

AMINOSIDES



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1^{ère} session – Janvier 2024*

PLAN

Histoire

Structure et mode d'action

Spectre d'action

PK-PD

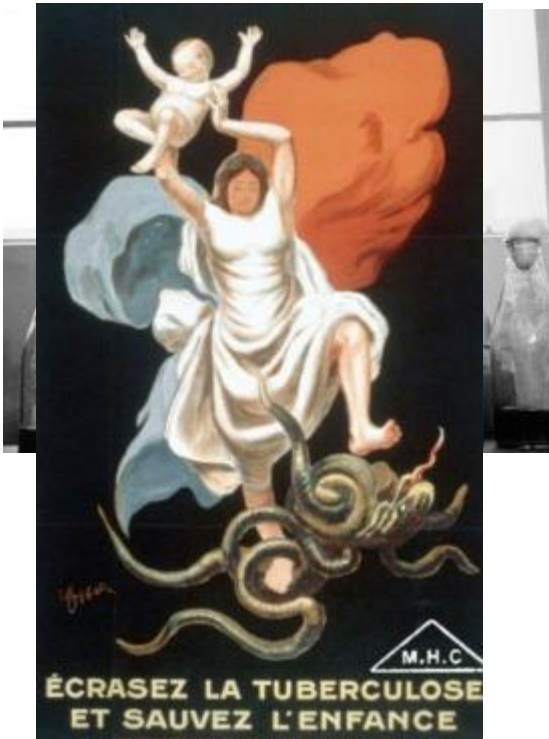
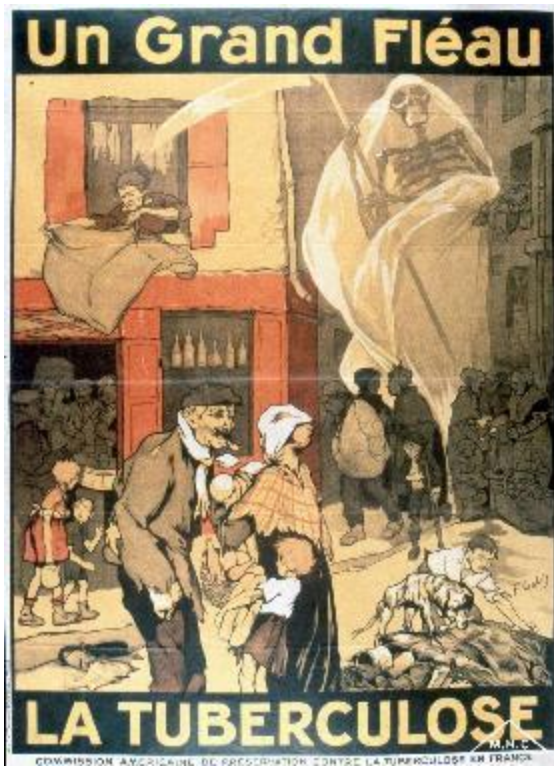
Indications

Effets secondaires

Surveillance

HISTOIRE

- 1944 : STREPTOMYCINE
 - Souche de *Streptomyces griseus*



Selman Abraham Waksman
Albert Schatz

Streptomycin, a Substance Exhibiting Antibiotic Activity Against Gram-Positive and Gram-Negative Bacteria.*†

ALBERT SCHATZ, ELIZABETH BUGIE, AND SELMAN A. WAKSMAN.
From the New Jersey Agricultural Experiment Station, New Brunswick, N.J.

HISTOIRE

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

HISTOIRE

- Groupes

Streptomycine : 33

Contrôle : 24

TABLE II.—*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission*

Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement ..	28	51%	4	8%
Moderate or slight improvement	10	18%	13	25%
No material change	2	4%	3	6%
Moderate or slight deterioration	5	9%	12	23%
Considerable deterioration ..	6	11%	6	11%
Deaths	4	7%	14	27%
Total	55	100%	52	100%

HISTOIRE

Contrôle

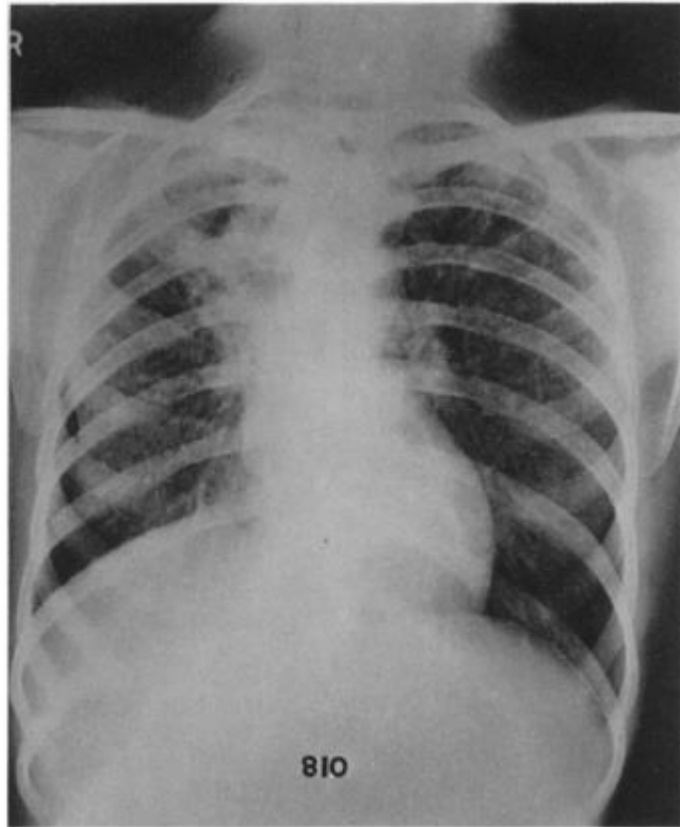


FIG. 7.—Case 81 (C). Feb. 27, 1947.

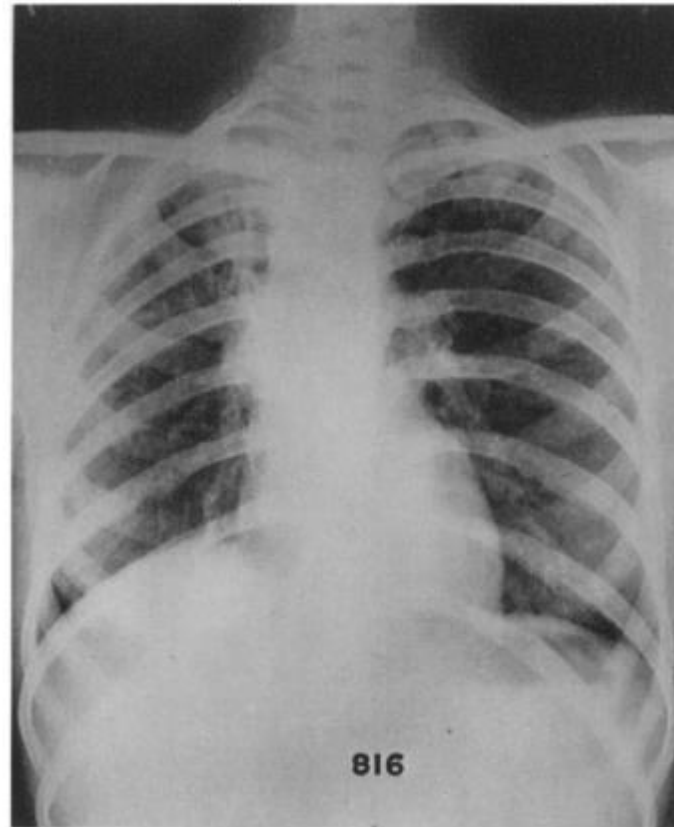


FIG. 8.—Case 81 (C). Aug. 27, 1947.

HISTOIRE

Streptomycine

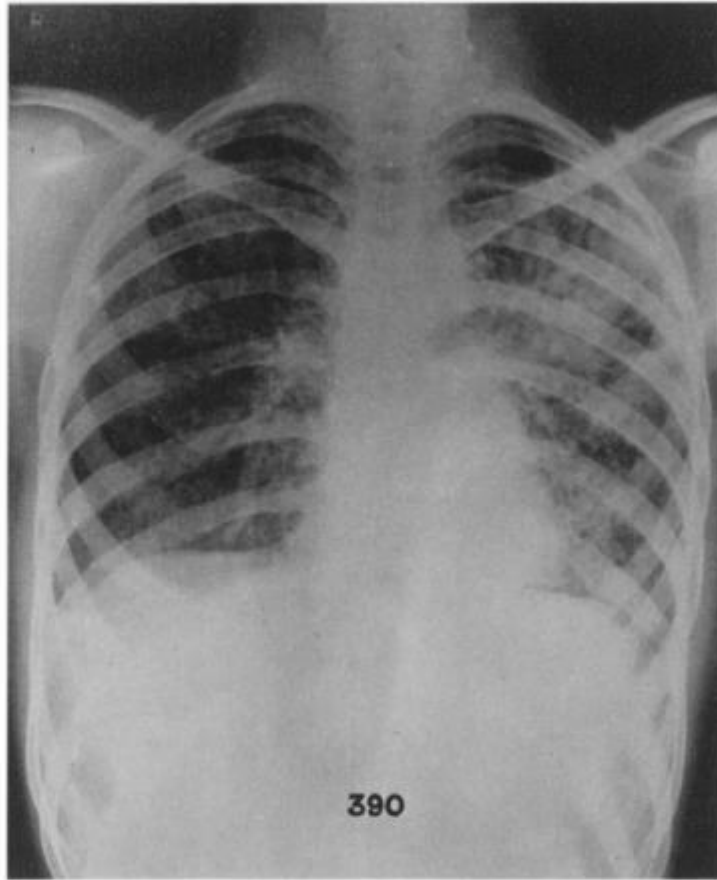


FIG. 5.—Case 39 (S). June 21, 1947.

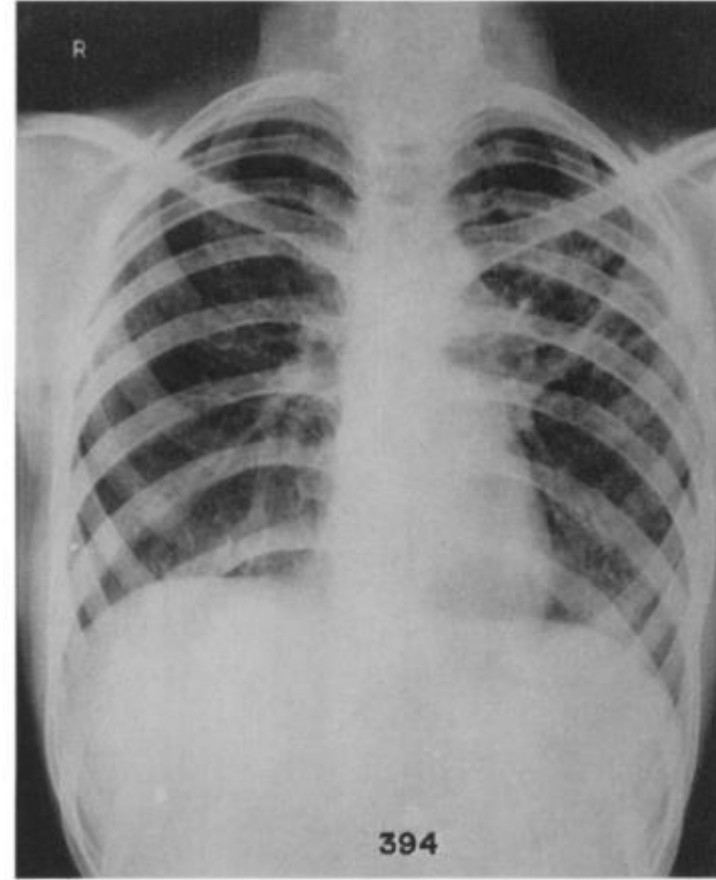


FIG. 6.—Case 39 (S). Oct. 20, 1947.

HISTOIRE

TABLE XIII.—*Presence of Tubercle Bacilli*

Results on Admission	Total	Deaths	Results in Third Month			
			Direct Smear		Smear Negative Culture Positive	Culture Negative
			Strongly Positive	Weakly Positive		
S Cases:						
Smear strongly positive	40	0	16	12	10	2
Smear weakly positive ..	11	0	1	3	1	6
Smear negative, culture positive	3	0	1	0	0	2
C Cases:						
Smear strongly positive	29	5	19	3	1	1
Smear weakly positive ..	17	1	6	8	2	0
Smear negative, culture positive	4	0	1	1	2	0
Results at End of 6 Months						
S Cases:						
Smear strongly positive	40	4	24	1	7	4
Smear weakly positive ..	11	0	3	3	2	3
Smear negative, culture positive	3	0	1	0	1	1
C Cases:						
Smear strongly positive	29	11	15	2	0	1
Smear weakly positive ..	17	3	4	7	3	0
Smear negative, culture positive	4	0	0	1	2	1

Streptomycine

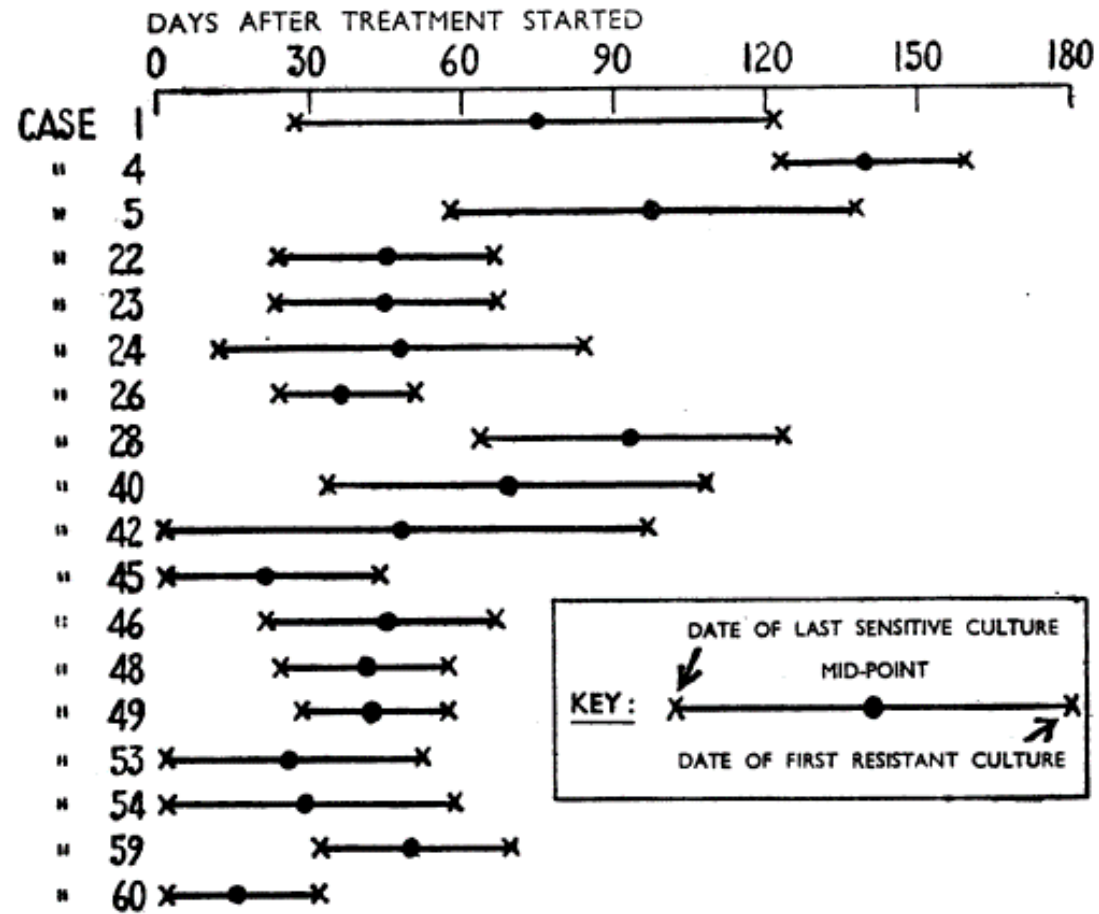
Contrôle

Streptomycine

Contrôle



INTRODUCTION



RESISTANCE

INTRODUCTION

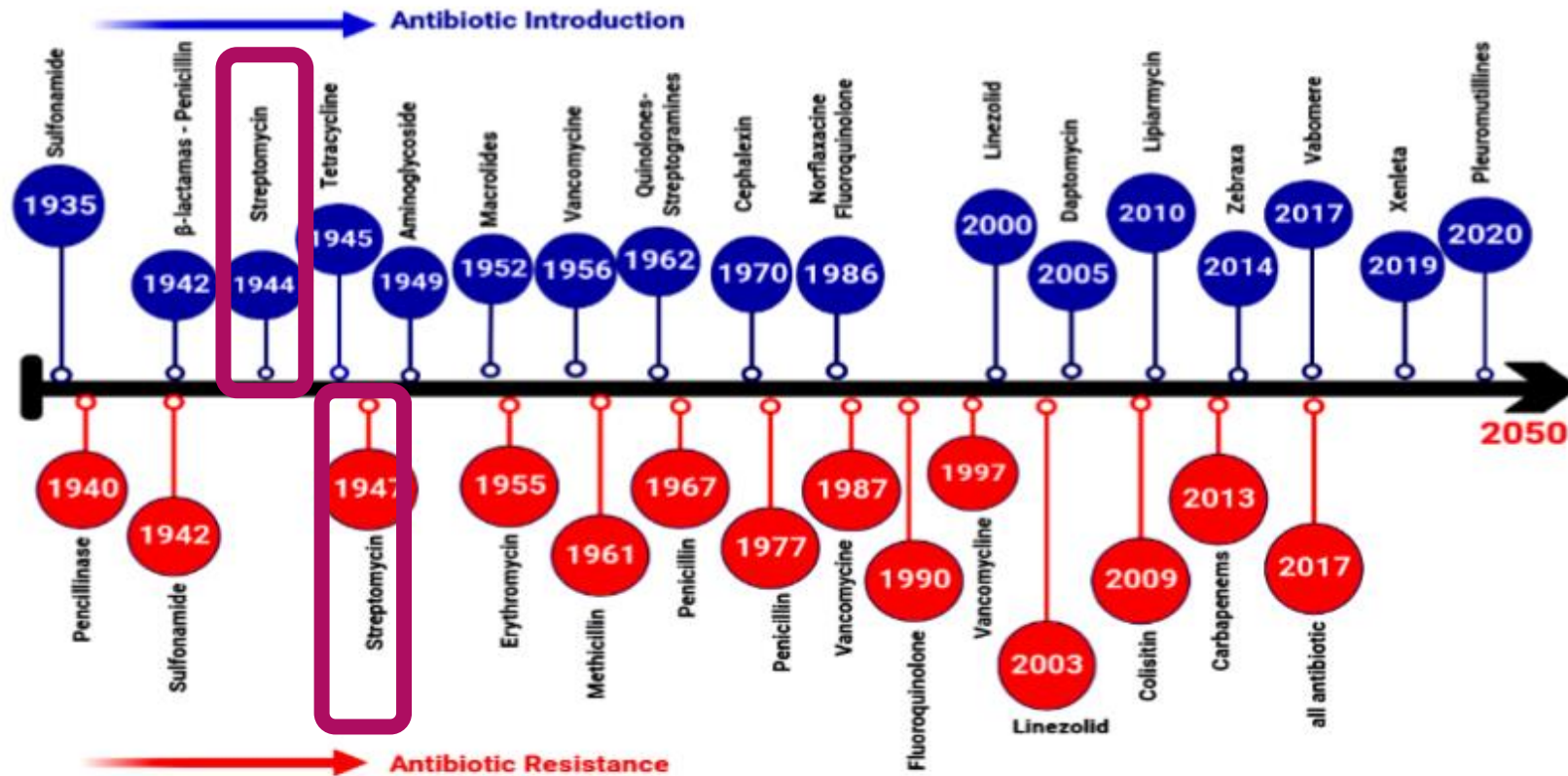


Figure 1. Timeline illustrates antibiotics evolution.

PLAN

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Structure et mode d'action

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PK-PD

Indications

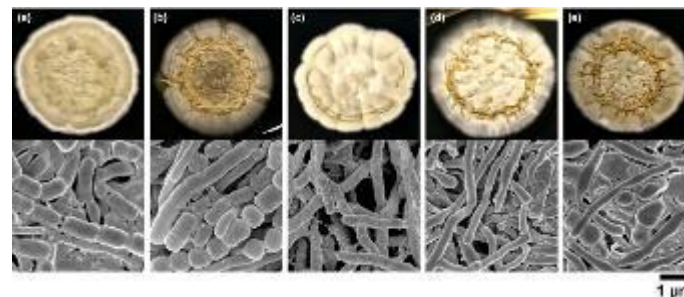
Effets secondaires

Surveillance

STRUCTURE ET MODE D ACTION

- 50 molécules → 9 utilisées en thérapeutique

Aminosides naturels		Aminosides hemi-synthétique
Extraits de <i>Streptomyces</i> (<i>y</i>)	Streptomycine	Amikacine
	Néomycine	Isepamycine
	Kanamycine	Netilmicine
	Tobramycine	
Extraits de <i>Actinomyces</i> (<i>i</i>)	Gentamicine	
	Sisomicine	



STRUCTURE ET MODE D ACTION

Quel est le mode d'action des aminosides ?

BACTERICIDE



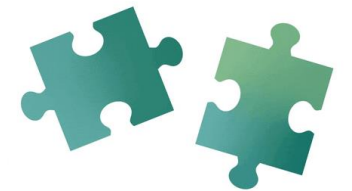
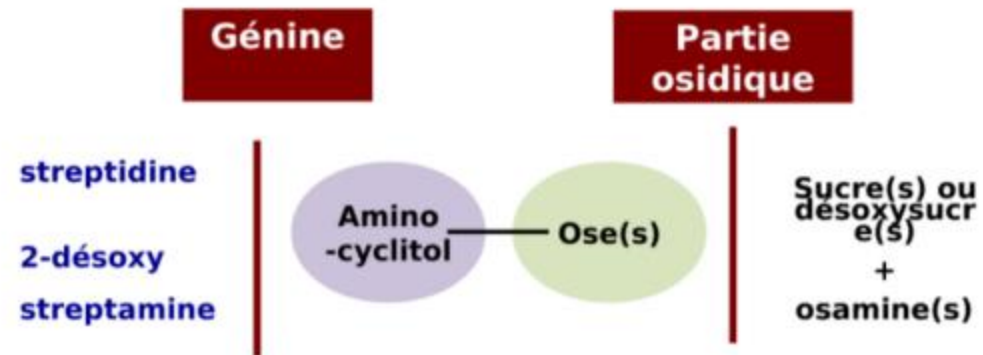
BACTERIOSTATIQUE



STRUCTURE ET MODE D ACTION

- Aminosides = Hétérosides

AMINO GLYCOSIDE



STRUCTURE ET MODE D ACTION

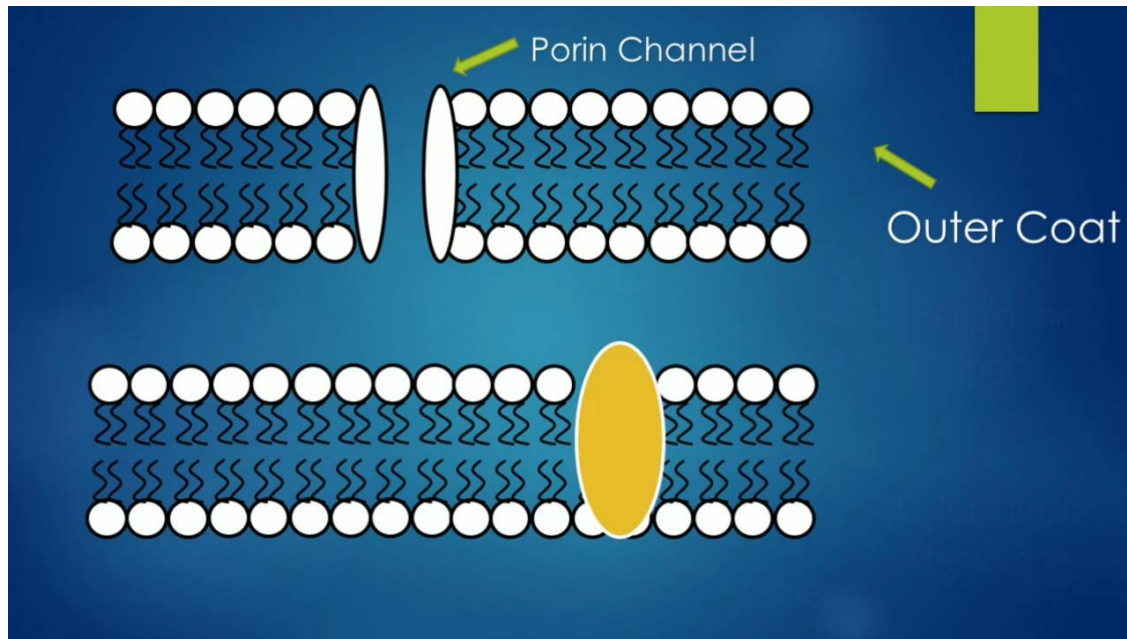
- Implications physico-chimique :
 - Fonctions azotés et hydroxyles → HYDROPHILE , peu LIPOPHILE
 - Utilisés sous forme de sels (sulfate) → solution ACIDE
 - Incompatibilité physico-chimique +++
 - **Ne pas mélanger avec d'autres traitements** → PRECIPITATIONS

STRUCTURE ET MODE D ACTION

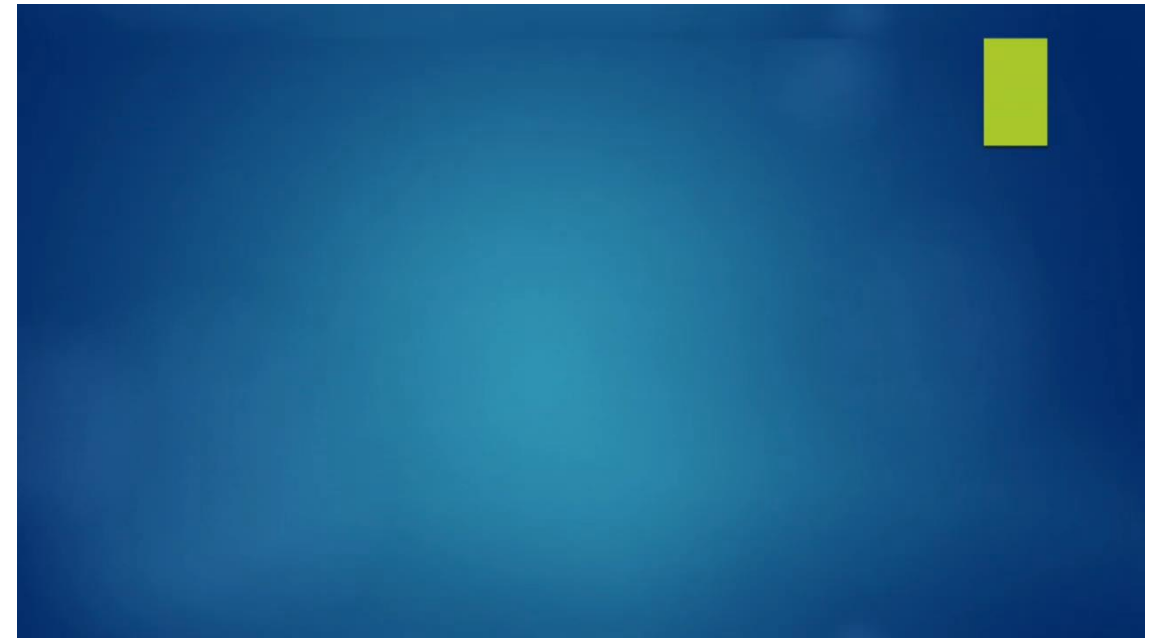
Quelle est la cible des aminosides ?

- A- Topo-isomérase
- B- Peptidoglicane
- C- Ribosome
- D- La réponse D

STRUCTURE ET MODE D ACTION



ENTREE : DEPENDANTE DE L OXYGENE



**LESION IRREVERSIBLE SOUS
UNITE 30S RIBOSOME**

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Surveillance

SPECTRE D'ACTION

Quelle(s) bactérie(s) sont sensible(s) [spectre sauvage] ?

A- E coli

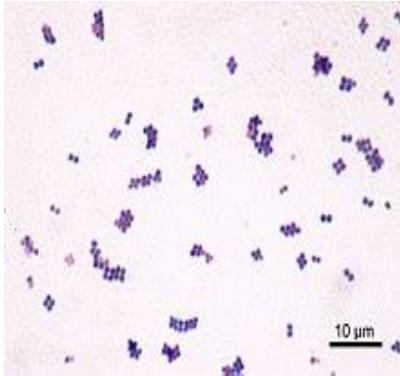
B- Listeria monocytogénès

C- Clostridium perfringens

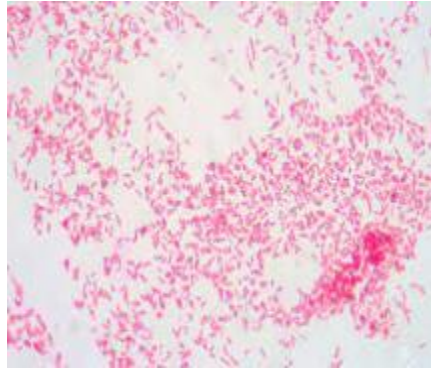
D- Mycobacterium tuberculosis

SPECTRE UTILE

Cocci +



**Bacilles
gram négatif**



*Listeria
monocytogénès*



Mycobateries



**GENTAMICINE
AMIKACINE**

SPECTRE UTILE

Pseudomonas spp.

Expert Rules and Intrinsic Resistance Tables

Aminoglycosides ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Amikacin (systemic infections)	(16) ¹	(16) ¹		30	(15) ^A	(15) ^A	
Amikacin (infections originating from the urinary tract)	16	16		30	15	15	
Gentamicin (systemic infections)	IE	IE			IE	IE	
Gentamicin (infections originating from the urinary tract)	IE	IE			IE	IE	
Netilmicin	IE	IE			IE	IE	
Tobramycin (systemic infections)	(2) ¹	(2) ¹		10	(18) ^A	(18) ^A	
Tobramycin (infections originating from the urinary tract)	2	2		10	18	18	

SPECTRE UTILE

***Pseudomonas* spp.**

Expert Rules and Intrinsic Resistance Tables

- **TOBRAMYCINE :**

- Le + bactéricide
- Le – de résistance



Resistance de haut niveau

- **AMIKACINE:**

- Resistance fréquente
- BAS NIVEAU (efflux) => OK forte posologie

SPECTRE UTILE

Acinetobacter spp.

Expert Rules and Intrinsic Resistance Tables

Aminoglycosides ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≥	R >	ATU		S ≥	R <	ATU
Amikacin (systemic infections)	(8) ¹	(8) ¹		30	(19) ^A	(19) ^A	
Amikacin (infections originating from the urinary tract)	8	8		30	19	19	
Gentamicin (systemic infections)	(4) ¹	(4) ¹		10	(17) ^A	(17) ^A	
Gentamicin (infections originating from the urinary tract)	4	4		10	17	17	
Netilmicin	IE	IE			IE	IE	
Tobramycin (systemic infections)	(4) ¹	(4) ¹		10	(17) ^A	(17) ^A	
Tobramycin (infections originating from the urinary tract)	4	4		10	17	17	

SPECTRE UTILE

Staphylococcus spp.

Expert Rules and Intrinsic Resistance Tables

Aminoglycosides ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Amikacin ² , <i>S. aureus</i>	(16) ¹	(16) ¹		30	(15) ^A	(15) ^A	
Amikacin ² , Coagulase-negative staphylococci	(16) ¹	(16) ¹		30	(15) ^A	(15) ^A	
Gentamicin, <i>S. aureus</i>	(2) ¹	(2) ¹		10	(18) ^A	(18) ^A	
Gentamicin, Coagulase-negative staphylococci	(2) ¹	(2) ¹		10	(22) ^A	(22) ^A	
Netilmicin	IE	IE			IE	IE	
Tobramycin, <i>S. aureus</i>	(2) ¹	(2) ¹		10	(18) ^A	(18) ^A	
Tobramycin, Coagulase-negative staphylococci	(2) ¹	(2) ¹		10	(20) ^A	(20) ^A	

SPECTRE UTILE

RESISTANCES NATURELLES

- ***Streptococcus sp, Enterococcus sp*** : BAS NIVEAU

Association avec un ATB actif sur la paroi

- ***Stenotrophomas maltophila***
- **Bactéries intracellulaires**
- **Anaerobies**



SPECTRE UTILE

RESISTANCE ACQUISE

- **MODIFICATION ENZYMATIQUE**
 - Plasmidique => diffusion
 - Haut niveau
- **DEFAUT DE PERMEABILITE**
 - Modification des porines
 - Altération du transport actif
 - Efflux
 - Haut niveau
- **MODIFICATION DE LA CIBLE**
 - Chromosomique et rare

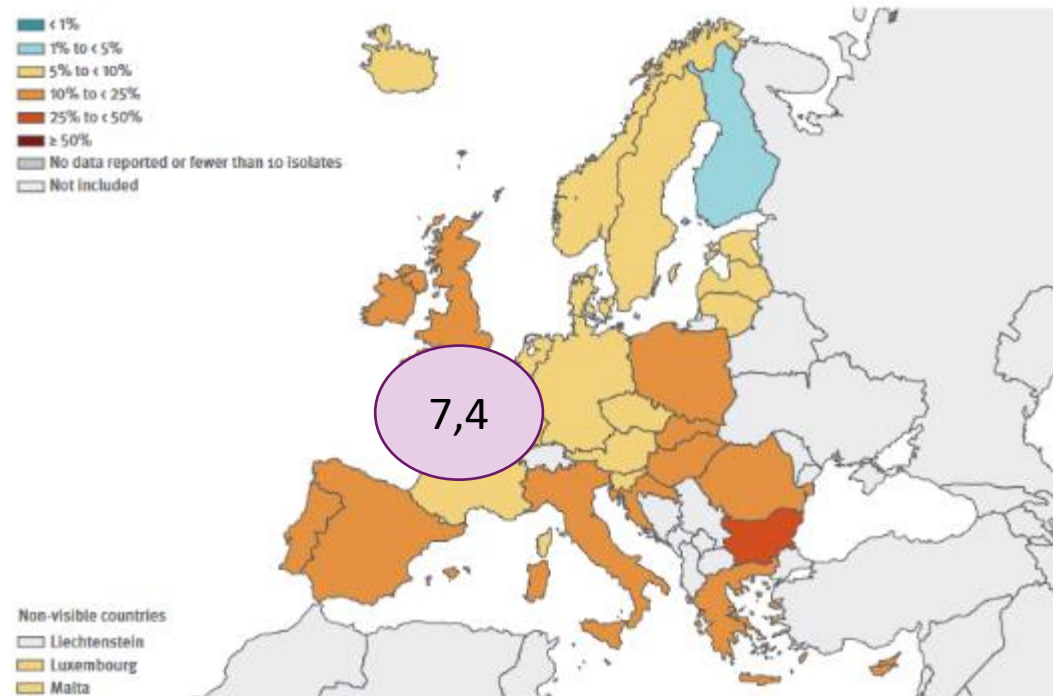
SPECTRE UTILE

Total number of invasive isolates tested (N) and percentage with resistance to aminoglycosides (%R), including 95 % confidence intervals (95 % CI), EU/EEA countries, 2015 to 2018

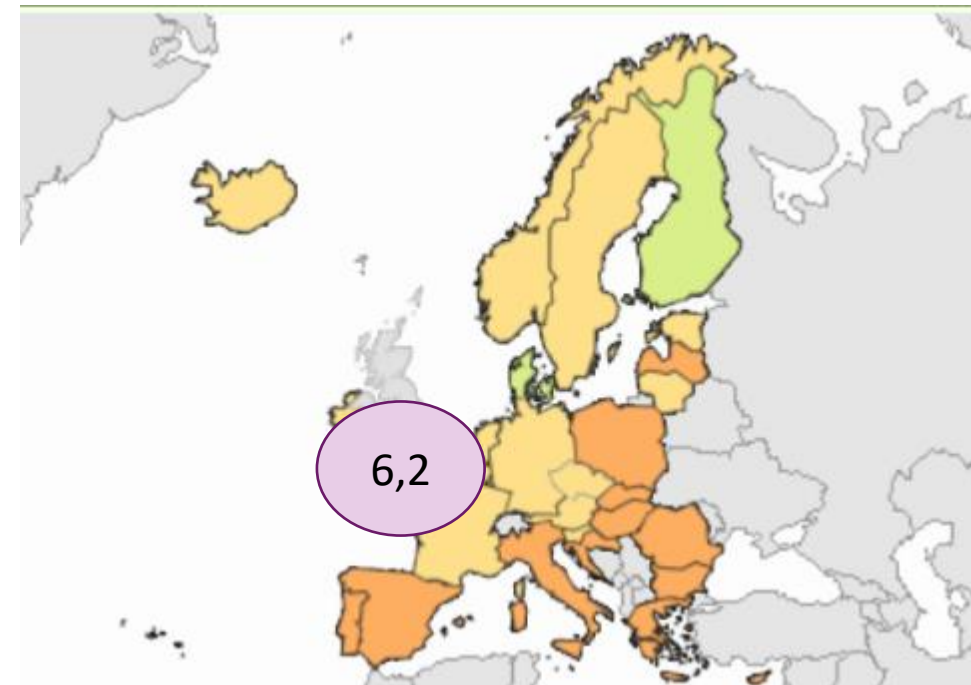
GERMES	2015		2016		2017		2018	
	N	%R (95%IC)	N	%R (95%IC)	N	%R (95%IC)	N	%R (95%IC)
<i>E.coli</i>	11 055	8.2 (8-9)	11 135	7.9 (7-8)	13 103	7.0 (7-7)	12 283	7.4 (7-8)
<i>K. pneumoniae</i>	2 337	26.3 (25-28)	2569	26.2 (25-28)	2 857	23.8(22-25)	2990	24.8 (23-26)
<i>P. Aeruginosa</i>	1950	14.1 (13-16)	1 976	10.7 (9-12)	1 713	10.9 (9-12)	1 898	9.3 (8-11=
<i>A. Spp</i>	431	11.1 (8-14)	449	12.2 (9-16)	474	9.1 (7-12)	482	8.9 (7-12)

SPECTRE UTILE

Figure 3-4. *Escherichia coli*. Percentage (%) of invasive isolates with resistance to aminoglycosides, by country, EU/EEA countries, 2018



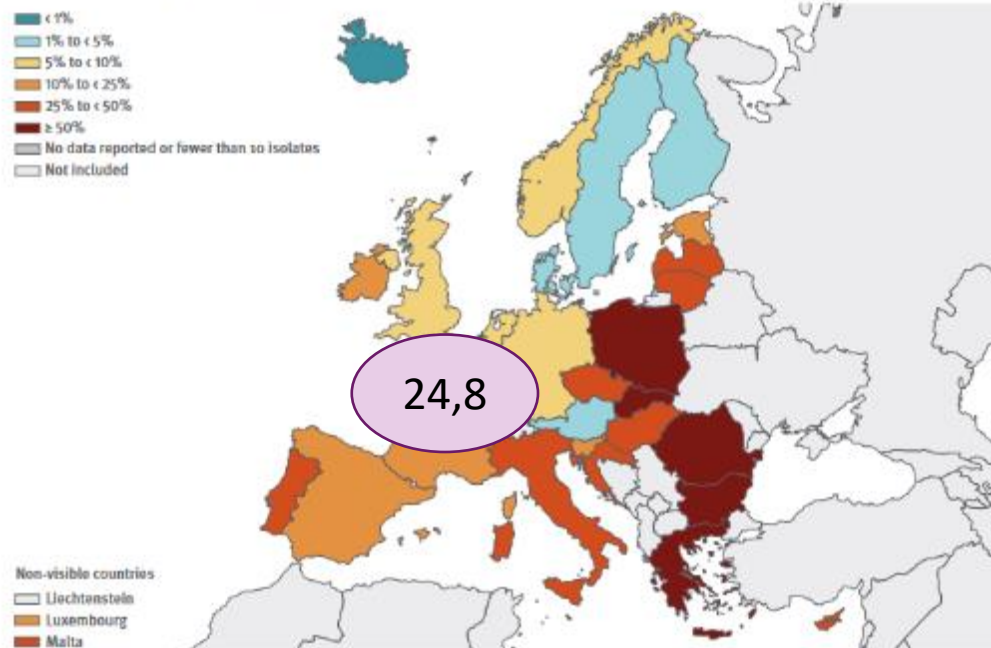
ECDC : Surveillance of antimicrobial resistance in Europe 2018



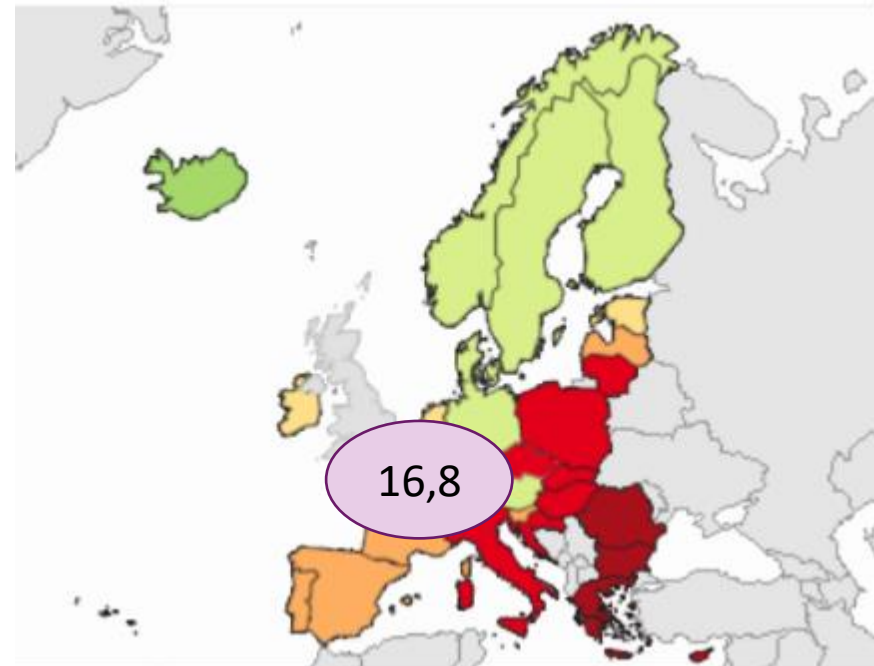
ECDC : Surveillance of antimicrobial resistance in Europe 2022

SPECTRE UTILE

Figure 3.10. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to aminoglycosides, by country, EU/EEA countries, 2018



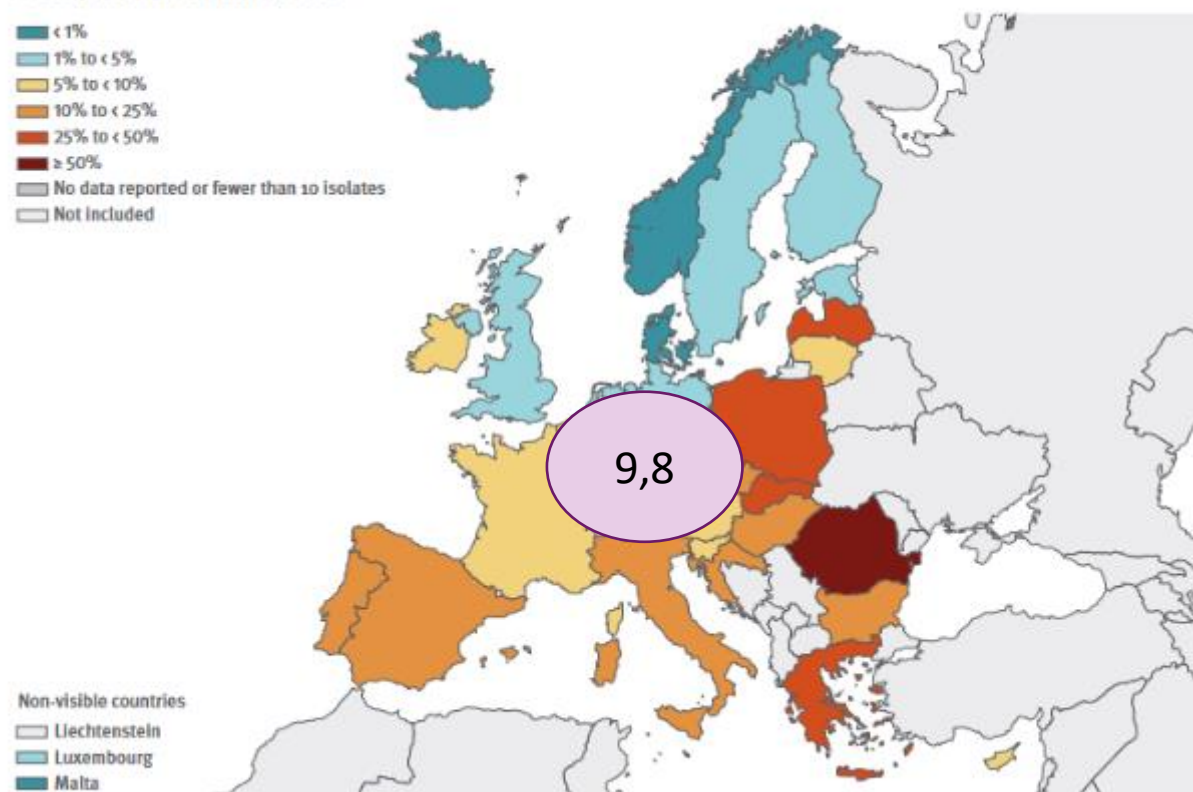
ECDC : Surveillance of antimicrobial resistance in Europe 2018



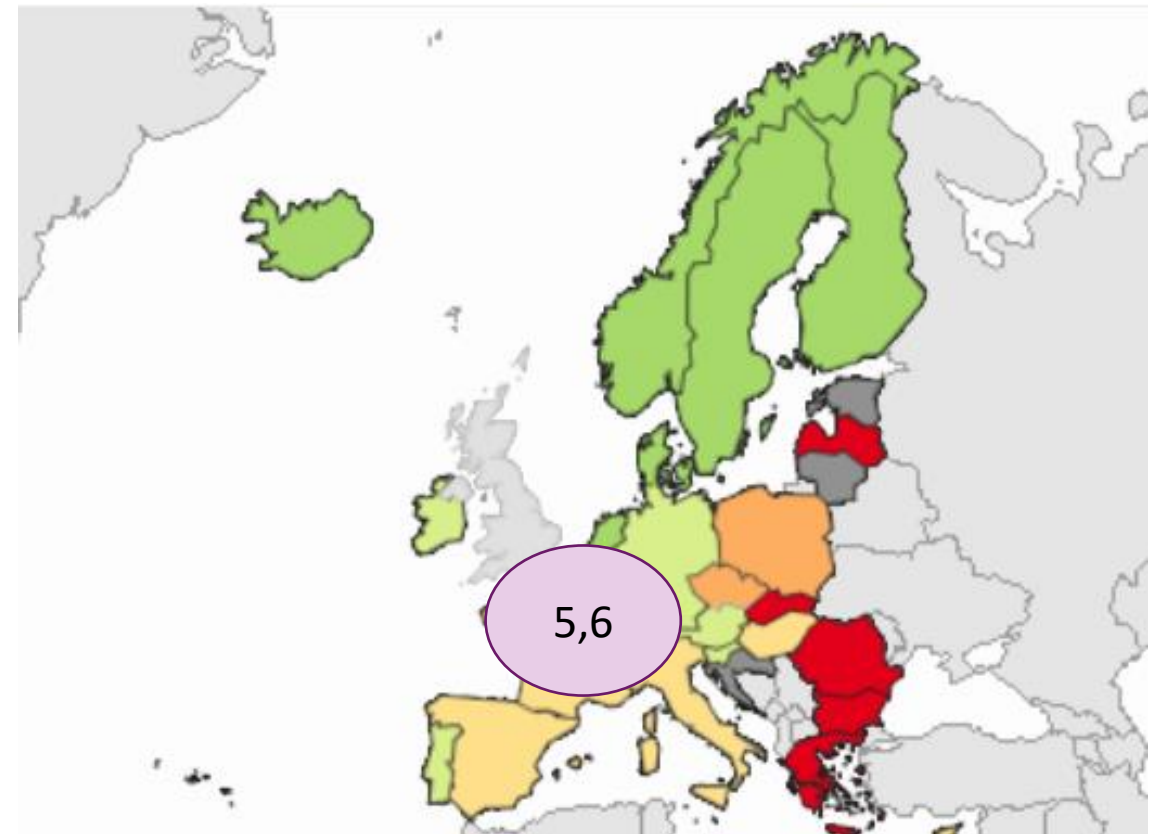
ECDC : Surveillance of antimicrobial resistance in Europe 2022

SPECTRE UTILE

Figure 3.16. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to aminoglycosides, by country, EU/EEA countries, 2018



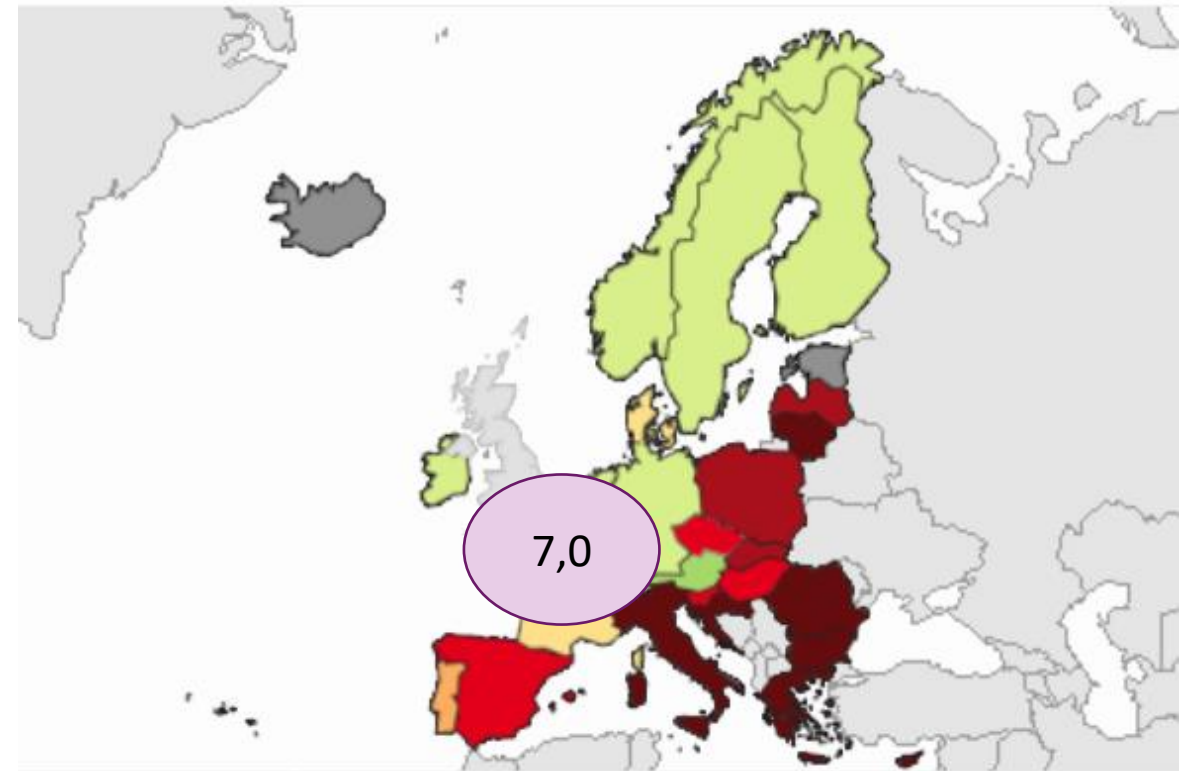
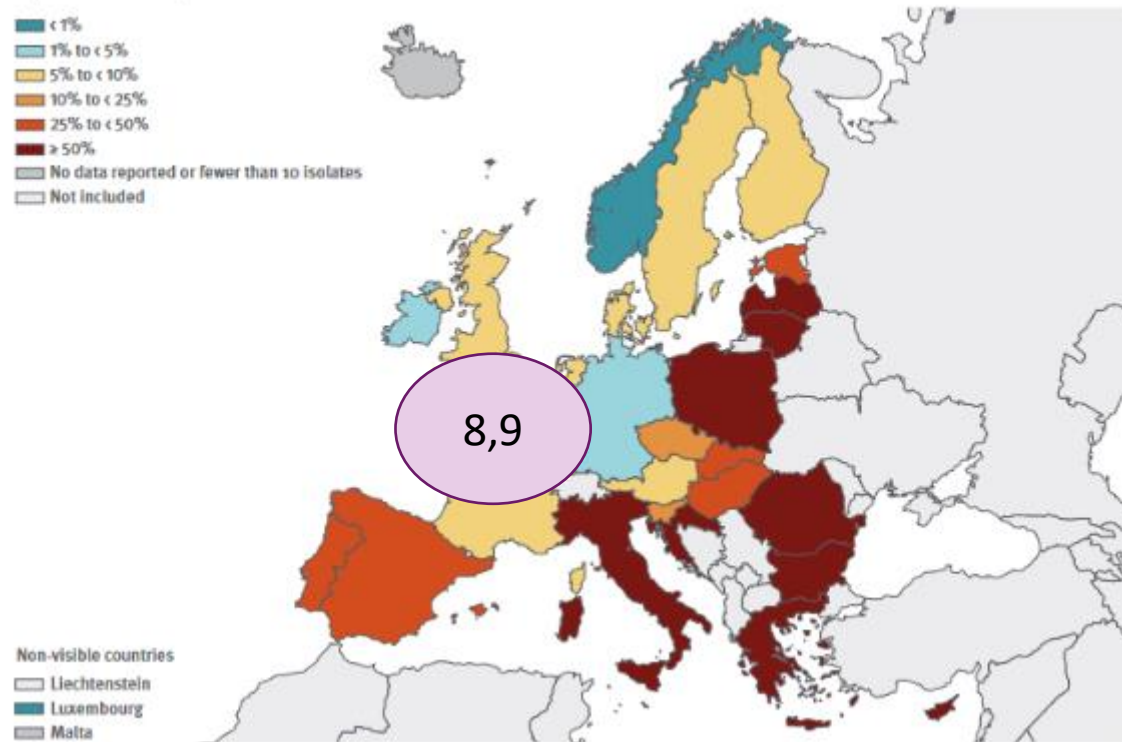
ECDC : Surveillance of antimicrobial resistance in Europe 2018



ECDC : Surveillance of antimicrobial resistance in Europe 2022

SPECTRE UTILE

Figure 3.21. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to aminoglycosides, by country, EU/EEA countries, 2018



ECDC : Surveillance of antimicrobial resistance in Europe 2018

ECDC : Surveillance of antimicrobial resistance in Europe 2022

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PK/PD

PHARMACOCINETIQUE (PK) :

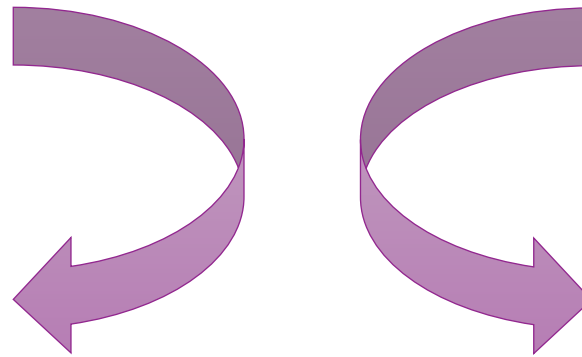
PHARMACODYNAMIE (PD)



PK/PD

Quelle est la pharmacodynamie des aminosides?

TEMPS DEPENDANT

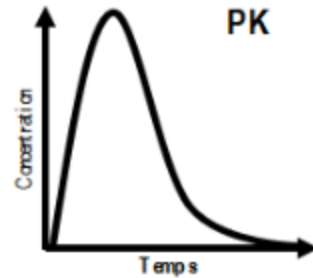


CONCENTRATION
DEPENDANT

PK/PD

PHARMACOCINETIQUE (PK) :

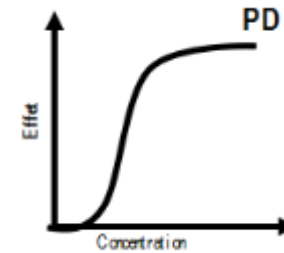
- Absorption
- Biodisponibilité
- Diffusion
- Demi-vie
- Métabolisme
- Elimination



CONCENTRATION

PHARMACODYNAMIE

Action de l'antibiotique



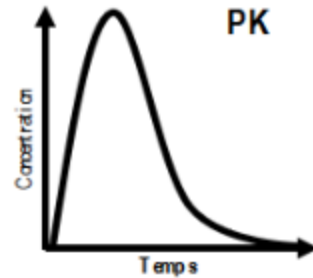
SITE INFECTION :
EFFICACITE

TISSUS :
TOXICITE

PK/PD

PHARMACOCINETIQUE (PK) :

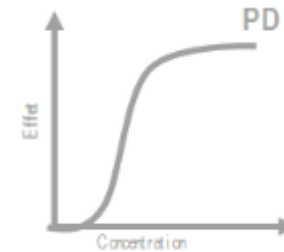
- Absorption
- Biodisponibilité
- Diffusion
- Demi-vie
- Métabolisme
- Elimination



CONCENTRATION

PHARMACODYNAMIE

Action de l'antibiotique



SITE INFECTION :
EFFICACITE

TISSUS :
TOXICITE

PK/PD

Mise au point • mars 2011



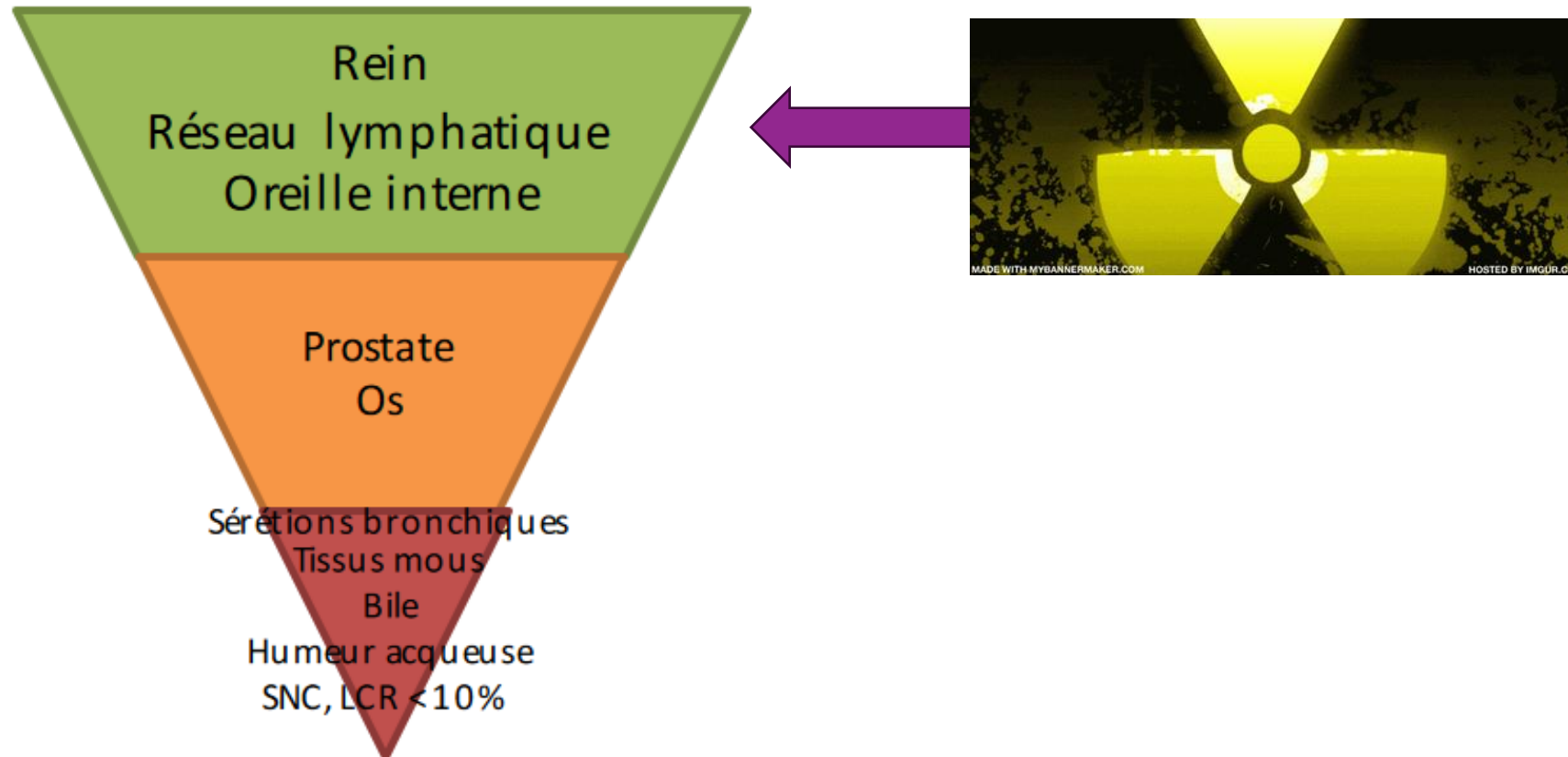
Mise au point sur le bon usage des aminosides administrés par voie injectable : gentamicine, tobramycine, nétilmicine, amikacine

PK/PD

- **ABSORPTION : Voie IV**
 - Absence d'absorption enterale
- **FIXATION AU PROTEINES :**
 - faible 20%
- **ELIMINATION**
 - Rénale (forme inchangée) → Toxicité !!!
 - Faible sécrétion biliaire
- **DEMI VIE D ELIMINATION : 2h**

PK/PD

- **VOLUME DE DISTRIBUTION : faible : 0,3-0,4L/kg**
 - diffusion médiocre : SNC, bronche et humeur aqueuse



PK/PD

PHARMACOCINETIQUE (PK) :

- Absorption
- Biodisponibilité
- Diffusion
- Demi-vie
- Métabolisme
- Elimination



• RISQUE DE MODIFICATION PK :

Insuffisance rénale

Nouveau né

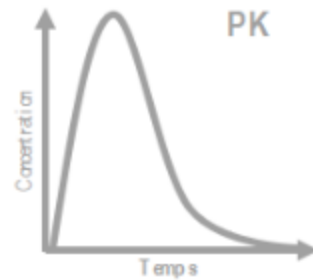
Sujet âgé

Modification du volume de distribution

PK/PD

PHARMACOCINETIQUE (PK) :

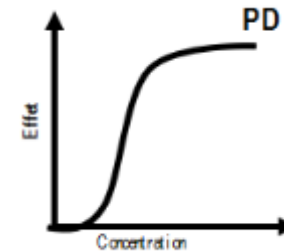
- Absorption
- Biodisponibilité
- Diffusion
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- Métabolisme
- Elimination



CONCENTRATION

PHARMACODYNAMIE

Action de l'antibiotique



SITE INFECTION :
EFFICACITE

TISSUS :
TOXICITE

PK/PD

TEMPS VERSUS CONCENTRATION DEPENDANT :

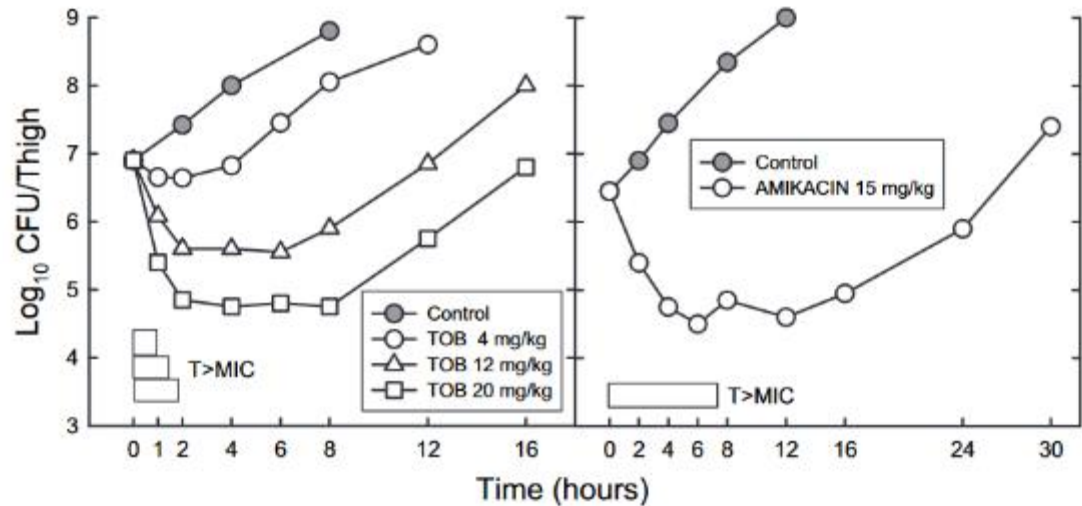
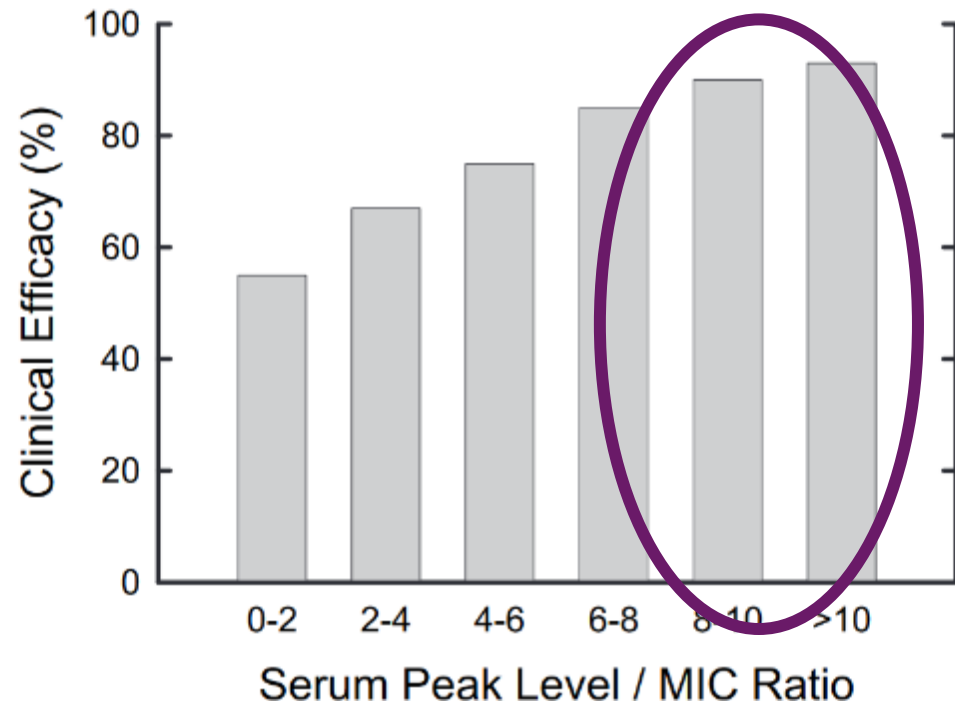


Fig. 1. The time course of killing and regrowth of *Pseudomonas aeruginosa* in thighs of neutropenic mice following 3 doses of tobramycin (TOB) in normal mice (*left panel*) and amikacin in mice with renal impairment (*right panel*). T>MIC, time above minimum inhibitory concentration.

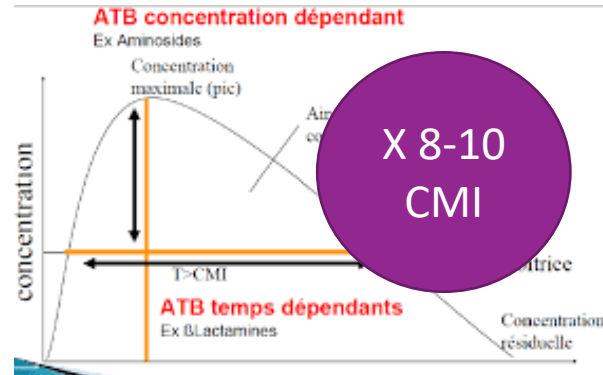


PK/PD

BACTERICIDE RAPIDE



CONCENTRATION DEPENDANT



EFFET POST ANTIBIOTIQUE



PK/PD

- **ADMINISTRATION :**

- IVL : 30 min (éviter sous cutanée et IM)

- **DOSE UNIQUE JOURNALIERE**

- 8-10 CMI
- Passage tissulaire
- Efficacité clinique
- Toxicité équivalente
- Diminution risque de mutants résistants

- **DUREE : COURTE**

- Inoculum important
- <5 jours

PK/PD

REFERENTIELS

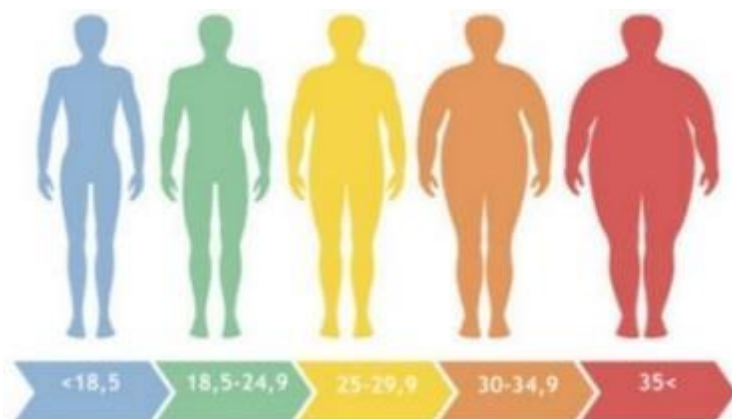
- gentamicine, tobramycine : 3 à 8 mg/kg/jour ;
- nétilmicine : 4 à 8 mg/kg/jour ;
- amikacine : 15 à 30 mg/kg/jou



PK/PD

REFERENTIELS

- gentamicine, tobramycine : 3 à 8 mg/kg/jour ;
- nétilmicine : 4 à 8 mg/kg/jour ;
- amikacine : 15 à 30 mg/kg/jou



Masse maigre !!!!!
Poids corrigé = poids idéale + 0,43x surcharge pondérale

PK/PD



- PEDIATRIE :

- Posologies identiques
- Dose unique journalière
- Cas particulier : prématurés
 - Volume distribution : poids de naissance
 - Poids faible = VD augmenté
 - Clairance : variation rapide
 - Nephrogénèse 32-33 semaines

ATTENTION

ESPACEMENT DES DOSES

Dosages

PLAN

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INDICATIONS THERAPEUTIQUES



**Dans quelles situations cliniques
utiliseriez-vous ces antibiotiques en
premiere intention ?**

- Bactériémie ?
- Choc septique ?
- Immunodéprimé ?
- Listeria ?
- Tuberculose ?

INDICATIONS THERAPEUTIQUES



**Dans quelles situations cliniques
utiliseriez-vous ces antibiotiques en
premiere intention ?**

- **Bactériémie ?**
- **Choc septique ?**
- **Immunodéprimé ?**
- **Listeria ?**
- **Tuberculose ?**

BACTERIEMIE

Etude de cohorte rétrospective : Inclusion toutes les bactériémies , 1 laboratoire en Suede

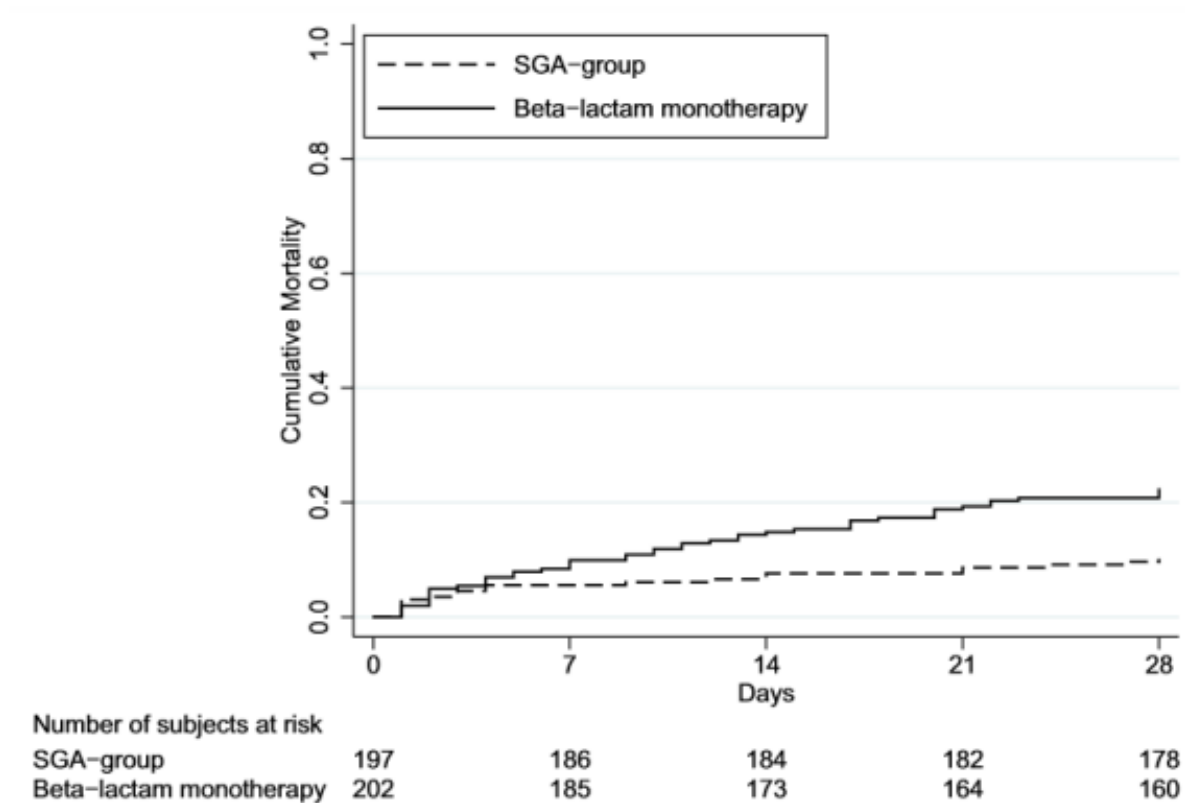


Fig 2. Kaplan Meier curve illustrating the significant difference in mortality between the monotherapy group (22%, 45/202) and SGA (10%, 20/197).

BACTERIEMIE

Table 3. Initial β -lactam treatment and 28-days mortality comparison between study groups.

	β -lactams	β -lactam monotherapy n = 202		SGA-group ¹ n = 197		β -Lactam monotherapy vs SGA groups			
		n	Mortality ³ (%)	n	Mortality ³ (%)	Unadjusted		Adjusted ²	
						HR (95% CI)	p	HR (95% CI)	p
Broad-spectrum β -lactams	Total	77	20 (26)	30	1 (3)	8.6 (1.1–64.2)	0.036	10.2 (1.3–76.9)	0.024
	Ceftazidime	6		2					
	Imipenem/cilastatin	16		7					
	Meropenem	6		1					
	Piperacillin/tazobactam	49	12 (24)	20	0 (0)	n/a ⁴	0.014	n/a ⁴	
Other β -lactams	Total	125	25 (20)	167	167 (11)	1.8 (1.0–3.3)	0.045	3.5 (1.8–6.8)	<0.001
	Benzylpenicillin	20	3 (15)	60	3 (5)	3.3 (0.7–16.3)	0.15	29.4 (2.6–335)	0.006
	Cefotaxime	94	19 (20)	105	16 (15)	1.3 (0.7–2.6)	0.38	2.2 (1.0–4.6)	0.038
	Cefuroxime	5		1					
	Cloxacillin	6		1					



BACTERIEMIE

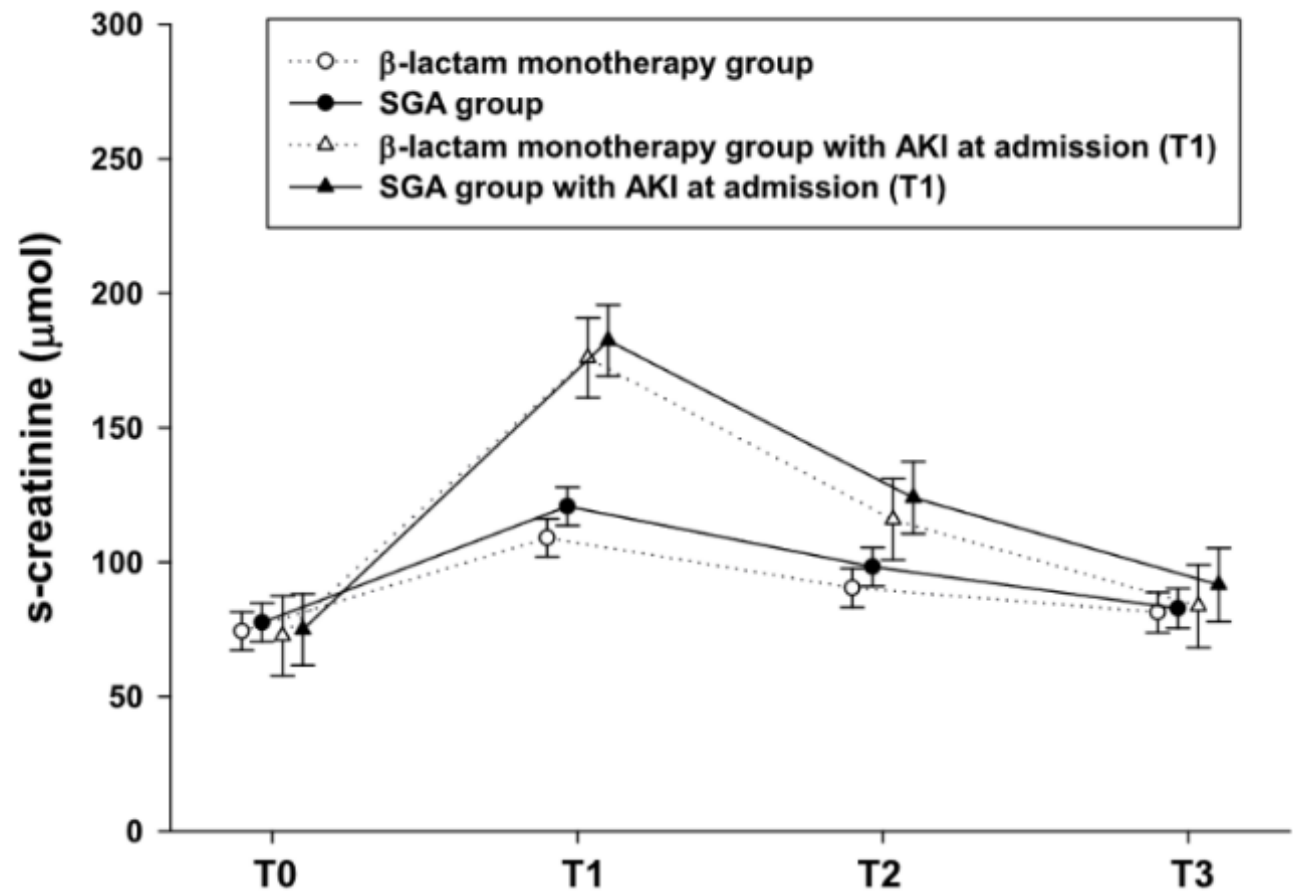
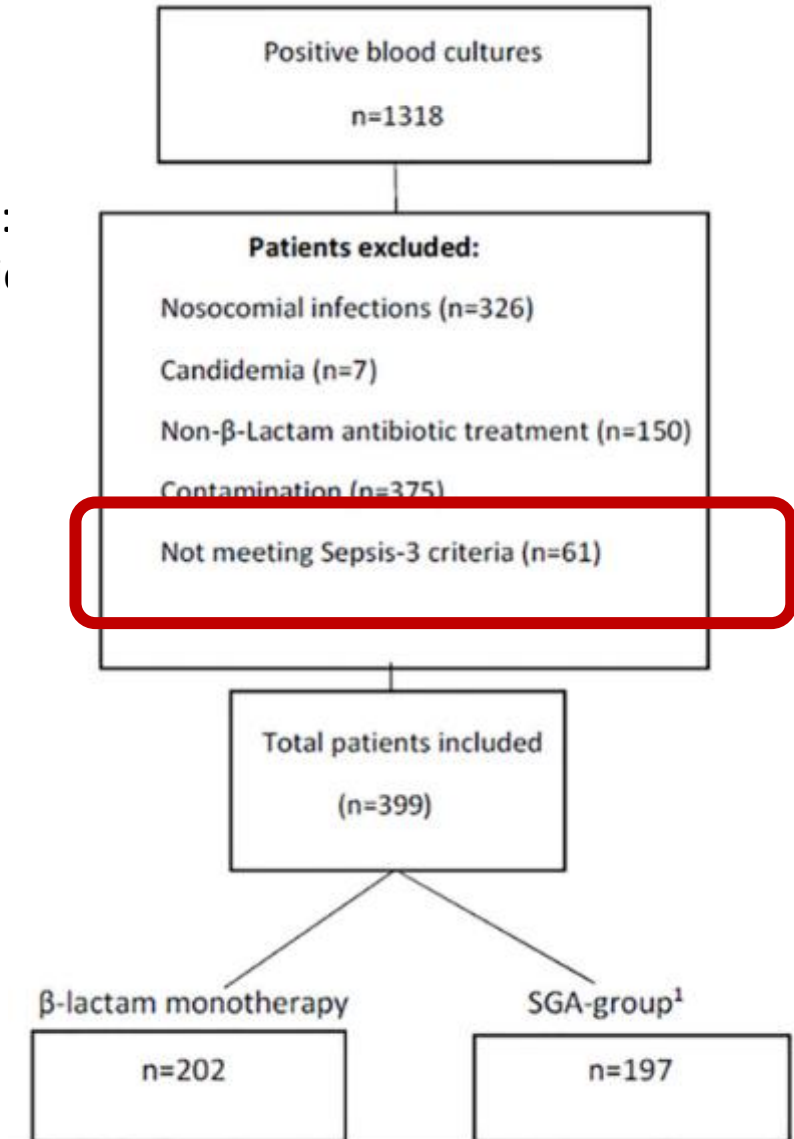


Fig 3. AKI. Mean creatinine from T0 to T3 in β-lactam monotherapy group and SGA group as well for each study group with only patients with AKI at admission (T1). Estimated mean creatinine with 95% confidence intervals by linear mixed model, see statistical section for details.

CHOC SEPTIQUE

Etude de cohorte retrospective :
- Inclusion toutes les bactérièmi



Sepsis-3 criteria :

- Dysfonction d'organe (SOFA ≥ 2)
- Choc septique
 - Besoin aminergique
 - Lactate supérieur à 2

BACTERIEMIE

THE LANCET Infectious Diseases Volume 4, Issue 8, August 2004, Pages 519-527



Review

Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis

Nasia Safdar ^a, Jo Handelsman ^b, Dr Dennis G Maki ^a  

BACTERIEMIE

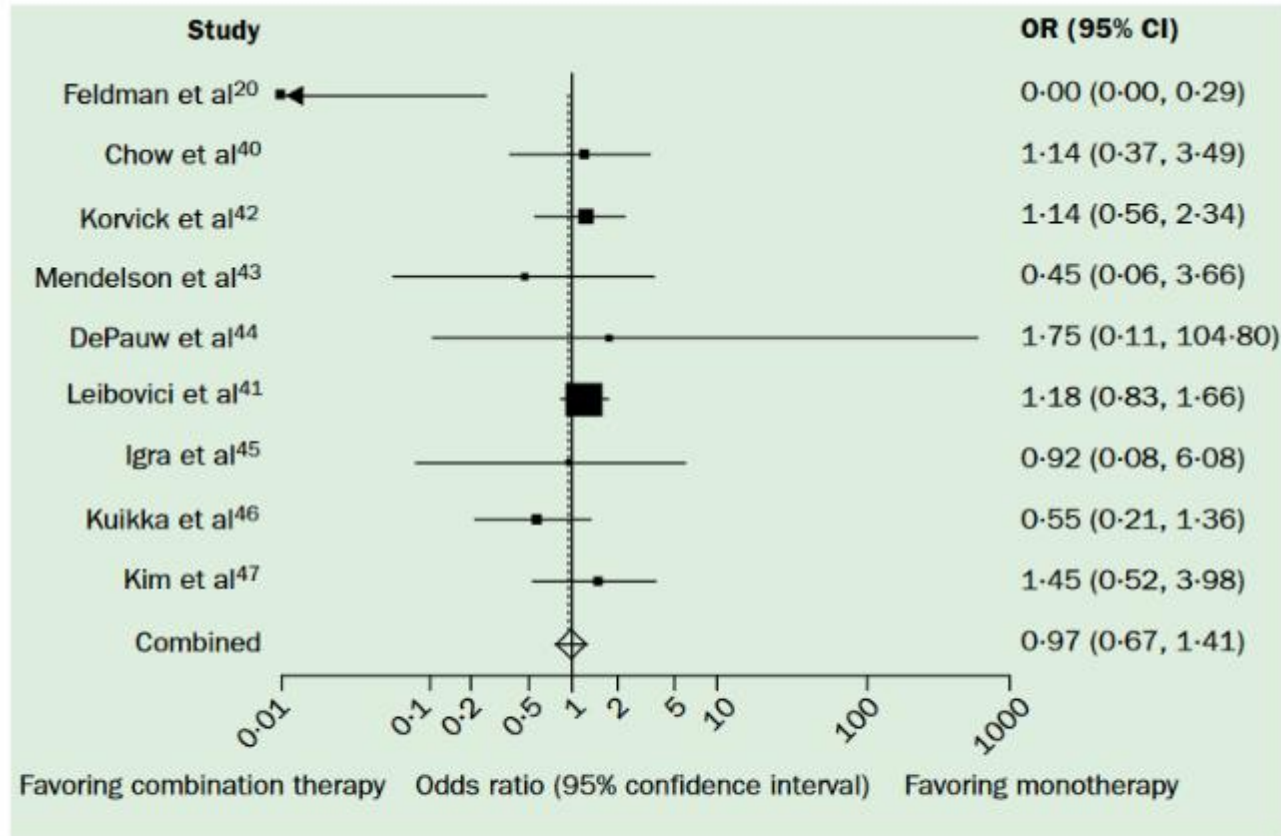


Figure 3. Analysis of studies done in or after 1990 comparing combination anti-infective therapy with monotherapy for reducing mortality of Gram-negative bacteraemia. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 0.97 (95% CI 0.67–1.41), indicating no mortality benefit with combination antimicrobial therapy.

BACTERIEMIE

*Pseudomonas
aeruginosa*

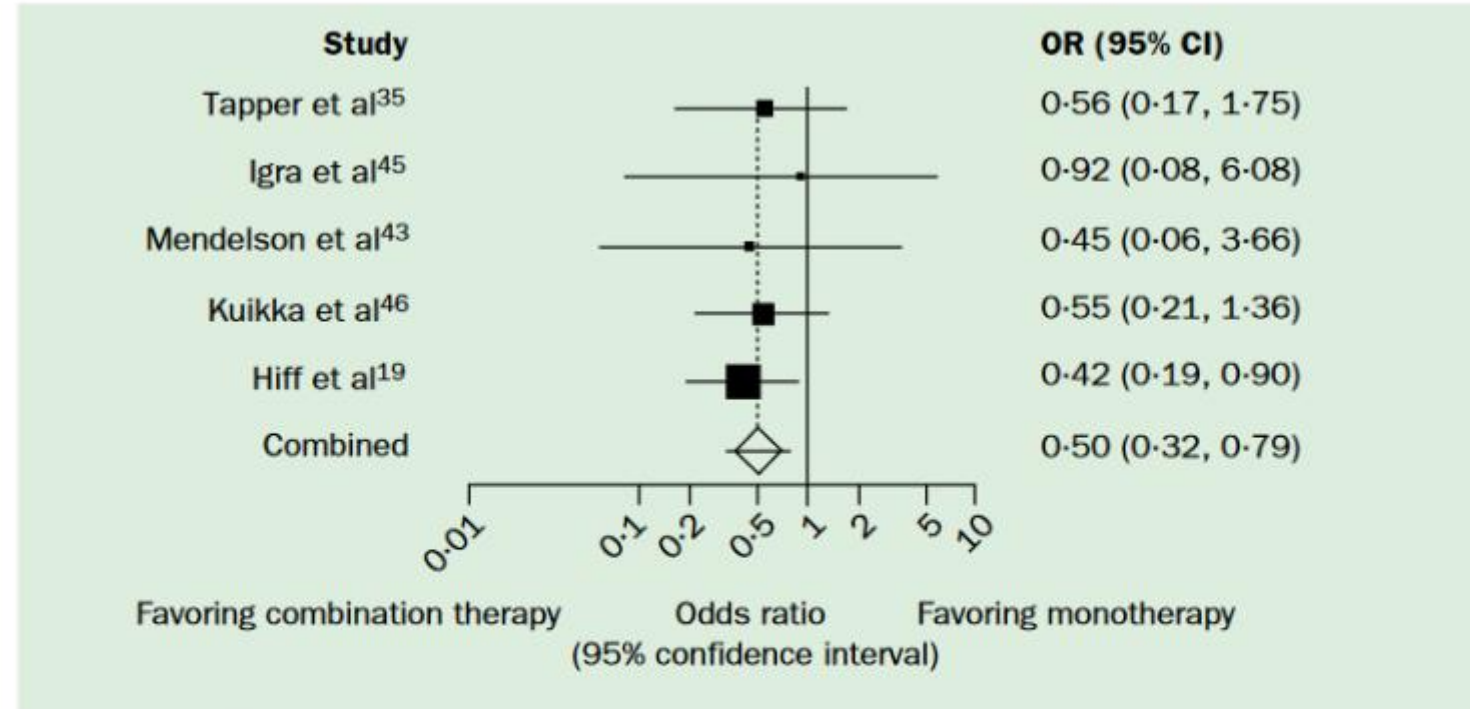


Figure 6. Analysis of studies comparing combination anti-infective therapy with monotherapy for reducing mortality of *Pseudomonas* spp bacteraemia. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 0.50 (95% CI 0.32–0.79), indicating a mortality benefit with combination antimicrobial therapy.

BACTERIEMIE



ELSEVIER

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Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com



Original article

Short-course aminoglycosides as adjunctive **empirical therapy** in patients with Gram-negative bloodstream infection, a cohort study

J.W. Timotëus Deelen ^{1,*}, W.C. Rottier ¹, A.G.M. Buiting ², J.W. Dorigo-Zetsma ³,
J.A.J.W. Kluytmans ⁴, P.D. van der Linden ⁵, S.F.T. Thijsen ⁶, B.J.M. Vlaminckx ⁷,
A.J.L. Weersink ⁸, H.S.M. Ammerlaan ^{1,9}, M.J.M. Bonten ^{1,10}, C.H. van Werkhoven ¹

BACTERIEMIE

- Etude de cohorte prospective
- Multicentrique (7) Pays Bas
- 2013-2015

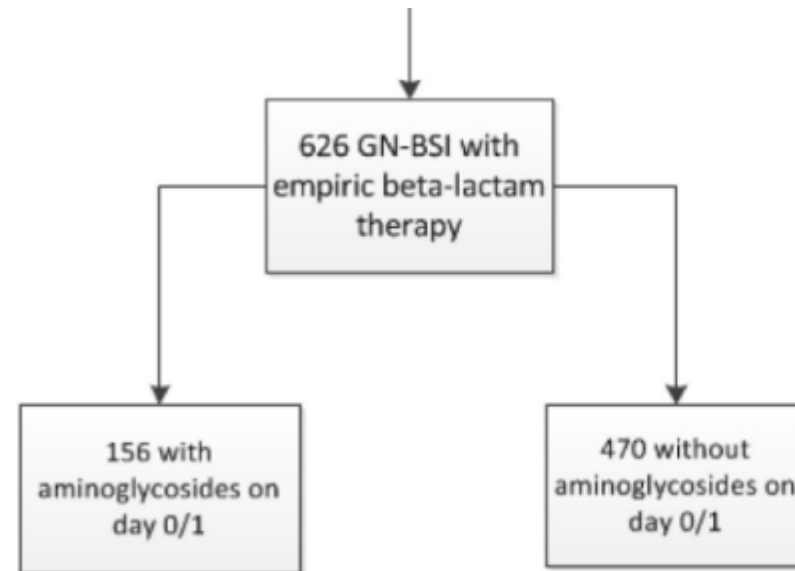


Fig. 1. Flow chart.

BACTERIEMIE

Regression analyses—30-day mortality

	Mortality: no aminoglycosides	Mortality: Aminoglycosides	Crude OR (95% CI)	Adjusted OR (95% CI)
Full analysis ($n = 626$)	64/470 (13.6%)	27/156 (17.3%)	1.33 (0.80–2.15)	1.57 (0.84–2.92)
Excluding patients with infection onset at ICU ($n = 597$)	57/447 (12.8%)	22/145 (15.3%)	1.24 (0.72–2.07)	1.52 (0.76–3.05)
Excluding CO/HA cases hospital B ($n = 558$)	58/441 (13.1%)	24/117 (20.5%)	1.70 (0.99–2.86)	1.84 (0.96–3.55)
Excluding patients with treatment restriction ($n = 453$)	29/327 (8.9%)	19/126 (15.1%)	1.82 (0.97–3.37)	1.93 (0.92–4.10)
Excluding patients with <i>Pseudomonas aeruginosa</i> BSI ($n = 591$)	59/444 (13.2%)	23/147 (15.6%)	1.21 (0.71–2.02)	1.43 (0.75–2.71)

BSI, bloodstream infection; CO, community-onset; HA, health-care-associated/hospital onset; ICU, intensive care unit; OR, odds ratio.

We report the crude and adjusted odds ratios of the impact of short-term adjunctive aminoglycosides on 30-day mortality, along with five sensitivity analyses (further explained in the methods). The adjusted OR was calculated by a logistic regression analysis, using inversed probability weighting to adjust for confounding. The confounders age, sex, culture ward, sepsis severity, Charlson co-morbidity score, chronic kidney disease, second-generation cephalosporin use, treatment restriction and community-onset/health-care-associated/hospital onset were included in the propensity score. Odds ratios reported with 95% confidence interval.

BACTERIEMIE

Infection (2011) 39:549–554
DOI 10.1007/s15010-011-0189-2

BRIEF REPORT

Combination therapy with an aminoglycoside for *Staphylococcus aureus* endocarditis and/or persistent bacteremia is associated with a decreased rate of recurrent bacteremia: a cohort study

T. L. Lemonovich · K. Haynes · E. Lautenbach ·
V. K. Amorosa

Table 2 Multivariable analysis of clinical variables associated with recurrent bacteremia

Variable	Unadjusted OR	Adjusted OR (95% CI)	<i>p</i> value
Aminoglycoside therapy	0.29	0.26 (0.07–0.98)	0.046
MRSA isolate	5.50	5.93 (1.19–29.47)	0.030

OR odds ratio, CI confidence interval

INDICATIONS THERAPEUTIQUES



Dans quelles situations cliniques
utiliseriez-vous ces antibiotiques en
premiere intention ?

- Bactériémie ?
- **Choc septique ?**
- Immunodéprimé ?
- Listeria ?
- Tuberculose ?

CHOC SEPTIQUE

Clinical Infectious Diseases

MAJOR ARTICLE



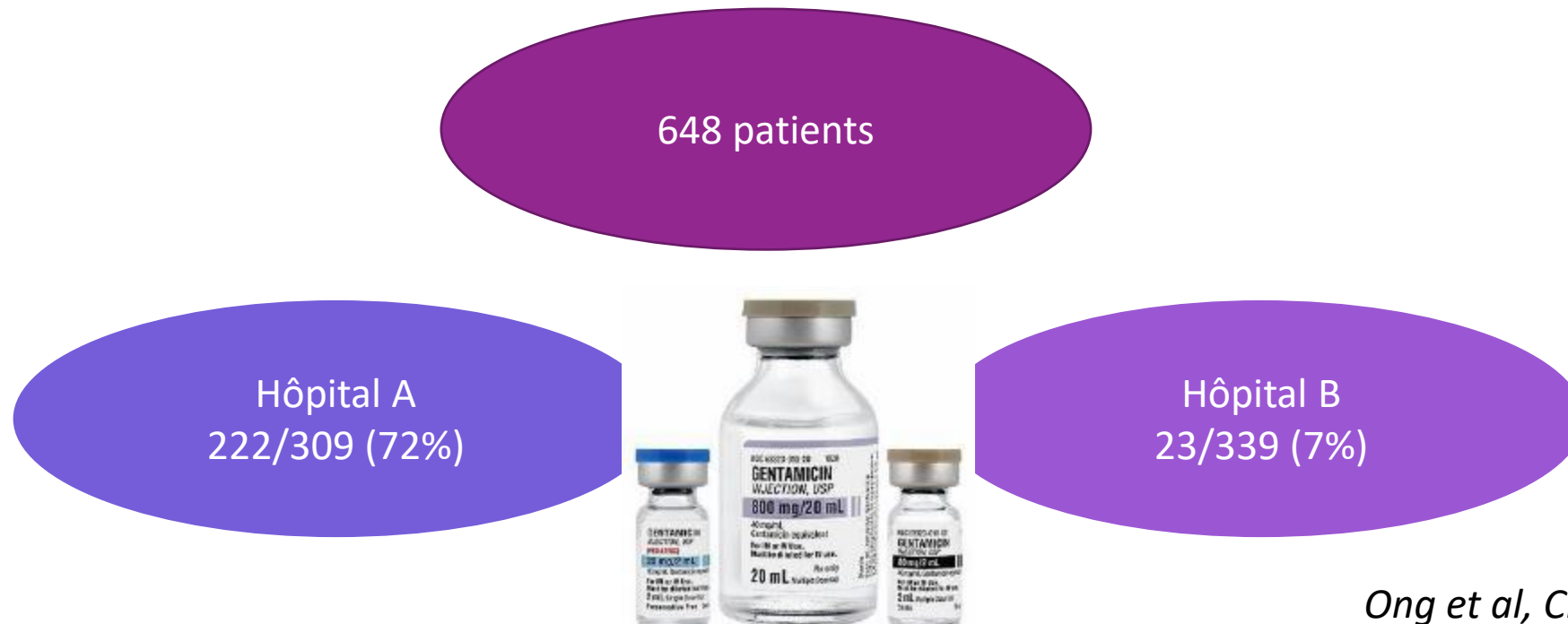
Short-Course Adjunctive Gentamicin as Empirical Therapy in Patients With Severe Sepsis and Septic Shock: A Prospective Observational Cohort Study

David S. Y. Ong,^{1,2} Jos F. Frencken,^{2,3} Peter M. C. Klein Klouwenberg,^{1,2} Nicole Juffermans,⁴ Tom van der Poll,⁵ Marc J. M. Bonten,^{1,3} and Olaf L. Cremer²; for the MARS consortium^a

¹Department of Medical Microbiology, ²Department of Intensive Care Medicine, and ³Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, ⁴Department of Intensive Care, Academic Medical Center, University of Amsterdam, and ⁵Center of Experimental and Molecular Medicine & Division of Infectious Diseases, Academic Medical Center, University of Amsterdam, The Netherlands

CHOC SEPTIQUE

- Etude prospective
- 2 ICU Pays Bas 2011-2015
 - Protocole différents : utilisation gentamicine dans 1 centre



CHOC SEPTIQUE

Table 4. Associations of Gentamicin Use With Renal Failure–Free Days, Shock-Free Days, and Death Before Day 14

Model	Primary Outcome	Secondary Outcome	
	Renal Failure–Free Days	Shock-Free Days	Death Before Day 14
Per protocol (primary) analysis			
Crude	1.35 (1.00–1.82)	1.30 (0.96–1.77)	1.41 (0.98 – 2.02)
Adjusted ^a	1.39 (1.00–1.94)	1.34 (0.96–1.86)	1.41 (0.94 – 2.12)
Intention-to-treat (sensitivity) analysis			
Crude	1.39 (1.04–1.86)	1.17 (0.87–1.57)	1.47 (1.03 – 2.10)
Adjusted ^a	1.70 (1.22–2.36)	1.28 (0.93–1.77)	1.76 (1.17 – 2.64)

CHOC SEPTIQUE

Table 2. Differences in Antimicrobial Management in the First 2 Days, Stratified by Gentamicin Use

Antibiotic ^a	Gentamicin Exposed (n = 245)	Non-Gentamicin Exposed (n = 403)	P Value
Cephalosporin ^b	207 (84)	332 (82)	.49
Penicillin ^c	64 (26)	85 (21)	.14
Carbapenem ^d	11 (4)	62 (15)	<.01
Metronidazole	159 (65)	204 (51)	<.01
Quinolone ^e	6 (2)	39 (9)	<.01
Vancomycin	101 (41)	73 (18)	<.01
Antifungal agent ^f	39 (16)	51 (13)	.24

CHOC SEPTIQUE

Table 3. Crude clinical outcomes by gentamicin exposure

	Gentamicin exposed (n=245)	Non gentamicin exposed (n=403)
Number of days alive and free of renal failure on day 14:		
0	74 (30)	102 (25)
1-13	61 (25)	89 (22)
14	110 (45)	214 (53)
Number of days alive and free of shock on day 14:		
0	75 (31)	95 (24)
1-13	123 (50)	222 (55)
14	47 (19)	86 (21)
Day 14 mortality	72 (29)	92 (23)

Data are presented in absolute number (percentage).

INDICATIONS THERAPEUTIQUES



**Dans quelles situations cliniques
utiliseriez-vous ces antibiotiques en
premiere intention ?**

- Bactériémie ?
- Choc septique ?
- **Immunodéprimé ?**
- Listeria ?
- Tuberculose ?

IMMUNODEPRIME

AMINOGLYCOSIDES IN IMMUNOCOMPROMISED CRITICALLY ILL PATIENTS WITH BACTERIAL PNEUMONIA AND SEPTIC SHOCK: *A POST-HOC ANALYSIS OF A PROSPECTIVE MULTICENTER MULTINATIONAL COHORT*

René Lopez,^{*} Jordi Rello,^{†‡§} Fabio Silvio Taccone,^{||} Omar Ben Hadj Salem,[¶]
Philippe R. Bauer,[#] Amélie Séguin,^{**} Andry van de Louw,^{††} Victoria Metaxa,^{‡‡}
Kada Klouche,^{§§} Ignacio Martin Loeches,^{||||} Luca Montini,^{¶¶} Sangeeta Mehta,^{##}
Fabrice Bruneel,^{***} T. Lisboa,^{†††} William Viana,^{‡‡‡} Peter Pickkers,^{§§§}
Lene Russell,^{|||||} Katerina Rusinova,^{¶¶¶} Achille Kouatchet,^{****}
François Barbier,^{††††} Djamel Mokart,^{‡‡‡‡} Elie Azoulay,^{*} and Michael Darmon^{*}

IMMUNODEPRIME

Secondary analysis of a prospective multicenter study.

- Patients immunodeprimés
- Pneumopathie bactérienne, choc septique
- CJP : mortalité hospitalière
- CJS: dialyse

the Efraim multinational
prospective cohort
study

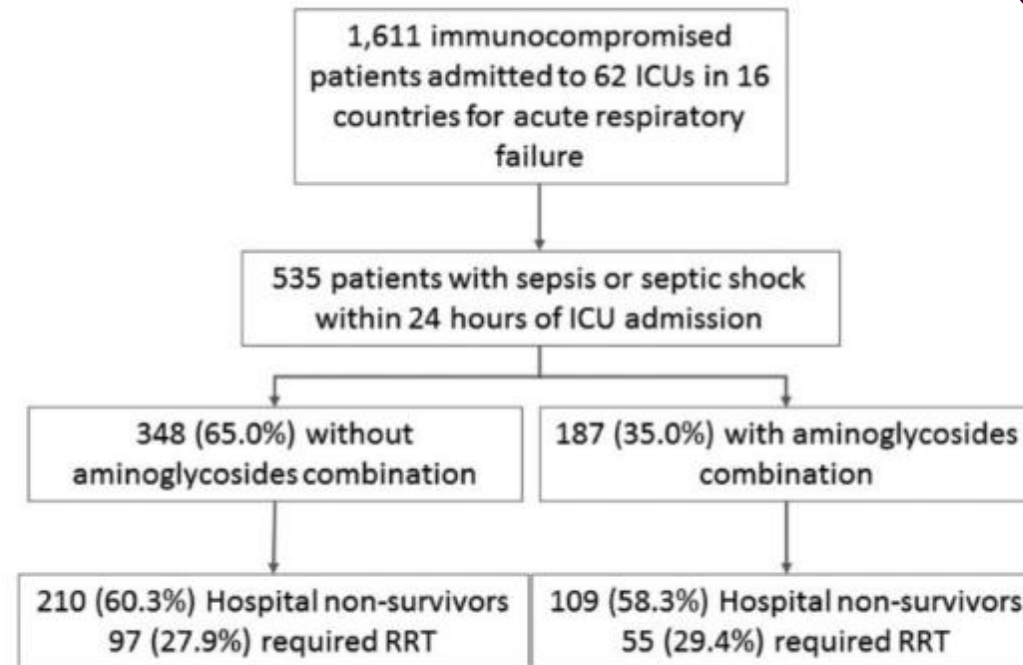


FIG. 1. Patients' flowchart modified from EFRAIM study (17).

IMMUNODEPRIME

TABLE 2. Results of the multivariable mixed regression model with center effect on subsequent mortality risk.

	Variable of interest: hospital mortality		
	Odds ratio	95% CI	P value
Fixed effect			
Performance status			
ECOG 0	Reference	–	–
ECOG 1	1.30	0.68–2.47	0.43
ECOG 2	2.45	1.26–4.78	0.009
ECOG 3	5.55	2.61–11.80	<0.001
Solid organ transplant	0.46	0.21–0.99	0.48
Renal replacement therapy	2.84	1.66–4.85	<0.001
Aminoglycosides	1.14	0.69–1.89	0.61
Model discrimination and calibration			
C-stat AUC (95% CI)		0.73 (0.68–0.77)	
Hosmer-Lemeshow-X ²		8.995	0.34

ECOG indicates Eastern Cooperative Oncology Group performance status (19).

TABLE 4. Results of the multivariable mixed regression model with center effect on subsequent renal replacement therapy risk.

	Renal replacement therapy		
	Odds ratio	Confidence interval	P value
Fixed effect			
Performance status			
ECOG 0	Reference	–	–
ECOG 1	0.45	0.24–0.87	0.02
ECOG 2	0.39	0.20–0.77	0.007
ECOG 3	0.41	0.20–0.82	0.01
Solid organ transplant	1.92	0.91–4.05	0.09
ARF etiology			
Bacterial	Reference	–	–
Fungal infection	1.40	0.66–2.99	0.38
Pneumocystis	1.65	0.46–5.83	0.44
Unknown etiology	0.51	0.20–1.29	0.16
Other etiology	0.53	0.31–0.91	0.02
Aminoglycosides	0.83	0.49–1.39	0.48
Model discrimination and calibration			
C-stat AUC (95% CI)		0.73 (0.69–0.77)	
Hosmer-Lemeshow-X ²		8.08	0.43

ARF, Acute Respiratory Failure; ECOG indicates Eastern Cooperative Oncology Group performance status (19).

IMMUNODEPRIMES

64 trials with 7586 patients

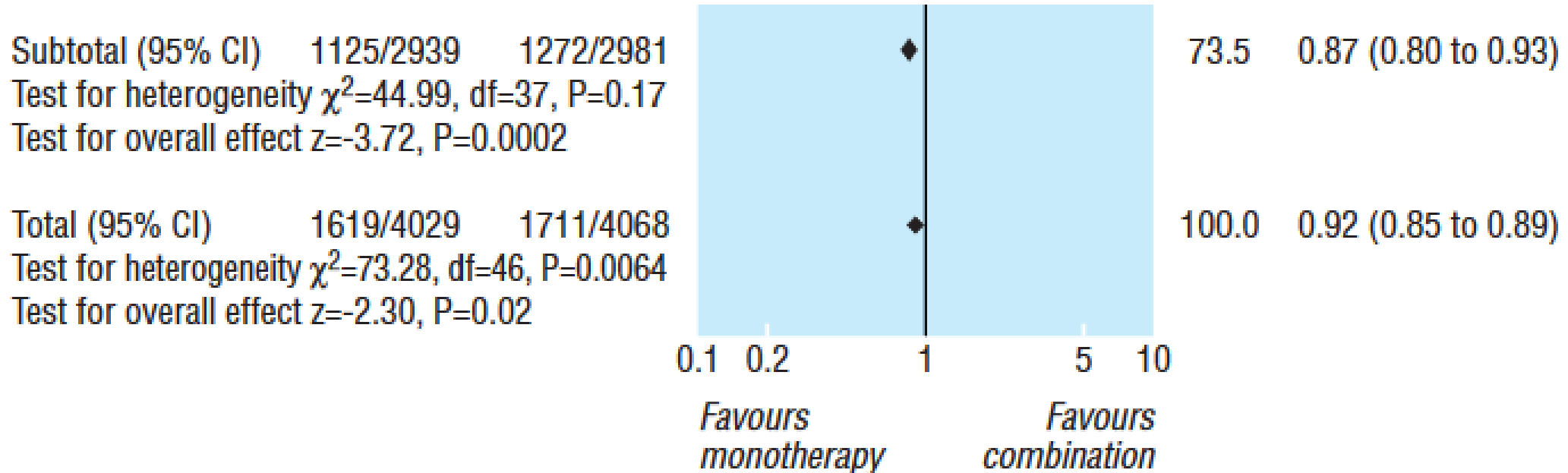


Fig 3 Treatment failure

IMMUNODEPRIME

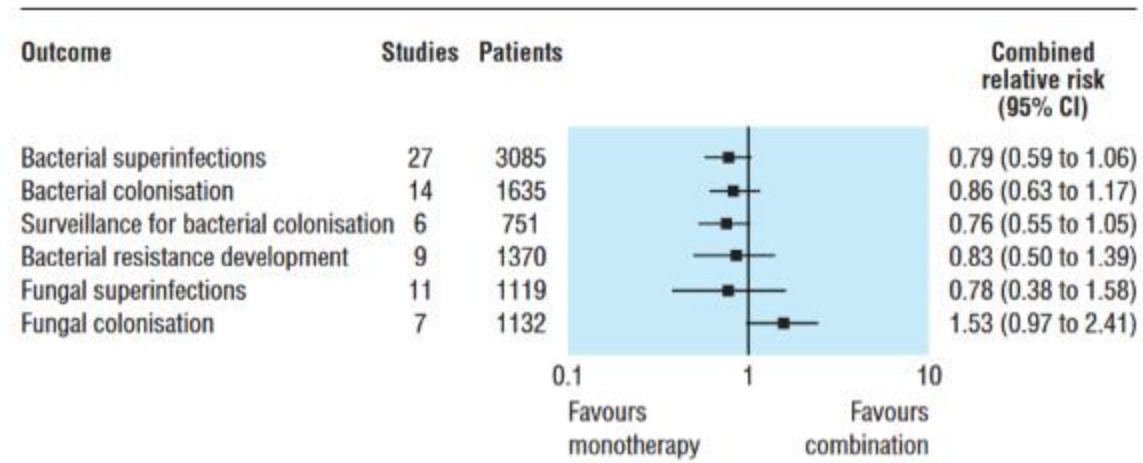


Fig 5 Summary relative risks for outcome relating to resistance development in comparison of β lactam monotherapy v β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

IMMUNODEPRIME

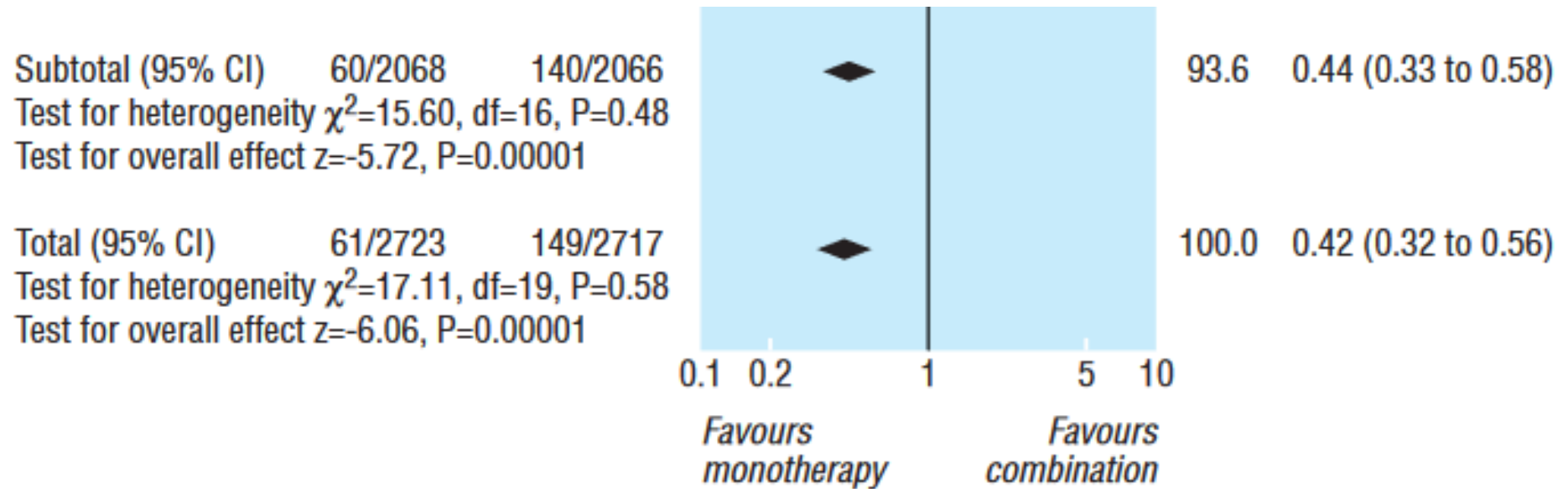


Fig 6 Nephrotoxicity

INDICATIONS THERAPEUTIQUES



Dans quelles situations cliniques
utiliseriez-vous ces antibiotiques en
premiere intention ?

- Bactériémie ?
- Choc septique ?
- Immunodéprimé ?
- **Listeria** ?
- Tuberculose ?

LISTERIA

- MONALISA, Charlier et al, Lancet infect Dis, 2017:
 - Cohorte nationale observationnelle
 - Cas déclarés de listera
 - Entre nov 2009 et juillet 2013



A: Treatment characteristics according to the form of infection*	Maternal [†] (N=107)	Bacteremia (N=427)	Neurolisteriosis (N=251)
Mean number of antibiotics	1.7±1.1	2.3±1.4	3.2±1.4
Median duration of antibiotics in days	15 [8; 21]	17 [9; 23]	22 [18; 25]
Amoxicillin – no. (%), median duration in days	91 (85), 15 [9; 22]	349 (82), 16 [11; 22]	244 (97), 22 [15; 23]
Imipenem – no. (%), median duration in days	0 (0)	13 (3), 8 [4; 16]	10 (4), 7 [5; 23]
Gentamicin – no. (%), median duration in days	32 (30), 3 [2; 4]	205 (48), 4 [3; 6]	200 (79), 7 [4; 8]
Cotrimoxazole – no. (%), median duration in days	0 (0)	49 (12), 11 [6; 22]	42 (17), 20 [14; 30]
Rifampicin – no. (%), median duration in days	0 (0)	6 (1), 21 [11; 25]	3 (1), 22 [19; 23]
Vancomycin – no. (%), median duration in days	1 (1), 3 [3; 3]	19 (4), 4 [2; 11]	24 (10), 2 [2; 6]
Linezolid – no. (%), median duration in days	1 (1), 15 [15; 15]	5 (1), 13 [10; 15]	4 (2), 14 [13; 21]
Amoxicillin+Gentamicin – no. (%), median duration in days	30 (28), 3 [2; 4]	170 (40), 4 [3; 6]	192 (76), 7 [4; 8]
Amoxicillin+Cotrimoxazole – no. (%), median duration in days	0 (0)	33 (8), 11 [6; 22]	37 (15), 20 [14; 30]
No treatment – no. (%)	10 (9) [‡]	30 (7)	1 (1)
Dexamethasone – no. (%)	-	-	32 (13)

LISTERIA

3-month death in bacteremias + neuroinfection (N=679)*

Factors	Odds ratio (95%CI) [†]	p-value
Female sex	1.60 (1.04-2.46)	0.034
Age – years	1.03 (1.01-1.05)	0.001
At least one immunosuppressing comorbidity	0.43 (0.15-1.22)	0.113
Ongoing organ neoplasia	5.19 (3.01-8.95)	<0.001
Recent weight loss >5kgs	1.74 (1.05-2.87)	0.031
Intensive care unit management	1.48 (0.90-2.41)	0.120
Multi-organ failure	7.98 (4.32-14.72)	<0.001
Aggravation of any pre existing organ dysfunction	4.35 (2.79-6.81)	<0.001
Diarrhea	0.58 (0.33-1.01)	0.053
Flu-like symptoms	0.47 (0.27-0.80)	0.006
Monocytopenia <200/mm ³	3.70 (1.82-7.49)	<0.001
Neutrophils – cells /mm ³	1.05 (1.01-1.08)	0.006
Cotrimoxazole therapy	0.49 (0.26-0.92)	0.027
Aminoglycoside therapy	0.60 (0.38-0.94)	0.024
Active betalactam therapy [‡] †	0.10 (0.04-0.26)	<0.001

LISTERIA

B· Univariable analysis of 3-month death in bacteremia + neuroinfection cases

Characteristic	No, n = 410	Yes, n = 269	p-value
Duration of bitherapy			
Anti-listeria betalactamin ^{**} + aminoglycoside			<0.001*
Missing data	0 (0)	0 (0)	
0 d	121 (45.1)	147 (54.9)	
<= 3 d	76 (59.8)	51 (40.2)	
> 3 d	213 (75)	71 (25)	

LISTERIA

Clinical Microbiology and Infection 22 (2016) 725–730

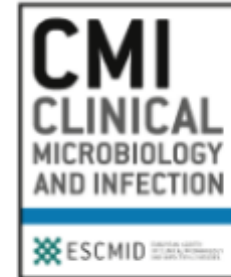


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Original article

Antibiotic treatment and mortality in patients with *Listeria monocytogenes* meningitis or bacteraemia

S. Thønnings^{1,2}, J.D. Knudsen¹, H.C. Schönheyder^{3,4}, M. Søgaard⁴, M. Arpi⁵,
K.O. Gradel^{6,7}, C. Østergaard^{1,*}, for the Danish Collaborative Bacteraemia Network
(DACOBAN)

LISTERIA

- Etude observationnelle rétrospective
 - 1997-2012
 - Nord du Danemark + Capital
 - Risk factor or fatal outcome
 - Impact de l'antibiothérapie ?



LISTERIA

Table 1

Risk of fatal outcome (30-day mortality) in patients with *Listeria monocytogenes* bacteraemia/meningitis

Characteristic	All patients (n = 229)	Non-survivors (n = 61) (26.6%)	Survivors (n = 168) (73.4%)	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI) p <0.2 and n >90%	p
Gender (female)	46.3% (106/229)	45.9% (28/61)	46.4% (78/168)	0.98 (0.54–1.76)	1.00		
Age	71 (62–79)	74 (65–84) (n = 61)	70 (60–79)	1.02 (1.00–1.04)	0.04	1.02 (1.00–1.05)	0.12
Body temperature (°C)	38.6 (37.9–39.4) (n = 215)	38.5 (37.6–39.0) (n = 56)	38.7 (37.9–39.6) (n = 159)	0.73 (0.56–0.95)	0.02	0.89 (0.85–0.94)	<0.01
Septic shock	23.1% (53/222)	43.9% (25/57)	17.0% (28/165)	3.82 (1.97–7.42)	<0.01	3.03 (1.43–6.39)	<0.01
Altered mental state	48.5% (111/228)	71.7% (43/60)	40.5% (68/168)	3.72 (1.96–7.06)	<0.01	3.59 (1.71–7.56)	<0.01
Meningitis	24.9% (57/229)	23.0% (14/61)	25.6% (43/168)	0.87 (0.43–1.73)	0.73		
Combination therapy with gentamicin	38.9% (89/229)	37.5% (12/32)	45.8% (77/168)	0.71 (0.33–1.54)	0.44		
Inadequate empiric antibiotic therapy	50.7% (116/229)	75.4% (46/61)	41.7% (70/168)	3.62 (1.91–6.86)	<0.01	3.81 (1.80–8.07)	<0.01
Days to adequate antibiotic therapy	0 (0–3) (n = 205)	2 (0–3) (n = 42)	0 (0–3) (n = 163)	1.22 (0.99–1.50)	0.62		

Data are shown as percentages or medians (25/75 percentiles).

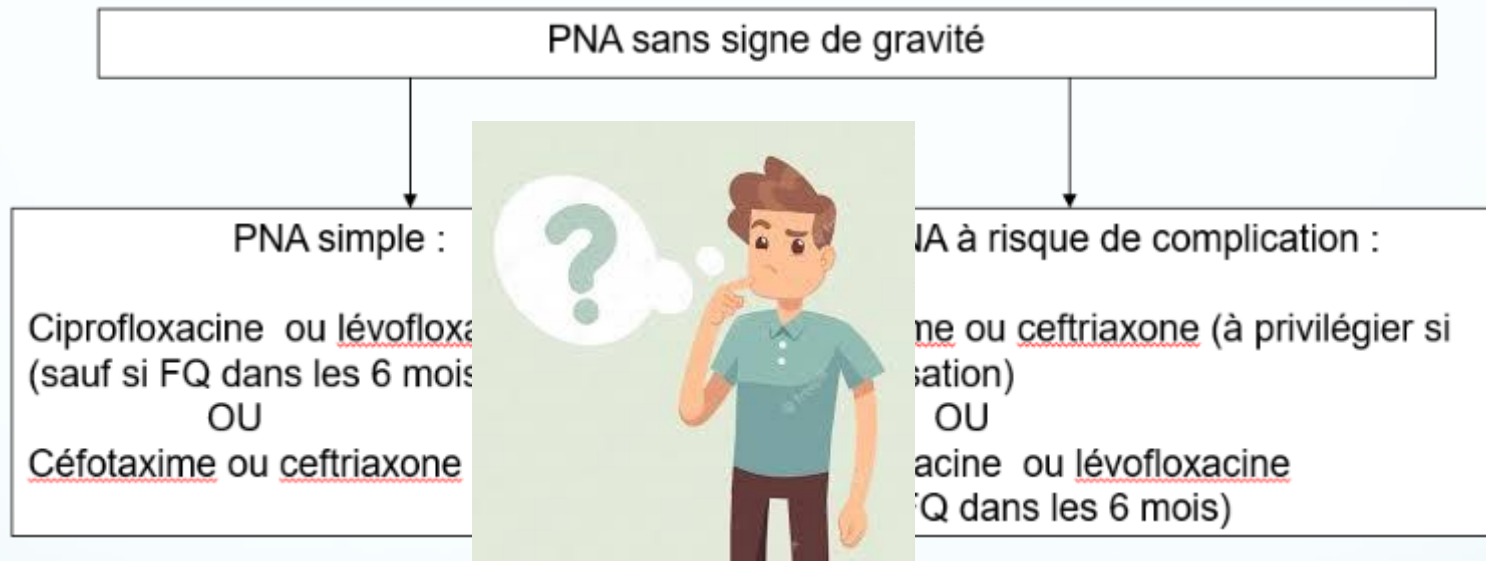
Statistical significance (p <0.05) are shown with bold font.

^a Median time from admission to blood/CSF culturing 9 days [IQR: 4 days, 18 days].

INDICATIONS THERAPEUTIQUES



PNA - stratégie probabiliste (1)



Si contre-indications : aminoside (amikacine, gentamicine ou tobramycine) ou aztréonam

INDICATIONS THERAPEUTIQUES

- BITHERAPIE :

- Monothérapie : Infections urinaires : allergie
- INDICATION :
 - Choc septique **non documentés**
 - Infection à risque en **probabiliste** :
 - Nosocomiales tardives
 - Sujets à risque : ID sévère, nouveau né, mucoviscidose
 - Bactériémie et **méningites** à *Listeria monocytogenes*
 - Infections documentées ou **suspectées** à *Pseudomonas aeruginosa*, *Acinetobacter sp.*, Enterobactéries groupe 3
 - **Endocardite** à cocci + et *Bartonella sp.*

GRAVITE

PROBABILISTE

SUJET A RISQUE

PLAN

Histoire

Structure et mode d'action

Spectre d'action

PK-PD

Indications

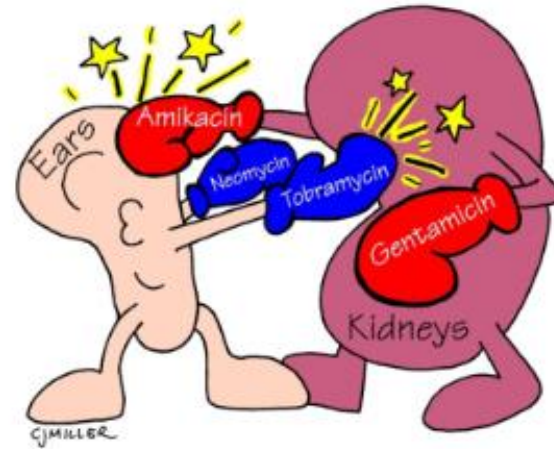
Effets secondaires

Surveillance

EFFETS SECONDAIRES



EFFETS SECONDAIRES

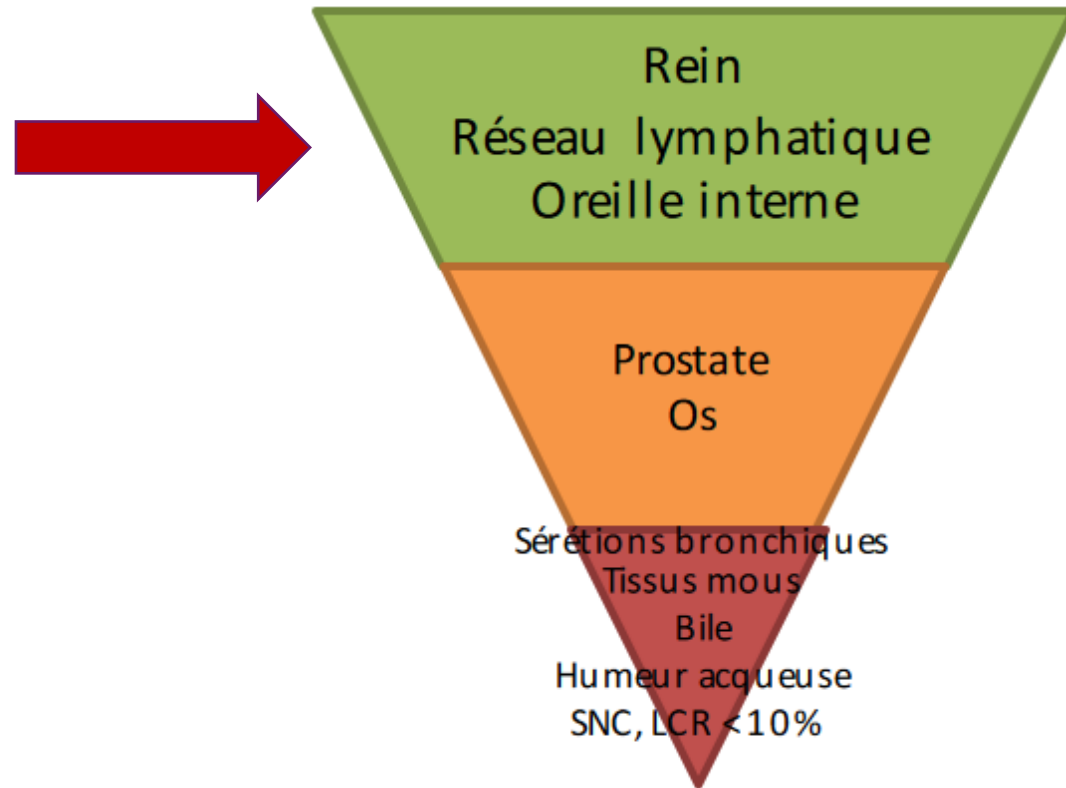


INDEX THERAPEUTHIQUE ETROIT

EFFETS SECONDAIRES

BONNE DIFFUSION REIN et OREILLE INTERNE

ELIMINATION LENTE



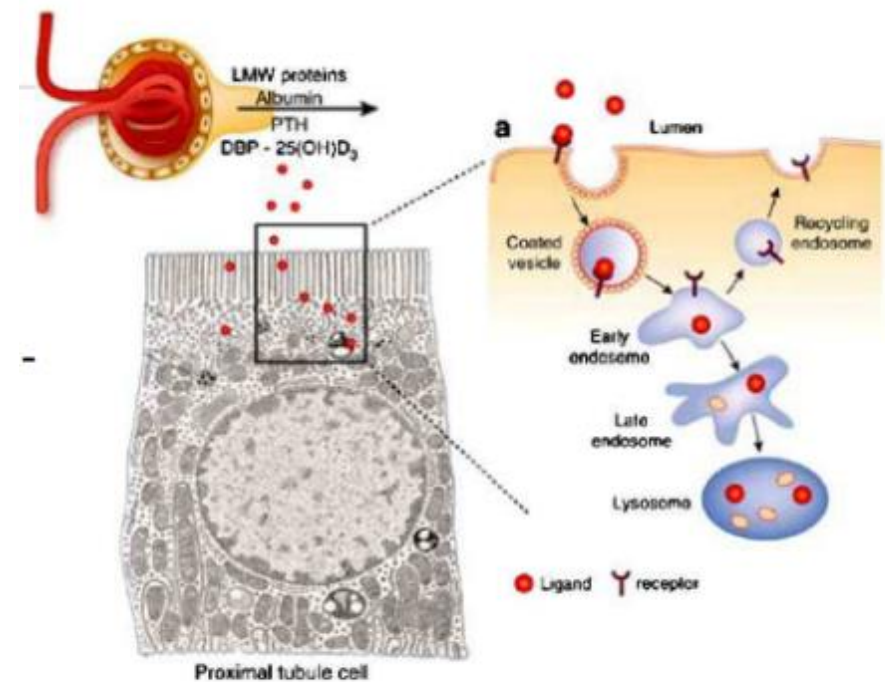
M. LENT



EFFETS SECONDAIRES

- **Néphrotoxicité**

- Epidémiologie : 1-2 % => jusqu' a 20%
- Facteurs de risque
 - Durée : >7 jours
 - Dose : résiduel >2 mg/L
 - Nombre d'injection par jour
 - Type : neo>genta>amikacine
- Accumulation TCP => nécrose tubulaire
- Réversible lente à l'arrêt
 - Accumulation jusqu'à 28 jours après l'arrêt
 - ➔ atteinte différée



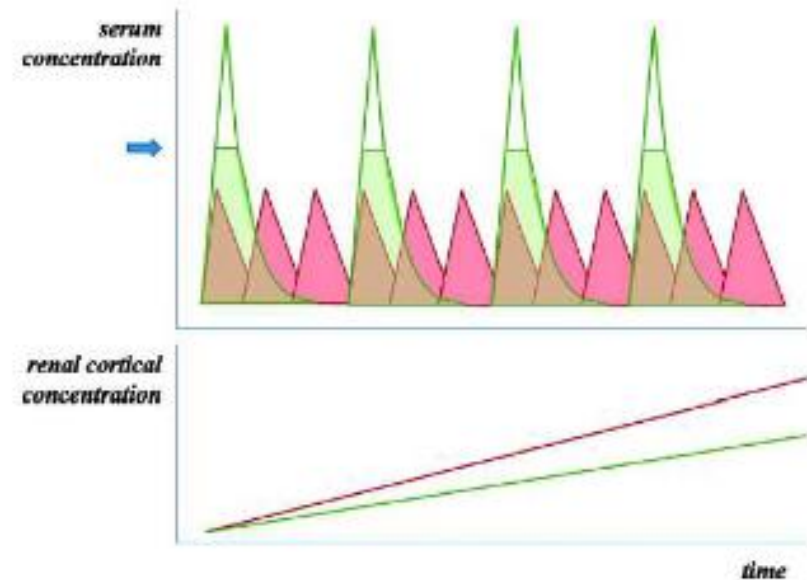
J Am Soc Nephrol, 2007

EFFETS SECONDAIRES

- **Néphrotoxicité**

- A surveiller : **FACTEURS DE RISQUE ASSOCIES DE NEPHROPATHIES**

- Age >75 ans
- Néphropathie sous jacente
- Diurétiques, IEC...
- Vancomycine
- Insuffisance cardiaque
- Déshydratation
- Hypovolémie, choc , cirrhose



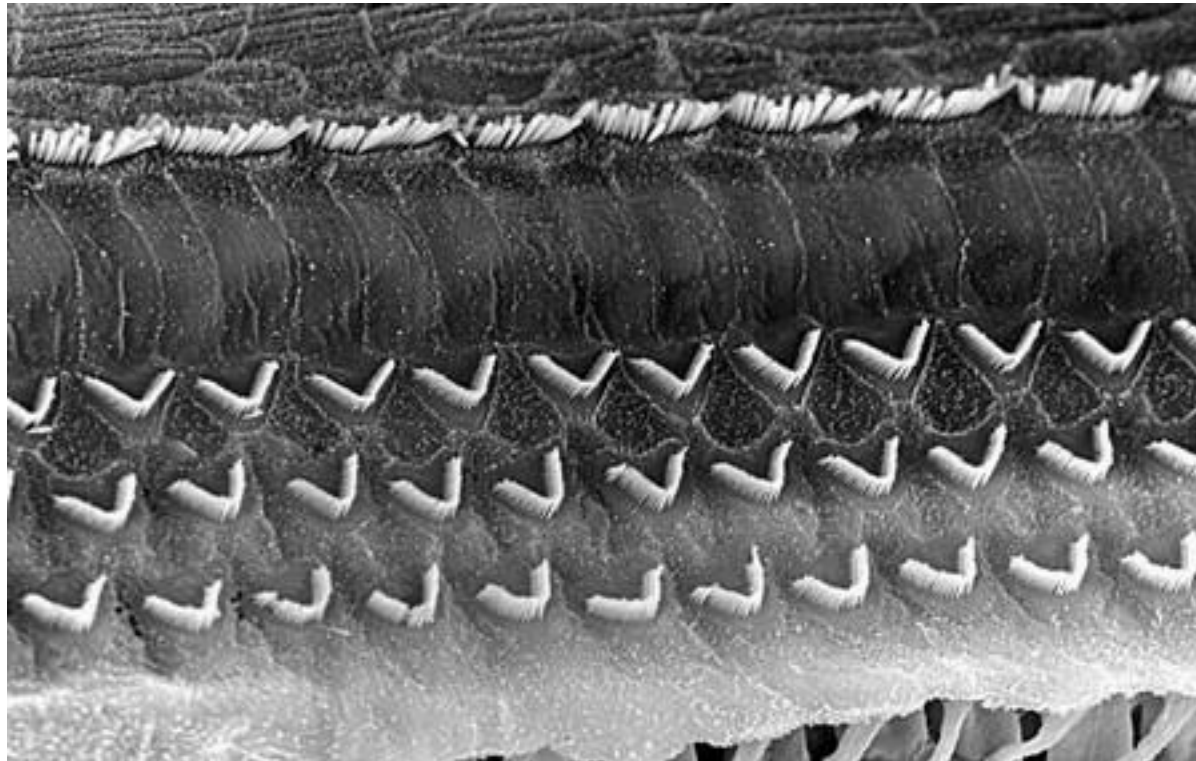
Nazareth, cystic fibrosis, 2013

EFFETS SECONDAIRES

- **Ototoxicité : IRREVERSIBLE**
 - Destruction progressive cellules ciliées + canaux semi circulaires
 - surdité, acouphènes
 - Vertiges, ataxie, troubles de l'équilibre
 - Facteurs de risque :
 - Durée dépendant : >7 jours
 - Dose dépendant (insuffisance rénale)
 - Nombre d'injection par jour

EFFETS SECONDAIRES

- Ototoxicité : IRREVERSIBLE



Cellules ciliées
internes

Cellules ciliées
Externes

Image en microscopie électronique à balayage (MEB) , Marc Lenoir

EFFETS SECONDAIRES

- Ototoxicité : IRREVERSIBLE

+ AMINOSIDES

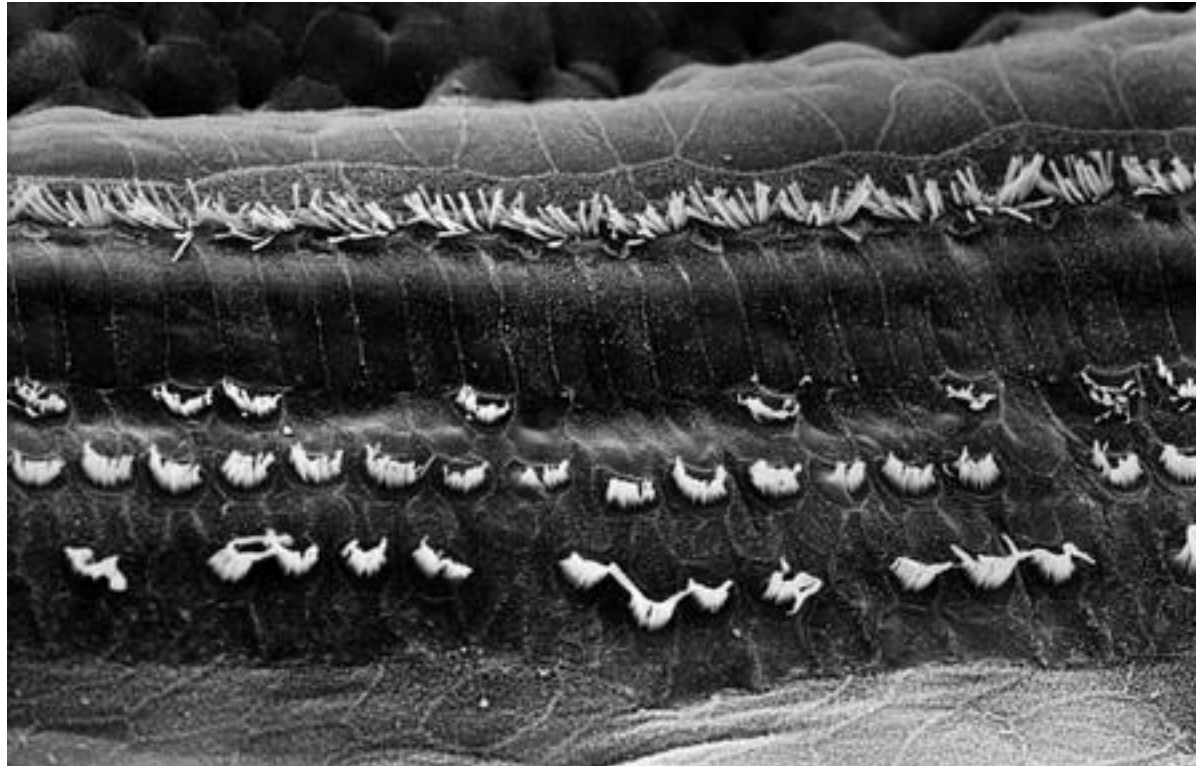


Image en microscopie électronique à balayage (MEB) , Marc Lenoir

EFFETS SECONDAIRES

- Ototoxicité : IRREVERSIBLE

+ AMINOSIDES

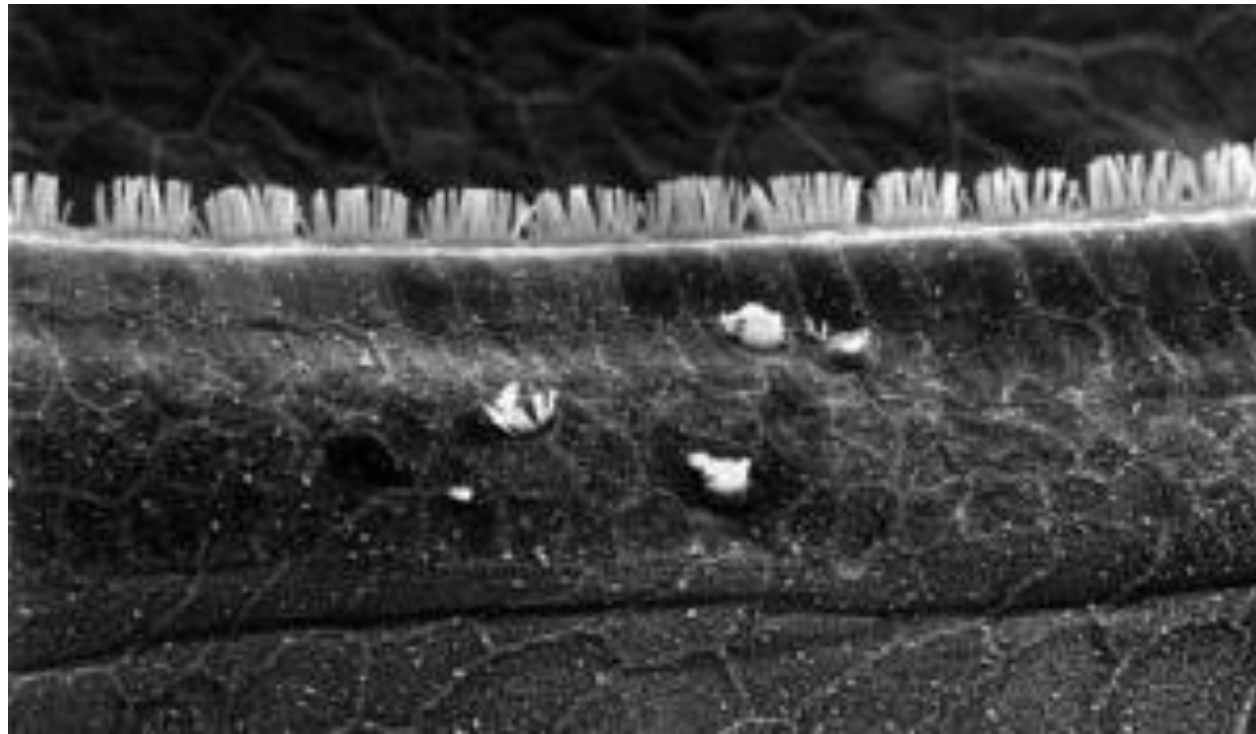
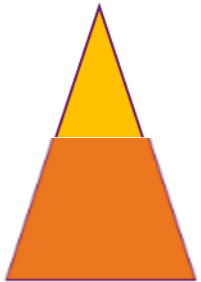


Image en microscopie électronique à balayage (MEB) , Marc Lenoir

EFFETS SECONDAIRES

- Ototoxicité : IRREVERSIBLE

+ AMINOSIDES

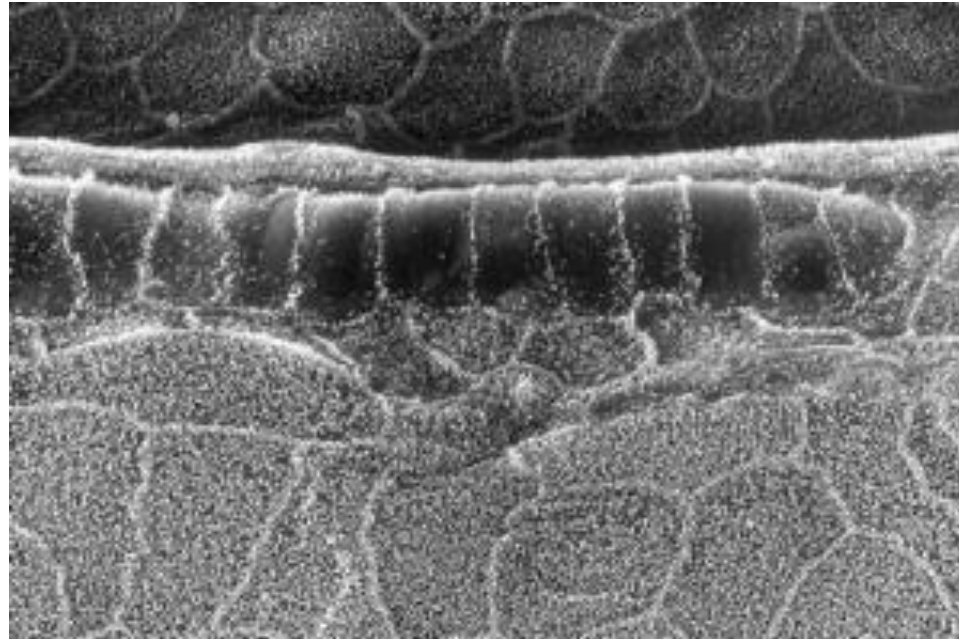


Image en microscopie électronique à balayage (MEB) , Marc Lenoir

EFFETS SECONDAIRES

- Potentialisation effet sur la plaque motrice : contre indication MYASTHENIE

Encadré 8.1

Médicaments contre-indiqués

Tous les médicaments susceptibles d'altérer la transmission neuromusculaire sont contre-indiqués au cours de la myasthénie, en distinguant les contre-indications absolues et relatives et en appréciant le rapport bénéfice-risque.

Contre-indications absolues

Aminosides, colimycine, polymyxine, telithromycine, cyclines injectables, macrolides, fluoroquinolones, quinine, quinidine, hydroxychloroquine, procainamide, bêtabloquants (même en collyre), diphényl-hydantoïne, triméthadione, dantrolène, D-pénicillamine, magnésium.

Contre-indications relatives

Curarisants (l'usage de molécules non dépolarisantes de dégradation rapide, comme l'atracurium, est possible, nécessité d'un monitoring précis), benzodiazépines, neuroleptiques (phénothiazine), carbamazépine, lithium.

Vaccinations : le retentissement sur la myasthénie est mal documenté. La vaccination contre la poliomyélite, le tétanos et la grippe n'entraîne pas d'aggravation lorsque la myasthénie est bien contrôlée. Les vaccins vivants (par exemple polio buccal) sont formellement contre-indiqués chez les patients sous corticoïdes ou immunosuppresseurs.

PLAN

Histoire

Structure et mode d'action

Spectre d'action

PK-PD

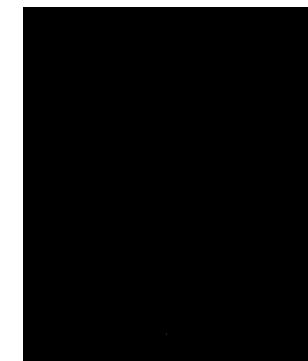
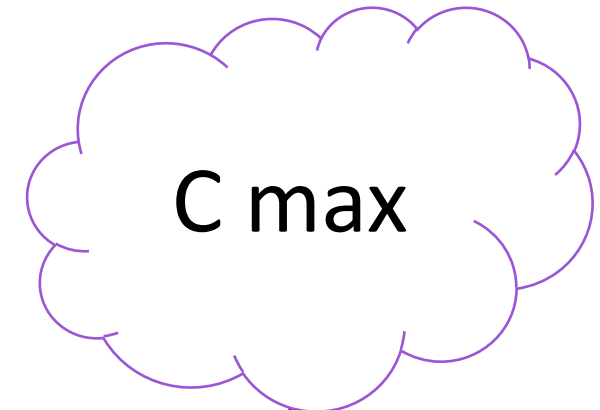
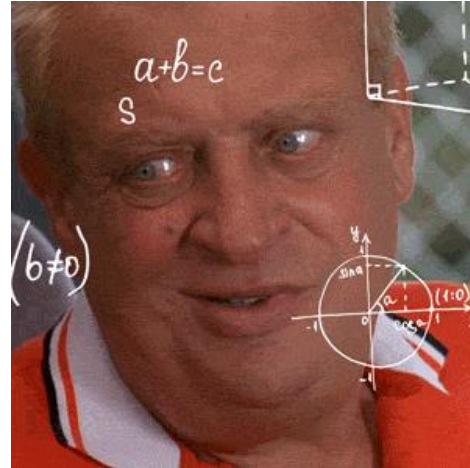
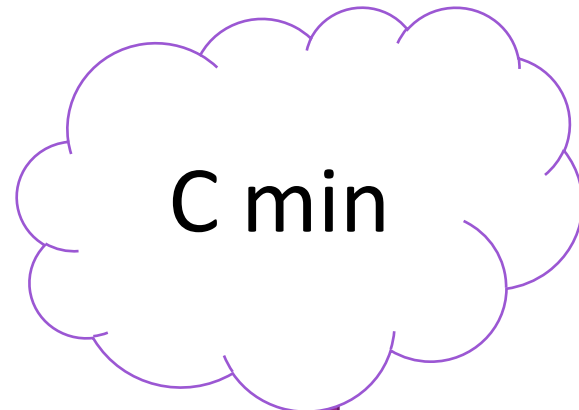
Indications

Effets secondaires

Surveillance

SURVEILLANCE

- DOSAGES PLASMATIQUES



SURVEILLANCE

- Quels propositions concernant les dosages sont correctes ?
 - Le Cmax est dosé à 30 min
 - Le Cmax est dosé à 48h
 - Le C min est dosé à 30 min
 - Le C min est dosé à 48h

SURVEILLANCE

- DOSAGES PLASMATIQUES



Tableau 1: Objectifs de concentrations

	Pic (Cmax) en mg/l	Résiduelle (Cmin) en mg/l
Gentamicine, nétilmicine, tobramycine	30 à 40	< 0,5
Amikacine	60 à 80	< 2,5

- QUAND :

- Cmax

- Modification PK/PD : Choc, brûlés, obésité morbide, VM
 - 30 min après l'injection

< C max



AUGMENTATION DOSE

SURVEILLANCE

- QUAND :

- Cmin

- Si plus de 5 jours ou insuffisants rénaux
 - A 48 h initiation
 - 2/sem

> C min attendu



ESPACEMENT DES DOSES