Aminoglycosides in treatment of pneumonia

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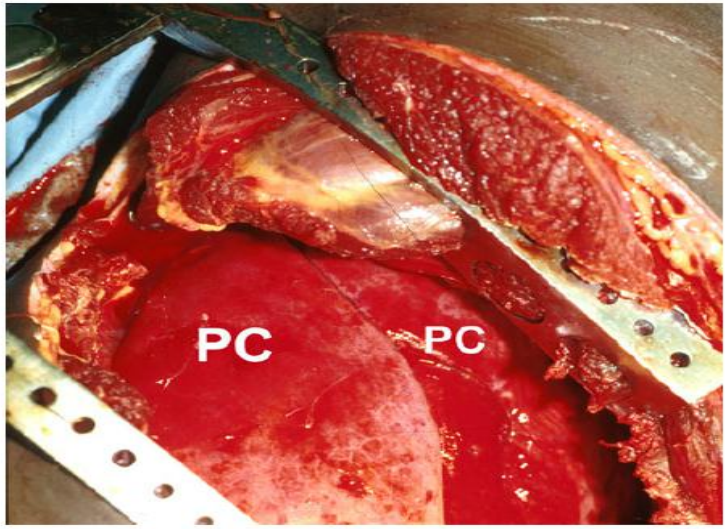
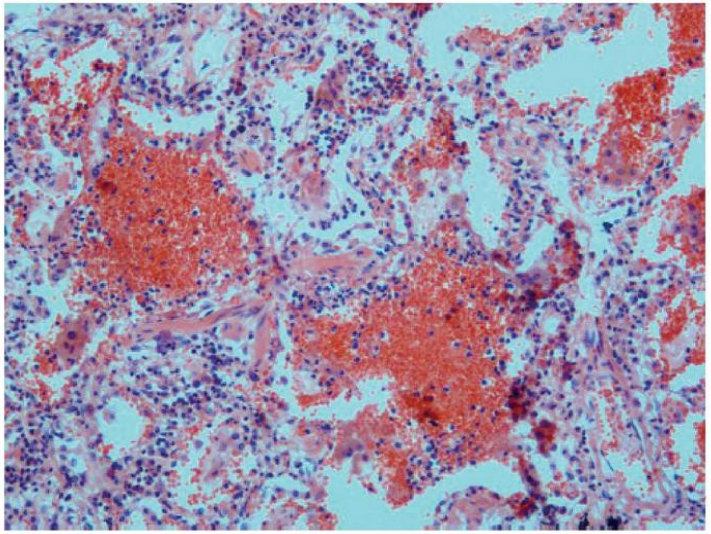
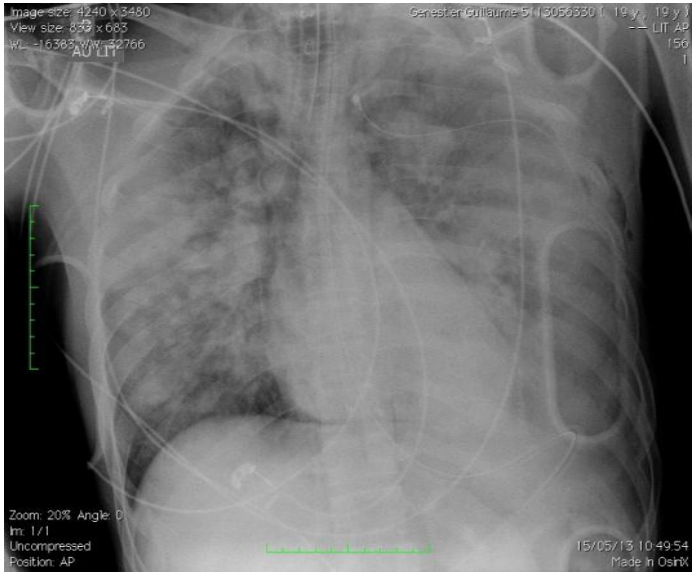
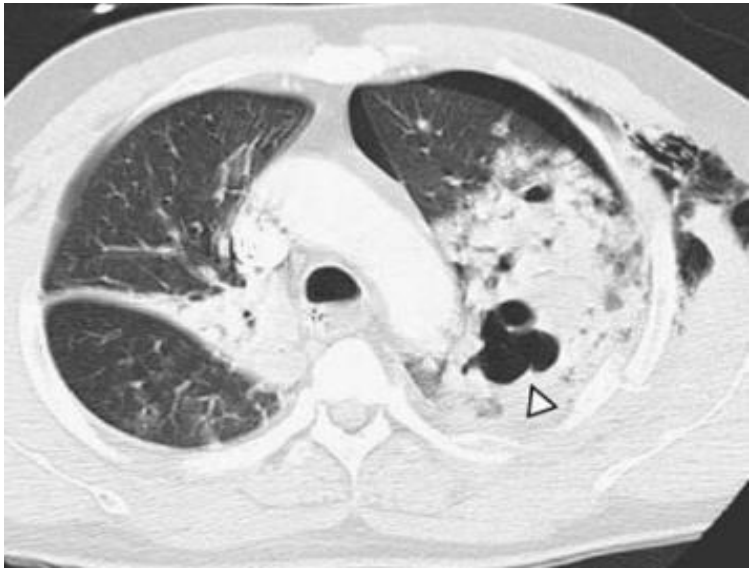
Severe lung contusion and pneumonia







24 hours



2-7 days

New guidelines on antibiotics in hospital-acquired or ventilator associated pneumonia

Kalil et al, Clinical Infectious Diseases 2016

4. We suggest prescribing 2 antipseudomonal antibiotics from different classes for the empiric treatment of suspected VAP only in patients with any of the following: a risk factor for

β-lactams and

Risk factors for MDR VAP	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Prior intravenous antibiotic use within 90 d	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
Septic shock at time of VAP	
ARDS preceding VAP	OR
Five or more days of hospitalization prior to the occurrence of VAP	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
Acute renal replacement therapy prior to VAP onset	OR
Risk factors for MDR HAP	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
Prior intravenous antibiotic use within 90 d	
Risk factors for MRSA VAP/HAP	
Prior intravenous antibiotic use within 90 d	
Risk factors for MDR *Pseudomonas* VAP/HAP	
Prior intravenous antibiotic use within 90 d	

Main thérapeutique indications for combined therapy

ATS 2005

- Intial empirical therapy in patients with VAP associatd with septic choc to provid broad spectrum
- Prevent the emergence of resistance during therapy
- Suspected or documented some specific bacteria
  - Pseudomonas aeruginosa
  - Enterobacteria secreting of a cephalosporinase

→ Use often aminoglycoside

History of aminoglycoisides

- 1944: discovery of Streptomycin by Waksman and Schatz
- Action against GNB and Mycobacterium tuberculosis
- Nobel Prize en 1952

1949: Neomycin

1957: Kanamycin

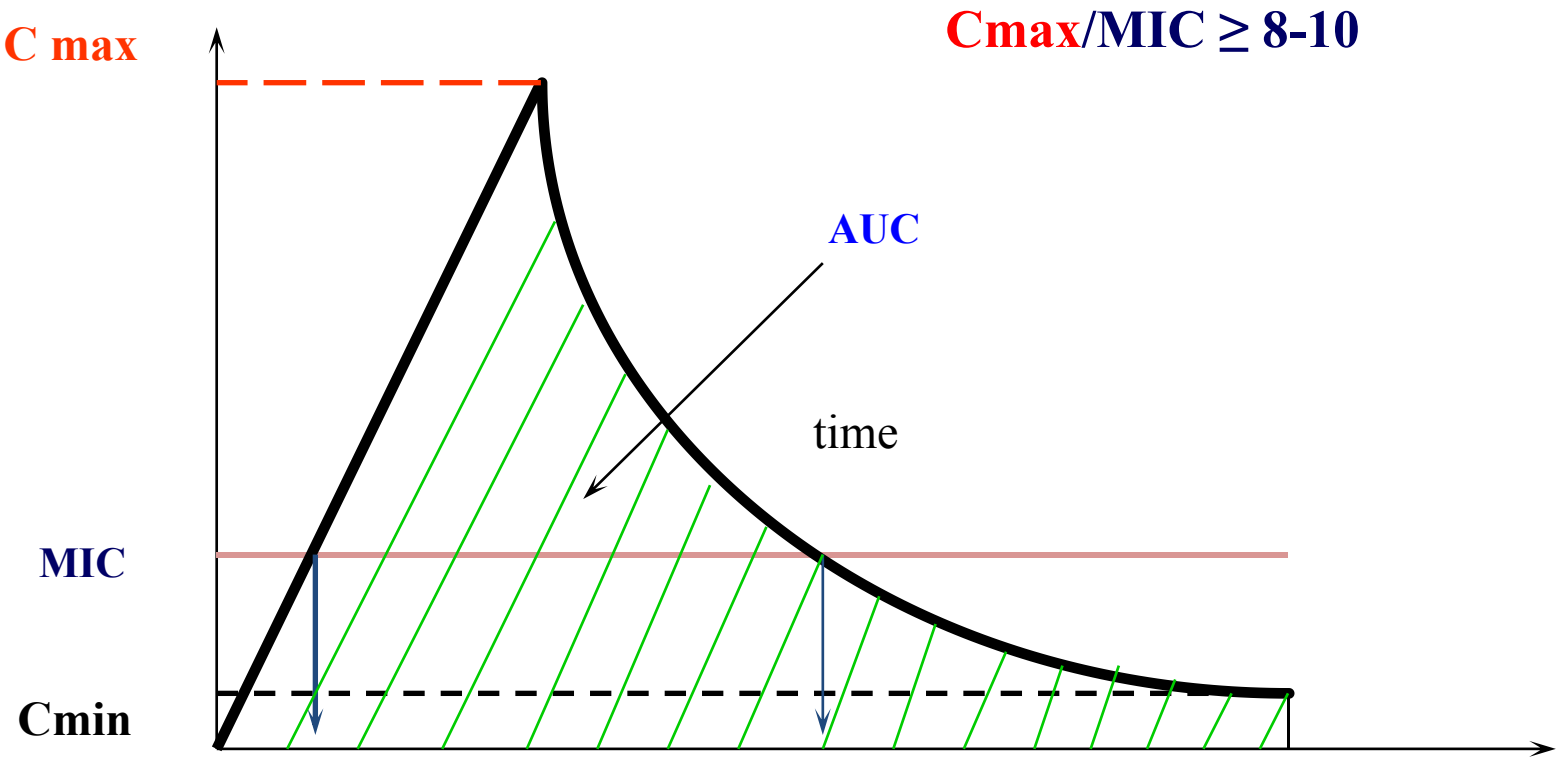
1963: Gentamycin

1970 th : Amikacin and Tobramycin

Aminioglycosides: Mechanism of action

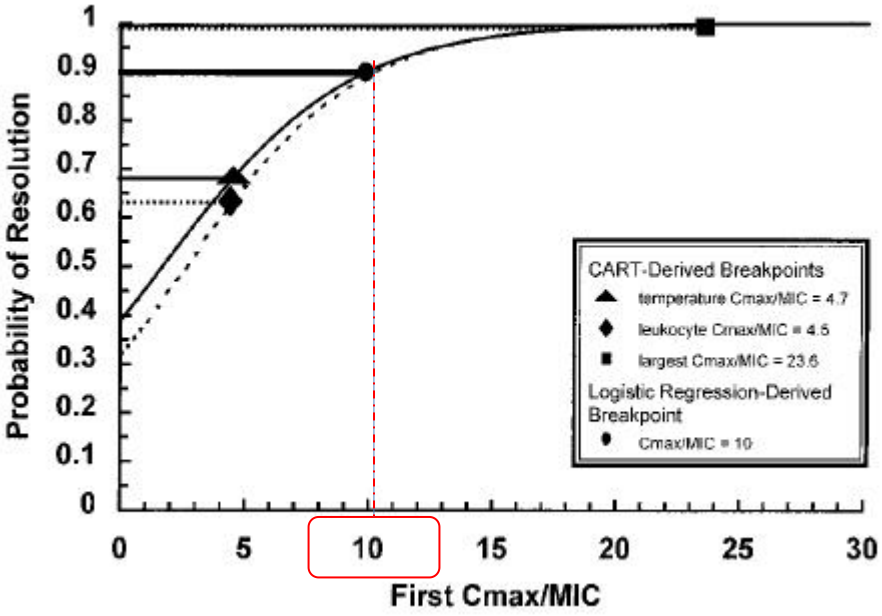
- Rapide bactericidal effet and concentraion dependent killing activity through inhibition of protein synthesis
- Prolonged post-antibiotic effect through irreversible fixation on ribosomes
- Hydrosolubles, elimination half time: 2 hours
- Renal elimination

Pharmacodynamics of aminoglycosides aministered intravenously



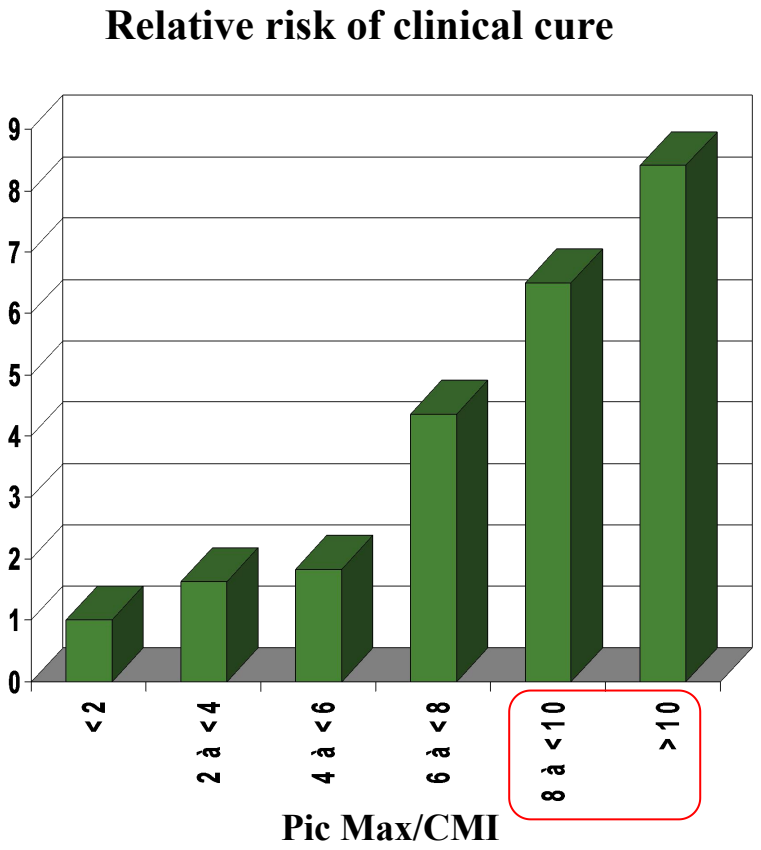
MIC: Lowest concentration of an antibiotic that prevents visible growth of bacerium

Relationship between Cmax/MIC and clinical evolution



A 90% probability of temperature resolution and leukocyte count resolution by day 7 if a Cmax/MIC of >10 is achieved within the first 48 h of aminoglycoside therapy.

Kashuba et al, Antimicrobial Agents and Chemotherapy, 1999



Moore et al, JID, 1987, 155, 93-99

Break-points (EUCAST)

Gentamycin/Netilmycin/Tobramycin

Staphylococcus

S si MIC ≤ 1 mg/L — R if MIC > 1 mg/L

Enterobacteriaceae

S si MIC ≤ 2 mg/L — R if MIC > 4 mg/L

P aeruginosa, A baumannii

S si MIC ≤ 4 mg/L — R if MIC > 4 mg/L

Amikacin

S si MIC ≤ 8 mg/L — R if MIC > 8 mg/L

→ Cmax > 64 mg/L

Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock

Taccone et al, Crit Care 2010

Cmax of amikacin

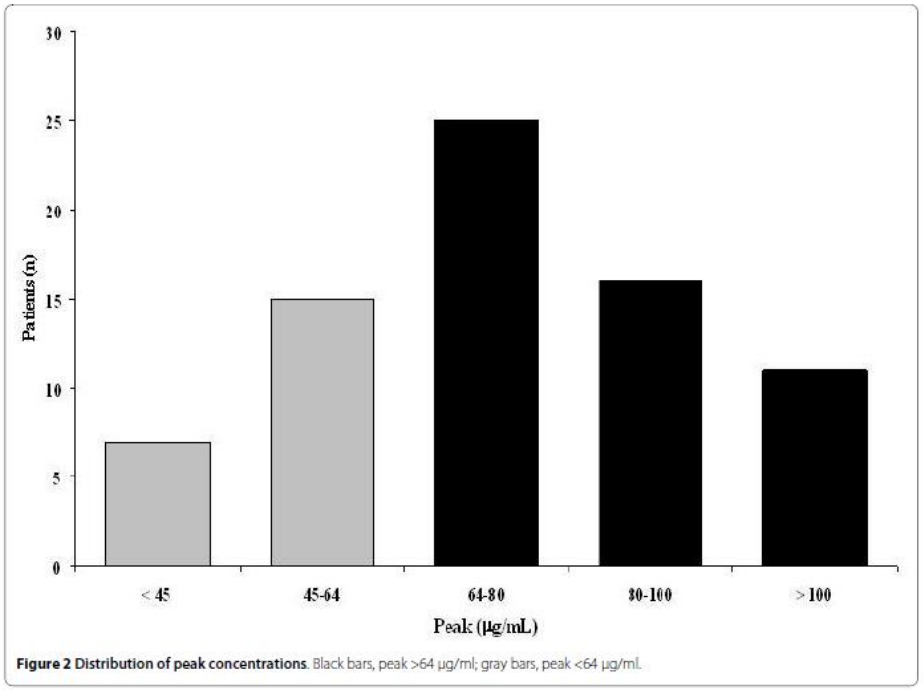


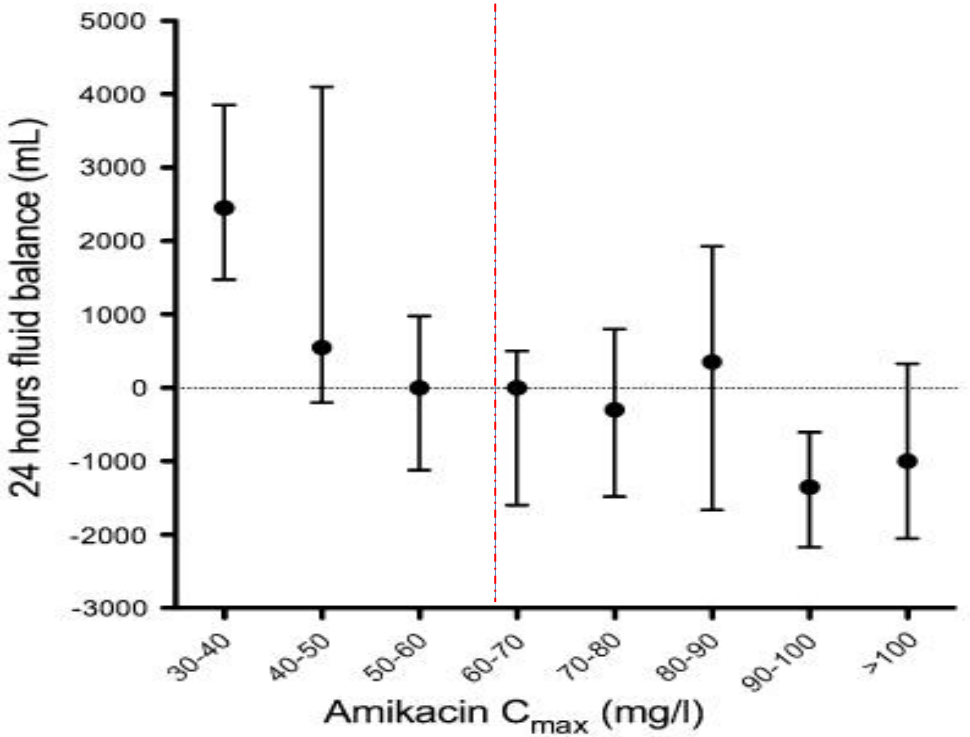
Figure 2 Distribution of peak concentrations. Black bars, peak >64 µg/ml; gray bars, peak <64 µg/ml.

25-30 mg/kg

- -Cmax > 64 µg/ml in **70 %**
- -Cmax/MIC 64 = 8 times for Enterobacteriaceae and *Pseudmonsa aeruginosa* S <8

Predictors of insufficient amikacin peak concentration in critically ill patients receiving a 25 mg/kg total body weight regimen

Montmollin et al, Intensive Care Med 2014



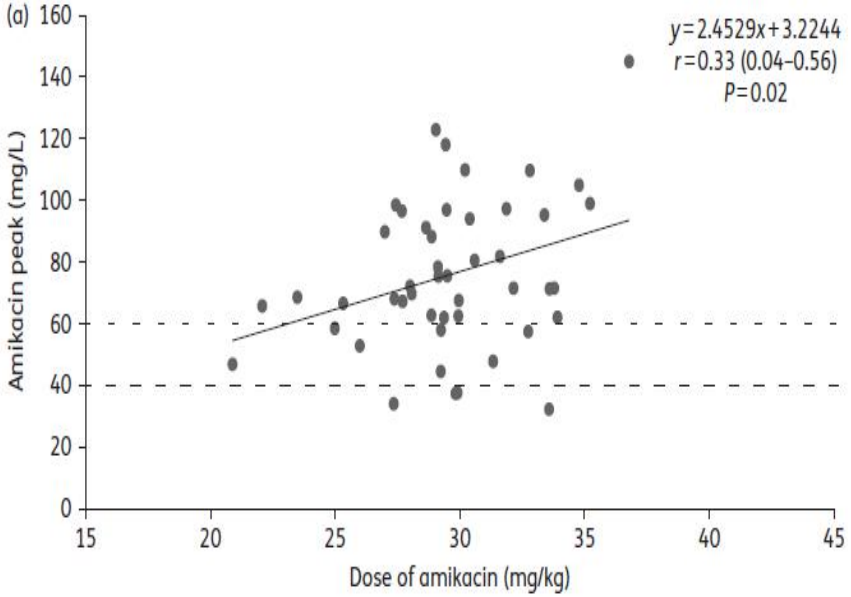
- 33% episodes had Cmax < 60 mg/L
- Positive fluid blalance was a predictive factor of Cmax >60

Corrleation between dose of aminoglycosides and Cmax

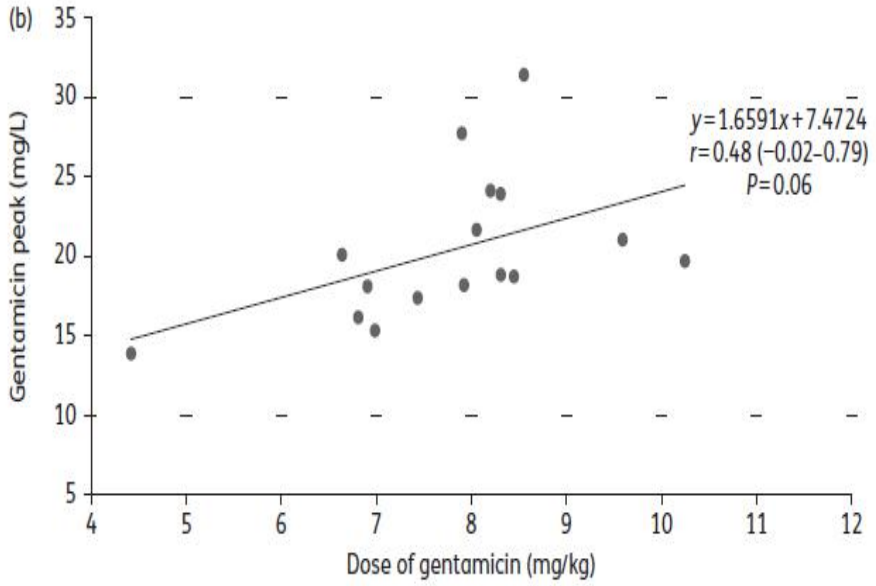
Roger et al, J Antimicrob Chemother 2016

63% of the patients with VAP

30 mg/kg amikacin



8 mg/kg gentamycin



30 mg/kg amikacin and 8 mg/kg gentamicin led to target peak serum concentrations in 59% of patients.

Tobramycin penetration into epithelial lining fluid of patients with pneumonia

Boselli et al, ICM 2007

Patients with late onset VAP, tobramycin IV 7-10 mg/kg for obtaining serum peak levels of 20-30 mg/L

Table 1 Patients' characteristics at enrolment, individual tobramycin concentrations and ELF/serum tobramycin concentration ratios

Patient	Gender (M/F)	Age (years)	Weight (kg)	Creatinine clearance (ml/min)	SAPS II	PO_2/FiO_2 (mmHg)	Tobramycin concentration (mg/l) Serum	BAL sampling BAL fluid[a]	BAL sampling ELF[b]	BAL sampling ELF/serum ratio (%)	Mini-BAL sampling BAL fluid[a]	Mini-BAL sampling ELF[b]	Mini-BAL sampling ELF/serum ratio (%)
1	M	30	98	70	55	135	39.2	0.5	4.4	11.2	0.4	4.2	10.7
2	M	39	67	107	42	60	22.0	0.2	2.5	11.3	0.2	2.4	10.7
3	F	75	60	66	38	200	19.5	0.2	2.1	10.8	0.2	2.2	11.1
4	F	80	58	82	65	120	24.3	0.9	2.9	11.9	0.9	3.1	12.6
5	M	29	71	186	52	118	22.3	0.8	2.6	11.5	0.8	2.6	11.5
6	M	71	103	104	66	125	21.2	0.5	3.6	17.0	0.4	2.6	12.5
7	M	25	70	118	59	162	19.1	0.3	1.7	9.0	0.4	2.3	11.9
8	M	25	70	127	38	340	25.8	0.5	2.9	11.0	0.6	3.3	12.8
9	M	65	84	62	41	178	17.2	0.2	2.0	11.9	0.2	1.9	10.9
10	M	56	75	76	55	254	19.8	0.2	2.4	11.9	0.2	2.3	11.5
11	F	73	62	82	32	98	20.4	0.2	2.7	13.3	0.2	2.6	12.5
12	F	68	65	56	48	286	17.4	0.1	2.2	12.4	0.1	2.0	11.7
Mean	8/4	53	74	95	49	173	22.4	0.4	2.7	11.9	0.4	2.6	11.7
SD		22	14	37	11	83	5.9	0.3	0.7	1.9	0.3	0.6	0.8

22 | 2,7 | 11,7

→ Poor penetration of tobramycin in ELF (12%)

→ Peudomonas aeruginosa MIC= 4 mg/L

Penetration of Gentamicin Into the Alveolar Lining Fluid of Critically Ill Patients With Ventilator-Associated Pneumonia*

Panidis et al, Chest 2005

Gentamycin 240 mg (8 mg/kg) once daily IV

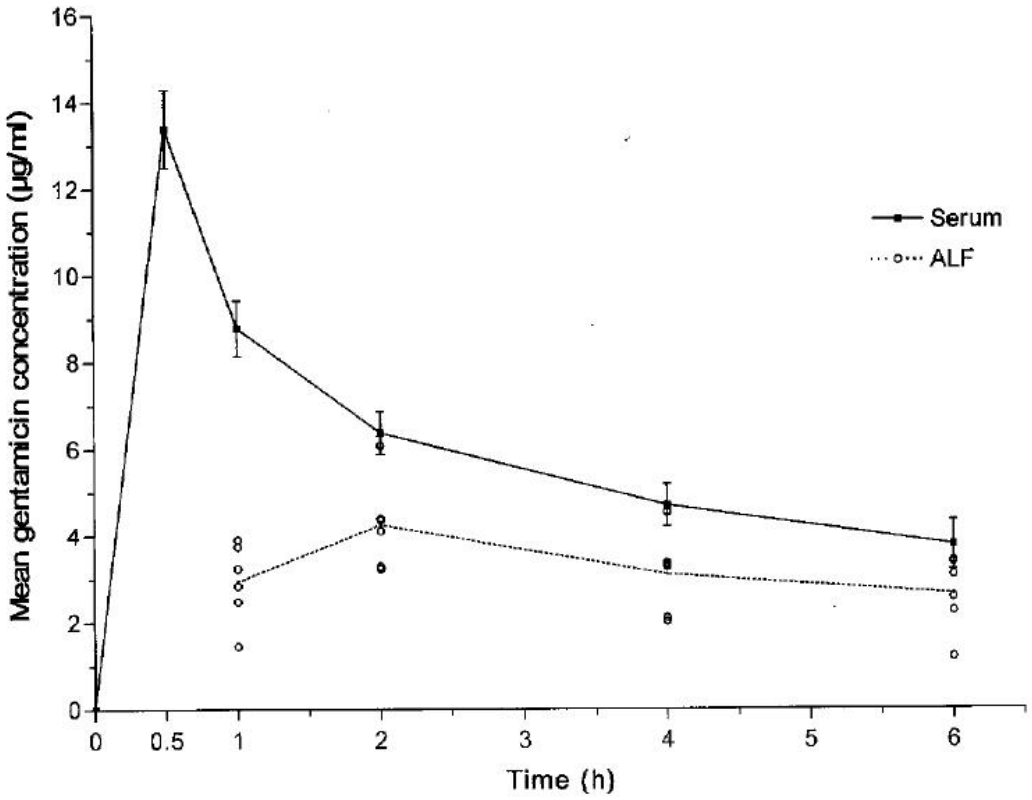


FIGURE 1. Mean gentamicin concentration in serum vs time (n = 24) and ALF concentrations (n = 6) at 1, 2, 4, and 6 h, respectively (dotted line represents mean ALF concentrations vs time).

- ELF/serum penetration ratio = 32%
- Dose insufficient for bacteria with MIC ≥ 4 mg/L

Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis

Paul et al, Cochrane Database Syst Rev 2014

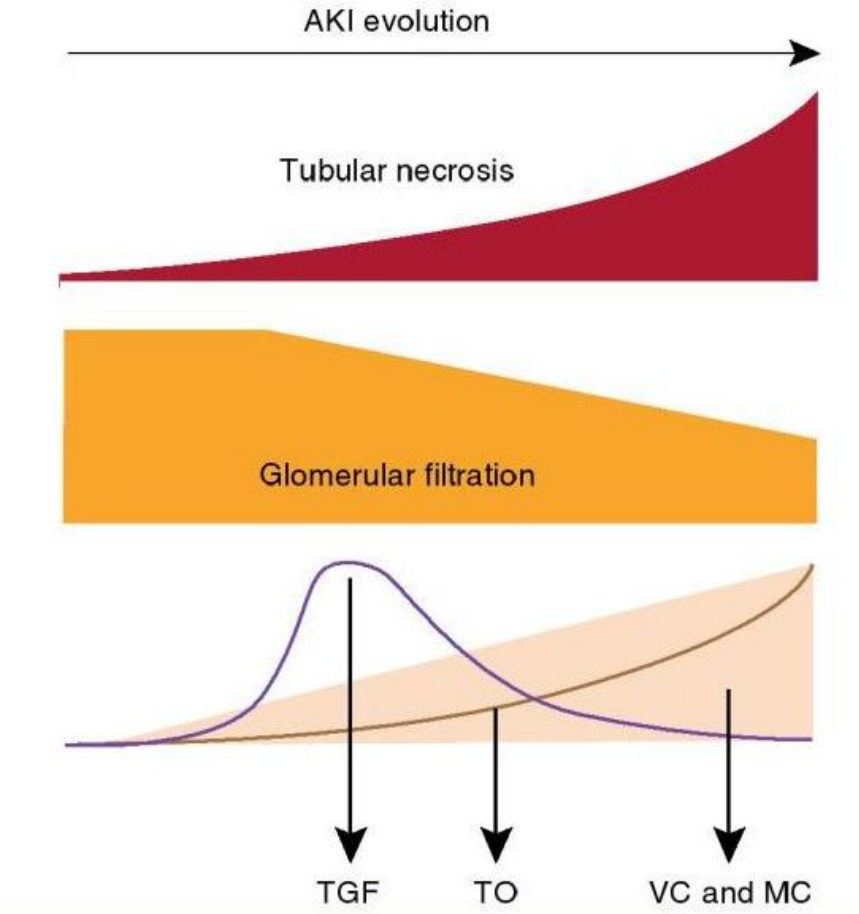
- 64 trials with 7586 patients
- 20 trials compared the same β-lactams
- No difference with regard of all cause-mortality
- No difference with regard of clinical faliure
- No difference in patients infected by P aeruginosa
- No difference in the rate of resistance development
- Nephrotoxicity is more frequent with combined therapy

Authors' conclusions

The addition of an aminoglycoside to beta lactams for sepsis should be discouraged. All-cause mortality rates are unchanged. Combination treatment carries a significant risk of nephrotoxicity.

Nephrotoxicity and aminoglycosides

- Duration of treatment >5-7 day
- Renal: toxicity independently of Cmax
- Tubular effect
- Glomerular effect
- Vascular effect
- Tubular damage and tubular dysfunction are the main cause of renal insufficiency.

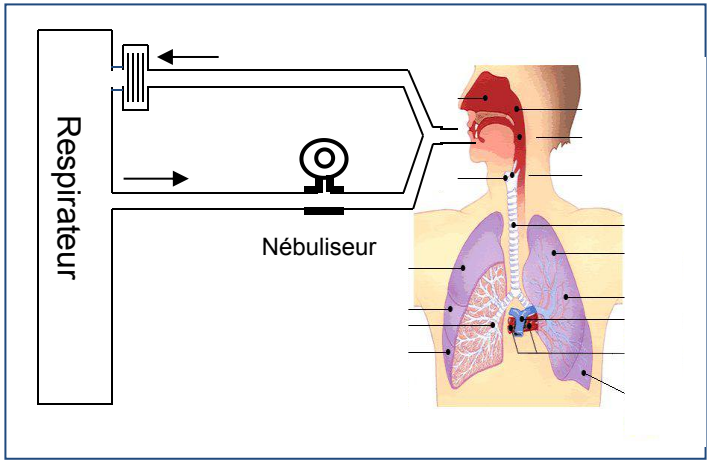


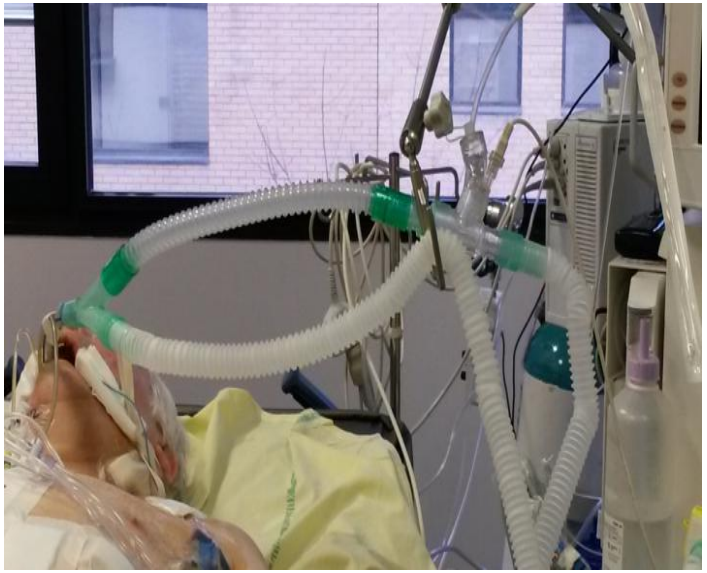
Nebulized amikacin and pneumonia

-Target the affected organ: lung

-Increase bactericidal activity by increasing the lung tissue concentration of the antibiotic.

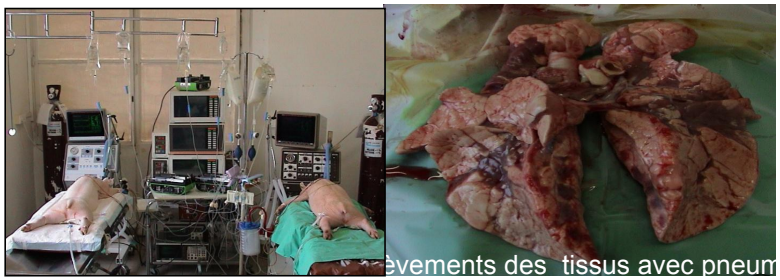
-Decrease systemic toxicity (?)



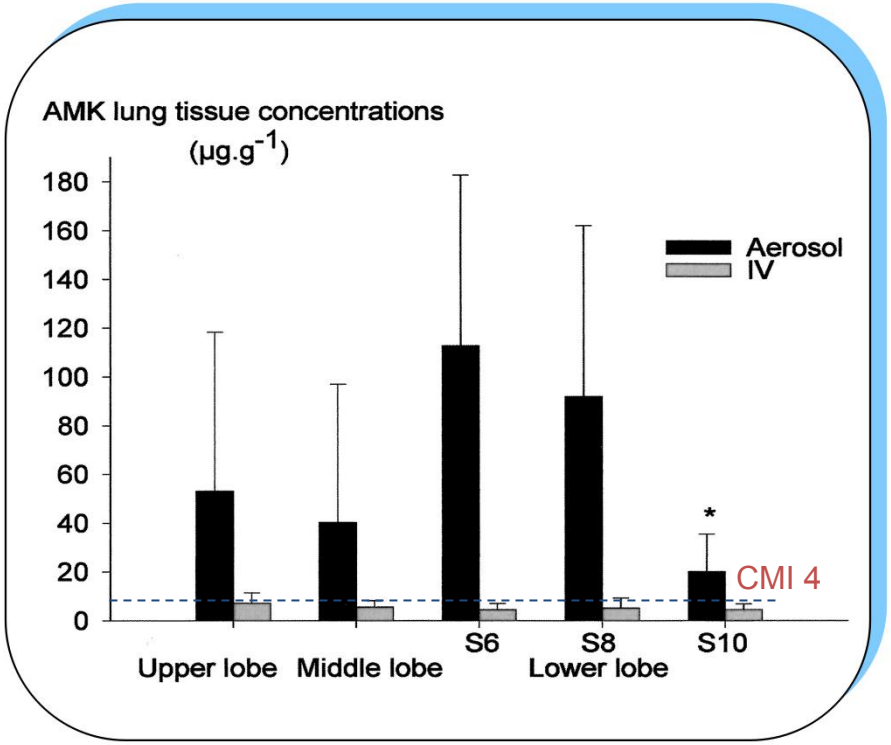


Lung Deposition and Efficiency of Nebulized Amikacin during *Escherichia coli* Pneumonia in Ventilated Piglets

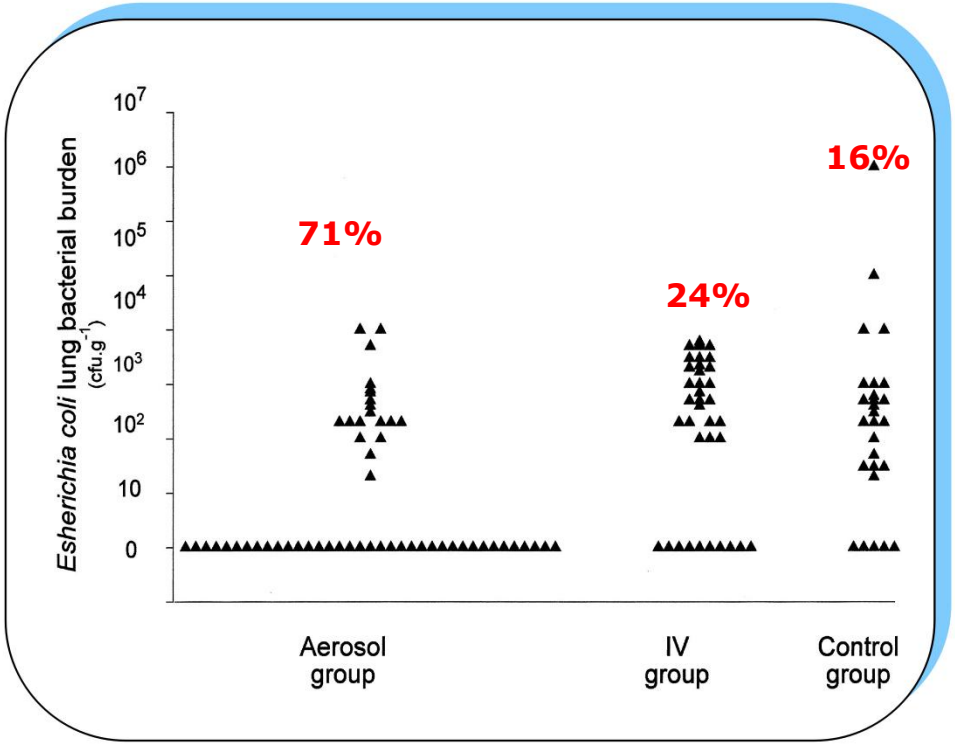
Amikacin IV vs. Nebulization (15 mg/kg)



Lung tissue concentration of Amikacin (Peak))



Sterilized pulmonary segments



Goldstein et al, Am J Respir Crit Care Med, 2002

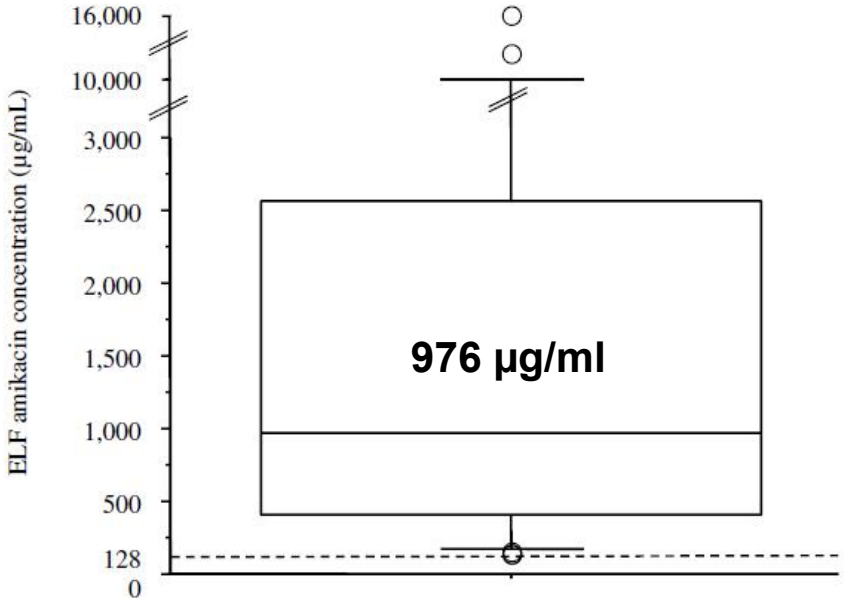
Nebulized Amikacin in lung epithelial lining fluid in patients with VAP

Nebulized Amikacin 400 mg bid

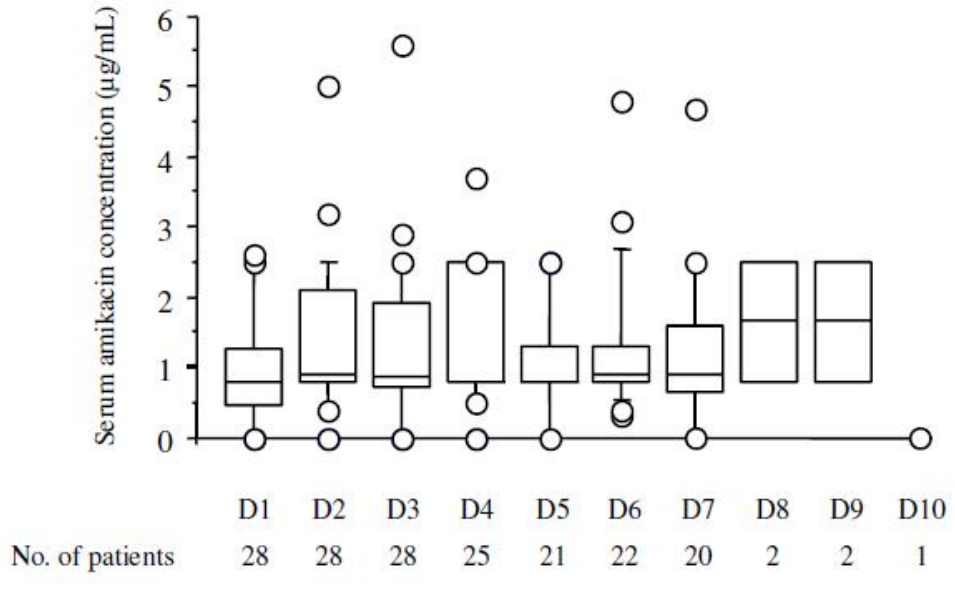
Breath-synchronized vibrating mesh nebulizer

Luyt et al, Crit Care 2009

ELF amikacin peak concentration



Serum amikacin trough concentration

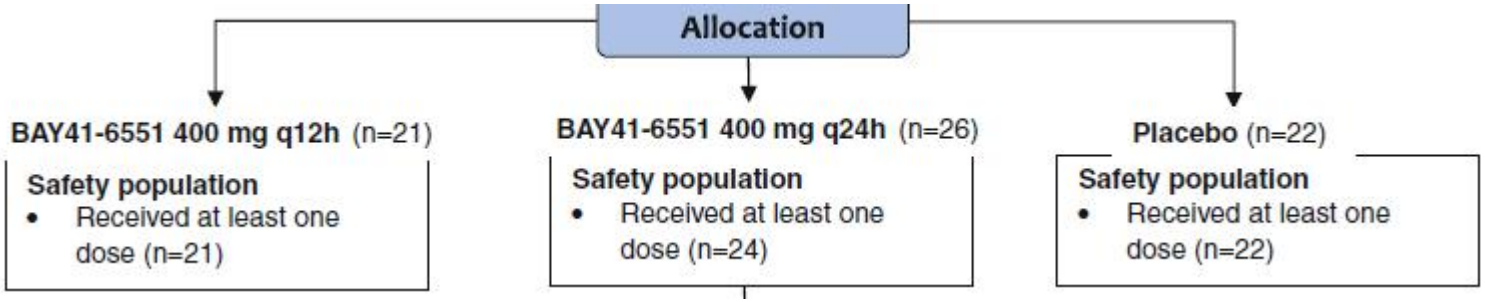


Michael S. Niederman
Jean Chastre
Kevin Corkery
James B. Fink
Charles-Edouard Luyt
Miguel Sánchez García

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

ICM 2015

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



Tracheal
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%**

Phase III study…

Vibrating mesh nebulizer: breath-synchronized

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 + amk300mg+120mg fosfomycine

- 143 patients were randomized, 71 to AFIS, 72 to placebo.
- Primary endpoint: CPIS change from baseline between treatment groups was not different (P=0.70).
- 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.

Vibrating mesh nebulizer: continous delivery

Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit*

Palmer LB, Critical Care Med 2008

Inhaled antibiotic:: Vanco, genta + antibiotic IV

Aerosol antibiotic (n = 19) vs. Placebo (n = 24)

- ❑ Reduced signs of respiratory infections
- ❑ Reduced clinical pulmonary infection score
- ❑ Lower WBC at day 14
- ❑ Reduced bacterial resistance
- ❑ Reduce use of systemic antibiotics
- ❑ Increase weaning

Jet nebulizer breath-synchronized delivery

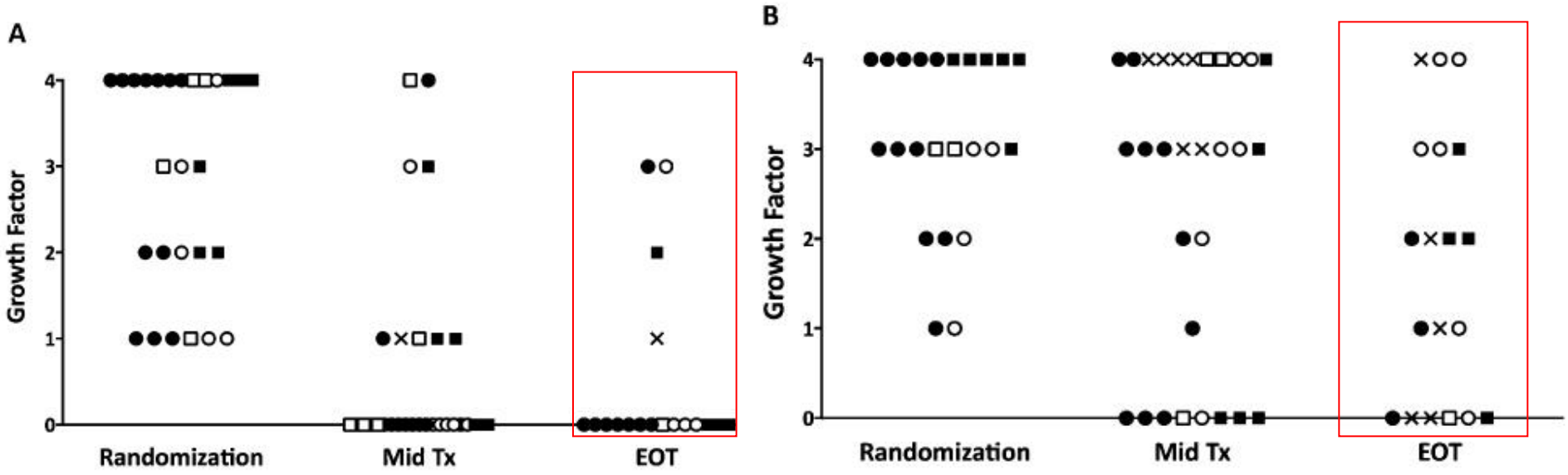
Reduction of Bacterial Resistance with Inhaled Antibiotics in the Intensive Care Unit

Lucy B. Palmer and Gerald C. Smaldone

Am J Respir Crit Care med 2014

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

Aerosol antibiotic (n = 18) vs. Placebo (n = 24)



Aerosol group (n = 24)

Placebo group (n = 23)

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

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

Lu et al, AJRCCM 2011

Etude de phase II, n = 40, taux de guérison: groupe aérosol 70% vs groupe IV 55%

Groupe aérosol

	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				

Groupe IV

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

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

Lu et al, AJRCCM 2011

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

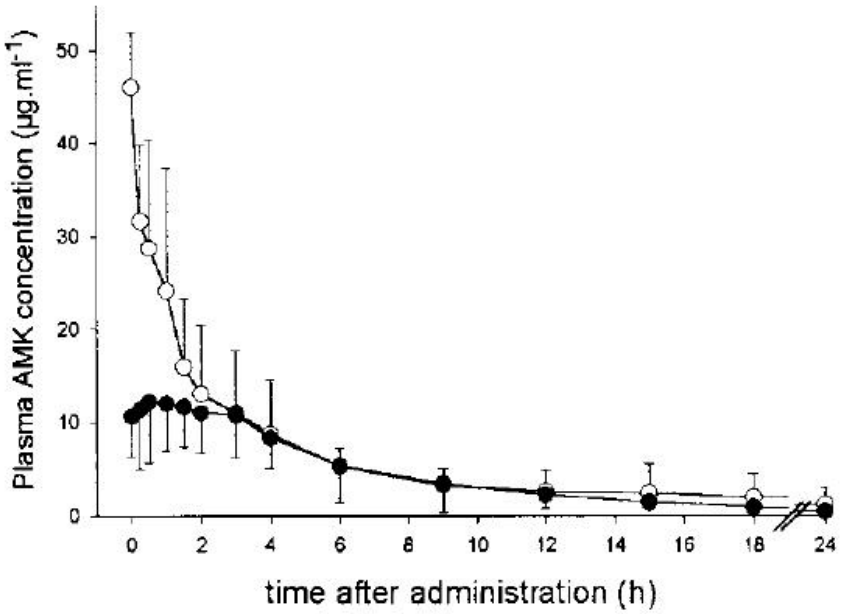
IV group: Ceftazidime IV (90 mg/kg)
AMK 1 x/j (15 mg/kg)

Table 3 Antibiotic treatment efficiency.

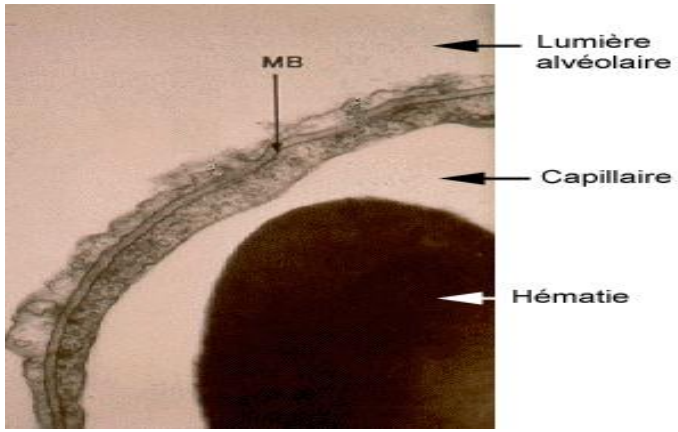
	Aerosol n=20	Intravenous n=20	p Value
Cure of *P aeruginosa* VAP at day 9 (n, %)	14 (70)	11 (55)	0.33
Day 9 : Positive BAL≥10^4 or miniBAL≥10^3 (n)	3	6	
Persisting *P aeruginosa* VAP at day 9 (n, %)	3 (15%)	6 (30%)	0.26
VAP caused by superinfection at day 9 (n, %)	3 (15%)	3 (15%)	NS
Recurrence of *P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

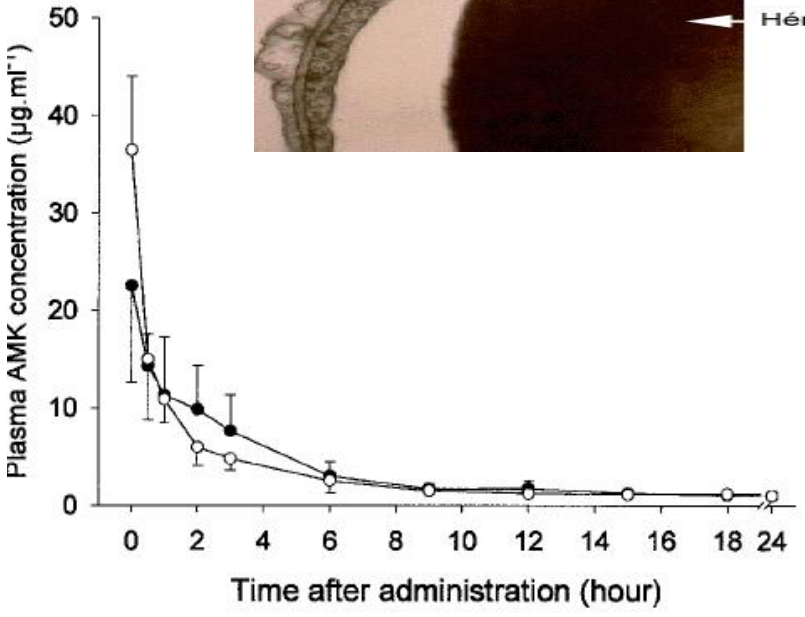
Vibrating mesh nebulizer: continous delivery

Systemic exposure of Amikacin after inhaled or intravenous Amikacin



Healthy Piglets





Piglets with pneumonia

Golstein et al, AJRCCM 2002

Concentration plasmatique d'amikacine

Lu et al, AJRCCM 2011

Table 5 Amikacin and ceftazidime plasma concentrations measured on days 3 and 4

	Aerosol	IV	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

→ Monitoring of trough amikacin trough concentration in patients with renal insufficienct is recommended

Pharmacokinetics of high-dose nebulized amikacin in ventilated critically ill patients

A. Petitcollin[1], P.-F. Dequin[2], F. Darrouzain[1], L. Vecellio[3,4], T. Boulain[5], D. Garot[2], G. Paintaud[1], D. Ternant[1]* and S. Ehrmann[2–4]

J Antimicrob Chemoter, 2016

Nebulized amikacin: 60 mg/kg

Conclusions: Our pharmacokinetic model provided an accurate description of amikacin concentrations following nebulization. There was wide interindividual and interoccasion variability in the absorption and elimination of amikacin. Nevertheless, systemic exposure after nebulization was always much lower than after infusion, an observation suggesting that nebulized high doses are safe in this regard and may be used to treat ventilator-associated pneumonia.

New guidelines on inhaled antibiotic therapy

Kalil et al, Clinical Infectious Diseases

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 MDR.

Conclusion

- Lung tissue penetration of aminoglycosides is poor
- Cmax/Mic is positively correlated to the IV dose, but increasing IV dose could increase the risk of nephrotoxicity
- Results of the recent meta-analysis didn't find the beneficial effect of using combined β-lactams and aminoglycosides for sepsis
- Nebulization of aminoglycosides generates high lung concentrations and may reduce emergence of bacterial resistance
- Further investigations are required to assess the effectiveness of inhaled aminoglycosides as mono or adjunctive therapy in VAP.