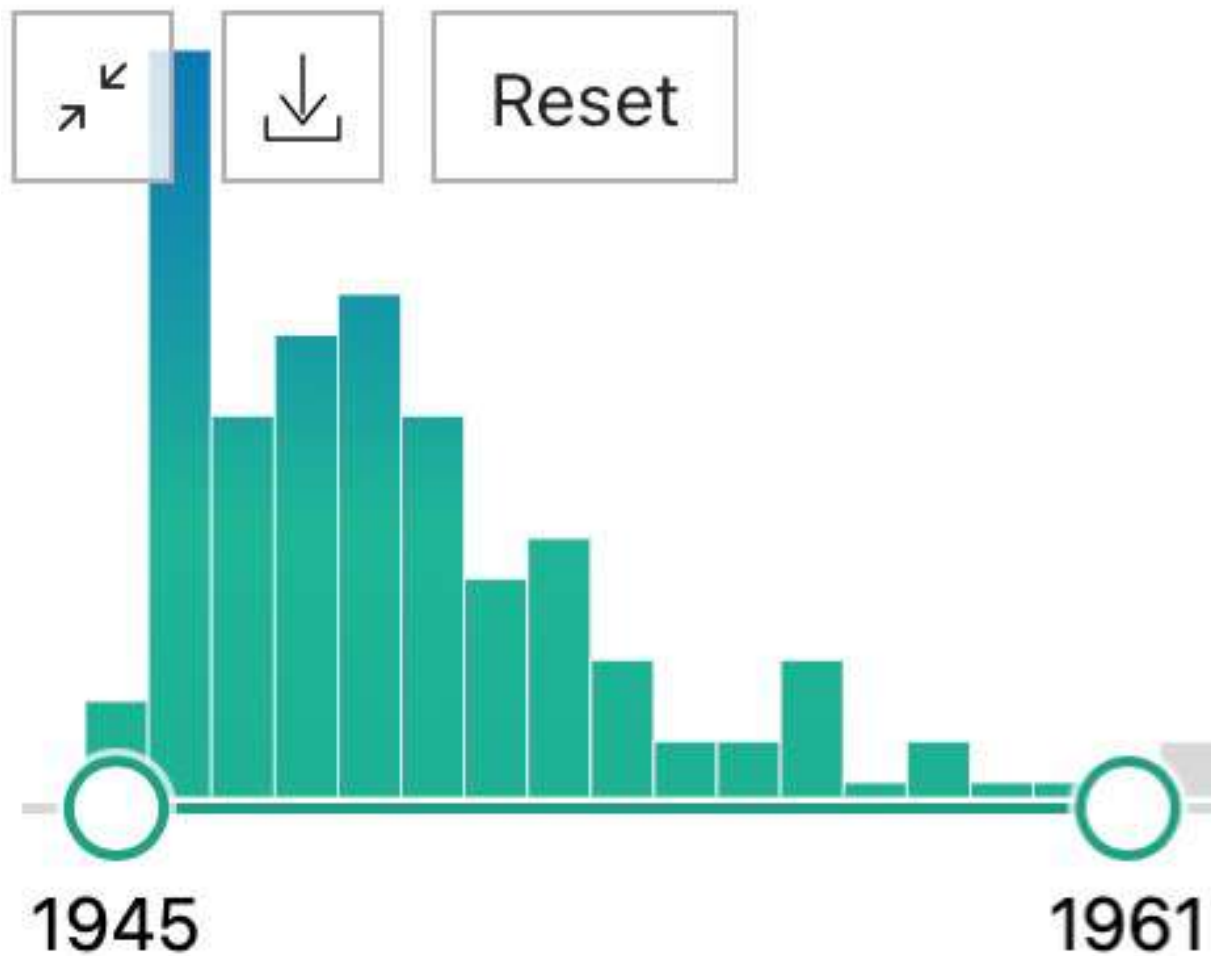


FIGURE 1. *Conventional Vaponefrin Nebulizer.*

This is capable of producing sprays with a particulate size of less than one micron.

SEGAL, et al “Penicillin inhalation therapy.” *NEJM (*1947)


Reset
1945
1961

The Diagnosis and Management of Acute Infectious Pneumonia

GEORGE W. MORROW, JR., M.D.

HOWARD A. ANDERSEN, M.D.

JOSEPH E. GERACI, M.D.

Morrow, G W Jr et al. *The Medical clinics of North America* vol. 48 (1964):

In pneumococcal and streptococcal infections, penicillin G remains the agent of choice. Erythromycin may be substituted if the patient is allergic to penicillin.

In staphylococcal pneumonia, if the organism is sensitive to penicillin G, then aqueous crystalline penicillin G is the agent of choice. Infections caused by staphylococci resistant to penicillin G are treated with one of the semisynthetic penicillins. Parenteral therapy with methicillin (Staphcillin) is best initially; sodium oxacillin (Prostaphlin) is reserved for oral administration after the infection has been brought under control. Since penicillin G and the semisynthetic penicillins are cross-allergenic, the latter agents cannot be used in patients who previously have had a serious untoward reaction to penicillin G. In patients with mild to moderate infections who are allergic to penicillin G, erythromycin or novobiocin may be substituted; but in the moderate to severe infections and those caused by strains resistant to penicillin G, vancomycin and kanamycin are the agents of second and third choice.

In infections due to H. influenzae, K. pneumoniae, or brucellar organisms, combined tetracycline-streptomycin therapy is effective. Streptomycin alone suffices in infections due to Pasteurella tularensis, as this species remains uniformly sensitive to it. Chloramphenicol continues as the drug of choice for infections due to Salmonella typhosa. Tetracycline is used in rickettsial infections such as Rocky Mountain spotted fever and Q fever, and also in psittacosis and ornithosis.

Morrow, G W Jr et al. *The Medical clinics of North America* vol. 48 (1964):

Un Changement de Paradigme

Landecker, Hannah. “Antibiotic Resistance and the Biology of History.” *Body & society* vol. 22,4 (2016)

Antibiotiques inhalés

Quels rôle dans la gestion des infections pulmonaires?

Technique de nébulisation

Aerosolized Antibiotics for Ventilator-associated Pneumonia

Lessons from Experimental Studies

Use ultrasonic or vibrating plate nebulizer, producing aerosols whose particles have a mass median aerodynamic diameter < 5 µm.

Remove heat and moisture exchanger and conventional humidifier and stop humidification during the period of nebulization.

Place the nebulizer on the inspiratory limb, 20 cm from the Y p

Determine in vitro the extrapulmonary deposition in the ventilator circuits using ventilator settings applied during the nebulizati period:

The amount of antibiotic deposited into inspiratory and expiratory circuits should be measured after lavage of each part of the circuit with a known volume of water.

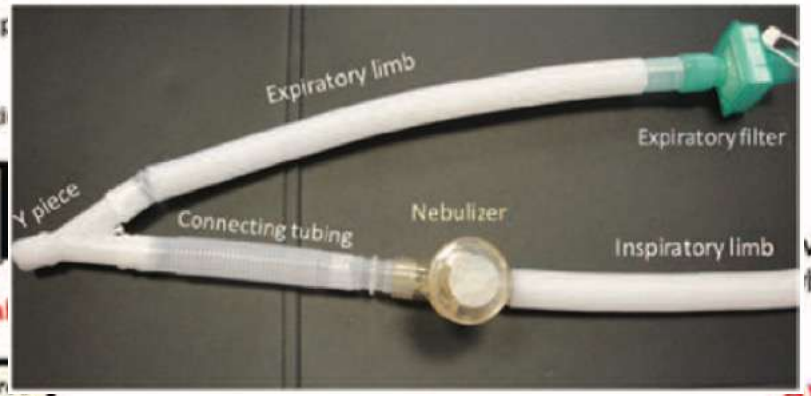
Determine the daily dose to be placed in the nebulizer cham

If the aminoglycoside is administered exclusively by nebulization, the dose should be calculated as the intravenous dose x 1/extrapulmonary deposition (%). If the aminoglycoside is concomitantly intravenously administered, then the determination of the appropriate dosage is difficult. Through plasma concentrations should be daily monitored in order to avoid systemic accumulation.

If colistin is administer exclusively by nebulization, the dose should range between 6 and 15 millions International Units / day. If it is also intravenously administered, then the determination of the appropriate dosage is difficult. Through plasma concentrations should be daily monitored in order to avoid systemic accumulation.

Determine the interval between each nebulization:

For aminoglycosides, a single daily nebulization.
For colistin, 3 daily nebulizations (every 8 h).



Use a controlled mode of mechanical ventilation with the following ventilator settings:

- *Constant inspiratory flow*
- *Tidal volume of 7- 9 ml/kg*
- *Respiratory frequency 12 bpm*
- *Inspiratory to Expiratory ratio 1/1*
- *Inspiratory plateau pressure 20 %*
- *Remove any humidification system*
- *Optimize alveolar recruitment*

void assisted modes of mechanical ventilation here the patient triggers flow during spontaneous inspiratory efforts

Avoid discoordination of the patient with the ventilator

If necessary, provide sedation with a continuous infusion of propofol during the nebulization period

Rouby, Jean-Jacques et al. *Anesthesiology* (2012)

Hypothèses

+

- Meilleure action locale?
- Moins de résistances?
- Moins de toxicité?

-

- Moins bonne action locale?
- Plus de résistances?

Aminosides

Caractéristiques

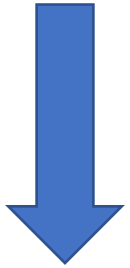
- Bactéricidie très rapide, très intense.
- Concentration dépendant.
- Associations synergiques
- Elimination rénale
- Toxicité rènale et cochléovestibulaire
- Vd = Liquides extracellulaires

Mécanisme d’action

Transport intracellulaire par la Chaine respiratoire

Sensibilité

Ensemble des
bactérie aérobies



Résistances Naturelle

Anaérobies strict
Streptocoques et Entérocoques

Fixation Ribosome

Résistances acquise

Inactivation enzymatique
Cible
Perméabilité cellulaire

Effet post antibiotique marqué.

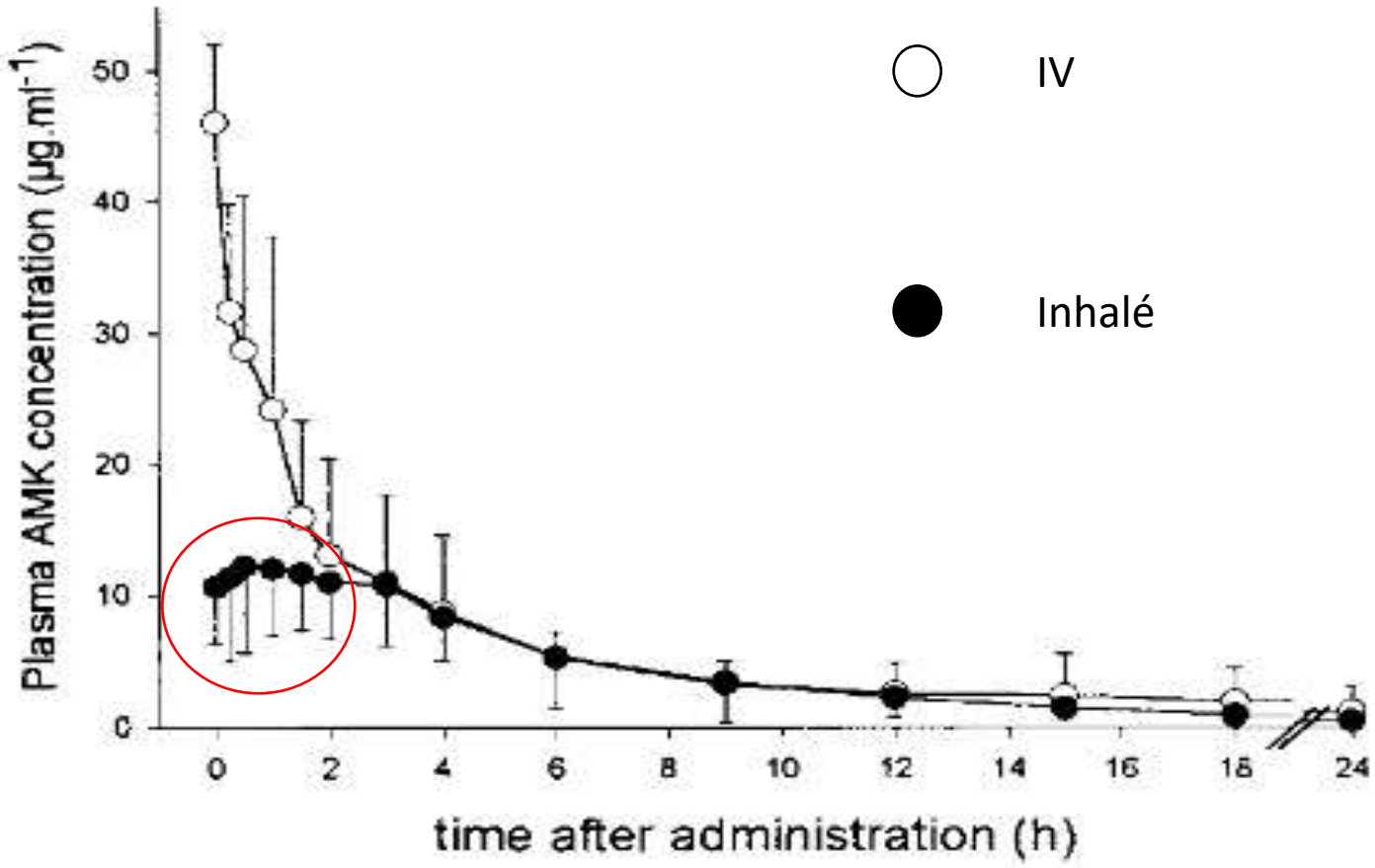
Diffusion pulmonaire?

Tableau III. Diffusion pulmonaire des aminosides et des fluoroquinolones.

	Réf.	*Posologie*	*Valeur en µg·mL^{-1} ou µg·g^{-1} de tissu*					
			Sérum	*Muqueuse bronchique*	*Biopsies pulmonaires*	*Film alvéolaire*	*Macrophages alvéolaires*	*Liquide pleural*
Gentamicine	52	1,5 mg·kg^{-1} IV	5,1					2,9 (57)**
	2	5 mg·kg^{-1} IV DM	5		6 (120)			0,6 (12)
Nétilmicine	52	2 mg·kg^{-1} IV	5,4					3,7 (69)*
Tobramycine	2	1,7 mg·kg^{-1}	6		6–9 (100–150)			3 (50)
	53					2,33–0,77 (30–153)		
	54	300 mg IM	5,3–5,5			3 (55)	3,3 (61)	
Amikacine	23	500 mg IV	11–20		6-9 (45–54)			
	55	500 mg IV	20,7		8,3 (40)			
	56	7,5 mg·kg^{-1} IV DM	17		14,9 (88)**			
					16,2 (95)*			

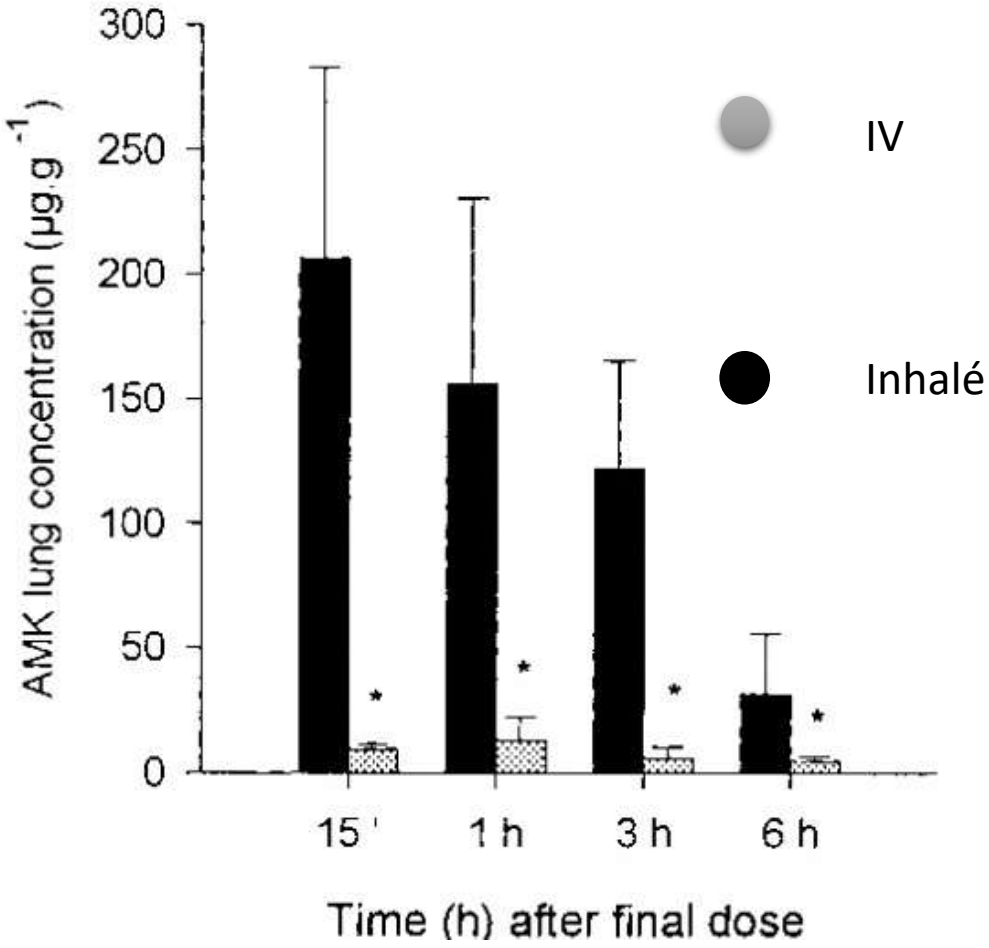
Boselli, E, and B Allaouchiche. *Annales francaises d'anesthesie et de reanimation* ol. 20,7 (2001)

Passage systémique?



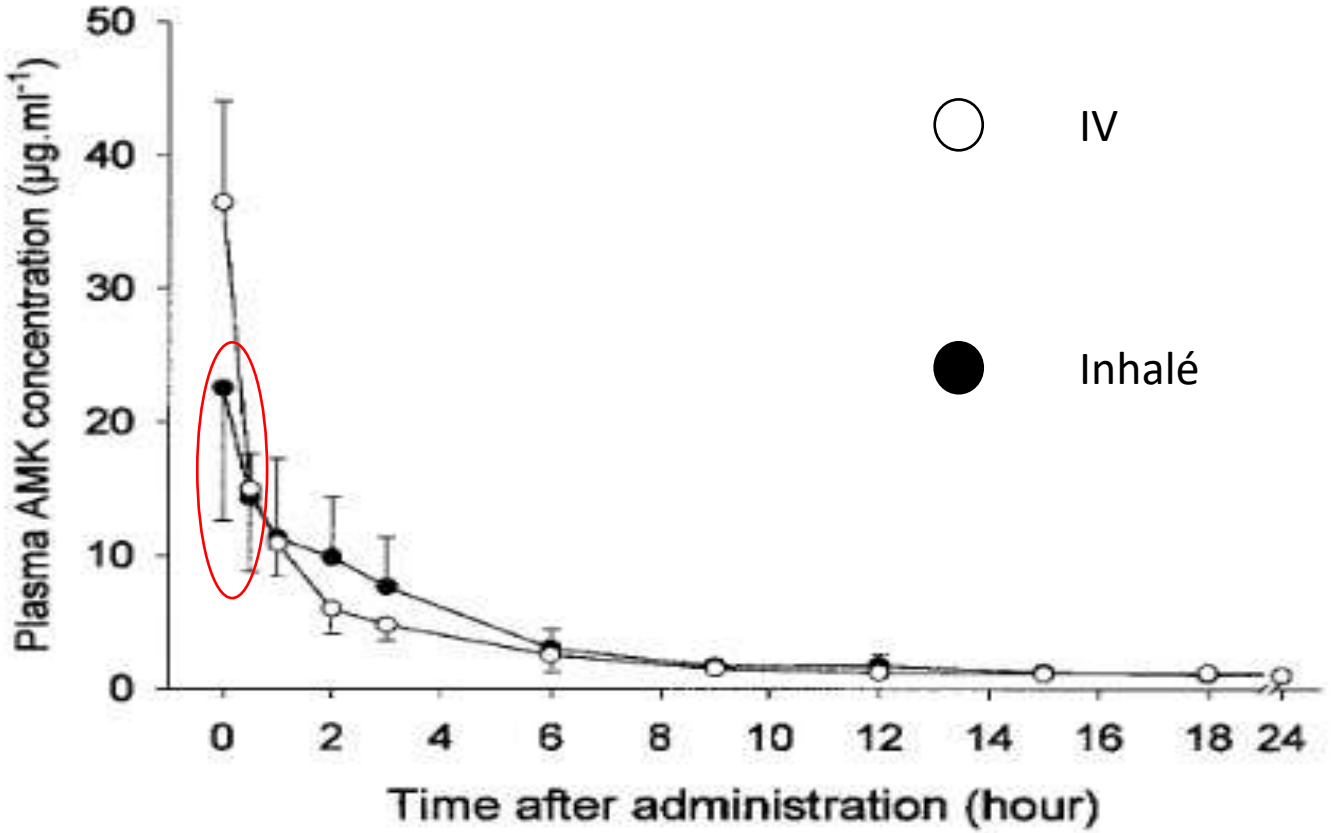
Goldstein, Ivan et al. “Lung tissue concentrations of nebulized amikacin during mechanical ventilation in piglets with healthy lungs.” AJRCCM (2002)

Concentrations locales?

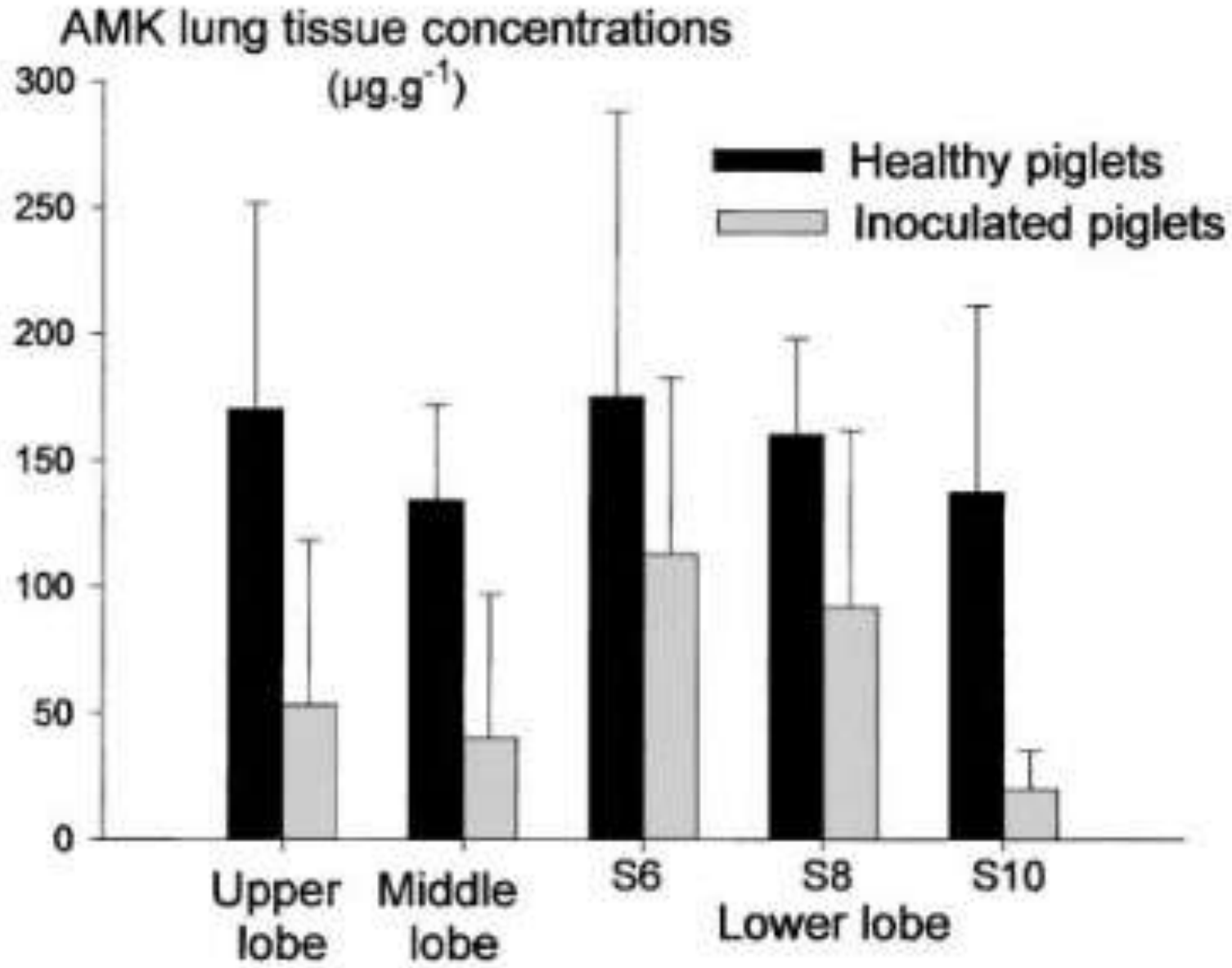


Goldstein, Ivan et al. “Lung tissue concentrations of nebulized amikacin during mechanical ventilation in piglets with healthy lungs.” AJRCCM (2002)

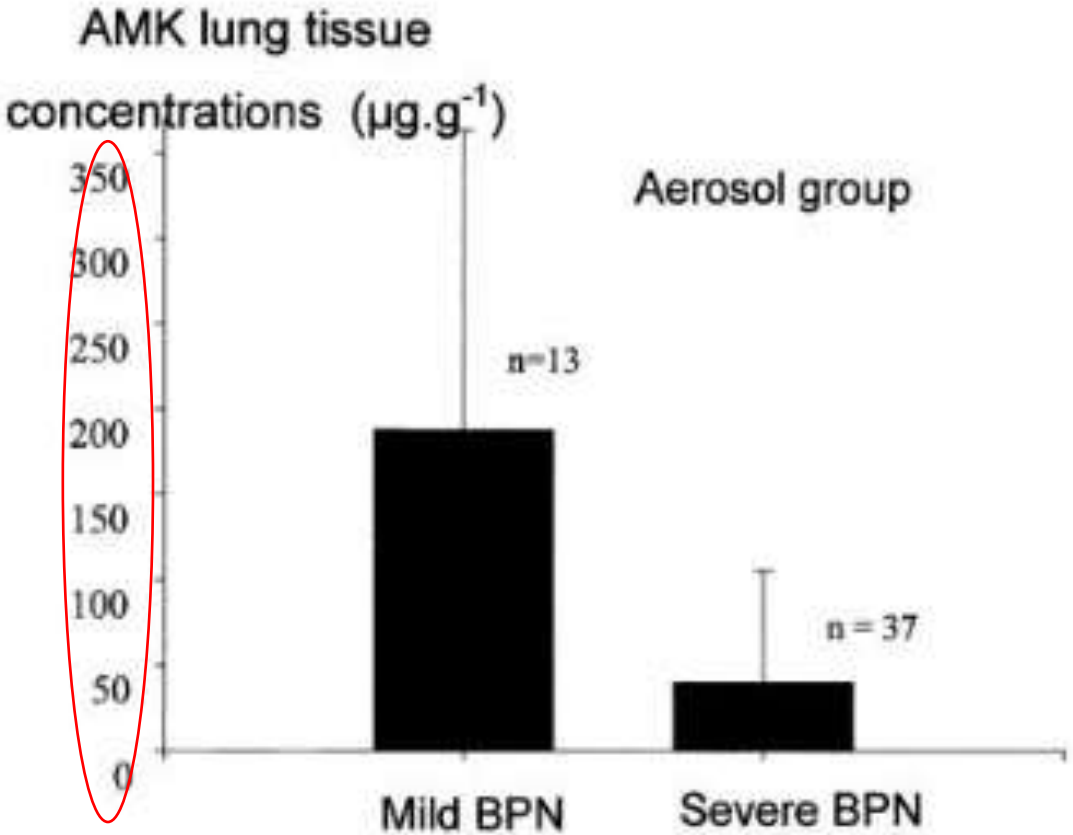
Chez le poumon infecté?

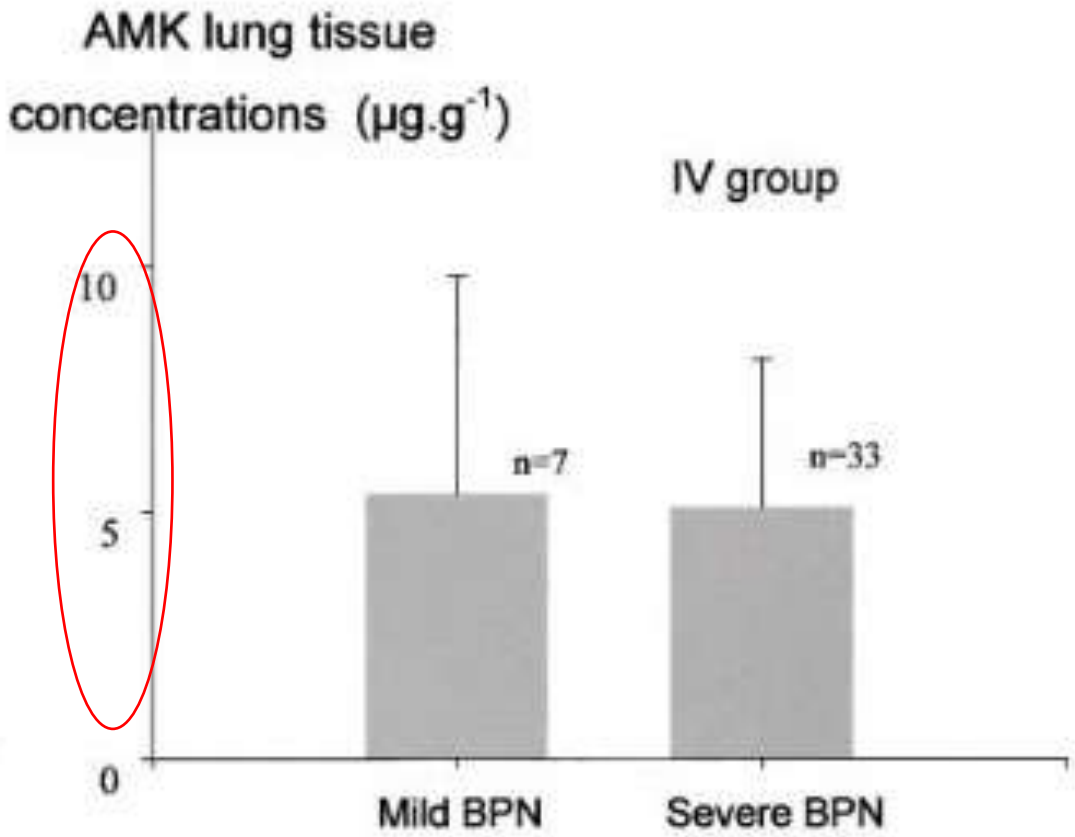


Goldstein, Ivan et al. “Lung deposition and efficiency of nebulized amikacin during Escherichia coli pneumonia in ventilated piglets.” AJRCCM 2002



Goldstein, Ivan et al. "Lung deposition and efficiency of nebulized amikacin during Escherichia coli pneumonia in ventilated piglets." AJRCCM 2002





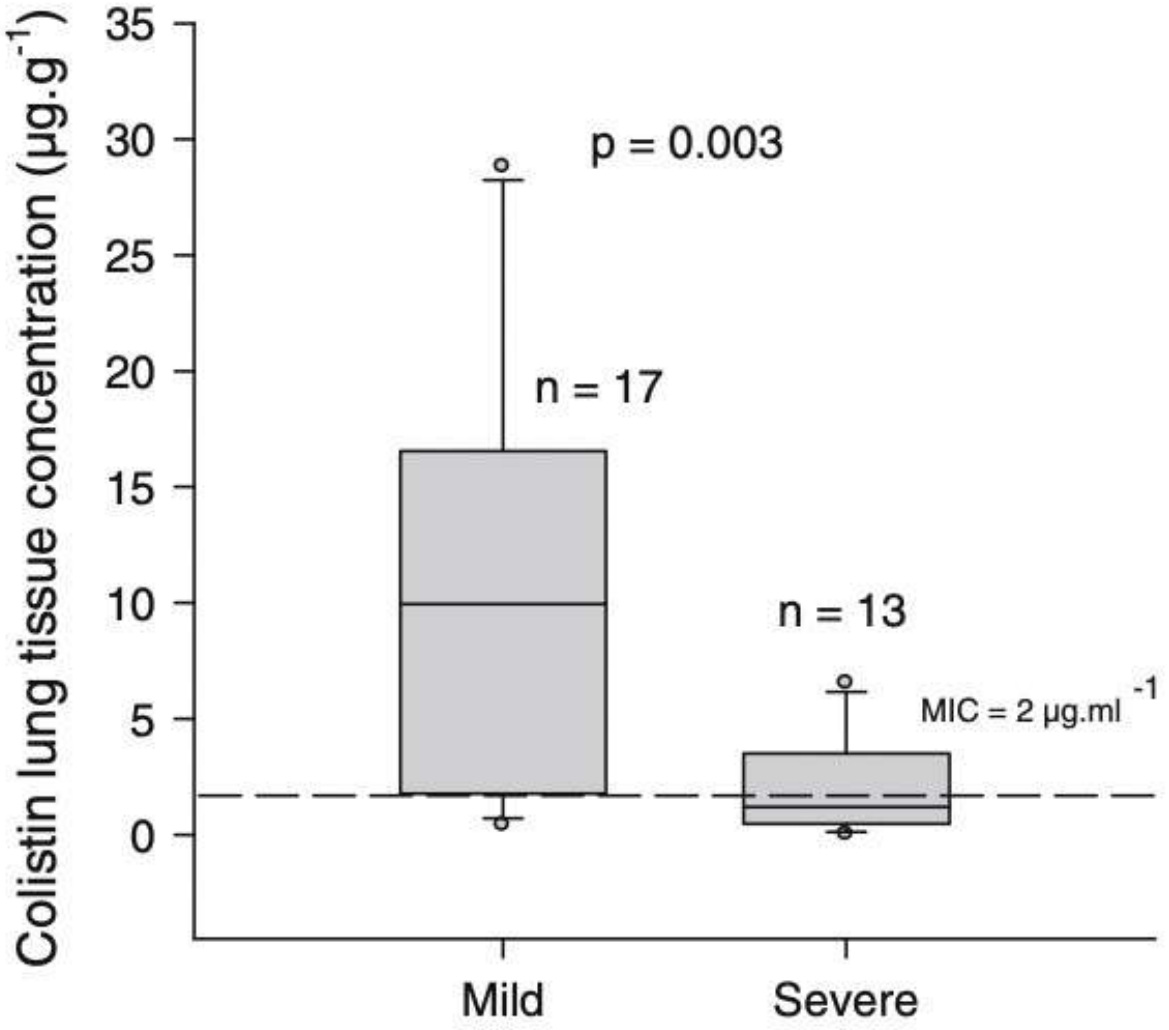
Goldstein, Ivan et al. "Lung deposition and efficiency of nebulized amikacin during Escherichia coli pneumonia in ventilated piglets." AJRCCM 2002

Conséquence?

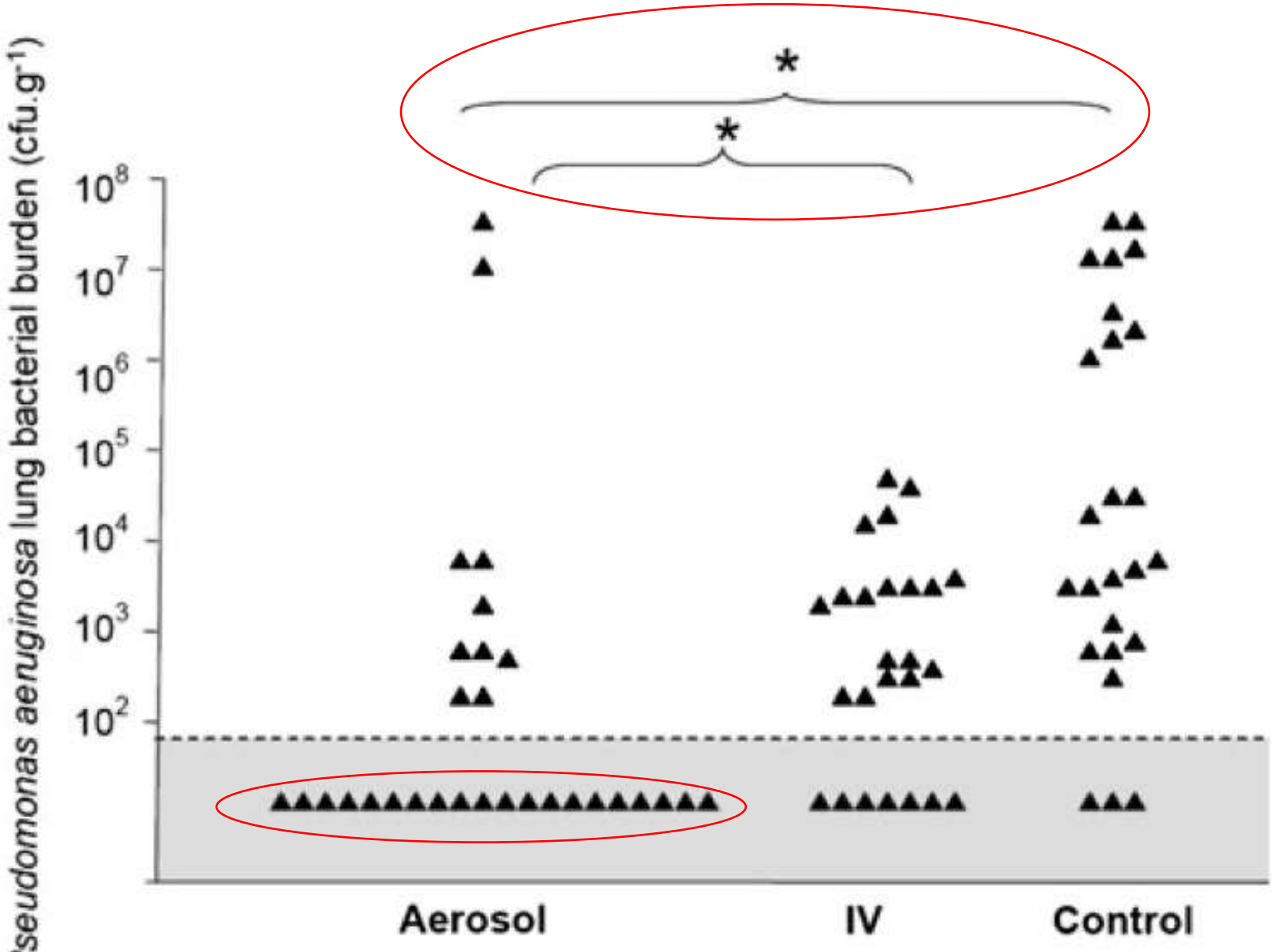
- Meilleure concentration locale
  - Meilleure efficacité?
  - Moins de sélection de R?
- Moindre diffusion systémique
  - Moindre toxicité?
  - Quelles conséquence sur les foyers d’infection périphérique?

Colimycine

- Toxicité rénale et neurologique
- Bactéricide, Concentration dépendant
- Très mauvaise diffusion pulmonaire.
- Efficacité ++ Pyocyanique



Lu, Qin et al. “Nebulized and intravenous colistin in experimental pneumonia caused by Pseudomonas aeruginosa.” *Intensive care medicine* (2010)



Lu, Qin et al. “Nebulized and intravenous colistin in experimental pneumonia caused by Pseudomonas aeruginosa.” *Intensive care medicine* (2010)

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

	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 (13–31)	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

Lu, Qin et al. "Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by Pseudomonas aeruginosa." *AJRCCM (*2011)

	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			1	2	1
R–S			2	1	1
R–I					1

Lu, Qin et al. “Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by Pseudomonas aeruginosa.” *AJRCCM (*2011)

Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults

A Systematic Review and Meta-analysis

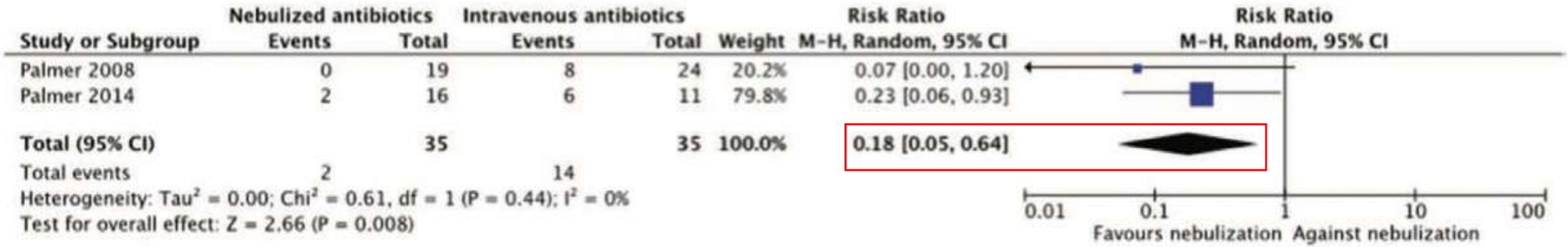


Fig. 3. Emergence of resistant strains n patients treated with nebulized antibiotics for ventilator-associated tracheobronchitis. I = heterogeneity index; M–H = Mantel–Haenszel.

Solé-Lleonart, Candela et al. *Anesthesiology* (2017)

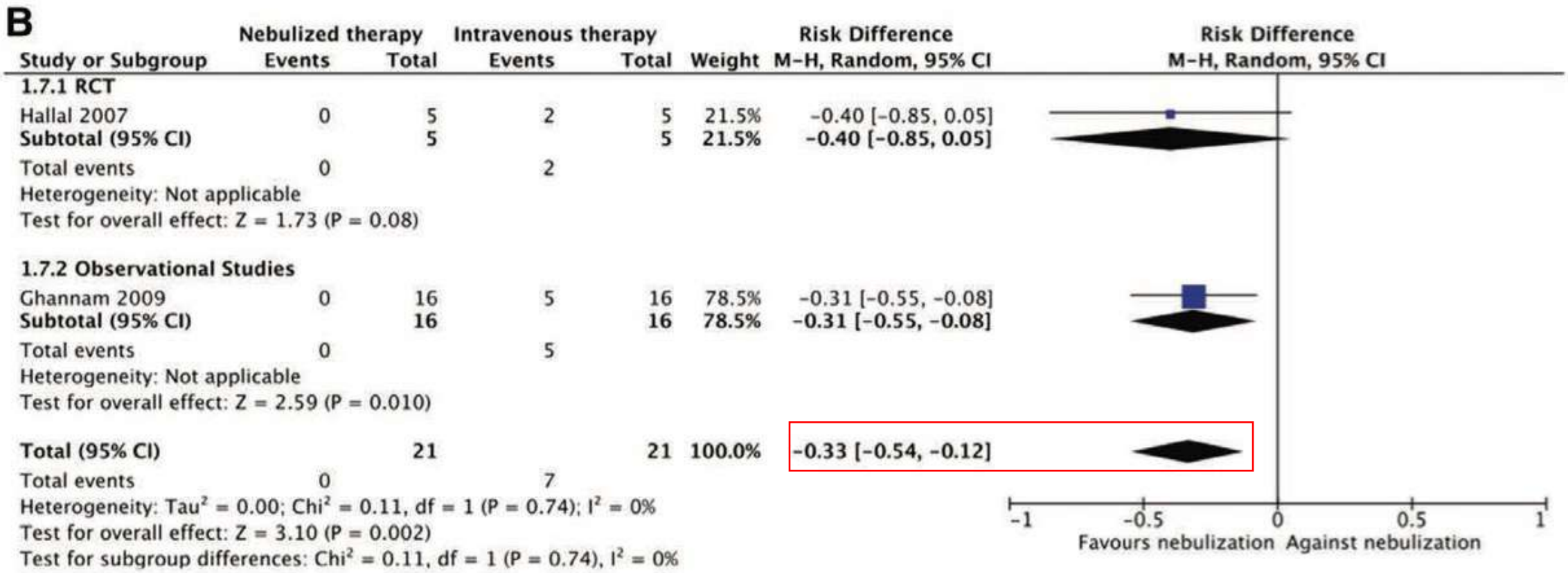


Fig. 7. Nephrotoxicity in patients treated with nebulized antibiotics for ventilator-associated pneumonia—(*A*) adjunctive administration strategy and (*B*) substitution administration strategy. I = heterogeneity index; M–H = Mantel–Haenszel; RCT = randomized controlled trial.

Solé-Lleonart, Candela et al. *Anesthesiology* (2017)

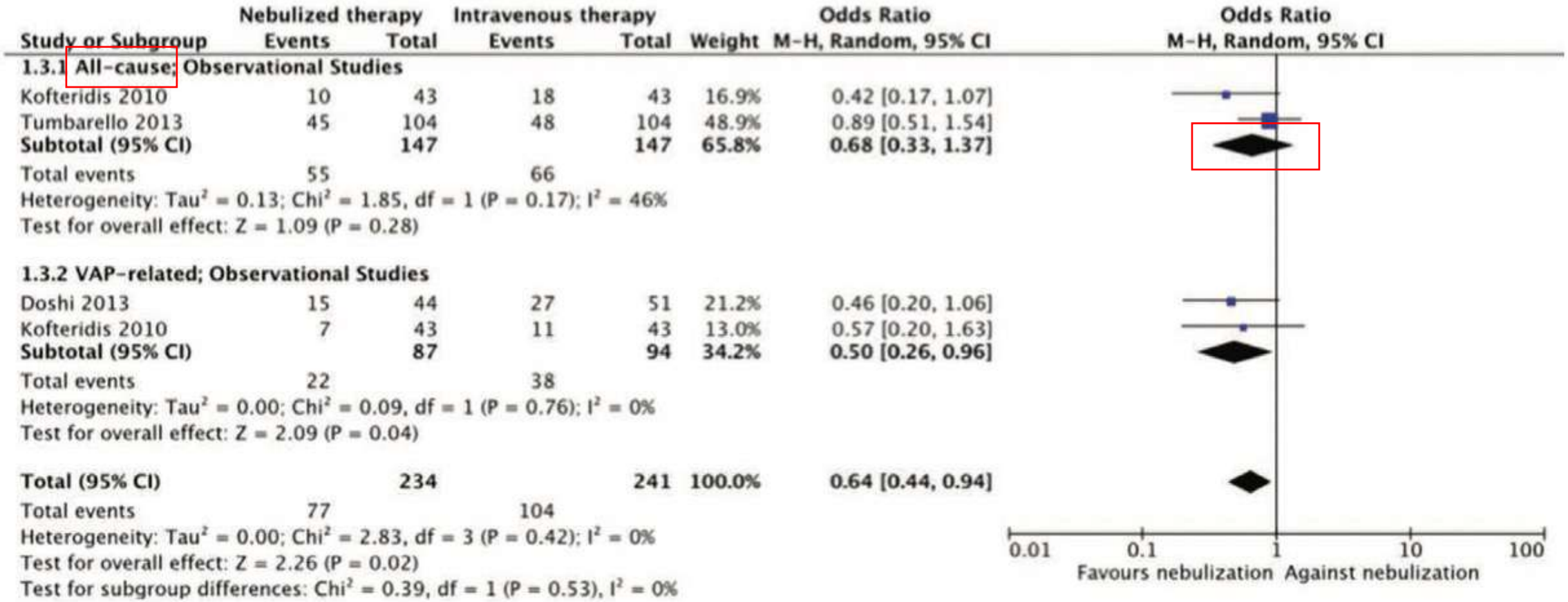


Fig. 5. Mortality of patients treated with nebulized antibiotics for ventilator-associated pneumonia (VAP) caused by resistant pathogens—adjunctive administration strategy. I = heterogeneity index; M–H = Mantel–Haenszel.

Solé-Lleonart, Candela et al. *Anesthesiology* (2017)

Hypothèses

+

- Meilleure action locale?
- Moins de résistances?
- Moins de toxicité?

-

- Moins bonne action locale?
- Plus de résistances?

Clinical Infectious Diseases

IDSA GUIDELINE

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

Kalil, Andre C et al. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* (2016)

ROLE OF INHALED ANTIBIOTIC THERAPY

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)*.

   Values and Preferences: This recommendation places a high value on achieving clinical cure and survival; it places a lower value on burden and cost.

   Remarks: It is reasonable to consider adjunctive inhaled antibiotic therapy as a treatment of last resort for patients who are not responding to intravenous antibiotics alone, whether the infecting organism is or is not multidrug resistant (MDR).

Kalil, Andre C et al. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* (2016)

Recommandations formalisées d'experts

PNEUMONIES ASSOCIÉES AUX SOINS DE RÉANIMATION

RFE commune SFAR – SRLF

Société Française d'Anesthésie et de Réanimation

Société de Réanimation de Langue Française

En collaboration avec les Sociétés ADARPEF et GFRUP

Association des Anesthésistes Réanimateurs Pédiatriques d'Expression Française,

Groupe Francophone de Réanimation et Urgences Pédiatriques

HEALTHCARE ASSOCIATED PNEUMONIA IN INTENSIVE CARE UNIT

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 lorsque 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

Depuis?

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

Niederman, Michael S et al. *The Lancet. Infectious diseases (2019)*

	Amikacin Inhale group (n=255)	Placebo group (n=253)
(Continued from previous column)		
Most common pathogens (≥10% of patients)		
Pseudomonas aeruginosa	75 (29%)	88 (35%)
Acinetobacter baumannii	77 (30%)	69 (27%)
Klebsiella pneumoniae	53 (21%)	44 (17%)
Escherichia coli	28 (11%)	29 (11%)
Other	22 (9%)	23 (9%)
Monomicrobial or polymicrobial infection		
Monomicrobial	172 (67%)	165 (65%)
Polymicrobial	82 (32%)	87 (34%)
Data missing	1 (<1%)	1 (<1%)
Gram-stain status of infection		
Gram-negative only	230 (90%)	230 (91%)
Gram-negative and Gram-positive	24 (9%)	22 (9%)
Data missing	1 (<1%)	1 (<1%)
Drug-resistance designation of pathogens		
Not multidrug-resistant	126 (49%)	112 (44%)
Multidrug-resistant	44 (17%)	61 (24%)
Extensively drug-resistant	81 (32%)	77 (30%)
Pandrug-resistant	3 (1%)	2 (1%)
Data missing	1 (<1%)	1 (<1%)

Table 1: **Baseline characteristics of efficacy population**

	Amikacin Inhale group	Placebo group
Primary endpoint*		
Survival at days 28–32 (n=255 *vs* n=253)		
Treatment successful	191 (75%)	196 (77%)
Treatment unsuccessful	64 (25%)	57 (23%)
Secondary endpoints		
Mortalities (n=255 *vs* n=253)	64 (25%)	57 (23%)
Pneumonia-related deaths	43 (67%)	36 (63%)
Pneumonia-unrelated deaths	21 (33%)	21 (37%)
Early clinical response (n=255 *vs* n=253)†		
Achieved early response	149 (58%)	145 (57%)
Did not achieve early response	106 (42%)	108 (43%)
Duration of mechanical ventilation, days (n=255 *vs* n=252)		
Mean (SD)	20·6 (10·1)	20·2 (10·2)
Median (IQR)	28·0 (9·0–28·0)	28·0 (8·5–28·0)
Duration of intensive care unit stay, days (n=247 *vs* n=249)		
Mean (SD)	21·3 (8·2)	21·9 (8·0)
Median (IQR)	28·0 (13·0–28·0)	28·0 (14·0–28·0)

Table 2: **Primary and secondary outcomes in the efficacy population**

	Amikacin Inhale group (n=353)	Placebo group (n=359)	Total (n=712)
TEAEs of special interest			
Local-effect adverse events, excluding bronchospasm	31 (9%)	26 (7%)	57 (8%)
Bronchospasm	15 (4%)	4 (1%)	19 (3%)
Device-related adverse event	7 (2%)	3 (1%)	10 (1%)
Hypersensitivity	21 (6%)	19 (5%)	40 (6%)
Nephrotoxicity	39 (11%)	44 (12%)	83 (12%)
Ototoxicity	0	1 (<1%)	1 (<1%)
Neuromuscular blockade	4 (1%)	6 (2%)	10 (1%)

***Table 3*: TEAEs in the safety population**

	Amikacin Inhale group	Placebo group
Microbiological response		
Pseudomonas aeruginosa		
Eradication	55/75 (73%)	44/88 (50%) *
Persistence	20/75 (27%)	44/88 (50%)
Clinical response		
Not multidrug-resistant*		
Survived	98/126 (78%)	88/112 (79%)
Died	28/126 (22%)	24/112 (21%)
Multidrug-resistant†		
Survived	34/44 (77%)	48/61 (79%)
Died	10/44 (23%)	13/61 (21%)
Extensively drug-resistant‡		
Survived	56/81 (69%)	58/77 (75%)
Died	25/81 (31%)	19/77 (25%)
Pandrug-resistant§		
Survived	3/3 (100%)	2/2 (100%)
Died	0/3	0/2

Table 4: **Microbiological response at test-of-cure visit (days 17–19) for selected baseline respiratory pathogens and clinical response by drug resistance designation**

The INHALE trial: multiple reasons for a negative result

Rouby, Jean-Jacques et al. *The Lancet. Infectious diseases* (2020)

The INHALE trial: multiple reasons for a negative result

- PAVM BGN MDR
- Bithérapie IV + Amikacine vs Bithérapie IV + Placebo
- 40mg/Kg
- Dispositif non synchronisé
- Paramètre ventilateur optimisé

Rouby, Jean-Jacques et al. *The Lancet. Infectious diseases* (2020)

The INHALE trial: multiple reasons for a negative result

- PAVM BGN MDR
- Bithérapie IV + Amikacine vs Bithérapie IV + Placebo
- 40mg/Kg
- Dispositif non synchronisé
- Paramètre ventilateur optimisé

Rouby, Jean-Jacques et al. *The Lancet. Infectious diseases* (2020)

Authors' reply

- Inclusion des suspicions
- Dispositif synchronisé adapté

Although the design of future trials might lead to success, we do not think that the suggestions by Rouby and colleagues are an answer for how to move forward.[4]

Niederman, Michael S et al. *The Lancet. Infectious diseases* (2020)

Conclusion

Conclusion

Peu de preuve, peu d'études, peu de substrat clinique.

Place dans l'arsenal thérapeutique incertaine

Impact clinique nul dans la population de PAVM au sens large

Réduction des toxicité systémique

Bibliographie

1. Stein, Stephen W, and Charles G Thiel. “The History of Therapeutic Aerosols: A Chronological Review.” *Journal of aerosol medicine and pulmonary drug delivery* vol. 30,1 (2017): 20-41. doi:10.1089/jamp.2016.1297
2. Graeser, J B, and A H Rowe. “Inhalation of Adrenalin for the Relief of Asthma.” *California and western medicine* vol. 43,2 (1935): 110.
3. Segal, M S. “Inhalation therapy in treatment of serious respiratory disease..” *The New England journal of medicine* vol. 229:235-241 (1943)
4. Bryson, V et al. “Aerosolization of penicillin solutions.” *Science (New York, N.Y.)* vol. 100,2585 (1944): 33-5. doi:10.1126/science.100.2585.33
5. Segal, M S, and C M Ryder. “Penicillin Aerosolization in the Treatment of Serious Respiratory Infections — A Preliminary Report” *The New England journal of medicine* (1945); 233:747-756. doi: 10.1056/NEJM194512202332501
6. Segal, M S, and C M Ryder. “Penicillin inhalation therapy.” *The New England journal of medicine* vol. 236,4 (1947): 132-8. doi:10.1056/NEJM194701232360403
7. Morrow, G W Jr et al. “The diagnosis and management of acute infectious pneumonia.” *The Medical clinics of North America* vol. 48 (1964): 829-38. doi:10.1016/s0025-7125(16)33413-7
8. Landecker, Hannah. “Antibiotic Resistance and the Biology of History.” *Body & society* vol. 22,4 (2016): 19-52. doi:10.1177/1357034X14561341
9. Boselli, E, and B Allaouchiche. “Diffusion pulmonaire des antibiotiques. Analyse critique de la littérature” [Pulmonary diffusion of antibiotics. Critical analysis of the literature]. *Annales francaises d'anesthesie et de reanimation* vol. 20,7 (2001): 612-30. doi:10.1016/s0750-7658(01)00439-7
10. Goldstein, Ivan et al. “Lung tissue concentrations of nebulized amikacin during mechanical ventilation in piglets with healthy lungs.” *American journal of respiratory and critical care medicine* vol. 165,2 (2002): 171-5. doi:10.1164/ajrccm.165.2.2107025
11. Goldstein, Ivan et al. “Lung deposition and efficiency of nebulized amikacin during Escherichia coli pneumonia in ventilated piglets.” *American journal of respiratory and critical care medicine* vol. 166,10 (2002): 1375-81. doi:10.1164/rccm.200204-363OC
12. Lu, Qin et al. “Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by Pseudomonas aeruginosa.” *American journal of respiratory and critical care medicine* vol. 184,1 (2011): 106-15. doi:10.1164/rccm.201011-1894OC
13. Lu, Qin et al. “Nebulized and intravenous colistin in experimental pneumonia caused by Pseudomonas aeruginosa.” *Intensive care medicine* vol. 36,7 (2010): 1147-55. doi:10.1007/s00134-010-1879-4
14. Solé-Lleonart, Candela et al. “Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults: A Systematic Review and Meta-analysis.” *Anesthesiology* vol. 126,5 (2017): 890-908. doi:10.1097/ALN.0000000000001570
15. Rouby, Jean-Jacques et al. “Aerosolized antibiotics for ventilator-associated pneumonia: lessons from experimental studies.” *Anesthesiology* vol. 117,6 (2012): 1364-80. doi:10.1097/ALN.0b013e3182755d7a
16. Kalil, Andre C et al. “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.” *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* vol. 63,5 (2016): e61-e111. doi:10.1093/cid/ciw353
17. Niederman, Michael S et al. “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.” *The Lancet. Infectious diseases* vol. 20,3 (2020): 330-340. doi:10.1016/S1473-3099(19)30574-2
18. Rouby, Jean-Jacques et al. “The INHALE trial: multiple reasons for a negative result.” *The Lancet. Infectious diseases* vol. 20,7 (2020): 778-779. doi:10.1016/S1473-3099(20)30481-3
19. Zhang, Changsheng et al. “Should Aerosolized Antibiotics Be Used to Treat Ventilator-Associated Pneumonia?.” *Respiratory care* vol. 61,6 (2016): 737-48. doi:10.4187/respcare.04748