AMINOSIDES

Dr GALLET Salomé

Maladies infectieuses

CHU Grenoble Alpes

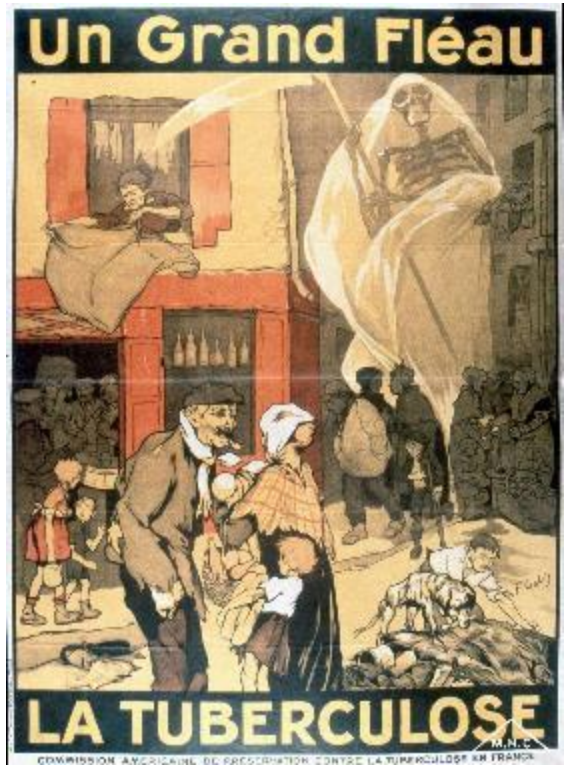
Diplôme Universitaire de Thérapeutiques Anti-Infectieuses
Université Grenoble Alpes
1ère session – Janvier 2025

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

Streptomycin in Tuberculosis Trials Committee, The British Medical Journal , 1948

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%

Streptomycin in Tuberculosis Trials Committee, The British Medical Journal , 1948

HISTOIRE

Contrôle

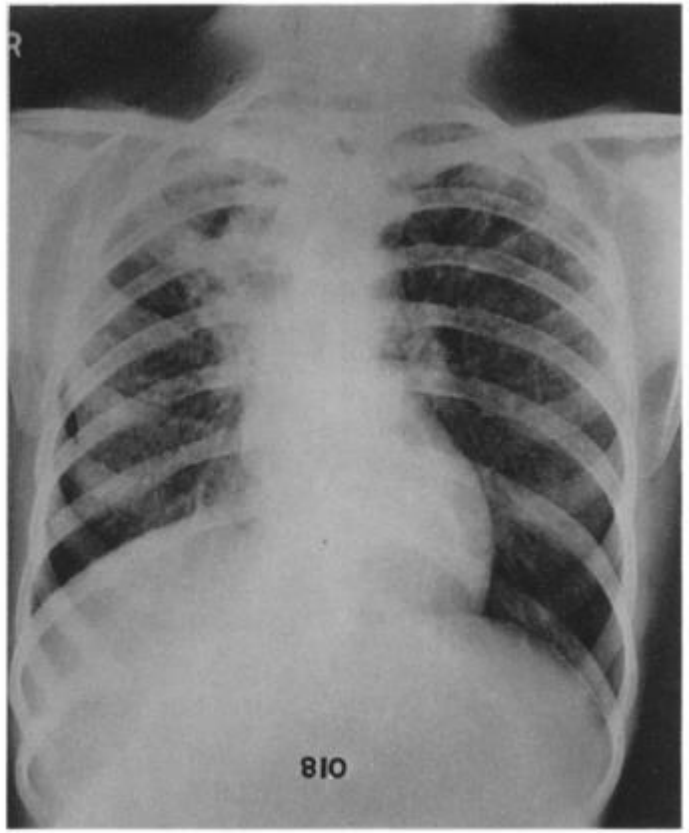


FIG. 7.—Case 81 (C). Feb. 27, 1947.

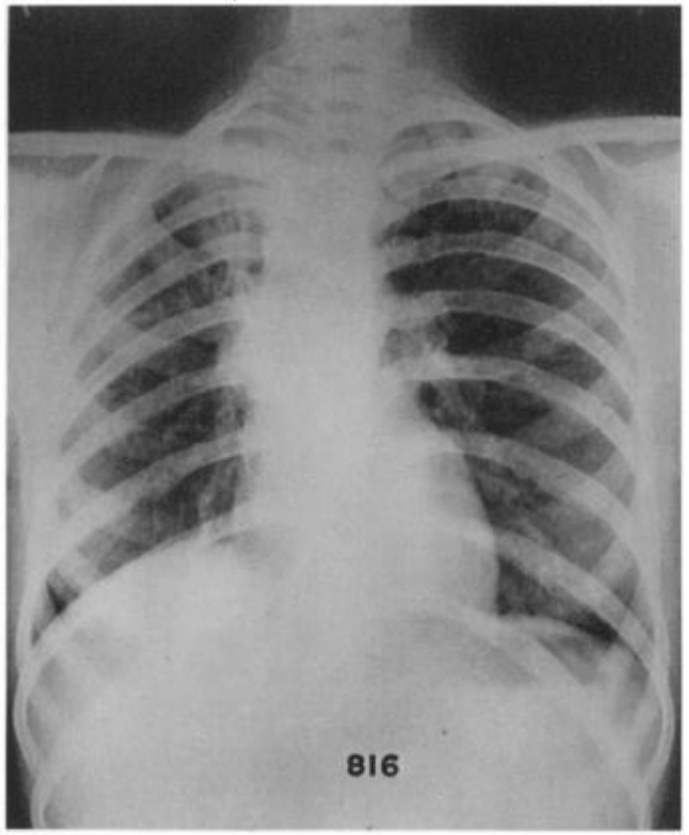


FIG. 8.—Case 81 (C). Aug. 27, 1947.

Streptomycin in Tuberculosis Trials Committee, The British Medical Journal , 1948

HISTOIRE

Streptomycine

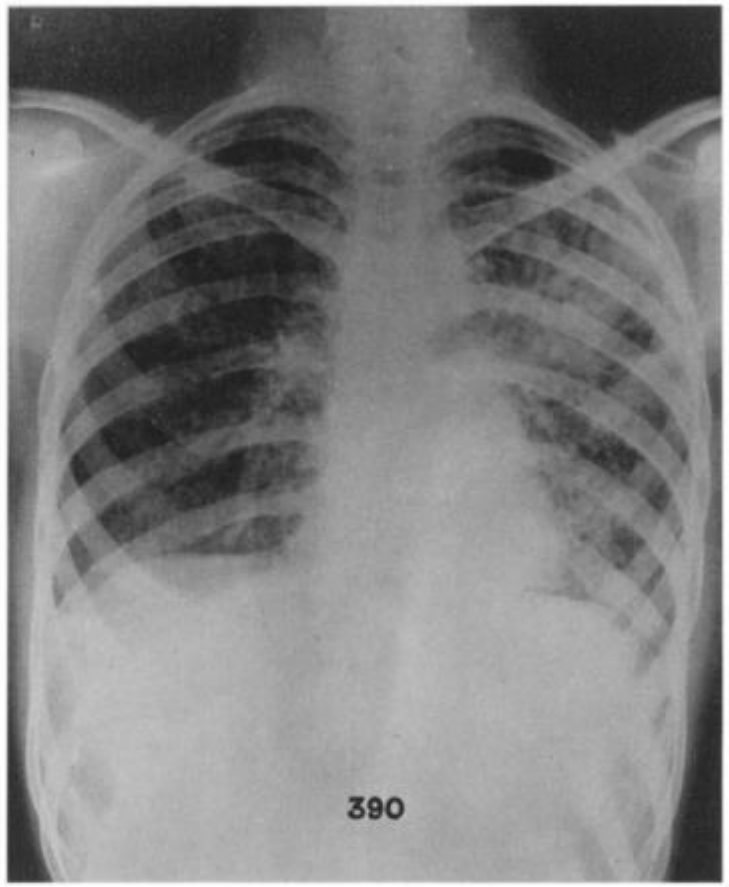


FIG. 5.—Case 39 (S). June 21, 1947.

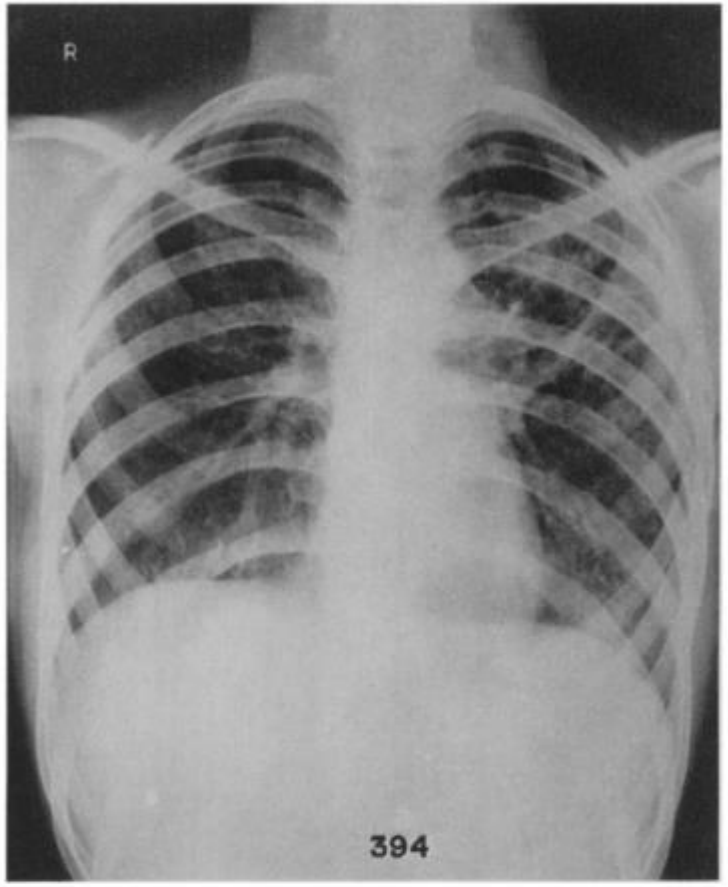


FIG. 6.—Case 39 (S). Oct. 20, 1947.

Streptomycin in Tuberculosis Trials Committee, The British Medical Journal , 1948

HISTOIRE

Streptomycine

Contrôle

TABLE XIII.—*Presence of Tubercle Bacilli*

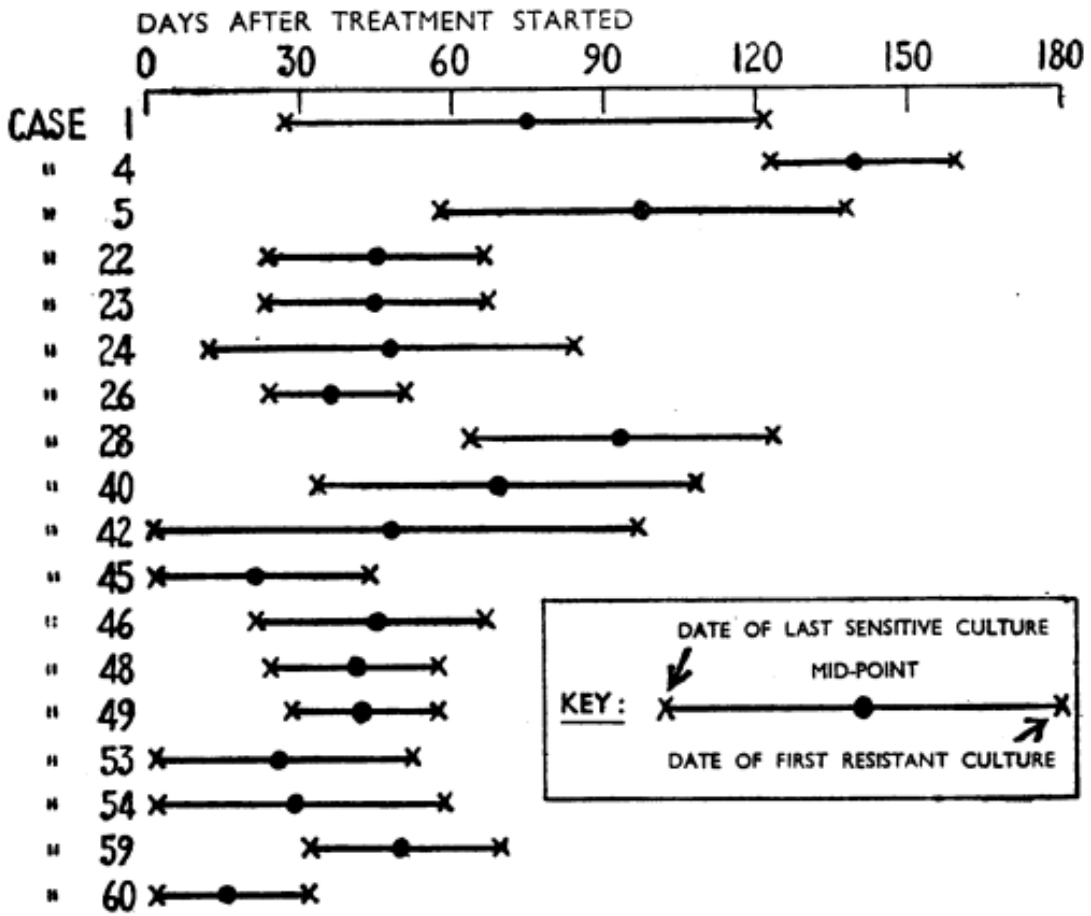
Results on Admission	Total	Deaths	Results in Third Month: Direct Smear: Strongly Positive	Results in Third Month: Direct Smear: Weakly Positive	Results in Third Month: Smear Negative Culture Positive	Results in Third Month: Culture Negative
S Cases:						
Smear strongly positive	40	0	16	12	10	2
Smear 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

Streptomycin in Tuberculosis Trials Committee, The British Medical Journal , 1948

INTRODUCTION



RESISTANCE

Streptomycin in Tuberculosis Trials Committee, The British Medical Journal , 1948

INTRODUCTION

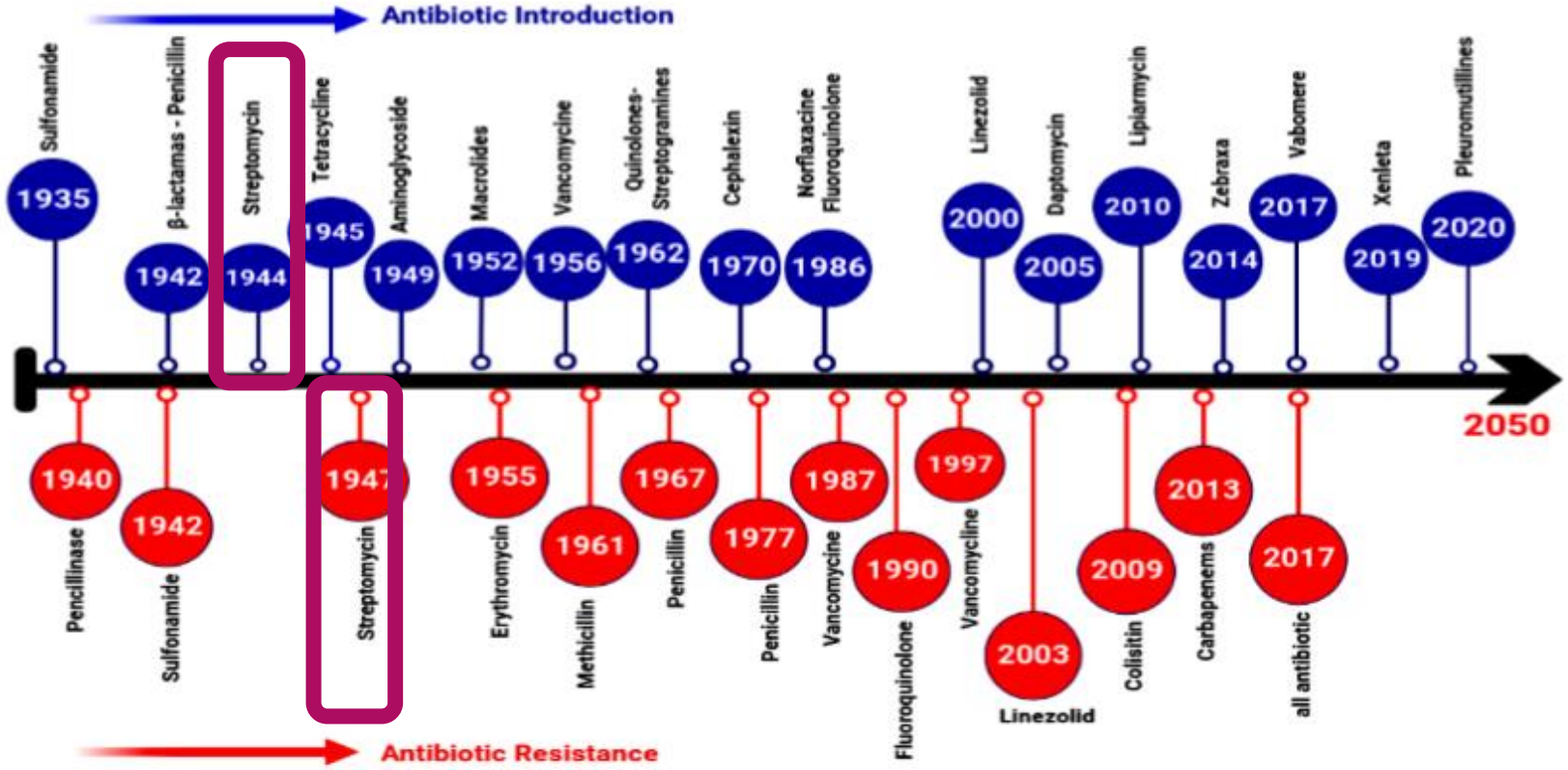


Figure 1. Timeline illustrates antibiotics evolution.

Helmy et al, antibiotic, 2023

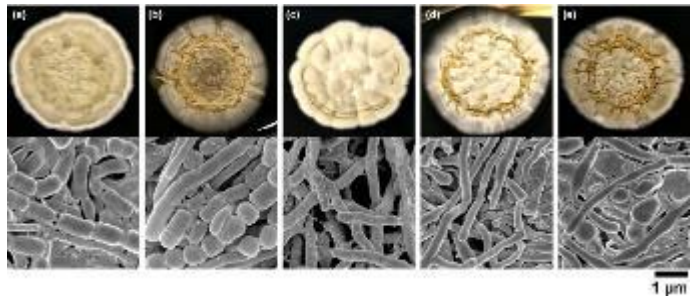
PLAN

- Histoire
- Structure et mode d’action
- Spectre d’action
- PK-PD
- Indications
- Effets secondaires
- Surveillance

STRUCTURE ET MODE D ACTION

- 50 molécules ➔ 9 utilisées en thérapeutique

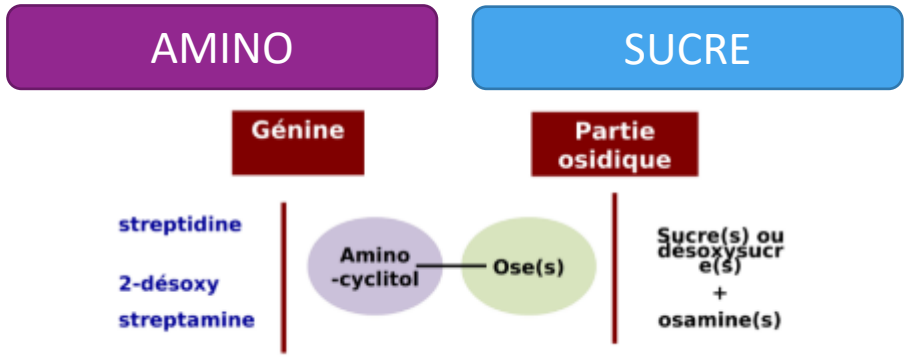
Aminosides naturels		Aminosides hemi-synthétique
Extraits de *Streptomyces* (y)	Streptom**y**cine	**Amikacine**
	Néom**y**cine	Isepamycine
	Kanam**y**cine	Netilmicine
	Tobram**y**cine	
Extraits de *Actinomyces (i)*	Gentam**i**cine	
	Sisomicine	



STRUCTURE ET MODE D ACTION

- Aminosides = Hétérosides

AMINO GLYCOSIDE



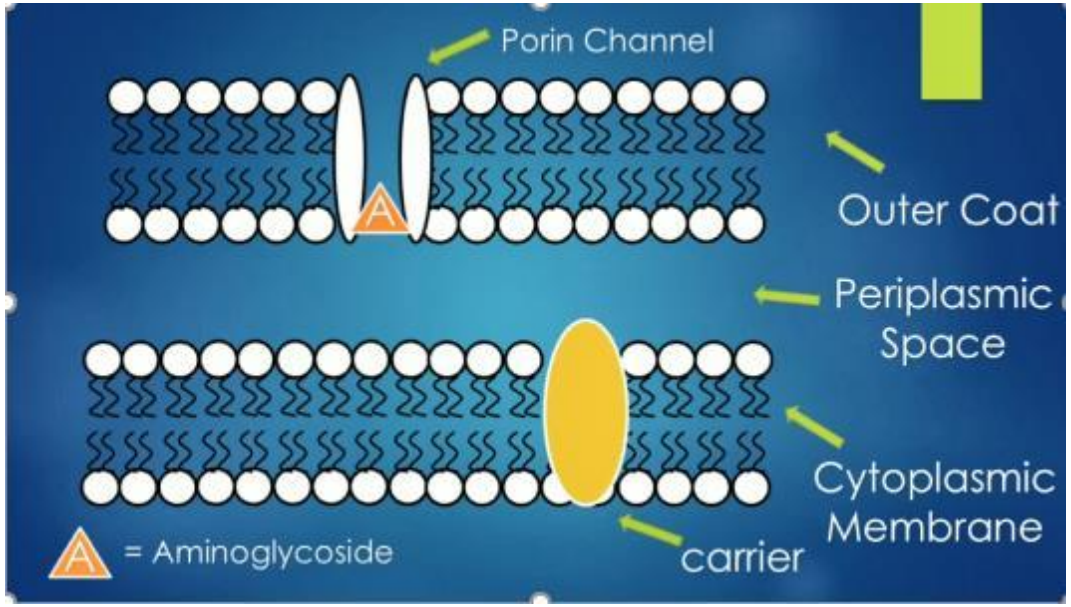
- Implications physico-chimique :
  - Fonctions azotés et hydroxyles ➔ HYDROPHILE , peu LIPOPHILE
  - Utilisés sous forme de sels (sulfate) ➔ solution ACIDE
    - Incompatibilité physico-chimique +++
    - Ne pas mélanger avec d'autres traitements ➔ PRECIPITATIONS

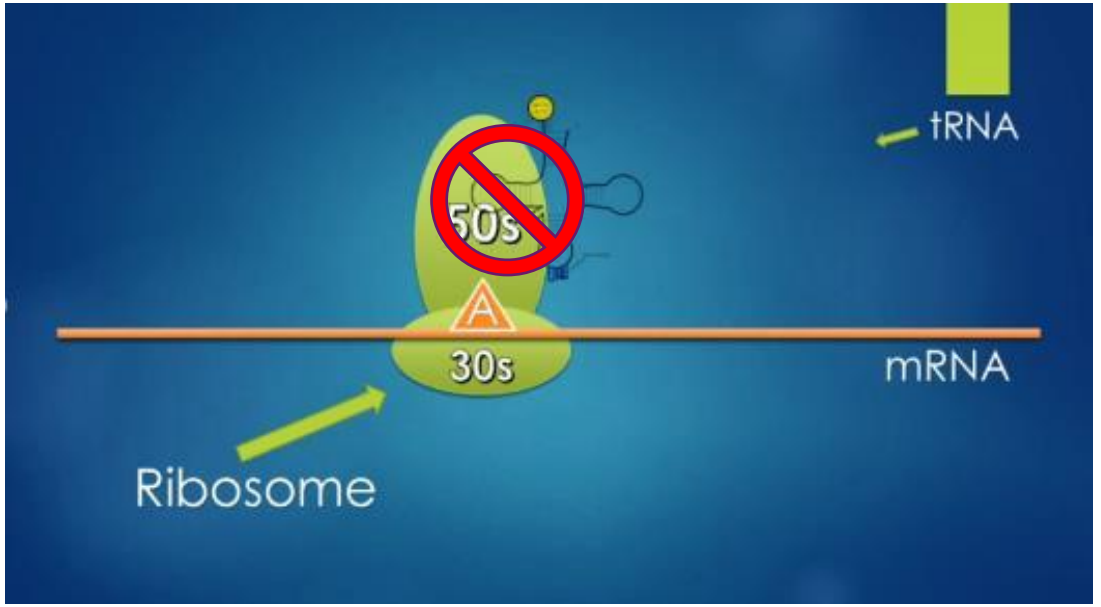
STRUCTURE ET MODE D ACTION

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

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

Quel est le mode d'action des aminosides ?

BACTERICIDE

BACTERIOSTATIQUE

STRUCTURE ET MODE D ACTION

Quel est le mode d'action des aminosides ?

BACTERICIDE

BACTERIOSTATIQUE

PLAN

- Histoire
- Structure et mode d’action
- Spectre d’action
- PK-PD
- Indications
- Effets secondaires
- Surveillance

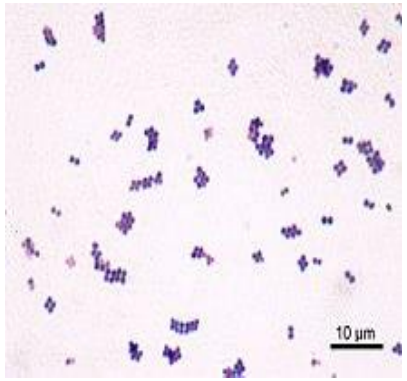
SPECTRE D'ACTION

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

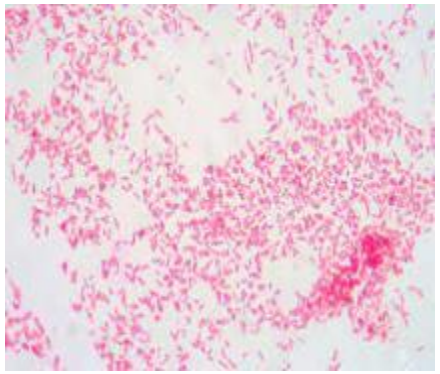
A- E coli
B- Listeria monocytogénès
C- Clostridium perfringens
D- Mycobacterium tuberculosis
E- Stenotrophomonas maltophila
F- Clostridium sp

SPECTRE UTILE

Cocci +

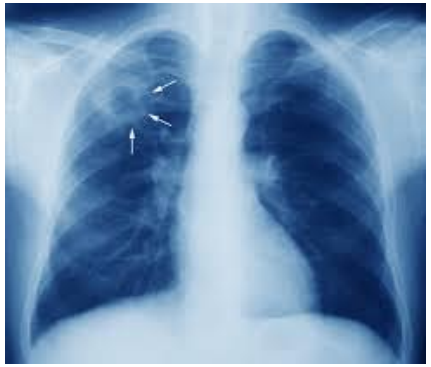


Bacilles gram négatif



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	

European Committee on Antimicrobial Susceptibility Testing, Jan 2022

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

European Committee on Antimicrobial Susceptibility Testing, Jan 2022

SPECTRE UTILE

RESISTANCES NATURELLES

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

Association avec un ATB actif sur la paroi

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

SPECTRE D'ACTION

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

*A- **E coli***
B- Listeria monocytogénès
C- Clostridium perfringens
D- Mycobacterium tuberculosis
E- Stenotrophomonas maltophila
F- Clostridium sp

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

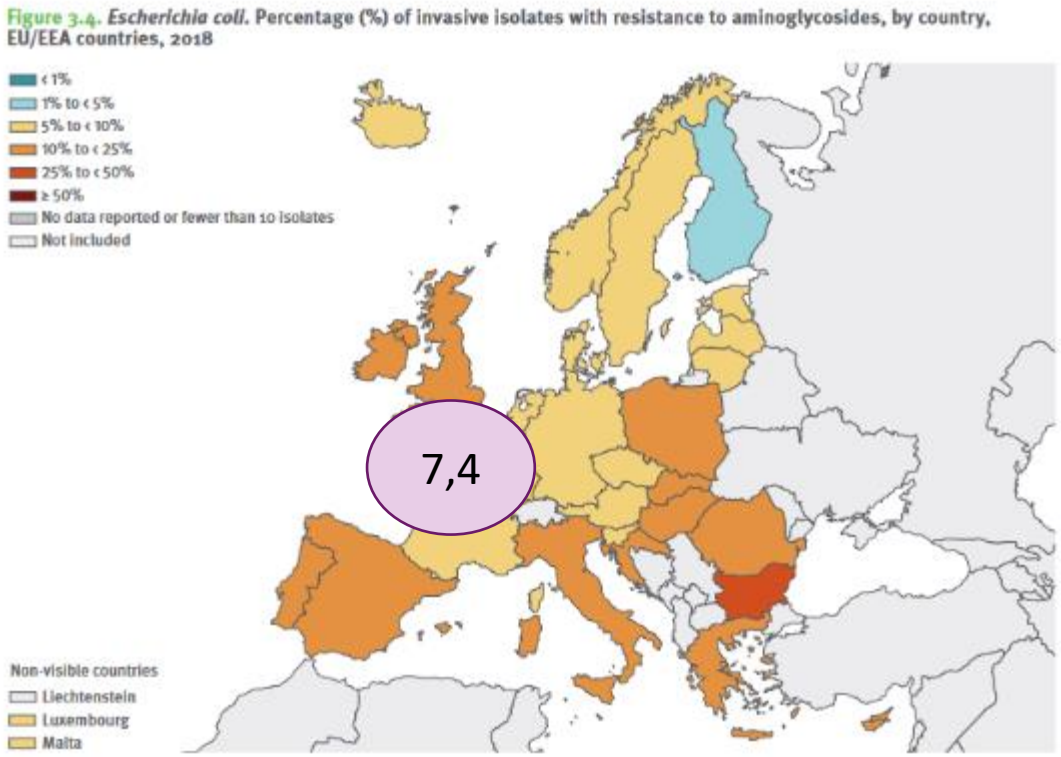
SPECTRE UTILE

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

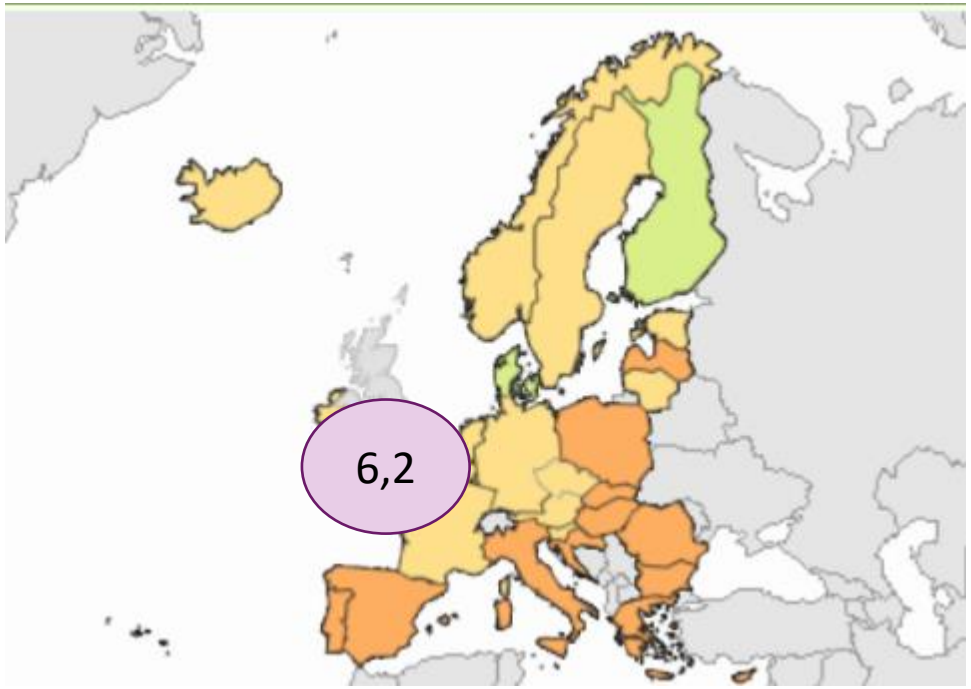
GERMES	2015		2016		2017		2018	
	N	%R (95%IC)	N	%R (95%IC)	N	%R (95%IC)	N	%R (95%IC)
E.coli	11 055	8.2 (8-9)	11 135	7.9 (7-8)	13 103	7.0 (7-7)	12 283	7.4 (7-8)
K. pneumoniae	2 337	26.3 (25-28)	2569	26.2 (25-28)	2 857	23.8(22-25)	2990	24.8 (23-26)
P. Aeruginosa	1950	14.1 (13-16)	1 976	10.7 (9-12)	1 713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

ECDC : Surveillance of antimicrobial resistance in Europe 2018

SPECTRE UTILE

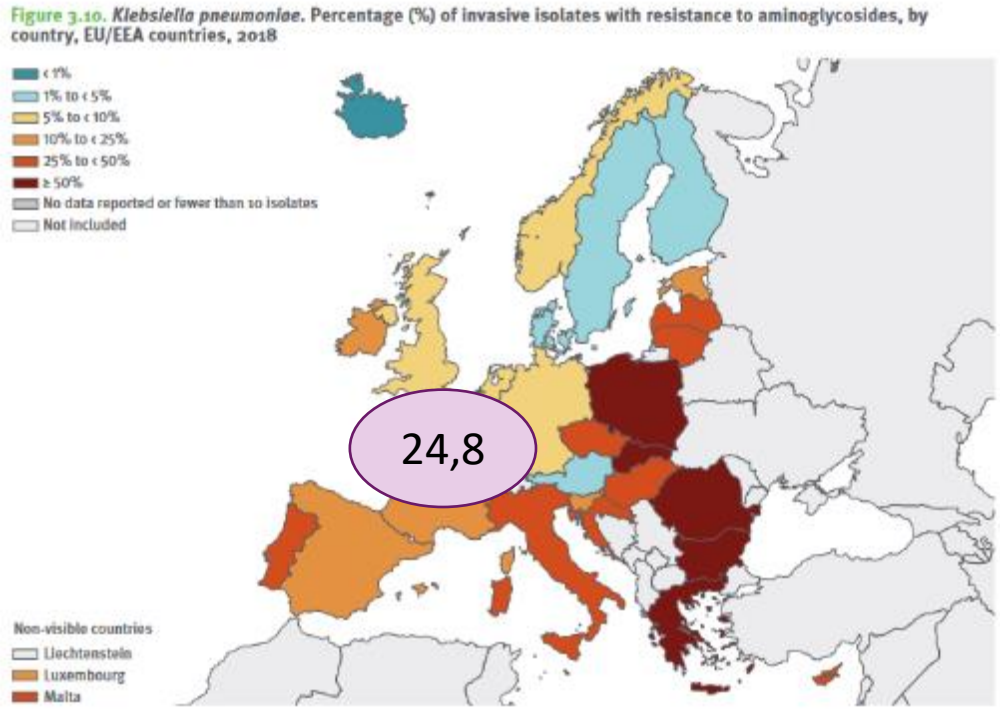


ECDC : Surveillance of antimicrobial resistance in Europe 2018

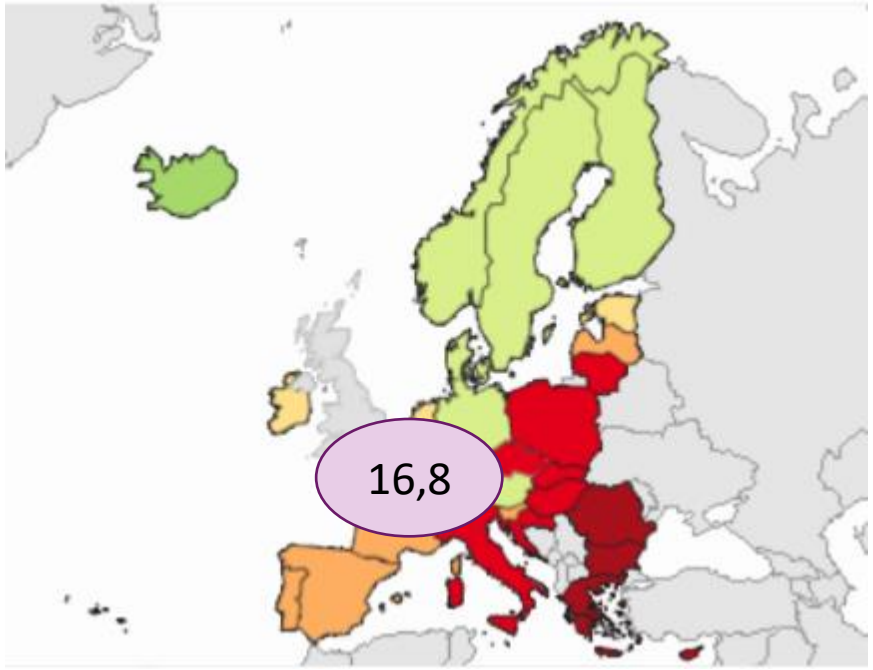


ECDC : Surveillance of antimicrobial resistance in Europe 2022

SPECTRE UTILE

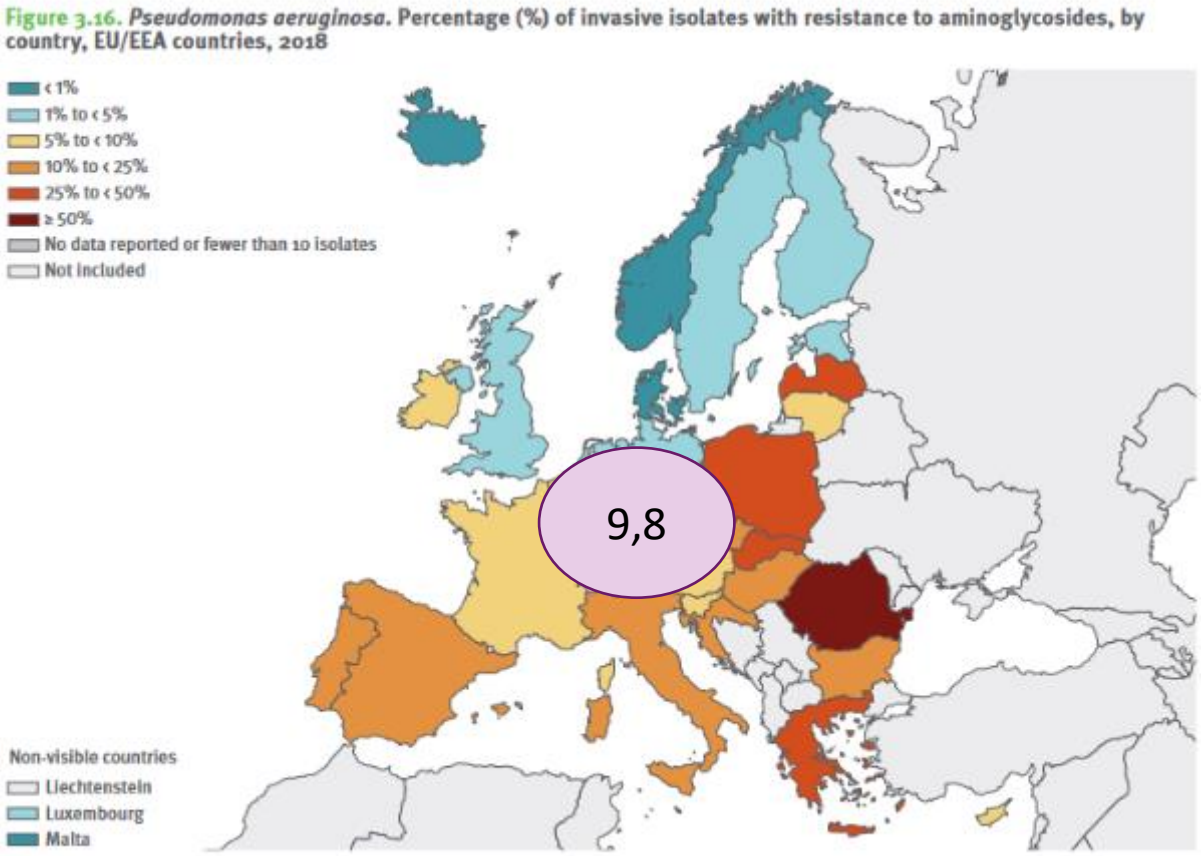


ECDC : Surveillance of antimicrobial resistance in Europe 2018

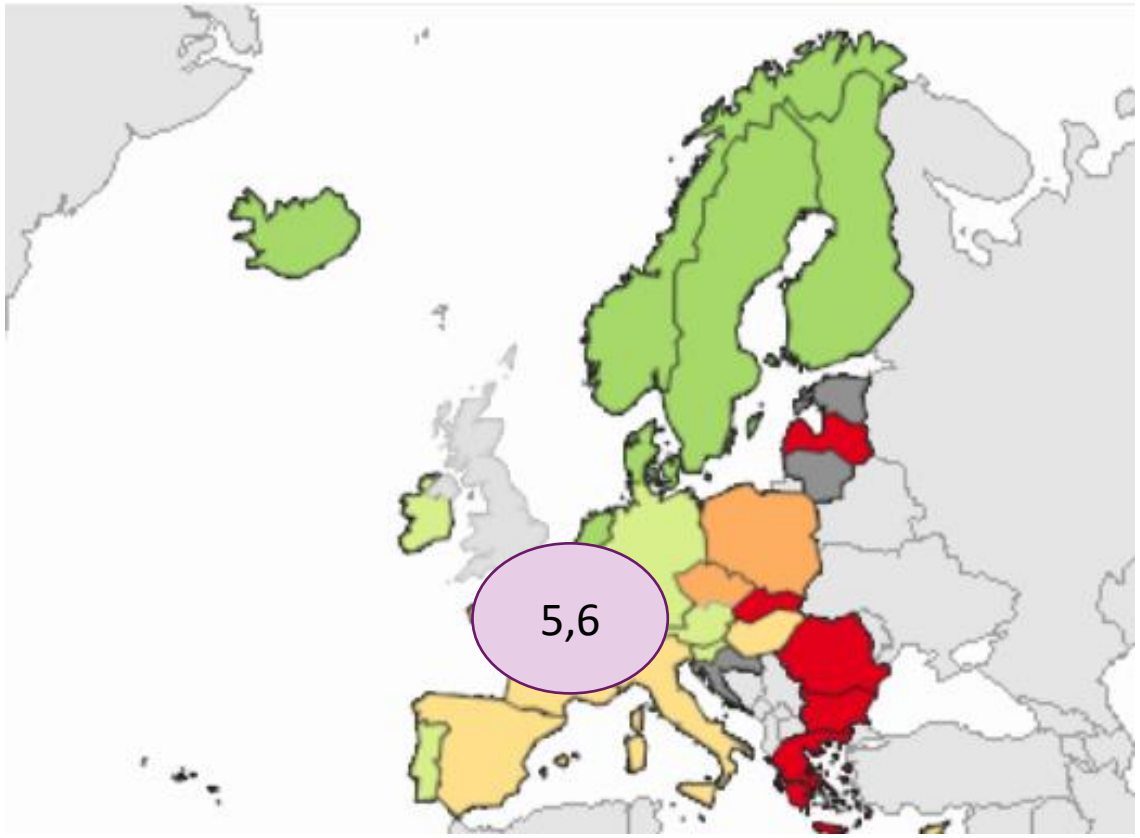


ECDC : Surveillance of antimicrobial resistance in Europe 2022

SPECTRE UTILE

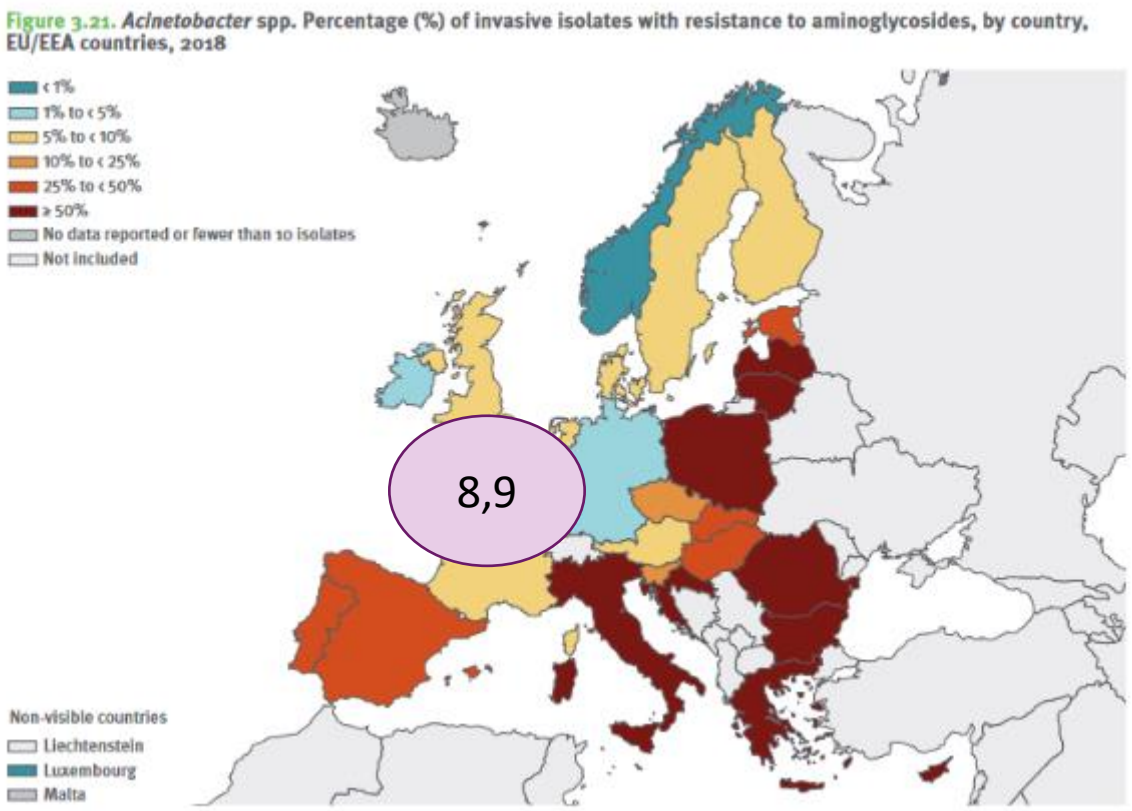


ECDC : Surveillance of antimicrobial resistance in Europe 2018

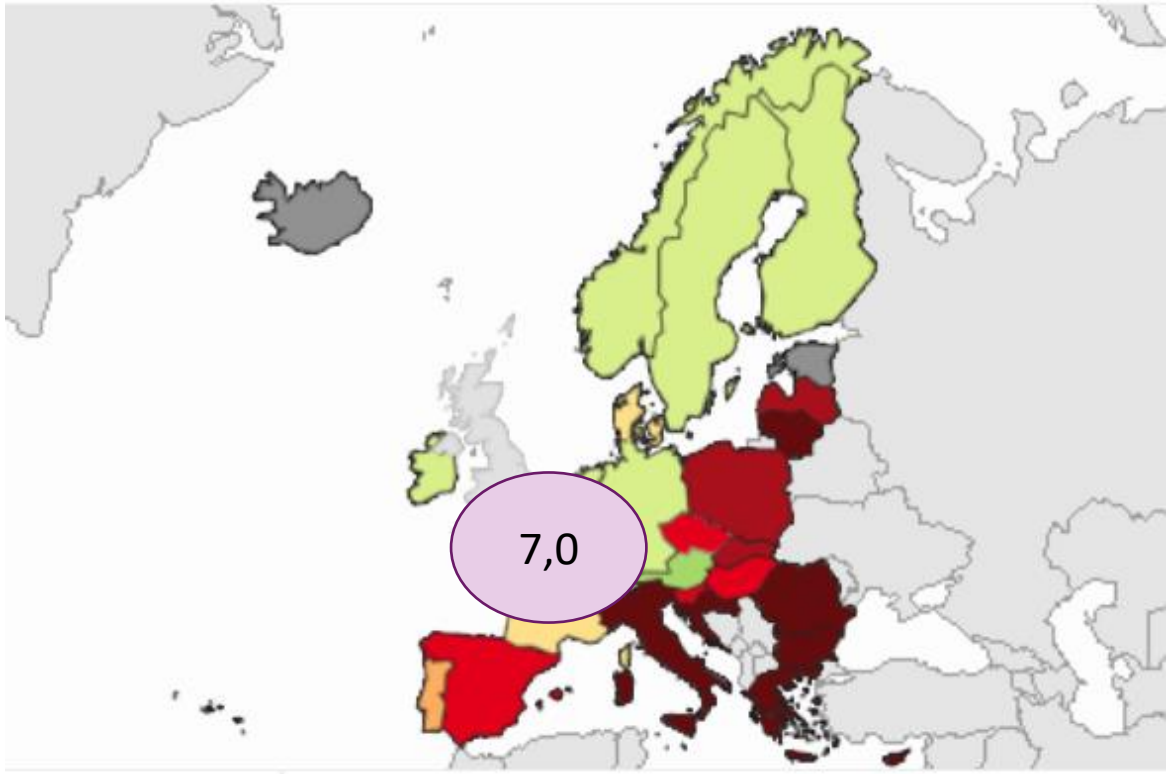


ECDC : Surveillance of antimicrobial resistance in Europe 2022

SPECTRE UTILE



ECDC : Surveillance of antimicrobial resistance in Europe 2018



ECDC : Surveillance of antimicrobial resistance in Europe 2022

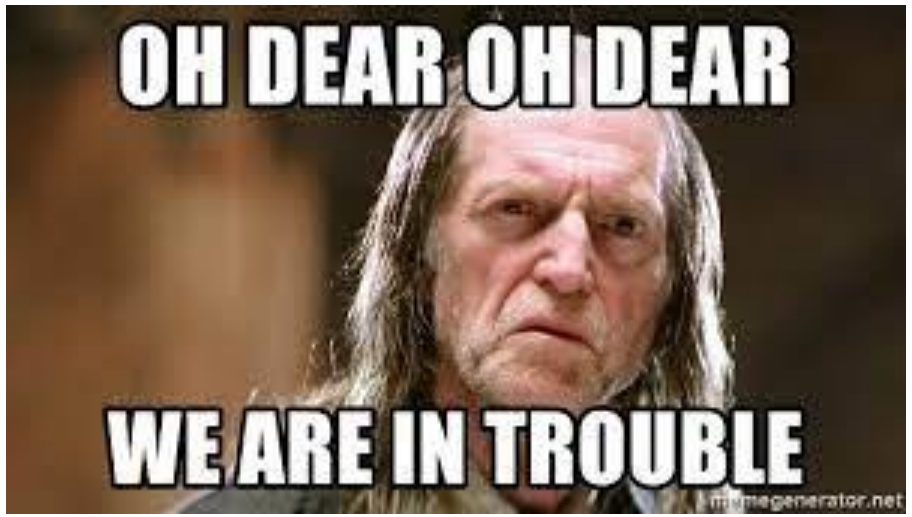
PLAN

- Histoire
- Structure et mode d’action
- Spectre d’action
- PK-PD
- Indications
- Effets secondaires
- Surveillance

PK/PD

PHARMACOCINETIQUE (PK) :

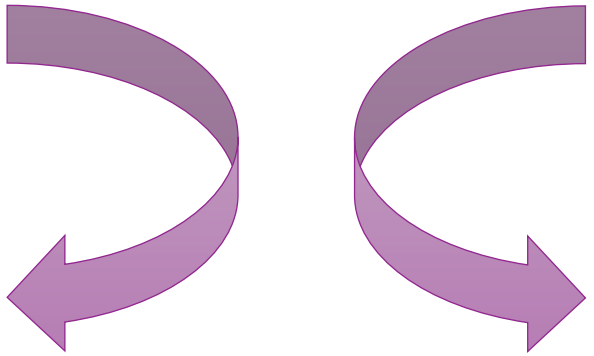
PHARMACODYNAMIE (PD)



PK/PD

Quelle est la pharmadynamie des aminosides?

TEMPS DEPENDANT

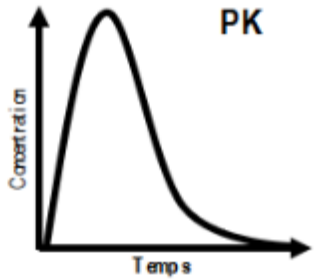


CONCENTRATION DEPENDANT

PK/PD

PHARMACOCINETIQUE (PK) :

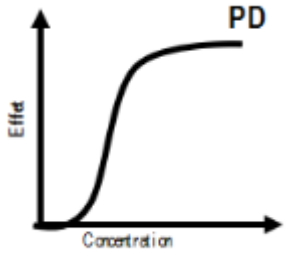
- Absorption
- Biodisponibilité
- Diffusion
- Demi-vie
- Métabolisme
- Elimination



CONCENTRATION

PHARMACODYNAMIE

Action de l'antibiotique



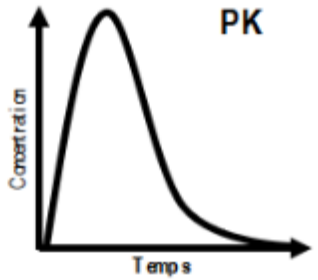
SITE INFECTION :
EFFICACITE

TISSUS :
TOXICITE

PK/PD

PHARMACOCINETIQUE (PK) :

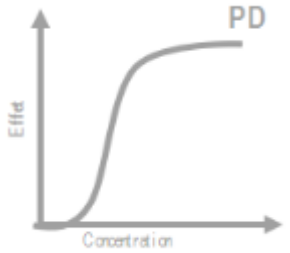
- Absorption
- Biodisponibilité
- Diffusion
- Demi-vie
- Métabolisme
- Elimination



CONCENTRATION

PHARMACODYNAMIE

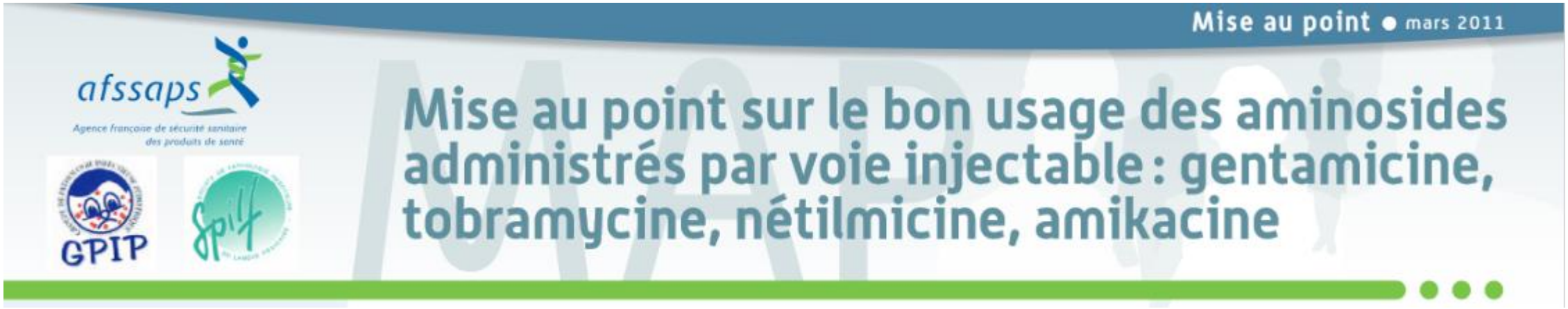
Action de l'antibiotique



SITE INFECTION : EFFICACITE

TISSUS : TOXICITE

PK/PD


Mise au point ● mars 2011
afssaps
Agence française de sécurité sanitaire des produits de santé
GPIP
Mise au point sur le bon usage des aminosides administrés par voie injectable : gentamicine, tobramycine, nétilmicine, amikacine

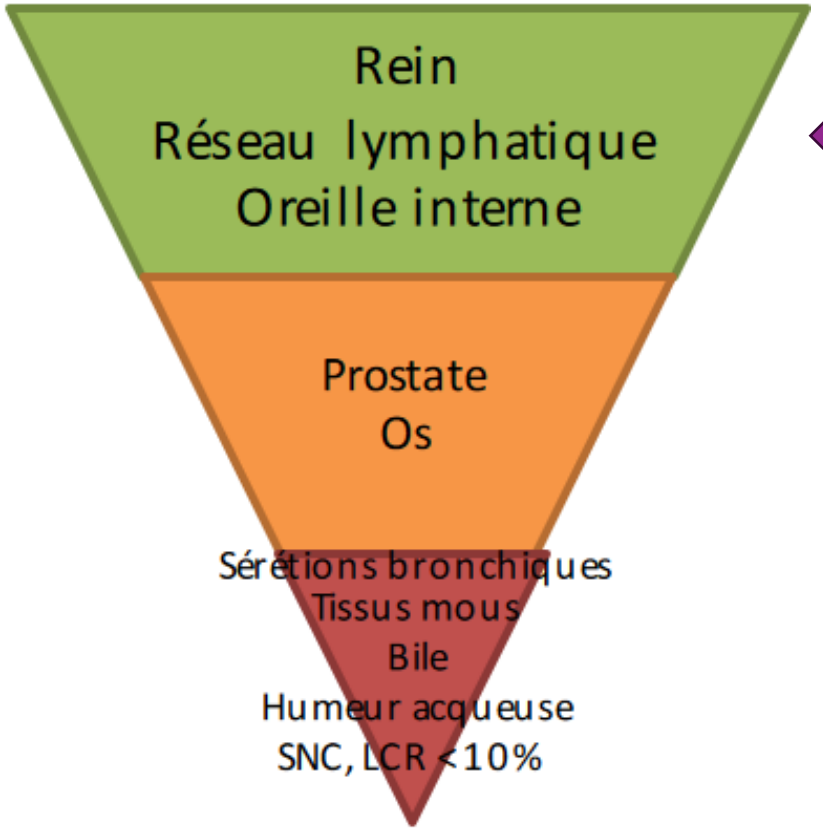
PK/PD

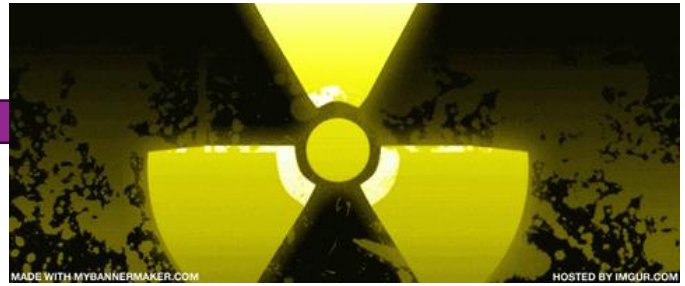
- **ABSORPTION :** **Voie IV**
  - Absence d'absorption enterale
- **FIXATION AU PROTEINES** :
  - faible 20%
- **ELIMINATION**
  - Rénale (forme inchangée) ➔ Toxicité !!!
  - Faible sécrétion biliaire
- **DEMI VIE D ELIMINATION** : 2h

Travail de thèse de science du Dr Vicens Quentin, 2002

PK/PD

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





Valour, Aminosides

PK/PD

PHARMACOCINETIQUE (PK) :

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

- **RISQUE DE MODIFICATION PK :**

Insuffisance rénale

Nouveau né

Sujet âgé

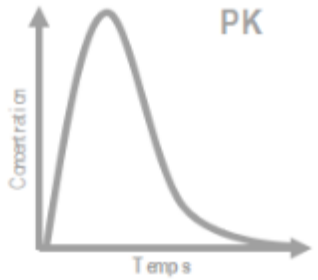
Modification du volume de distribution

Mise au point sur le bon usage des aminosides adminisitrés par voie injectable, AFSSAPS, 2011c

PK/PD

PHARMACOCINETIQUE (PK) :

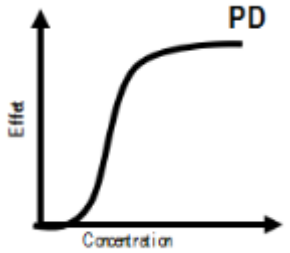
- Absorption
- Biodisponibilité
- Diffusion
- Demi-vie
- Métabolisme
- Elimination



CONCENTRATION

PHARMACODYNAMIE

Action de l'antibiotique



SITE INFECTION : EFFICACITE

TISSUS : TOXICITE

PK/PD

TEMPS VERSUS CONCENTRATION DEPENDANT :

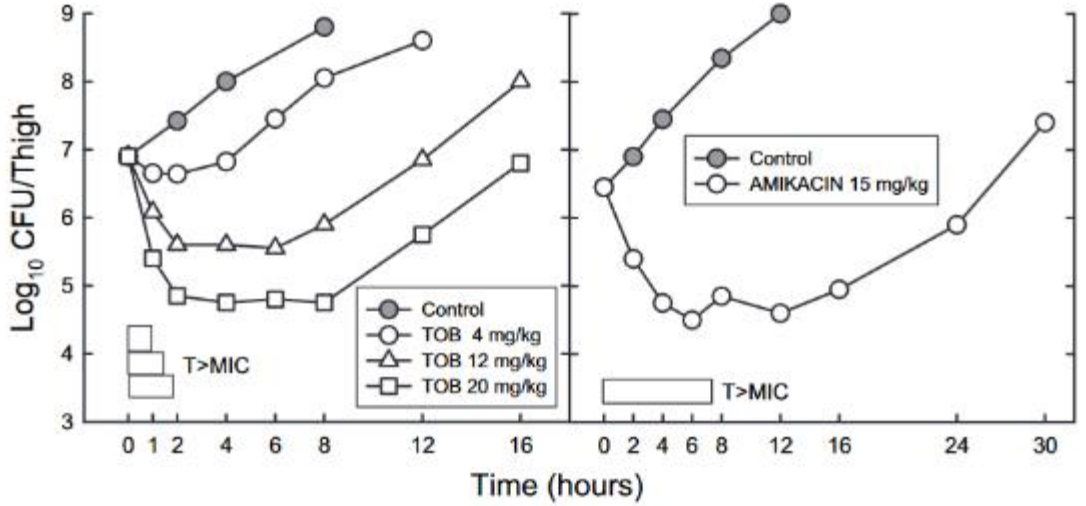
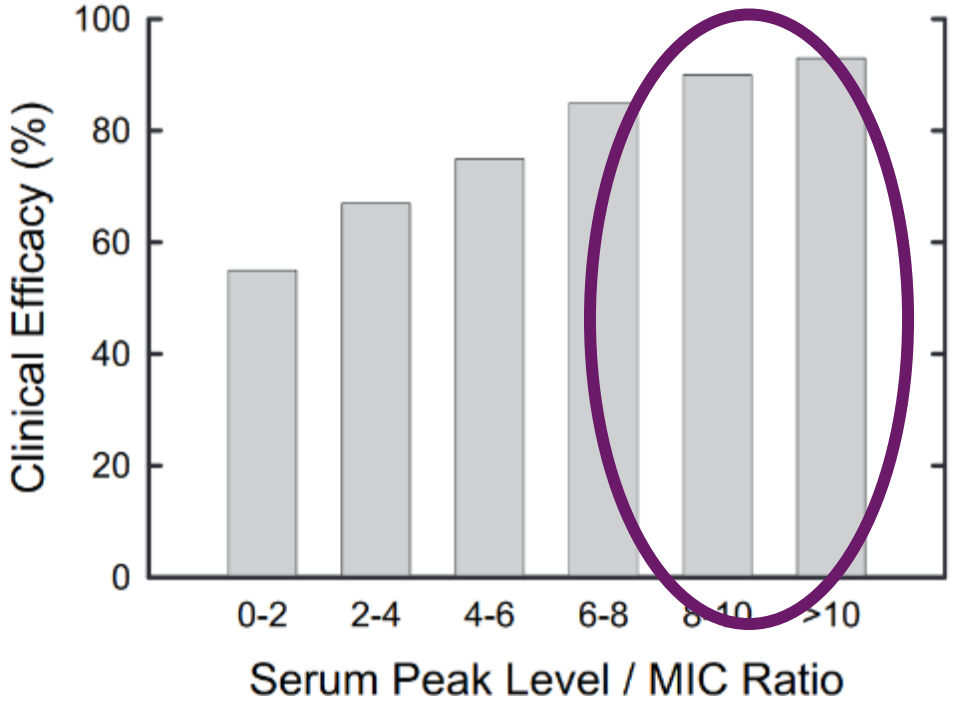


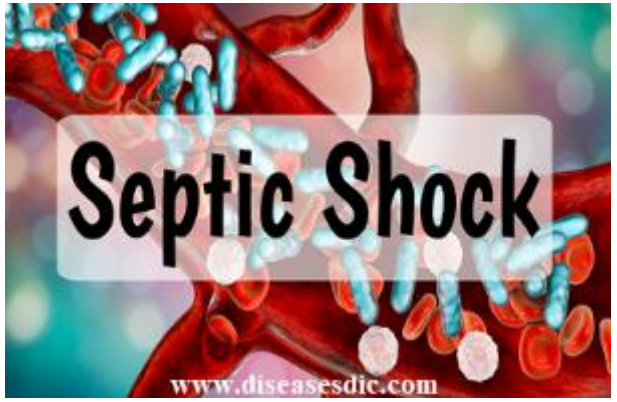
Fig. 1. The time course of killing and regrowth of *Pseudomonas aeruginosa* in thighs of neutropenic mice following 3 doses of tobramycin (TOB) in normal mice (*left panel*) and amikacin in mice with renal impairment (*right panel*). T>MIC, time above minimum inhibitory concentration.



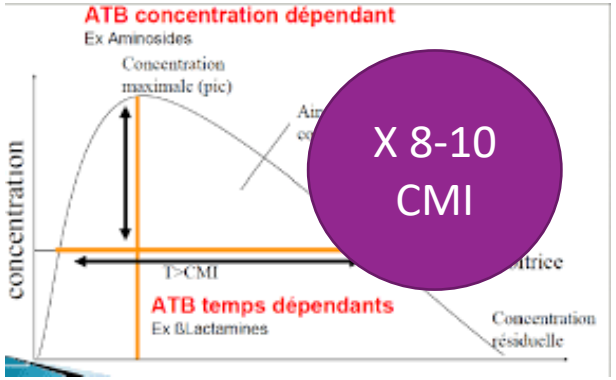
Optimizing aminoglycoside use. Crit Care Clin. 2011. Craig WA.

PK/PD

BACTERICIDE RAPIDE



CONCENTRATION DEPENDANT



EFFET POST ANTIBIOTIQUE

Resistance adaptative

PK/PD

- **ADMINISTRATION :**
  - IVL : 30 min (éviter sous cutanée et IM)
  - **DOSE UNIQUE JOURNALIERE**
    - 8-10 CMI
    - Efficacité clinique
    - Toxicité équivalente
    - Diminution risque de mutants résistants
  - **DUREE : COURTE**
    - Inoculum important
    - <5 jours

PK/PD

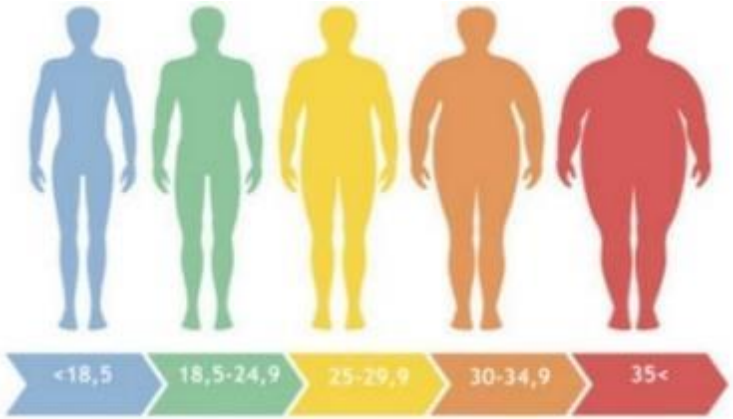
REFERENTIELS

- **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

ESPACEMENT DES DOSES

Dosages

PLAN

- Histoire
- Structure et mode d’action
- Spectre d’action
- PK-PD
- Indications
- Effets secondaires
- Surveillance

INDICATIONS THERAPEUTIQUES

<u>Dans quelles situations cliniques utiliseriez-vous ces antibiotiques en premiere intention</u> ?

- Bacteriémie ?
- Choc septique ?
- Immunodéprimé ?
- Listeria ?
- Tuberculose ?

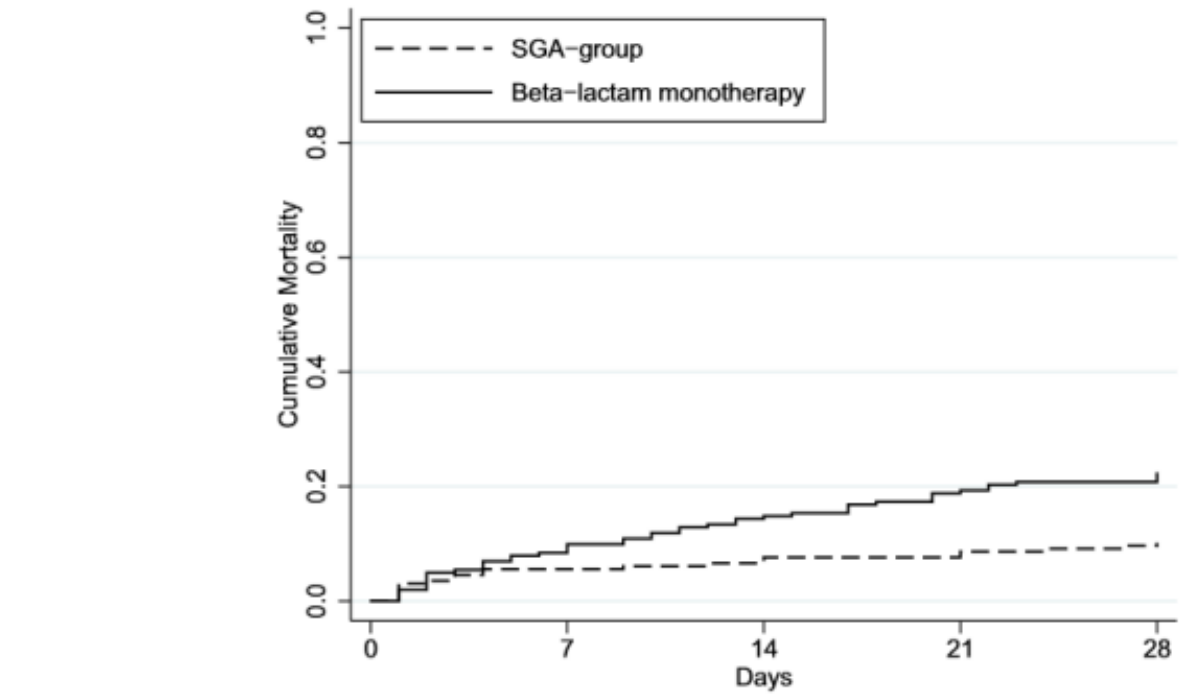
INDICATIONS THERAPEUTIQUES

<u>Dans quelles situations cliniques utiliseriez-vous ces antibiotiques en premiere intention</u> ?

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

BACTERIEMIE

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



Number of subjects at risk					
SGA−group	197	186	184	182	178
Beta−lactam monotherapy	202	185	173	164	160

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

Liljedahl Prytz et al, Plos, 2020

BACTERIEMIE

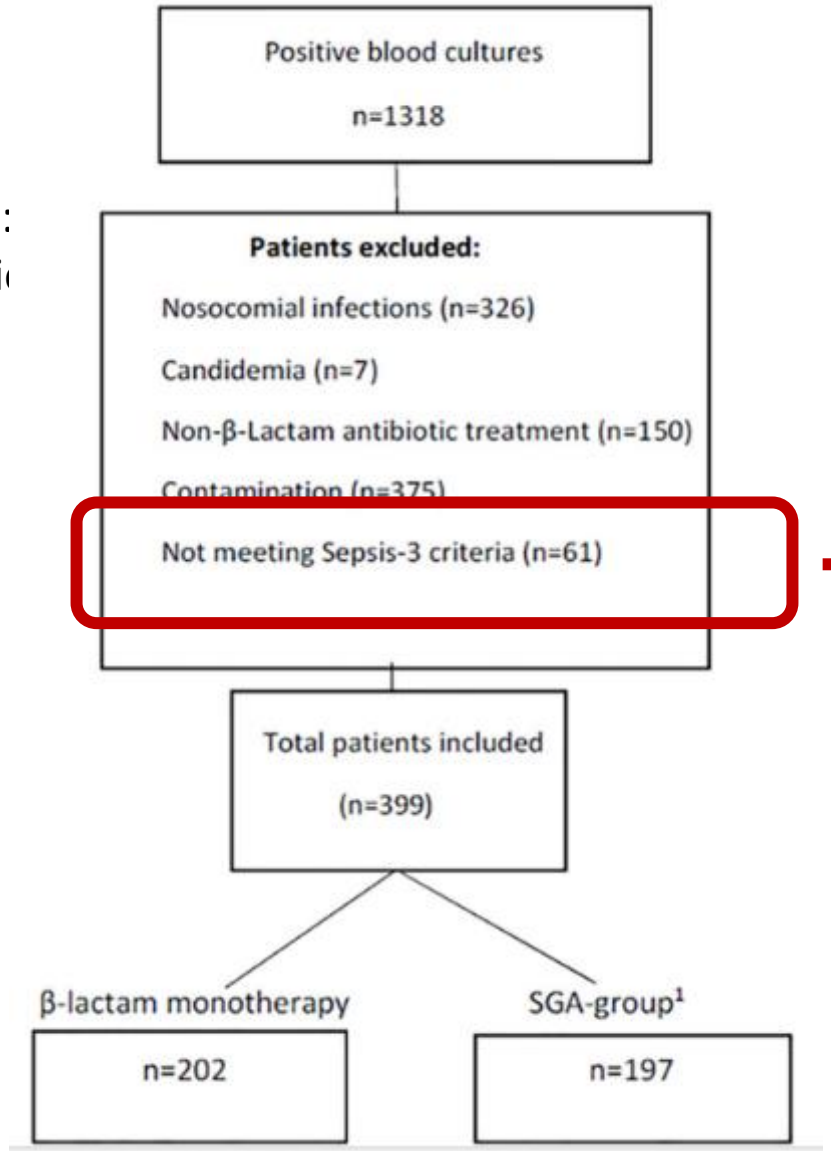
Table 3. Initial β-lactam treatment and 28-days mortality comparison between study groups.

	β-lactams	β-lactam monotherapy n = 202		SGA-group[1] n = 197		β -Lactam monotherapy vs SGA groups			
						Unadjusted		Adjusted[2]	
		n	Mortality[3] (%)	n	Mortality[3] (%)	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					

Liljedahl Prytz et al, Plos, 2020

CHOC SEPTIQUE

Etude de cohorte retrospective :
- Inclusion toutes les bactériémi



Sepsis-3 criteria :
- Dysfonction d'organe (SOFA >=2)
- Choc septique
  - Besoin aminergique
  - Lactate supérieur à 2

Liljedahl Prytz et al, Plos, 2020

BACTERIEMIE

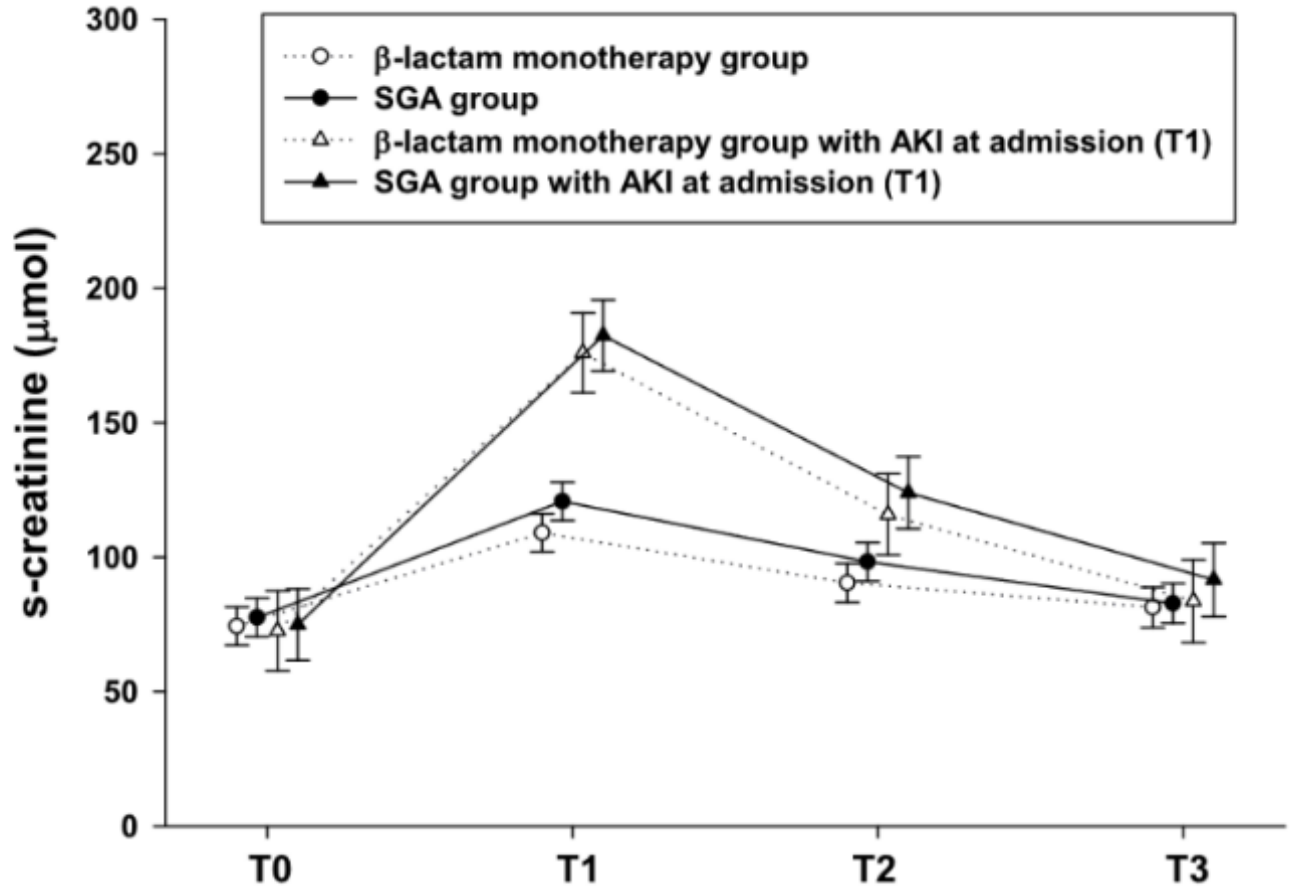


Fig 3. AKI. Mean creatinine from T0 to T3 in β-lactam monotherapy group and SGA group as well for each study group with only patients with AKI at admission (T1). Estimated mean creatinine with 95% confidence intervals by linear mixed model, see statistical section for details.

Liljedahl Prytz et al, Plos, 2020

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

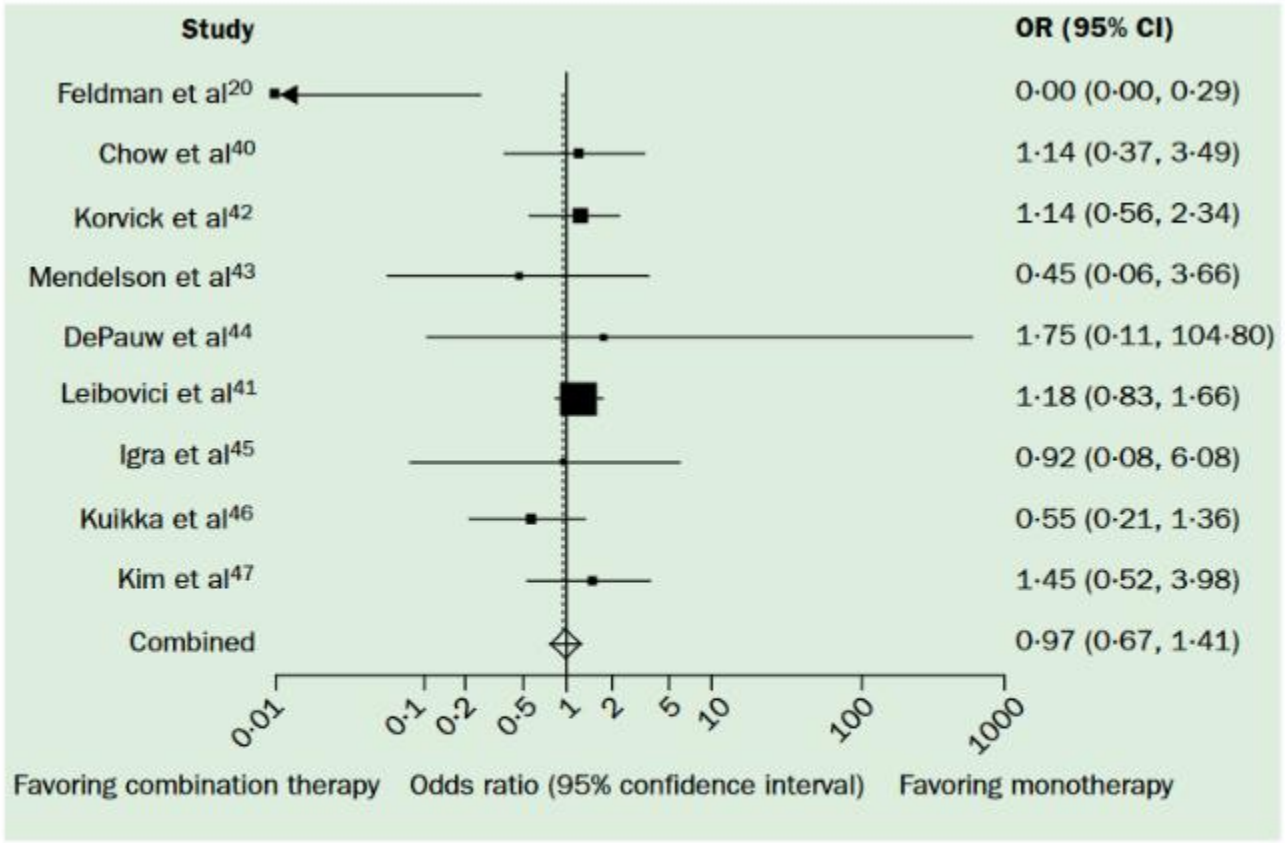


Figure 3. Analysis of studies done in or after 1990 comparing combination anti-infective therapy with monotherapy for reducing mortality of Gram-negative bacteraemia. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 0·97 (95% CI 0·67–1·41), indicating no mortality benefit with combination antimicrobial therapy.

17 études dont
- 5 cohortes prospectives
- 2 essais randomisés

BACTERIEMIE

Pseudomonas aeruginosa

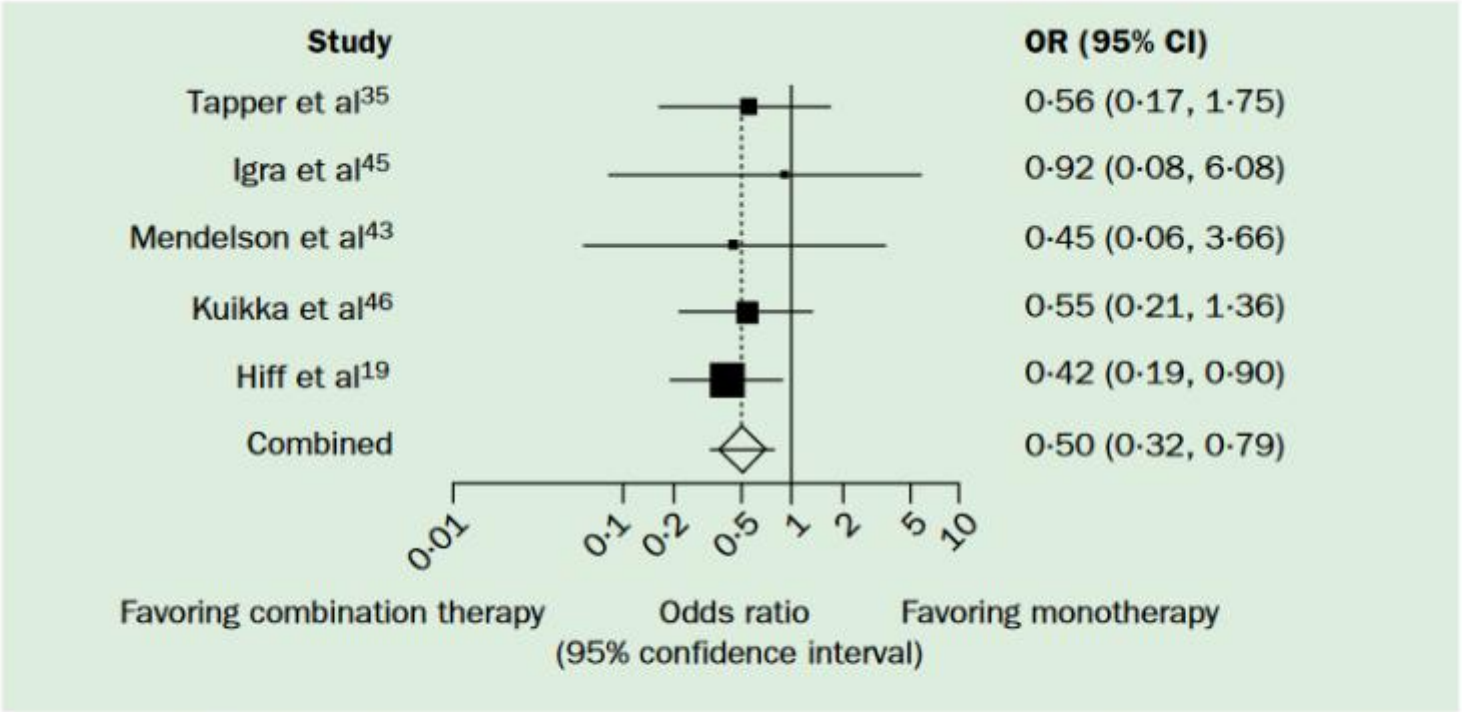


Figure 6. Analysis of studies comparing combination anti-infective therapy with monotherapy for reducing mortality of Pseudomonas *spp bacteraemia.The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 0·50 (95% CI 0·32–0·79), indicating a mortality benefit with combination antimicrobial therapy.*

BACTERIEMIE

Contents lists available at ScienceDirect

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]

Deelen et al, CMI, 2021

BACTERIEMIE

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

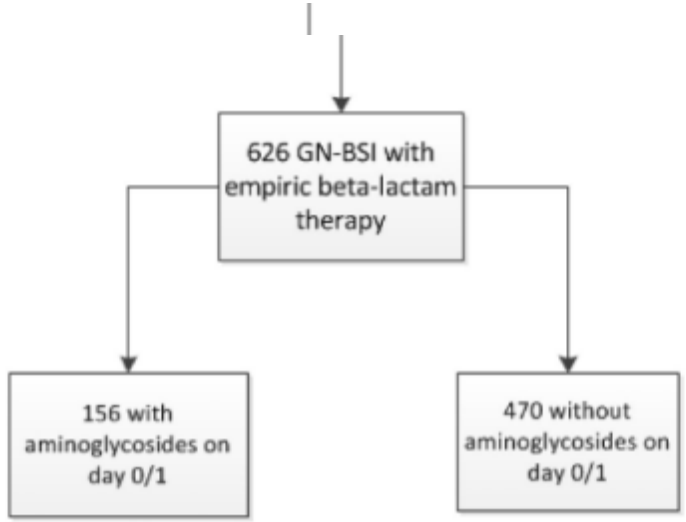


Fig. 1. Flow chart.

Deelen et al, CMI, 2021

BACTERIEMIE

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

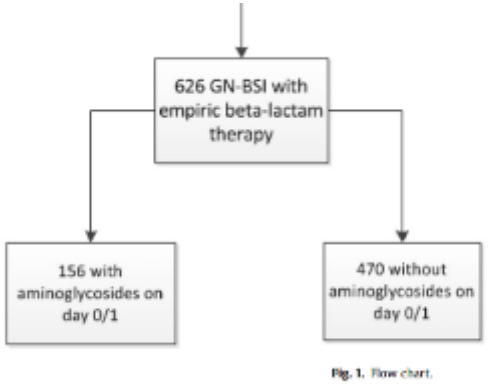


Fig. 1. Flow chart.

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 (0.76–3.03)
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 *Pseudomonas aeruginosa* 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.

Deelen et al, CMI, 2021

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)	*p* 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

<u>Dans quelles situations cliniques utiliseriez-vous ces antibiotiques en premiere intention</u> ?

- Bacteriémie ?
- **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

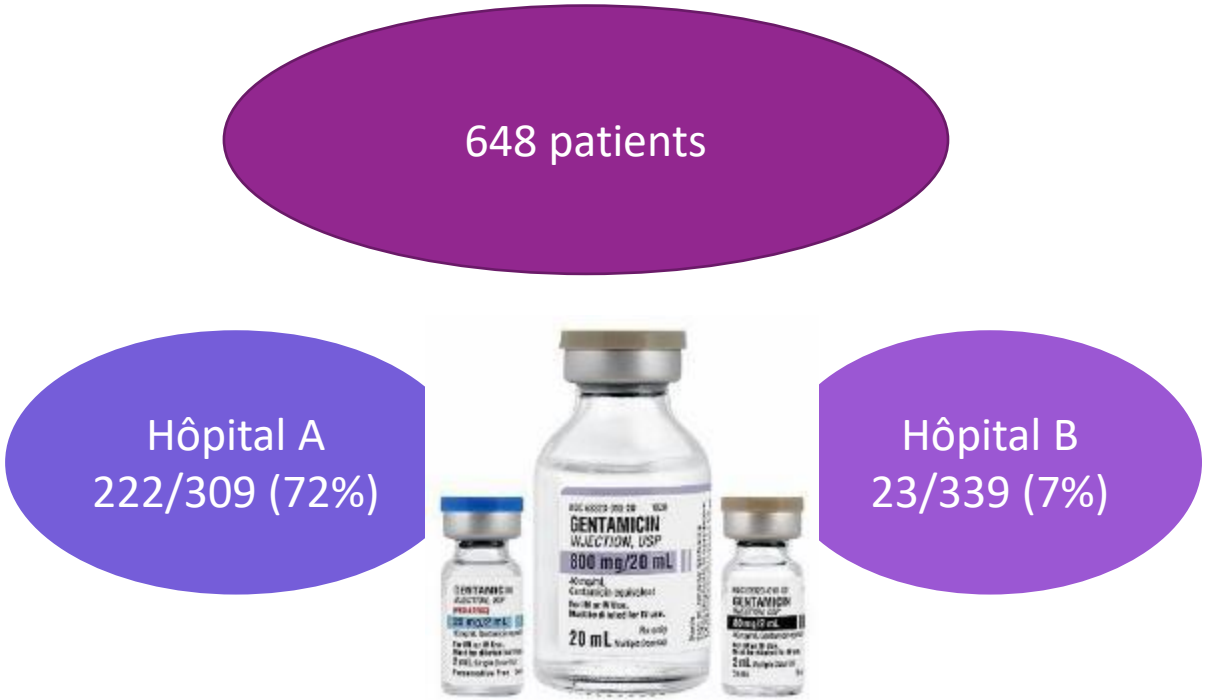
David S. Y. Ong,[1,2] Jos F. Frencken,[2,3] Peter M. C. Klein Klouwenberg,[1,2] Nicole Juffermans,[4] Tom van der Poll,[5] Marc J. M. Bonten,[1,3] and Olaf L. Cremer[2]; for the MARS consortium[a]

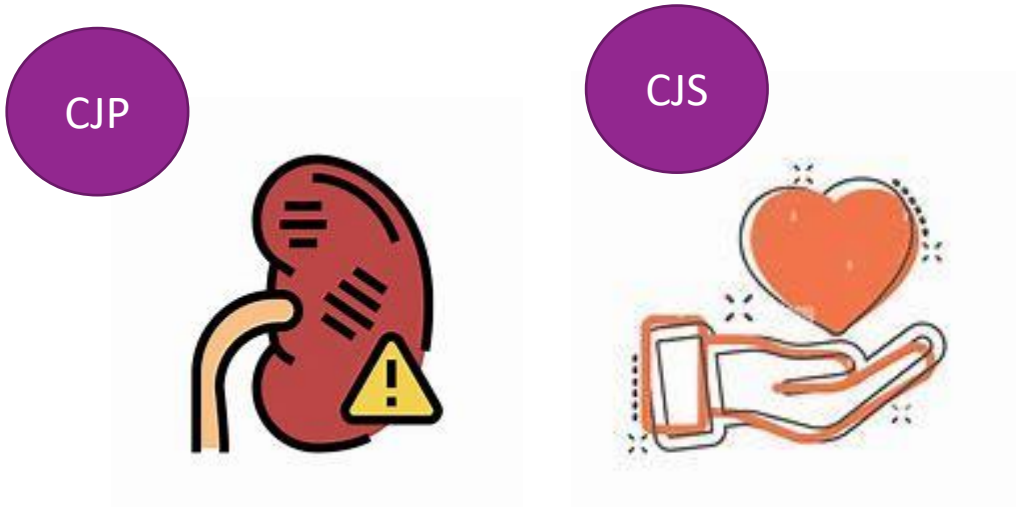
[1]Department of Medical Microbiology, [2]Department of Intensive Care Medicine, and [3]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, [4]Department of Intensive Care, Academic Medical Center, University of Amsterdam, and [5]Center of Experimental and Molecular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

Ong DSY et al, CID, 2017

CHOC SEPTIQUE

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





Ong et al, CID, 2017

CHOC SEPTIQUE

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

	Primary Outcome	Secondary Outcome	
Model	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)

Ong et al, CID, 2017

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

Ong et al, CID, 2017

INDICATIONS THERAPEUTIQUES

<u>Dans quelles situations cliniques utiliseriez-vous ces antibiotiques en premiere intention</u> ?

- Bacteriémie ?
- 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

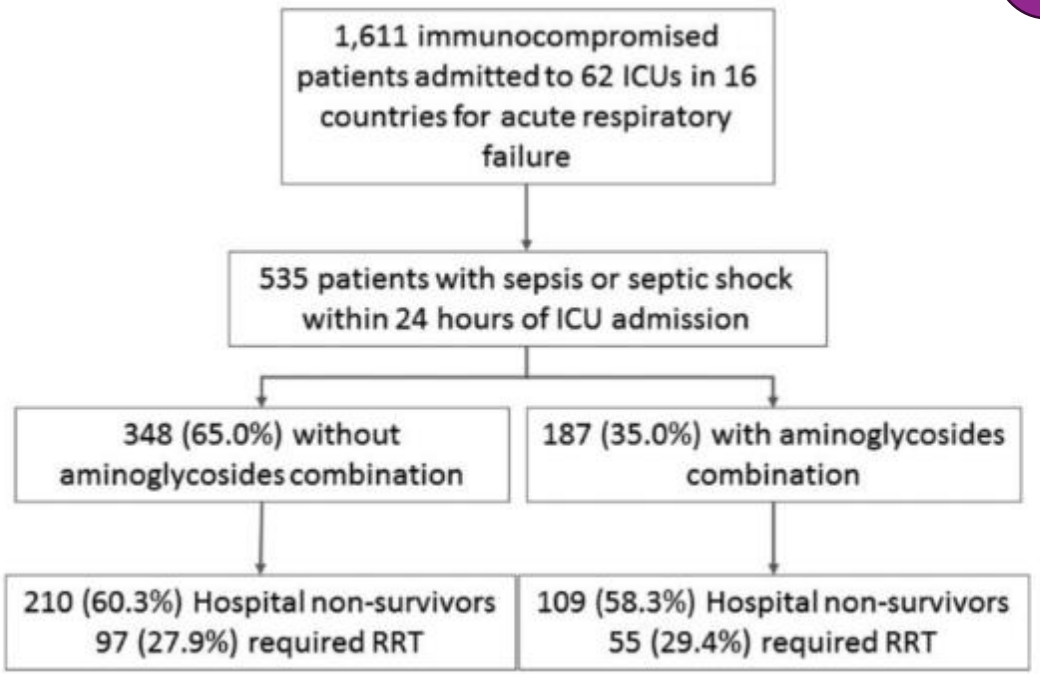


FIG. 1. **Patients' flowchart modified from EFRAIM study (17).**

Lopez et al, shock, 2020

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).

Lopez et al, shock, 2020

IMMUNODEPRIMES

64 etudes regroupant 7586 patients

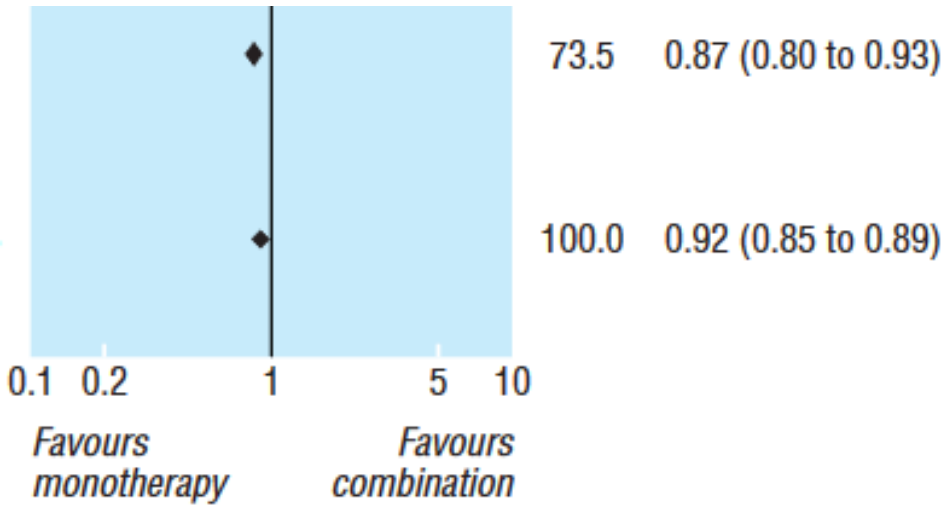


Fig 3 Treatment failure

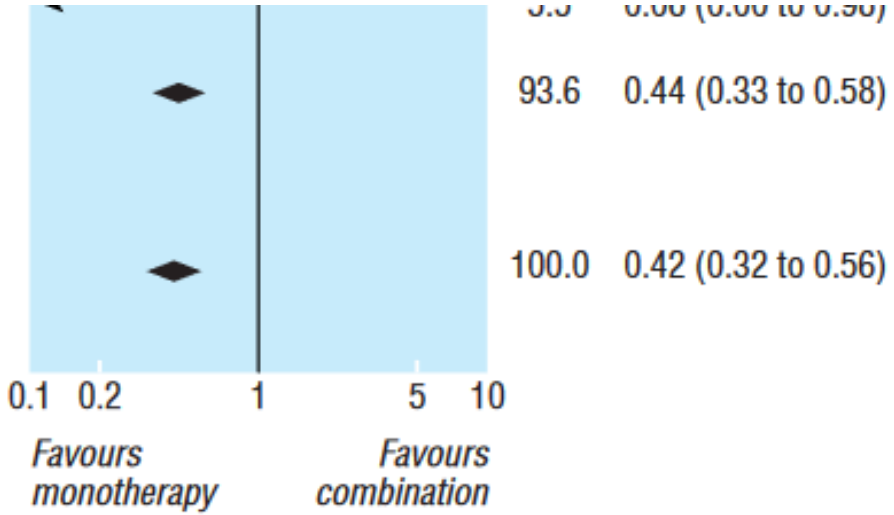


Fig 6 Nephrotoxicity

¨*Paul et al, BMJ,2003*

IMMUNODEPRIME

Outcome	Studies	Patients	Combined relative risk (95% CI)
Bacterial superinfections	27	3085	0.79 (0.59 to 1.06)
Bacterial colonisation	14	1635	0.86 (0.63 to 1.17)
Surveillance for bacterial colonisation	6	751	0.76 (0.55 to 1.05)
Bacterial resistance development	9	1370	0.83 (0.50 to 1.39)
Fungal superinfections	11	1119	0.78 (0.38 to 1.58)
Fungal colonisation	7	1132	1.53 (0.97 to 2.41)

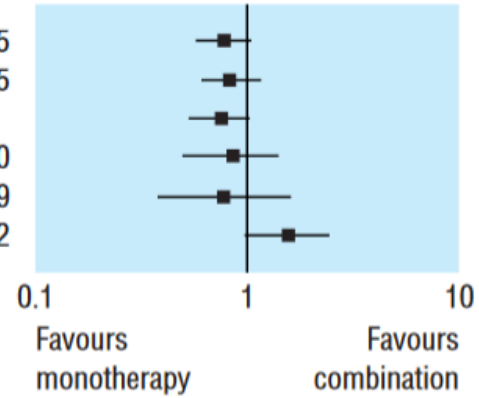


Fig 5 Summary relative risks for outcome relating to resistance development in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

¨*Paul et al, BMJ,2003*

INDICATIONS THERAPEUTIQUES

<u>Dans quelles situations cliniques utiliseriez-vous ces antibiotiques en premiere intention</u> ?

- Bacteriémie ?
- 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 + neurolisteriosis (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

MONALISA, Charlier et al, Lancet infect Dis, 2017

LISTERIA

B· Univariable analysis of 3-month death in bacteremia + neurolisteriosis 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)	

MONALISA, Charlier et al, Lancet infect Dis, 2017

INDICATIONS THERAPEUTIQUES

PNA - stratégie probabiliste (1)

PNA sans signe de gravité

PNA simple :

Ciprofloxacine ou lévofloxacine
(sauf si FQ dans les 6 mois)
OU
Céfotaxime ou ceftriaxone

PNA à risque de complication :

Céfotaxime ou ceftriaxone (à privilégier si hospitalisation)
OU
Ciprofloxacine ou lévofloxacine
(sauf si FQ dans les 6 mois)

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

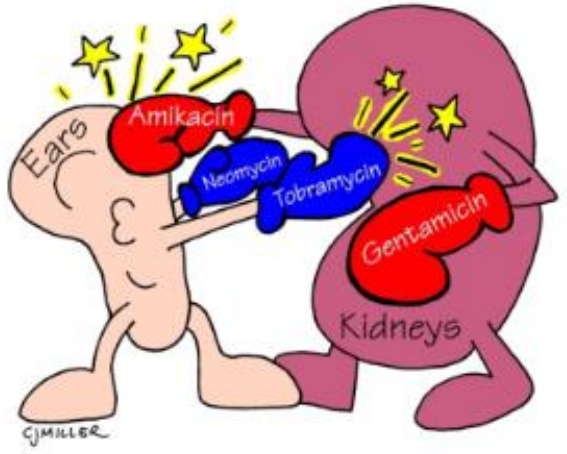
SUJET A RISQUE

PLAN

- Histoire
- Structure et mode d’action
- Spectre d’action
- PK-PD
- Indications
- Effets secondaires
- Surveillance

EFFETS SECONDAIRES

EFFETS SECONDAIRES

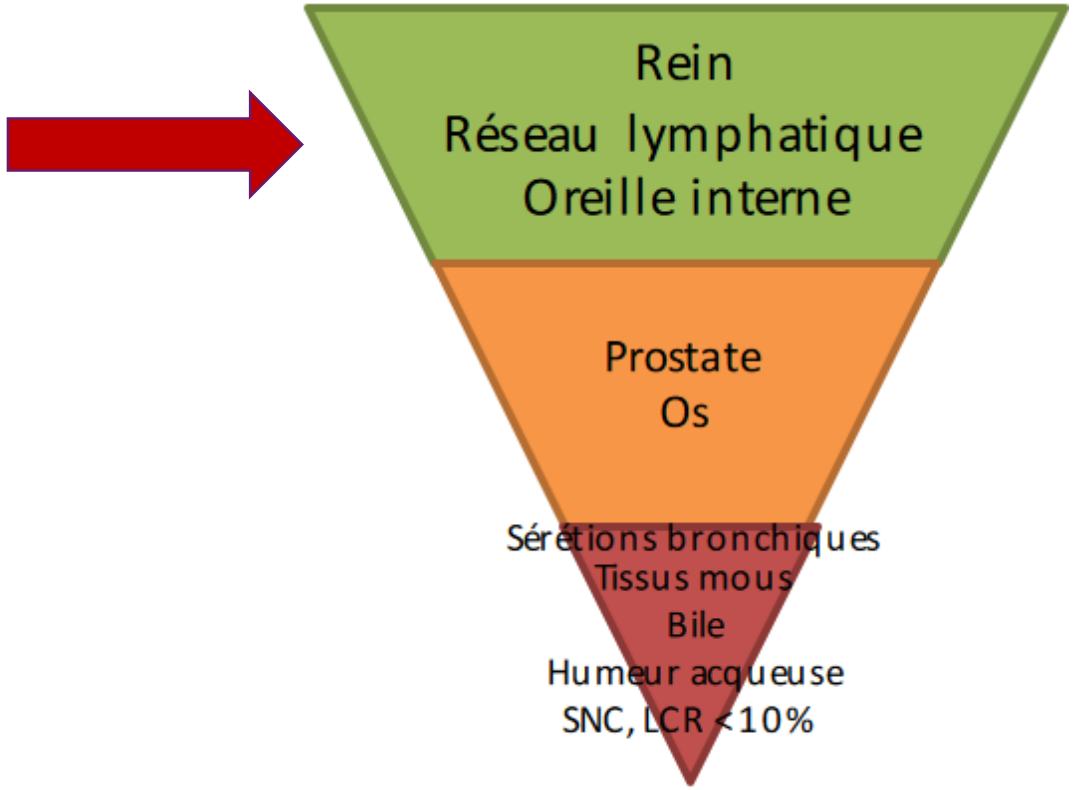


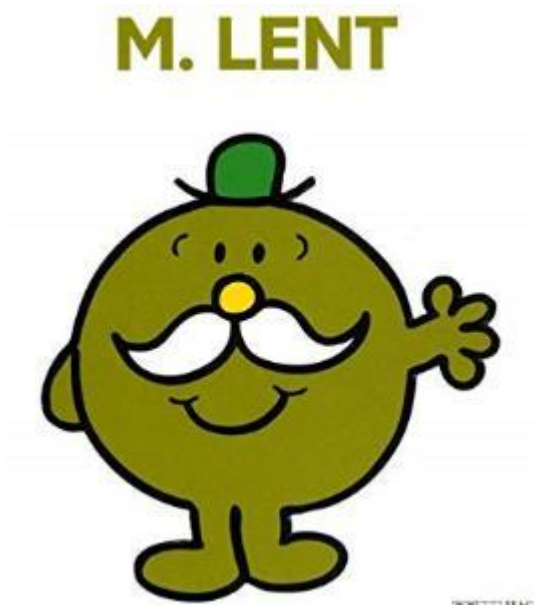
INDEX THERAPEUTHIQUE ETROIT

EFFETS SECONDAIRES

BONNE DIFFUSION REIN et OREILLE INTERNE

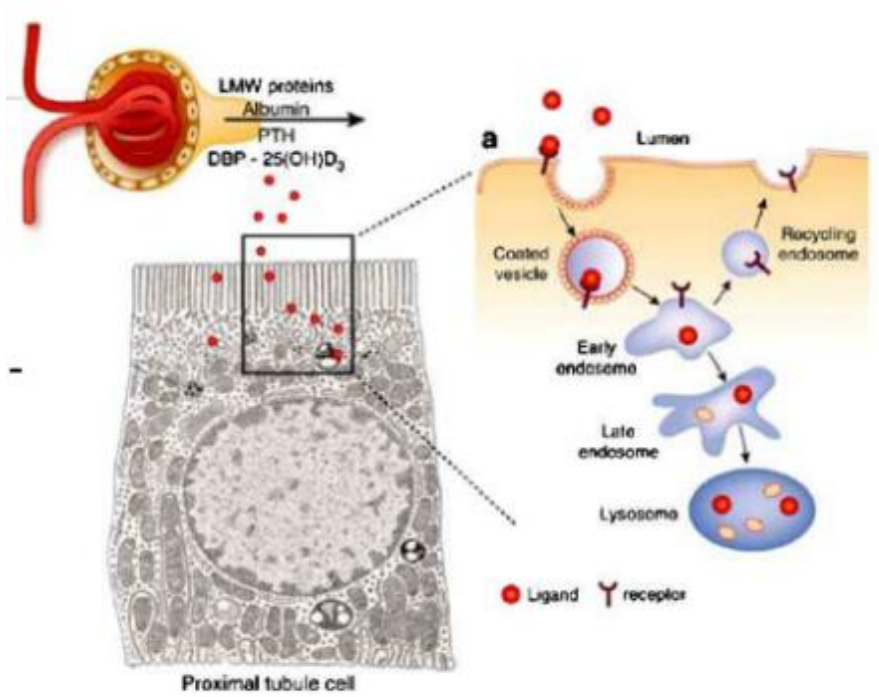
ELIMINATION LENTE





EFFETS SECONDAIRES

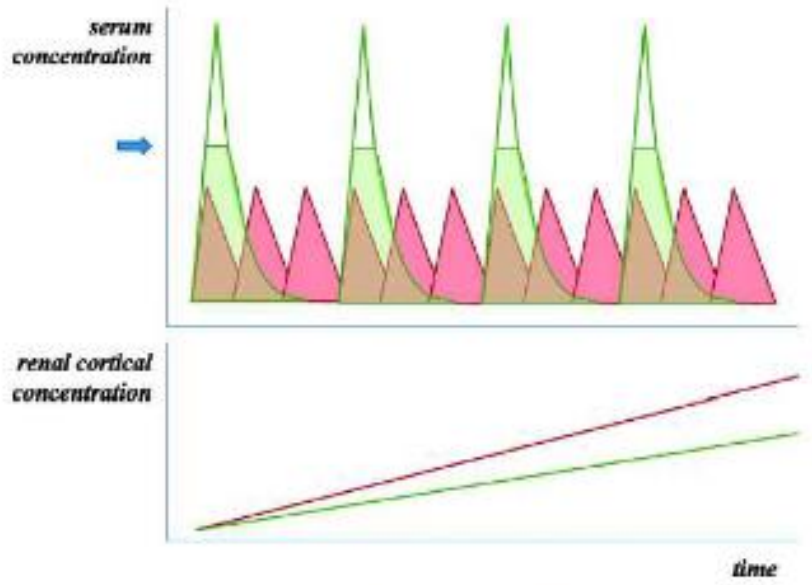
- Néphrotoxicité
  - Epidémiologie : 1-2 % => jusqu' a 20%
  - Facteurs de risque
    - Durée : >7 jours
    - Dose : résiduel >2 mg/L
    - Nombre d'injection par jour
    - Type : neo>genta>amikacine
  - Accumulation TCP => nécrose tubulaire
  - Réversible lente à l'**arret**
    - **Accumulation jusqu'à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



J Am Soc Nephrol, 2007

EFFETS SECONDAIRES

- Néphrotoxicité
  - A surveiller : **FACTEURS DE RISQUE ASSOCIES DE NEPHROPATHIES**
    - Age >75 ans
    - Nephropathie 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

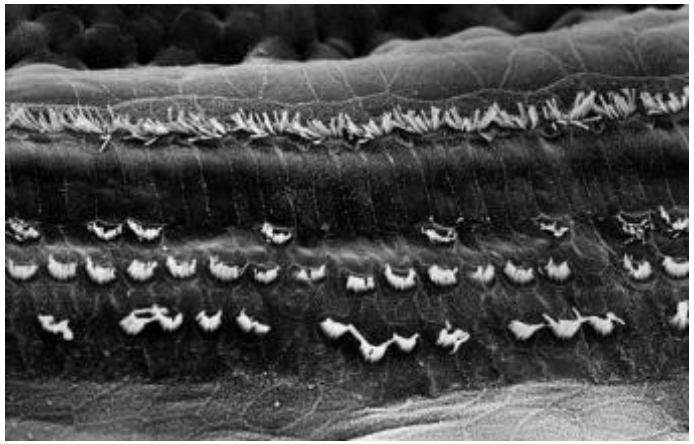
EFFETS SECONDAIRES

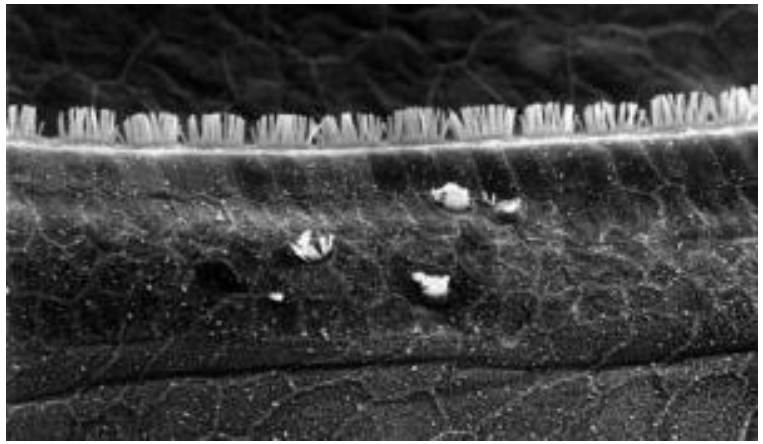
- Ototoxicité : IRREVERSIBLE

+ AMINOSIDES

+ AMINOSIDES

+ AMINOSIDES





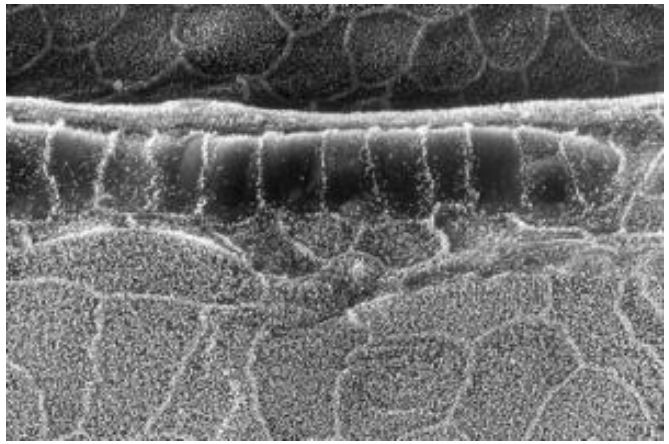


Image en microscopie électronique à balayage (MEB) , Marc Lenoir

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, quinines, quinidine, hydroxychloroquine, procaïnamide, 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 monitorage 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.

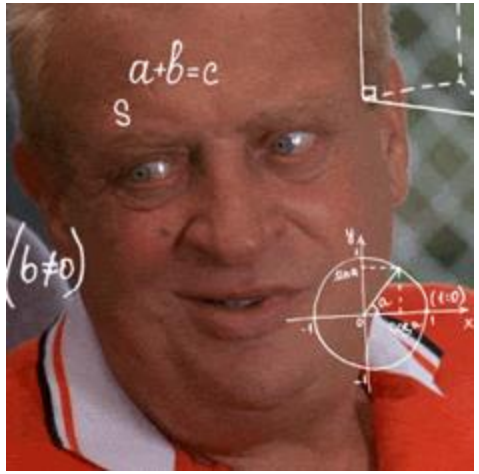
PLAN

- Histoire
- Structure et mode d’action
- Spectre d’action
- PK-PD
- Indications
- Effets secondaires
- Surveillance

SURVEILLANCE

- **DOSAGES PLASMATIQUES**

C min



C max

SURVEILLANCE

- **<u>Quels propositions concernant les dosages sont correctes ?</u>**
  - Le Cmax est dosé à 30 min
  - Le Cmax est dosé à 2h
  - Le C min est dosé à 24h
  - Le C min est dosé à 48h
  - Le C min est dosé à 72h

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, brulés, obésité morbidité, 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

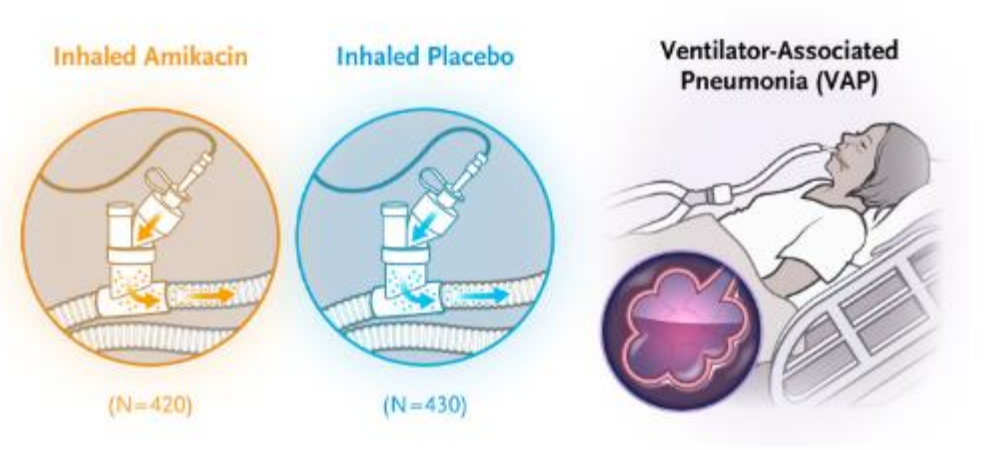
> C min attendu → ESPACEMENT DES DOSES

Et plus si affinités

NOUVEAUTES ?

- **PLACE DES TRAITEMENTS INHALES ?**

PAVM



Essai multicentrique, randomisé, double aveugle
Patient VM >72h
Randomisation :

- 20mg/kg d AMIKACINE
- placebo

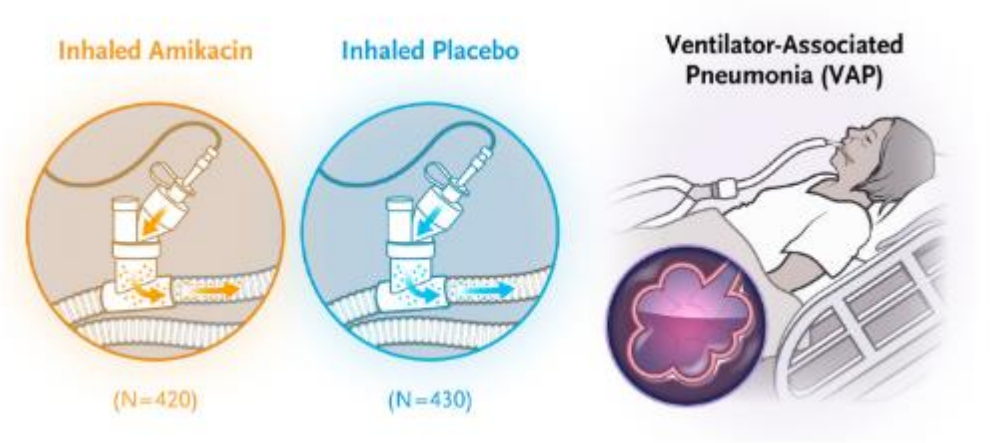
Invasive mechanical ventilation before randomization — days	3.5±0.3	3.5±0.3
Systemic antibiotic therapy at randomization — no. (%)	326 (78)	331 (77)

* Plus–minus values are means ±SD. To convert the values for creatinine to

Ehrmann S et al, N Engl J Med. 2023

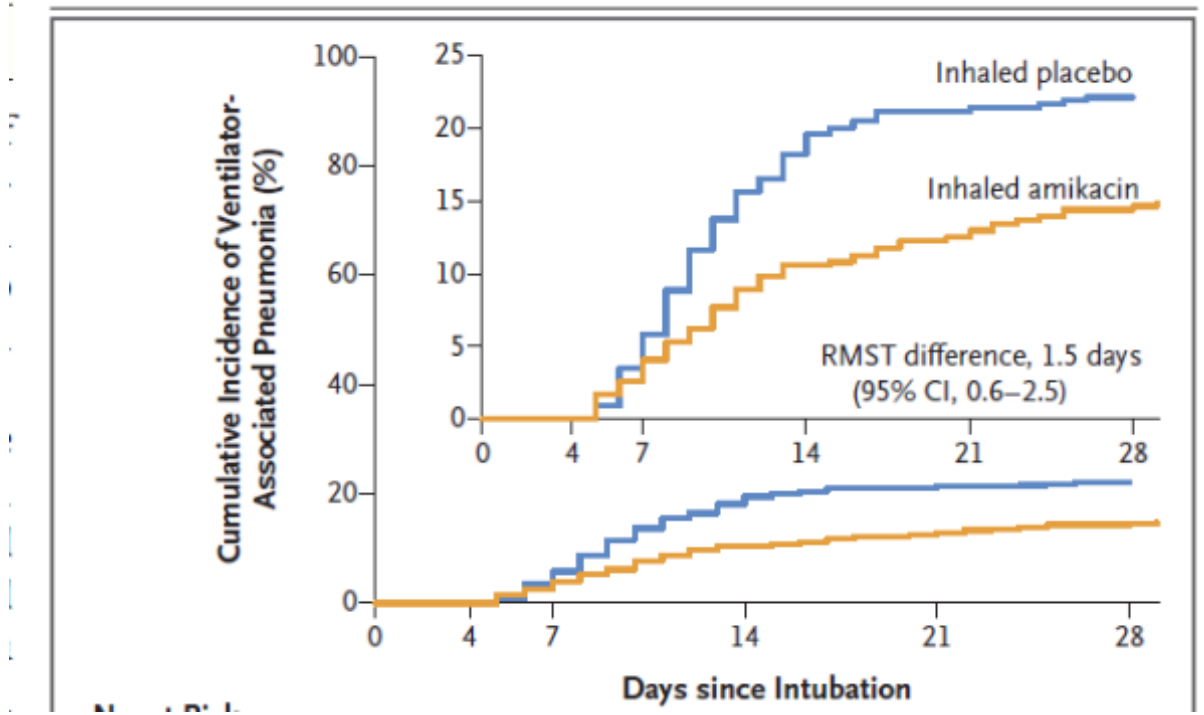
NOUVEAUTES ?

- **PLACE DES TRAITEMENTS INHALES ?**



- Evaluation des PAVM à J28

	0	4	7	14	21	28
Days since Intubation						
No. at Risk						
Inhaled placebo	430	288		85	40	18
Inhaled amikacin	420	269		120	60	28
No. of Deaths						
Inhaled placebo	0	21		65	85	106
Inhaled amikacin	0	20		47	78	92



Ehrmann S et al, N Engl J Med. 2023

NOUVEAUTES ?

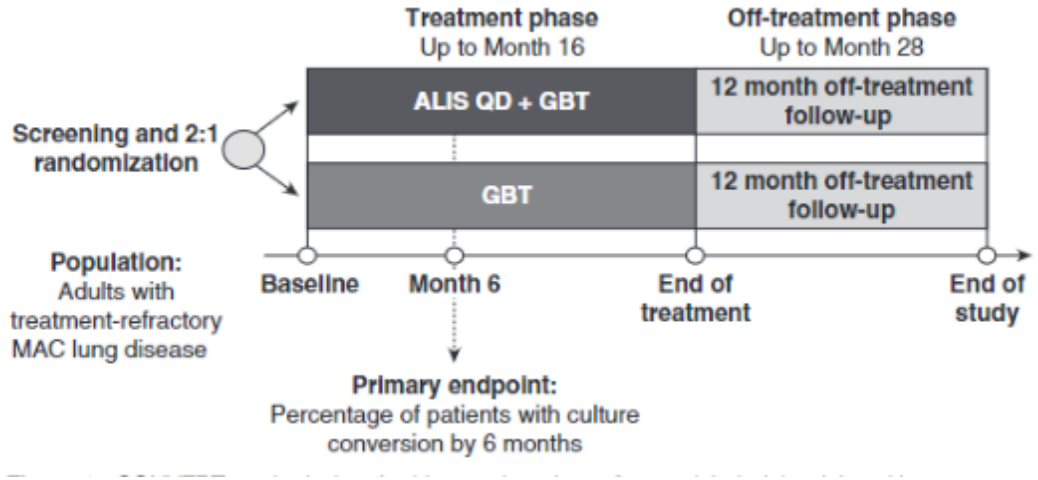
- **PLACE DES TRAITEMENTS INHALES ?**

Mycobacterie

PNP - MAC +
Tt standard
pendant 6 mois
Overall (n = 336)

ALIS 1 GBT
(n = 224)

GBT Alone
(n = 112)



Griffith DE et al, CONVERT study, Am J Respir Crit Care Med. 2018

NOUVEAUTES ?

- **PLACE DES TRAITEMENTS INHALES ?**

Mycobacterie

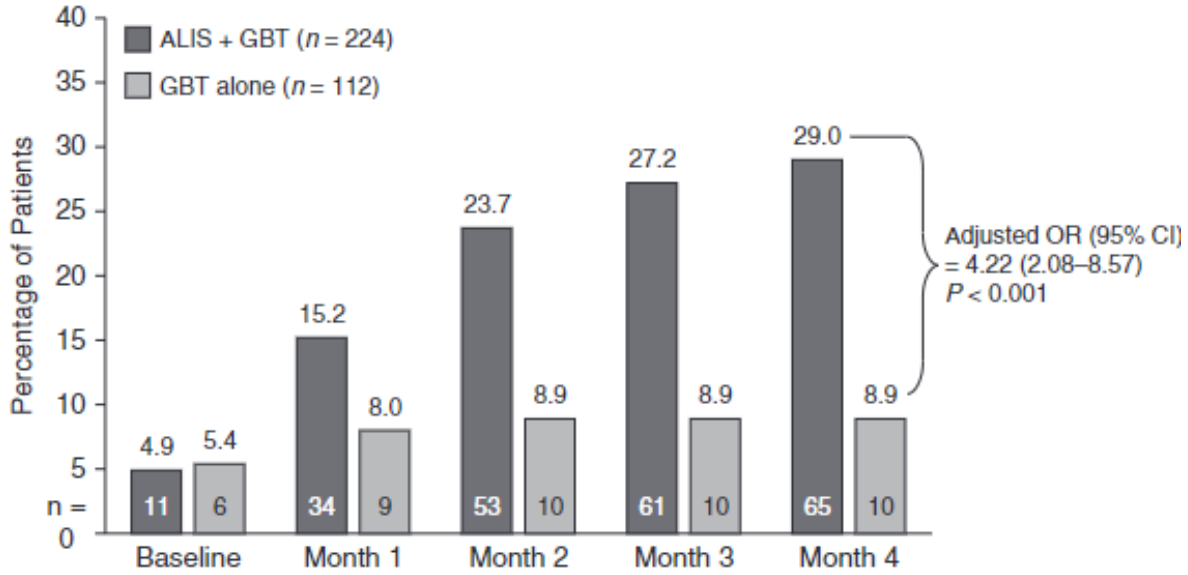


Figure 3. Proportion of patients achieving culture conversion, shown by the first month of conversion: intention-to-treat population. The cumulative proportion of patients achieving culture

Griffith DE et al, CONVERT study, Am J Respir Crit Care Med. 2018


NON DONALD.
PAS PLUS QUE DANS LA VRAIE VIE AUTORISER LE PORT D'ARME AUX ANTIBIOTIQUES NE SAURAIT ÊTRE LA SOLUTION!
Comment rendre les antibiotiques plus efficaces?
Rémi Malingrey.