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Traitement des infections liées à *P. aeruginosa*

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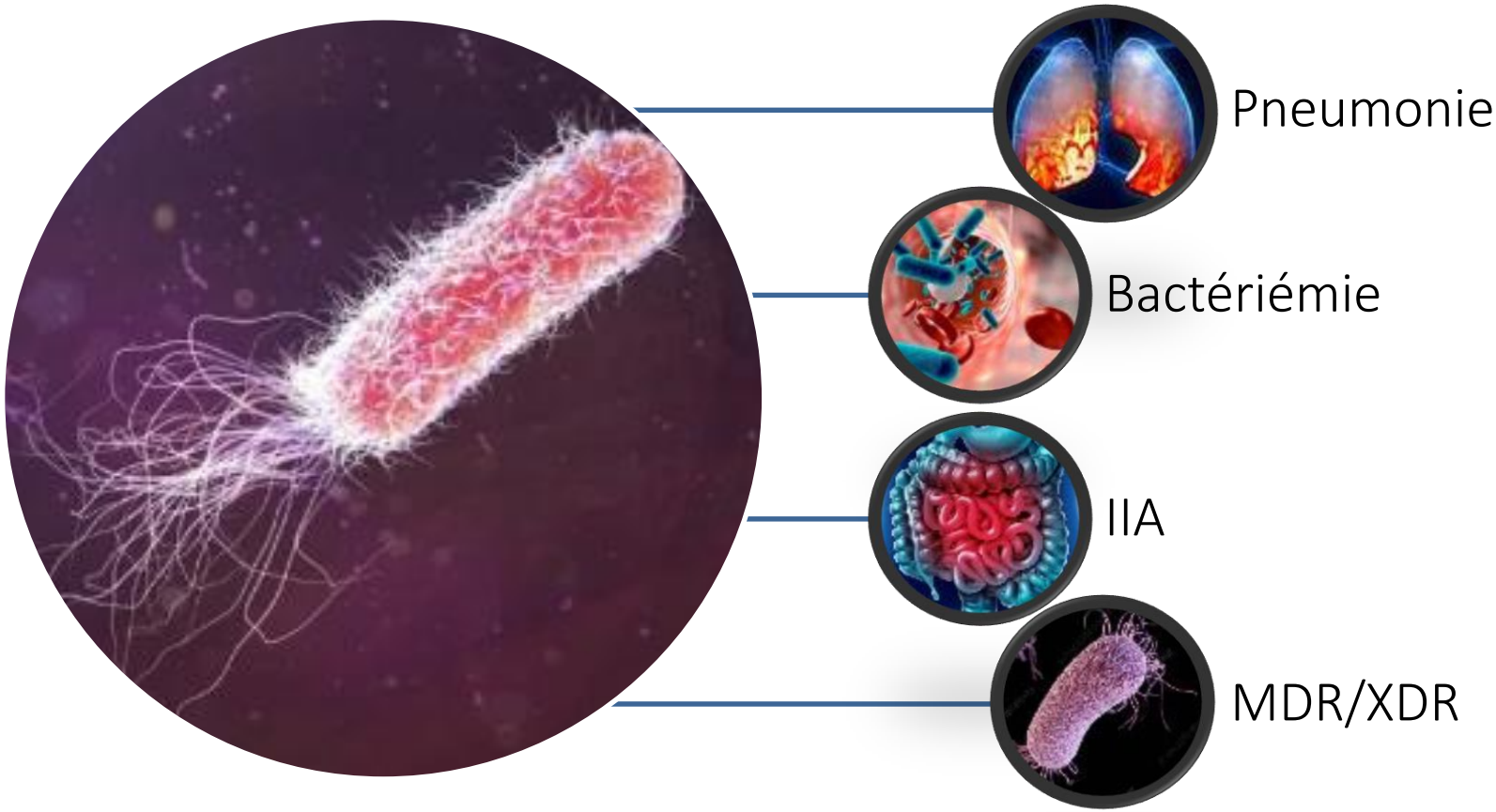
DU de Thérapeutiques anti-infectieuses
Grenoble
25 mars 2021

Epidémiologie



A comparison of microbiology and demographics among patients with healthcare-associated, hospital-acquired, and ventilator-associated pneumonia: a retrospective analysis of 1184 patients from a large, international study

- ✓ *Pseudomonas aeruginosa* was the most common Gram-negative organism isolated in all pneumonia classes
  - HCAP, 22/199 (11.1%)
  - HAP, 28/379 (7.4%)
  - VAP, 57/606 (9.4%);

Table 2 Microbiology grouped by HCAP, HAP, and VAP[a]

Microbiology	HCAP (n = 199) n (%)	HAP (n = 379) n (%)	VAP (n = 606) n (%)
Gram-positive pathogens	117 (58.8)	226 (59.6)	441 (72.8)
MRSA	82 (41.2)	125 (33.0)	259 (42.7)
MSSA	12 (6.0)	51 (13.5)	107 (17.7)
Pneumococcus	4 (2.0)	10 (2.6)	15 (2.5)
Other *Streptococcus* spp.	7 (3.5)	15 (4.0)	18 (3.0)
Gram-negative pathogens	53 (26.6)	113 (29.8)	222 (36.6)
Pseudomonas aeruginosa	22 (11.1)	28 (7.4)	57 (9.4)
Acinetobacter spp.	8 (4.0)	16 (4.2)	44 (7.3)
Haemophilus spp.	6 (3.0)	5 (1.3)	23 (3.8)
Moraxella catarrhalis	4 (2.0)	1 (0.3)	2 (0.3)
Klebsiella spp.	5 (2.5)	32 (8.4)	41 (6.8)
Escherichia coli	10 (5.0)	19 (5.0)	17 (2.8)
Enterobacter spp.	3 (1.5)	15 (4.0)	31 (5.1)
Proteus mirabilis	1 (0.5)	8 (2.1)	13 (2.1)
Stenotrophomonas maltophilia	0 (0)	2 (0.5)	13 (2.1)
Polymicrobial	111 (55.8)	191 (50.4)	387 (63.9)
Culture negative	50 (25.1)	101 (26.6)	79 (13.0)
Bacteremia	28 (14.1)	49 (12.9)	103 (17.0)

Quartin et al, BMC infectious diseases 2013, 13:561

Nosocomial pneumonia in 27 ICUs in Europe: perspectives from the EU-VAP/CAP study

Table 1. Most common etiological pathogens isolated from patients with VAP, as documented in a prospective observational study that enrolled patients from 27 ICUs in nine European countries

Causative pathogen	VAP[a] ($n=465$)	
	Early VAP (<5 days; $n=193$)	Late sVAP (≥5 days; $n=272$)
Unknown, *n* (%)	48 (24.9)	61 (22.4)
Other, *n* (%)	43 (22.3)	26 (9.6)
Staphylococcus aureus, *n* (%)	58 (30.1)	58 (21.3)
MRSA, *n* (%)	18 (9.3)	34 (12.5)
MSSA, *n* (%)	40 (20.7)	24 (8.8)
P. aeruginosa, *n* (%)	26 (13.5)	55 (20.2)
Acinetobacter spp., *n* (%)	16 (8.3)	56 (20.6)
Enterobacteriaceae, *n* (%)	61 (31.6)	92 (33.8)
Polymicrobial infection, *n* (%)	50 (25.9)	64 (23.5)

Koulenti et al, Eur J Clin Microbiol Infect Dis 2017; 36:1999–2006

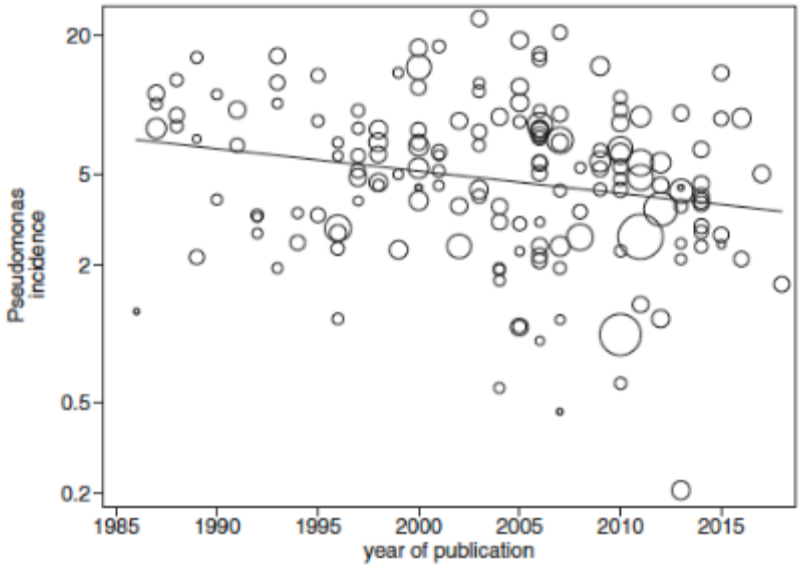
Table 2. Most common etiological pathogens grouped by type of pneumonia, as documented in a prospective observational study that enrolled patients from 27 ICUs in nine European countries

Causative pathogen	Very-early VAP[a] (*n* = 138)	VAP[b] (*n* = 465)	HAP[c] (*n* = 224)
Unknown, *n* (%)	59 (42.8)	109 (23.4)	84 (37.5)
Other, *n* (%)	31 (22.5)	69 (14.8)	20 (8.9)
Staphylococcus aureus, *n* (%)	26 (18.8)	116 (24.9)	44 (19.6)
MRSA, *n* (%)	10 (7.2)	52 (11.2)	30 (13.4)
MSSA, *n* (%)	16 (11.6)	64 (13.8)	14 (6.3)
P. aeruginosa, *n* (%)	16 (11.6)	81 (17.4)	36 (16.1)
Acinetobacter spp., *n* (%)	8 (5.8)	72 (15.5)	30 (13.4)
Enterobacteriaceae, *n* (%)	29 (21)	153 (32.9)	70 (31.3)
Polymicrobial infection, *n* (%)	25 (18.1)	114 (24.5)	46 (20.5)

Koulenti et al, Eur J Clin Microbiol Infect Dis 2017; 36:1999–2006

Worldwide variation in *Pseudomonas* associated ventilator associated pneumonia. A meta-regression

- ✓ *Pseudomonas* associated VAP incidence was reported in 162 studies from seven worldwide regions published over 30 years.
- ✓ Incidence varies by less than twofold with some decline by year of publication
- ✓ Variation not significantly associated with bronchoscopic sampling

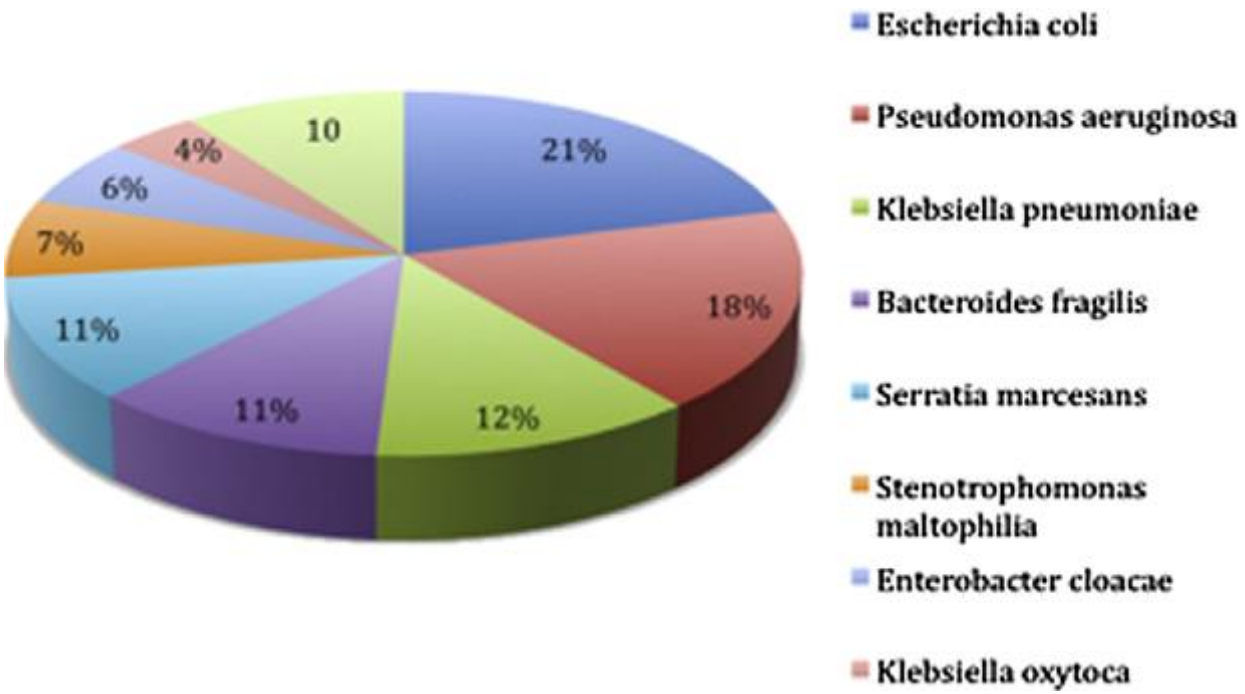


	Multinational & ungrouped[b]	Europe[c]	Mediterranean[d]	Asia[e]	Middle East[f]	Central & South America[g]	USA/Canada[h]
Bronchoscopic sampling[k]	2	28	17	1	2	3	11
Intervention period[l]	1	2	2	2	1	1	2
Study publication year (range)	1987–2015	1988–2018	1987–2015	2003–2016	1990–2017	1995–2014	1986–2014
Numbers of patients per study group; median (IQR)	850; 382–2238	496; 221–1004	184; 103–322	482; 333–1076	448; 100–1716	278; 233–508	340; 223–521
Duration of MV (days); median (IQR)	7; 5–9	11; 8–13	8; 7–12	9; 6–9	9; 7–10	9; 7–11	6; 5–10
Pseudomonas aeruginosa VAP incidence[i]							
Per 1000 MV days							
Mean[n]	5.8	4.5	6.9	4.4	6.8	4.2	3.7
95% CI	4.5–7.5	3.2–5.7	5.4–8.8	2.9–6.6	5.2–9.0	2.9–5.9	2.3–5.9

Hurley, Journal of Critical Care 51 (2019) 88–93

Nosocomial Gram-negative bacteremia in intensive care: epidemiology, antimicrobial susceptibilities, and outcomes

- ✓ Patients with ICU-acquired Gram-negative bacteremia from 2004 to 2012 reviewed retrospectively
- ✓ Seventy-eight cases of ICU-acquired Gram-negative bacteremia occurred in 74 patients.



Sligl et al, Int J Infect Dis 2015, 37:129-34

Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW Study

- ✓ Multicenter observational study
  - 68 medical institutions worldwide
  - six-month study period (October 2012-March 2013).
- ✓ 1898 patients
  - Mean age of 51.6 years (range 18-99)
  - 777 patients (41%) women
  - Community-acquired IAIs: 1,645 (86.7%)
  - Healthcare-associated infections: 253 (13.3%)
- ✓ Intraperitoneal specimens were collected from 1,190 (62.7%) of the enrolled patients

Total	**1.330 (100%)**
Aerobic Gram-negative bacteria	**957 (71.9%)**
Escherichia coli	548 (41.2%)
(Escherichia coli resistant to third generation cephalosporins)	75 (5.6%)
Klebsiella pneuumoniae	140 (10.5%)
(Klebsiella pneumoniae resistant to third generation cephalosporins)	26 (1.4%)
Klebsiella oxytoca	11 (0.8%)
(Klebsiella oxytoca resistant to third generation cephalosporins)	2 (0.1)
Enterobacter	64 (4.8%)
Proteus	47 (3.5%)
Pseudomonas	74 (5.6%)
Others	73 (5.6%)
Aerobic Gram-positive bacteria	**373 (29.1%)**
Enterococcus faecalis	153 (11.5%)
Enterococcus faecium	58 (4.4%)
Staphylococcus Aureus	38 (2.8%)
Streptococcus spp.	85 (6,4%)
Others	39 (2.9%)

Sartelli et al, World Journal of Emergency Surgery 2014, 9:37

Plan

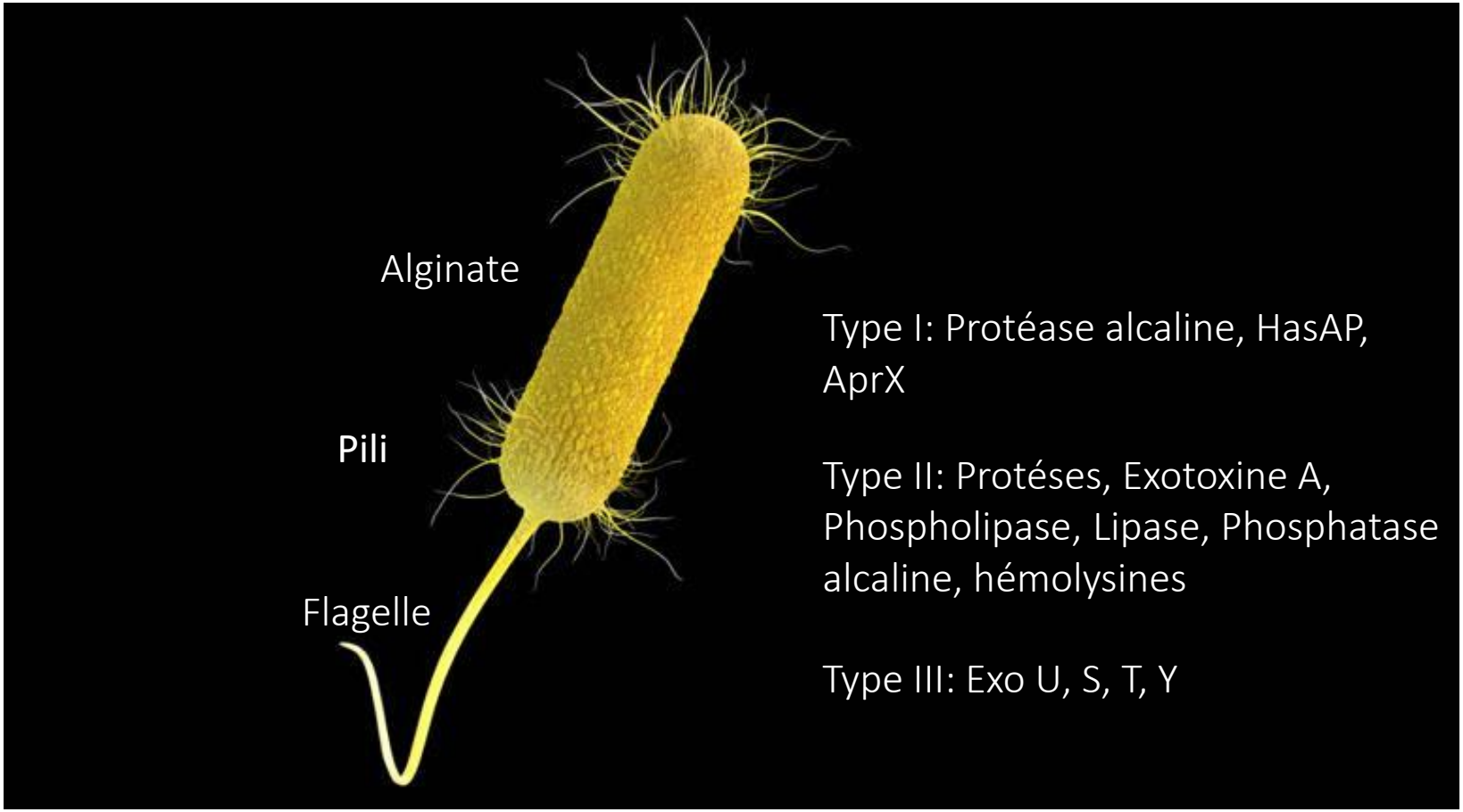
- ✓ Quelques éléments introductifs….
- ✓ Sensibilité aux principales molécules et nouvelles molécules
- ✓ PK/PD
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives

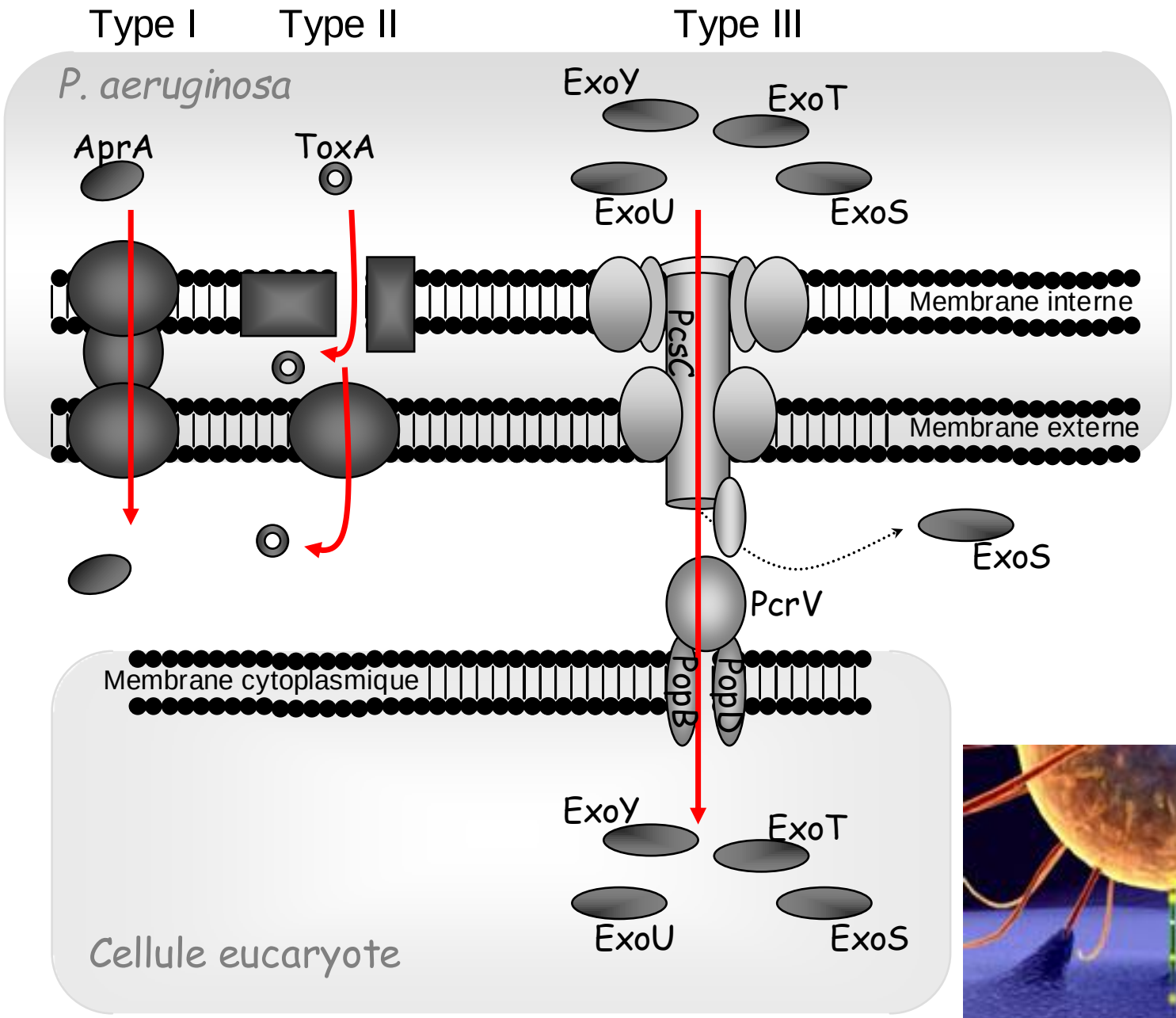
Table 1. Chromosomally encoded or imported resistance mechanisms of *P. aeruginosa*.

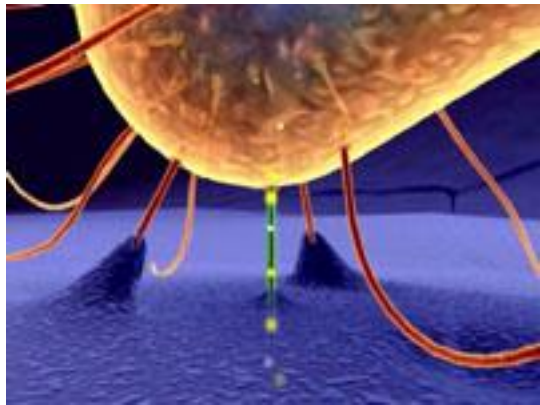
Location	Resistance mechanisms	Targeted antibiotics	Type of resistance
Intrinsic (chromosomal)	AmpC–type cephalosporinase	β-lactams	Antibiotic inactivation
	Class D oxacillinase OXA-50	β-lactams	Antibiotic inactivation
	Aminoglycosides inactivating enzymes	Aminoglycosides	Antibiotic inactivation
	Efflux systems (overexpression)	Multiple antibiotic classes	Efflux systems
	Decreased membrane permeability	Multiple antibiotic classes	Membrane impermeability and purines
	DNA gyrase and topoisomerase IV	Fluoroquinolones	Target modification
	LPS modification	Colistin	Target modification
Imported (Mobile genetic elements)	Class A serine β-lactamases (PSE, CARB, TEM)	β-lactams	Antibiotic inactivation
	Class A serine ESBL (TEM, SHV, CTX-M, PER, VEB, GES, IBC)	β-lactams	Antibiotic inactivation
	Class D ESBL (OXA-types)	β-lactams	Antibiotic inactivation
	Class B Metallo-β-lactamase (IMP, VIM, SPM, GIM)	Carbapenems	Antibiotic inactivation
	Class A serine carbapenemase (KPC)	Carbapenems	Antibiotic inactivation
	Class D carbapenemase (OXA-types: OXA-40)	Carbapenems	Antibiotic inactivation
	Aminoglycosides inactivating enzymes	Aminoglycosides	Antibiotic inactivation
	Ribosomal methyltransferase enzymes	Aminoglycosides	Target modification

Bassetti M, Vena A, Croxatto A, Righi E, Guery B. Drugs in Context 2018; 7: 212527.

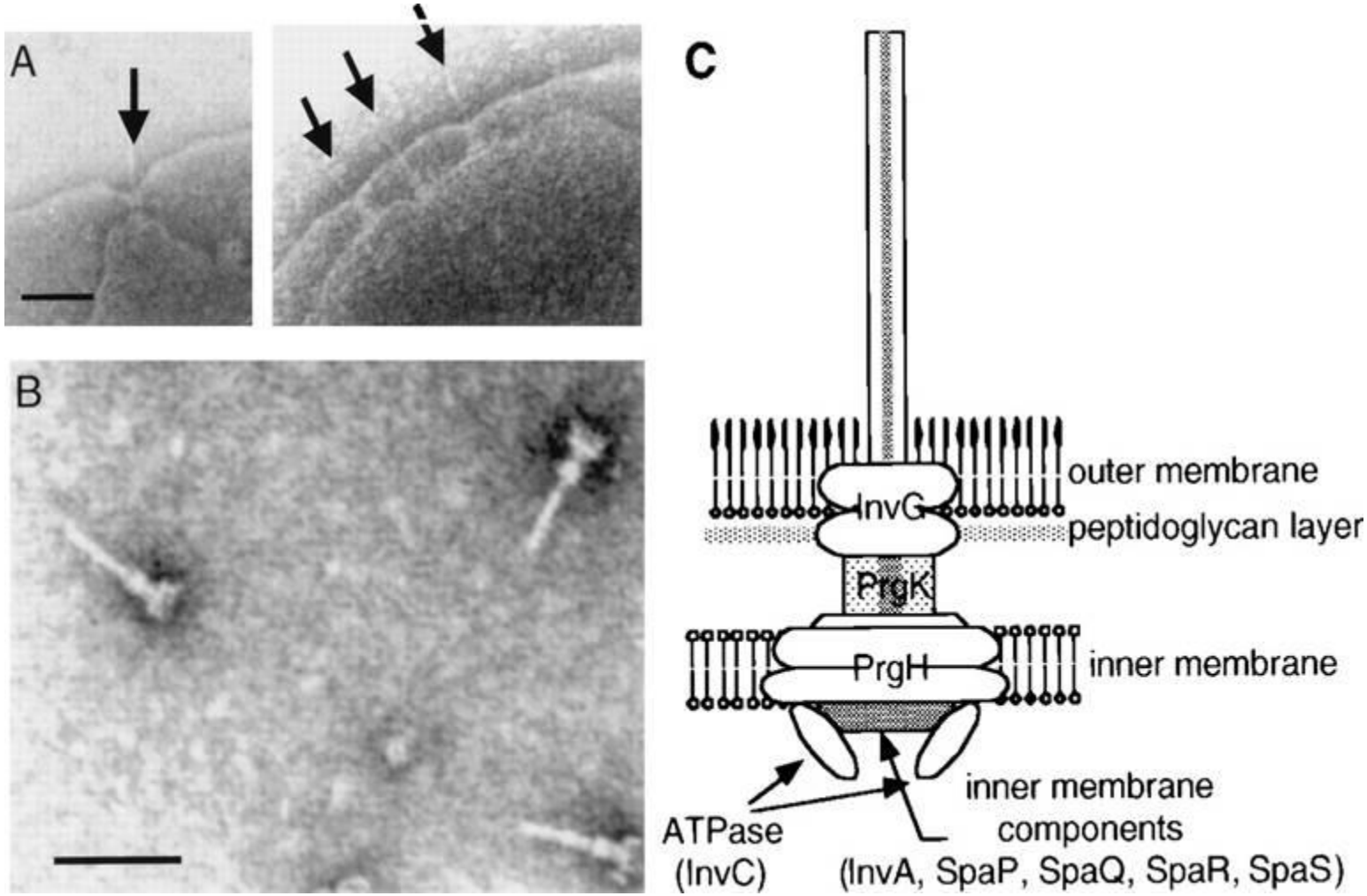
Facteurs de virulence



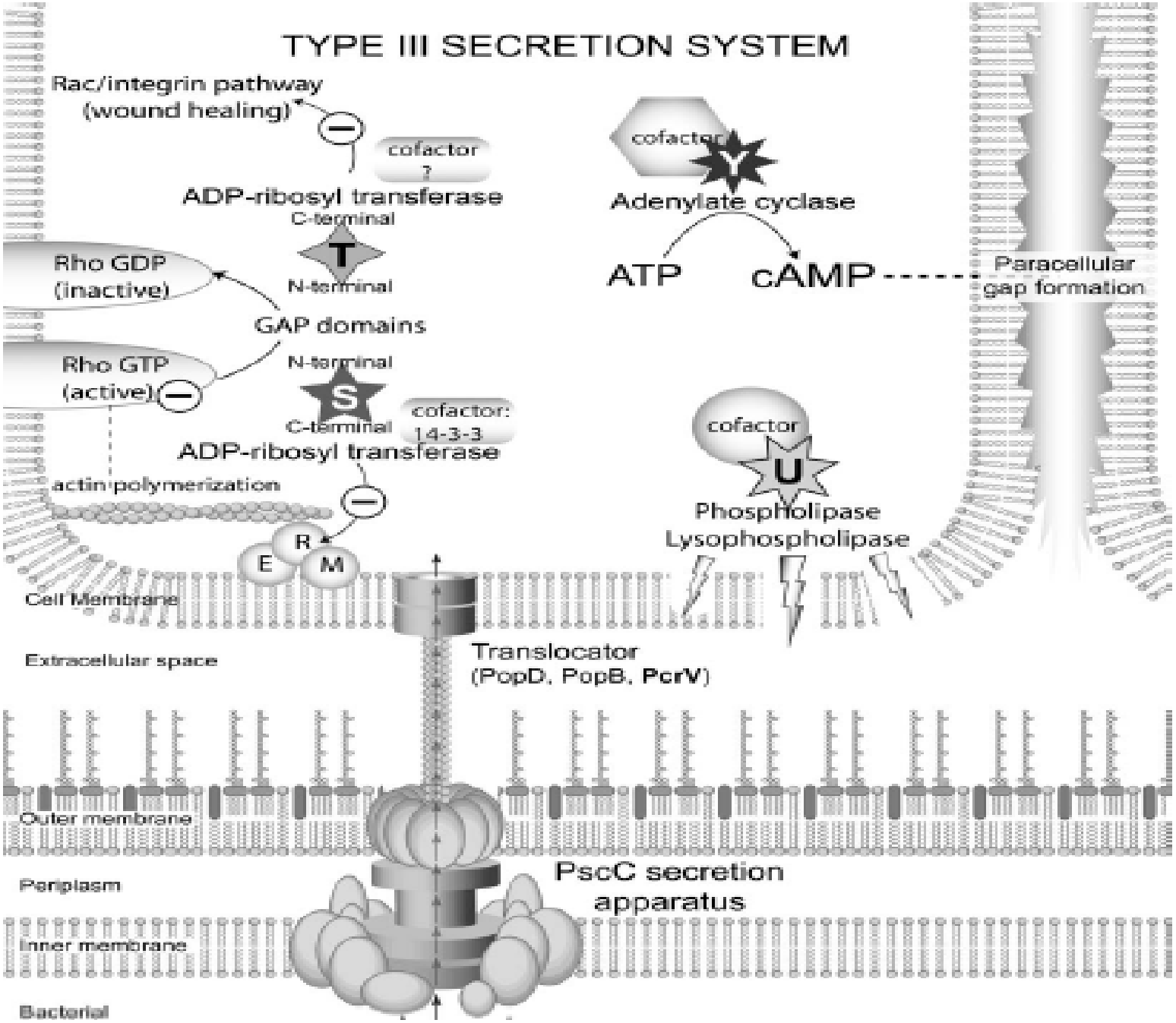

Type I
Type II
Type III
P. aeruginosa
AprA
ToxA
ExoY
ExoT
ExoU
ExoS
Membrane interne
PcsC
Membrane externe
ExoS
PcrV
Membrane cytoplasmique
PopB
PopD
ExoY
ExoT
ExoU
ExoS
Cellule eucaryote



TTSS: a needle

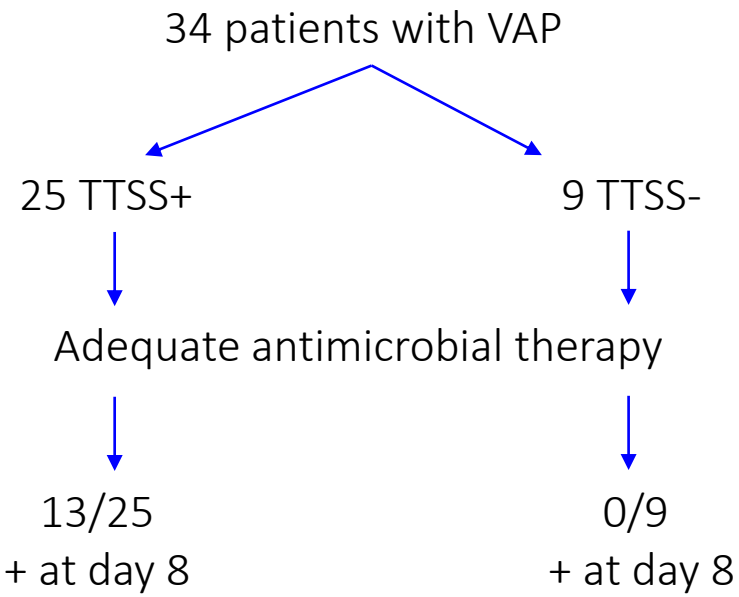


Kubori et al, Science 1998, 280, 602



Kipnis et al., Médecine et maladies infectieuses 36 (2006) 78–91

Persistent Infection with *Pseudomonas aeruginosa* in Ventilator-associated Pneumonia



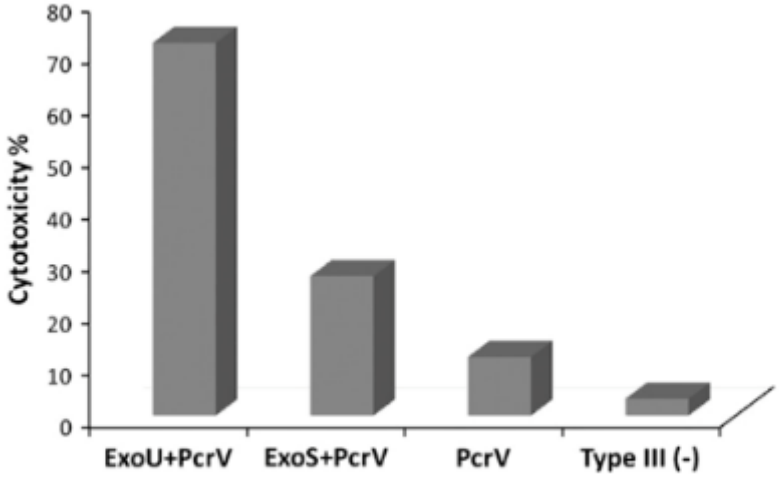
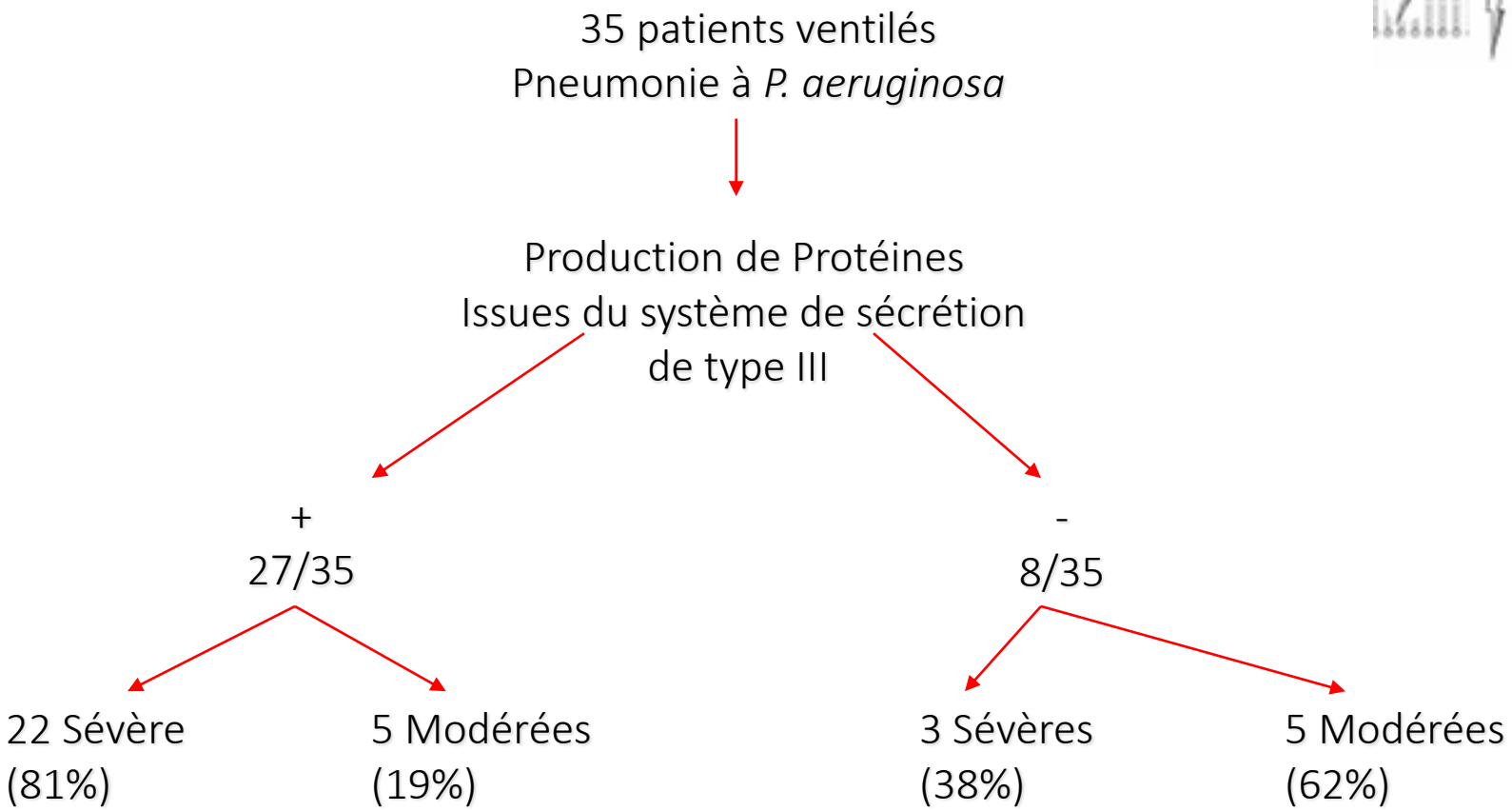


Figure 4. Cytotoxicity of *Pseudomonas aeruginosa* isolates toward human neutrophils. ExoS = exoenzyme S; ExoU = exoenzyme U.

El sohl et al, Am J Respir Crit Care Med 2008, 178:513-19

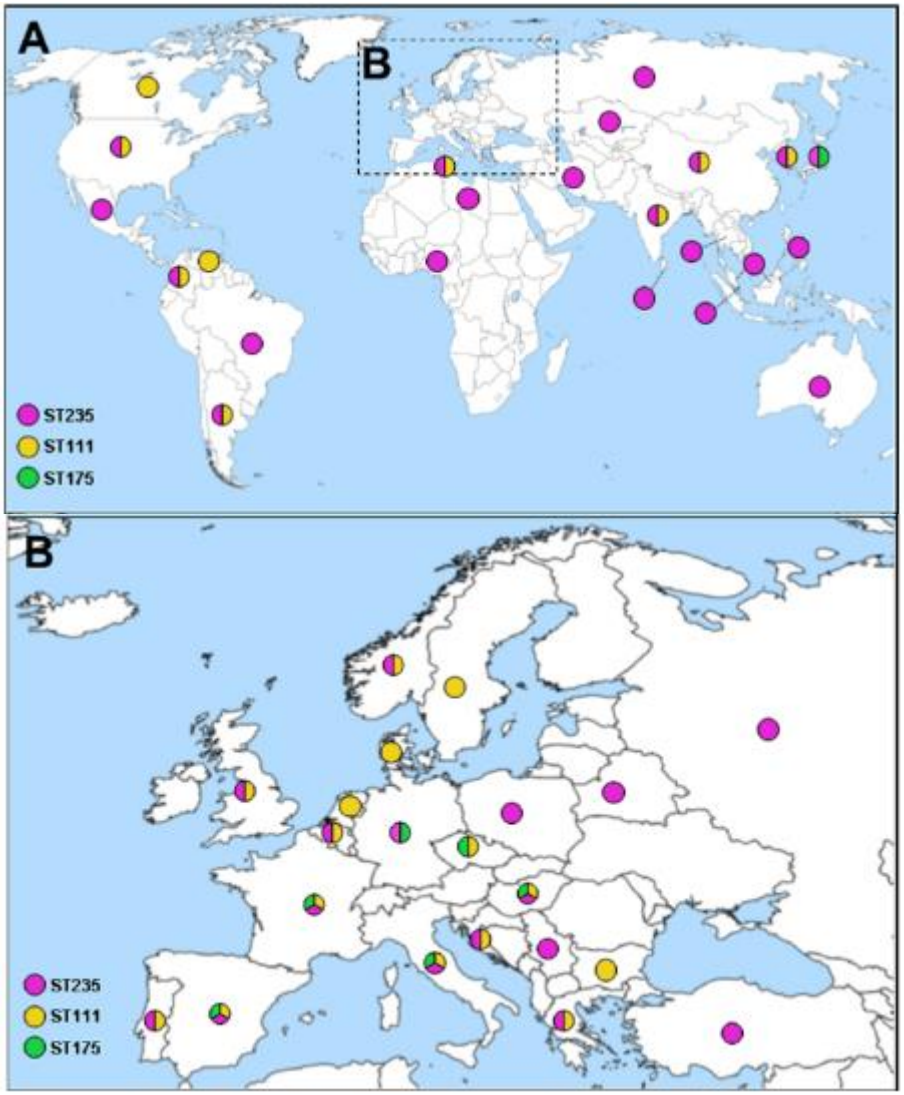
Type III protein secretion is associated with poor clinical outcomes in patients with ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*



ExoU : 10/35 (29%) associée à 90% de formes sévères

Hauser et al, Crit Care Med 2002, 30:521-28

The increasing threat of *Pseudomonas aeruginosa* high-risk clones



Horizontally-acquired β-lactamases described in *P. aeruginosa* ST235 high-risk clone isolates.

β-Lactamase		Countries
Type	Enzyme	
Class A		
BEL	BEL-1	Belgium
CTX-M	CTX-M-2	Brazil
GES	GES-1	France, Nigeria, Spain, Mexico
	GES-5	Russia, Spain
	GES-6	Portugal
	GES-9	Mexico
	GES-19	Mexico
KPC	KPC-2	Colombia
PER	PER-1	Turkey, Poland, Hungary, Serbia, Greece, Belgium, France, Croatia, Romania
PSE	PSE-1	Greece, Italy, United States
Class B		
FIM	FIM-1	Italia
IMP	IMP-1	Japan, Korea, Iran, Singapore, China
	IMP-4	Philippines
	IMP-6	Korea, China, Japan
	IMP-7	Singapore, Japan
	IMP-10	Japan
	IMP-26	Malaysia
	IMP-29	France
	IMP-31	Germany
NDM	NDM-1	Italia
VIM	VIM-1	Croatia, Greece, Philippines, Germany
	VIM-2	Sri Lanka, Korea, Serbia, Thailand, Singapore, Croatia, Malaysia, Greece, Russia, Kazakhstan, Belarus, United Kingdom, Belgium, Turkey, China, Spain
	VIM-4	Hungary, Norway, Greece, United Kingdom, Belgium, Iran
	VIM-6	United Kingdom
	VIM-11	Argentina
	VIM-13	Spain
Class D		
OXA	OXA-1	Korea
	OXA-2	Turkey, Poland, Hungary, Serbia, Korea, Spain, Mexico, Romania, Colombia, Italy, United States, Croatia, Argentina
	OXA-10	Korea, Philippines, Greece
	OXA-11	Romania
	OXA-17	Turkey, Poland, Argentina, Korea,
	OXA-19	Greece
	OXA-28	France
	OXA-35	Greece
	OXA-50	Turkey, Poland, Korea
	OXA-74	Poland, Romania
	OXA-129	Argentina, Brazil
	OXA-142	Korea

Oliver et al, Drug Resistance Updates 21–22 (2015) 41

Understanding the acute inflammatory response to *Pseudomonas aeruginosa* infection: differences between susceptible and multidrug-resistant strains in a mouse peritonitis model

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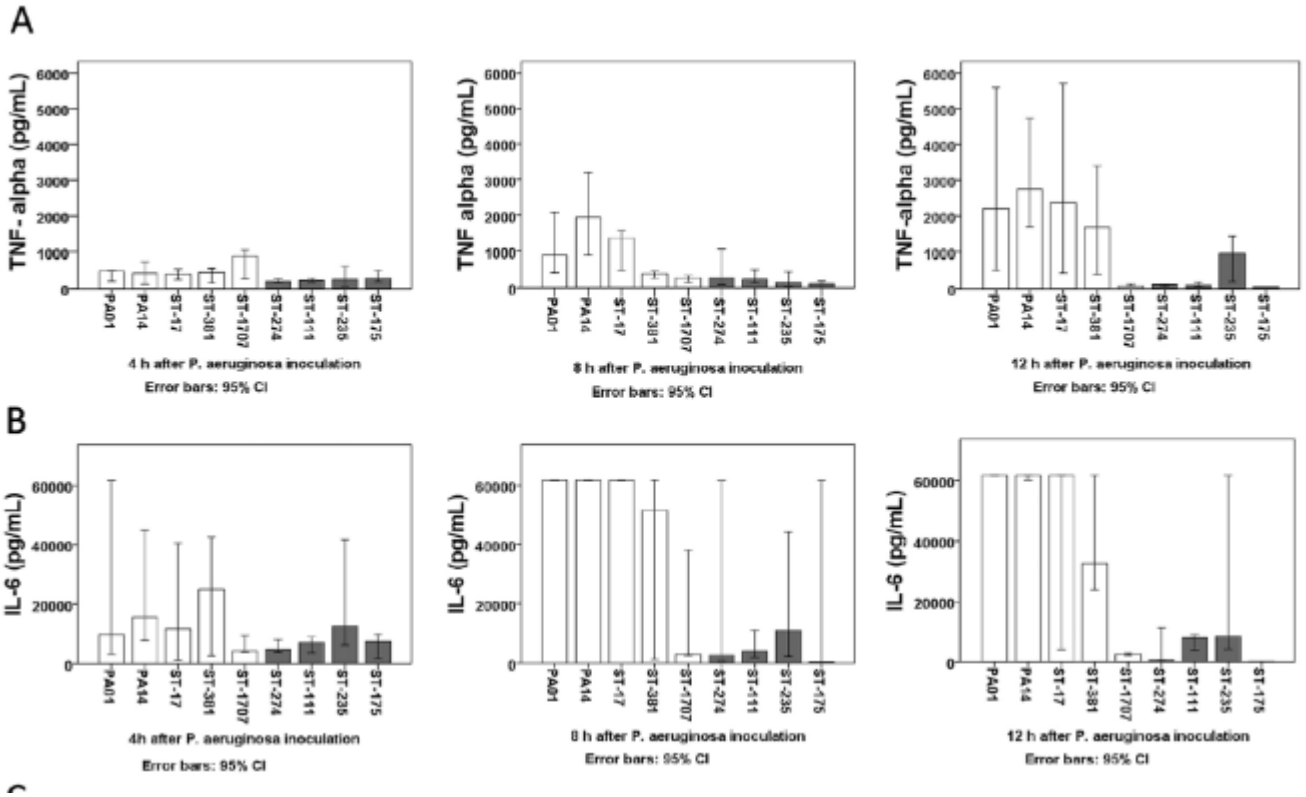
- ✓ Nine *P. aeruginosa* strains
  - 2 reference strains (PAO1 and PA14)
  - 7 clinical strains: 3 clinical multisusceptible strains, 1 MDR strain, 3MDR high-risk clones (ST111, ST235 and ST175).
- ✓ Mouse peritonitis model

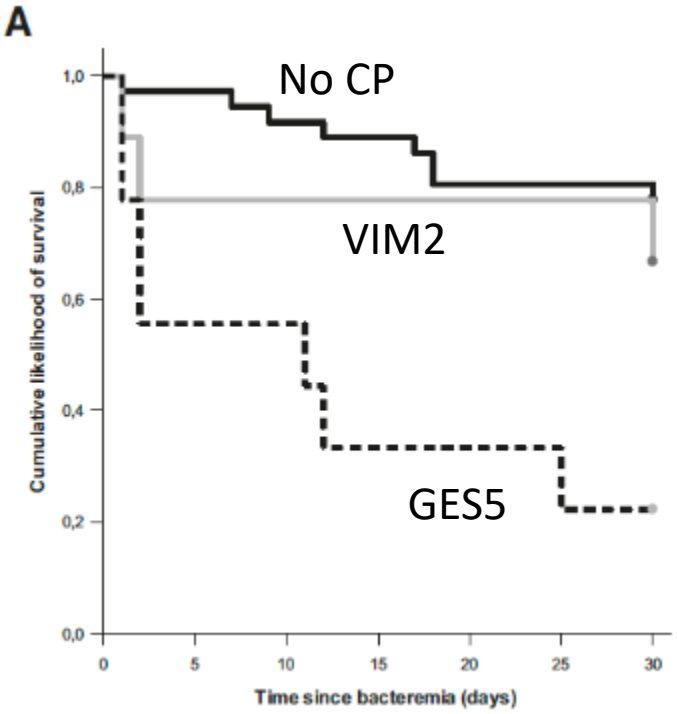


Gomez-Zorilla et al, International Journal of Antimicrobial Agents 2017, 49: 198

Bacteraemia due to extensively drug-resistant *Pseudomonas aeruginosa* sequence type 235 high-risk clone: Facing the perfect storm

- ✓ Retrospective analysis
- ✓ 64 patients with bacteremia
  - Non-XDR (40)
  - XDR
    - 10 VIM-2 CP (ST175)
    - 11 GES-5 CP (ST235)
    - 3 no CP
- ✓ ST235: 100 ExoU+
- ✓ Susceptibility XDR
  - Cefta-avi 58.3%
  - Cefto-tazo 12.5%
- ✓ 30d mortality
  - XDR: 62.5%
  - Non-XDR: 30%

- ✓ 30d mortality
  - ST175 30%
  - ST235 82%



Recio et al, International Journal of Antimicrobial Agents 52 (2018) 172

Plan

- ✓ Quelques éléments introductifs….
- ✓ Sensibilité aux principales molécules et nouvelles molécules
- ✓ PK/PD
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Antibiotiques avec une activité contre *Pseudomonas*

ß-lactamines

- ticarcilline ± clavu
- pipéracilline ± tazo
- aztréonam
- cefsulodine
- céfopérazone
- ceftazidime
- cefpirome
- céfépime
- ceftolozane-tazobactam
- ceftazidime-avibactam
- imipénème
- méropénème
- cefiderocol

Aminosides

- gentamicine
- nétilmicine
- tobramycine
- amikacine

Fluoroquinolones

- ciprofloxacine
- lévofloxacine
- delafloxacine

Autres

- colistine
- polymyxine B
- rifampicine
- fosfomycine

	Ceftazidime-avibactam	Ceftolozane-tazobactam
Statut	AMM juin 16 (IIA et IU) (2 g/500 mg x 3/j, en 2 h)	AMM oct 2015 (IIA et IU) (1 g/500 mg x 3/j, en 1 h)
Forces	Activité sur : • BLSE • AmpC • Carbapénèmases (KPC, OXA 48)	Activité sur : • BLSE (coli +++, Kp ±) • *P. aeruginosa* - R cefta et imipénème
Faiblesses	Pas d'activité sur : • Anaérobies • Metallo-carbapénémases • Oxacillinases d'Acinetobacter	Pas d'activité sur : • Anaérobies • Carbapénémases • AmpC hyperproduite • Oxacillinases d'Acinetobacter Pk ≠ molécule et l'inhibiteur

In vitro activity of ceftolozane/tazobactam versus antimicrobial non-susceptible *Pseudomonas aeruginosa* clinical isolates including MDR and XDR isolates obtained from across Canada as part of the CANWARD study, 2008–16

3229 *P. aeruginosa* isolates

Organism (*n*)/antimicrobial agents	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S	%I	%R
P. aeruginosa, all (*n* = 3229)					
ceftolozane/tazobactam	0.5	1	98.3	0.8	0.9
amikacin	4	16	93.3	3	3.8
ceftazidime	4	32	83	6	11.0
ciprofloxacin	0.25	4	77.3	7.7	15.0
colistin	1	2	95.2		4.8
gentamicin	2	8	83.5	7.3	9.2
meropenem	0.5	8	81	7.1	11.9
piperacillin/tazobactam	4	64	84.1	8.6	7.3
MDR *P. aeruginosa* (*n* = 462)					
ceftolozane/tazobactam	1	4	90.5	4.7	4.8
amikacin	8	64	76.4	9.1	14.5
ceftazidime	32	>32	19.5	22.7	57.8
ciprofloxacin	4	>16	24.9	20.6	54.5
colistin	1	2	93.5		6.5
gentamicin	8	>32	47	13.6	39.4
meropenem	8	32	22.5	20.6	56.9
piperacillin/tazobactam	64	256	21.4	38.3	40.3
XDR *P. aeruginosa* (*n* = 84)					
ceftolozane/tazobactam	2	16	78.6	8.3	13.1
amikacin	16	>64	51.2	14.3	34.5
ceftazidime	>32	>32	0	26.2	73.8
ciprofloxacin	8	>16	0	20.2	79.8
colistin	1	4	89.3		10.7
gentamicin	32	>32	1.2	19	79.8
meropenem	16	>32	0	15.5	84.5
piperacillin/tazobactam	128	512	0	42.9	57.1

Walkty et al, J Antimicrob Chemother 2018; 73: 703

Ceftolozane/Tazobactam Pharmacokinetic/ Pharmacodynamic-Derived Dose Justification for Phase 3 Studies in Patients With Nosocomial Pneumonia

The Journal of Clinical Pharmacology 2016, 56(1) 56–66

DOI: 10.1002/jcph.566

Alan J. Xiao, PhD[1], Benjamin W. Miller, PharmD[1], Jennifer A. Huntington, PharmD[1], and David P. Nicolau, PharmD, FCCP, FIDSA[2]

- ✓ Rapport concentration ceftolozane plasma/alvéole : 2/1
- ✓ *P. aeruginosa* dans plus de 30 % des PAVM
- ✓ *P. aeruginosa* R si CMI > 4 mg/l

J Clin Pharmacol 2015 Jun 2010

Ceftolozane/Tazobactam Pharmacokinetic/ Pharmacodynamic-Derived Dose Justification for Phase 3 Studies in Patients With Nosocomial Pneumonia

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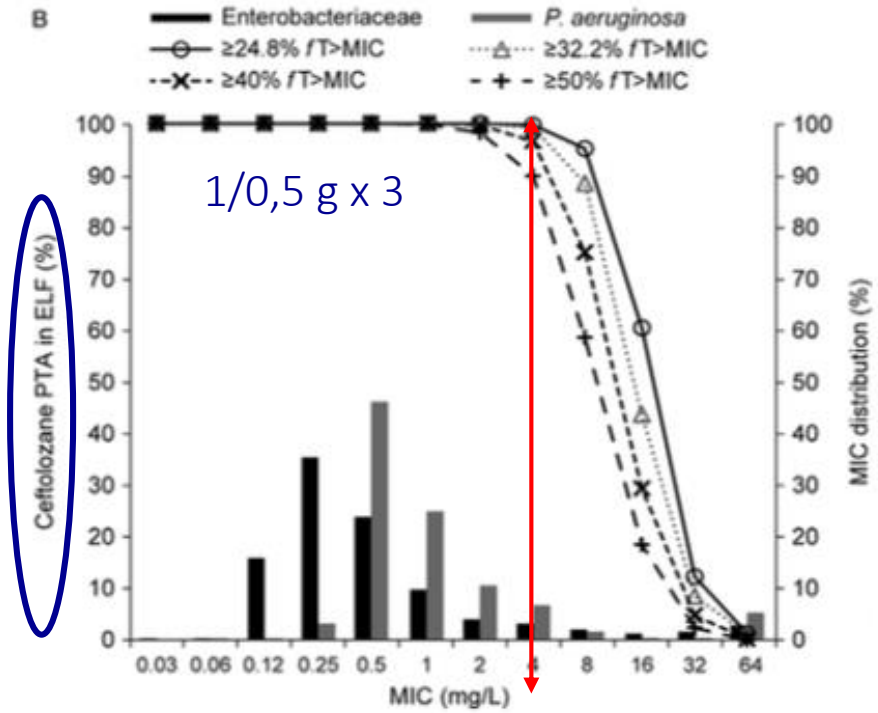

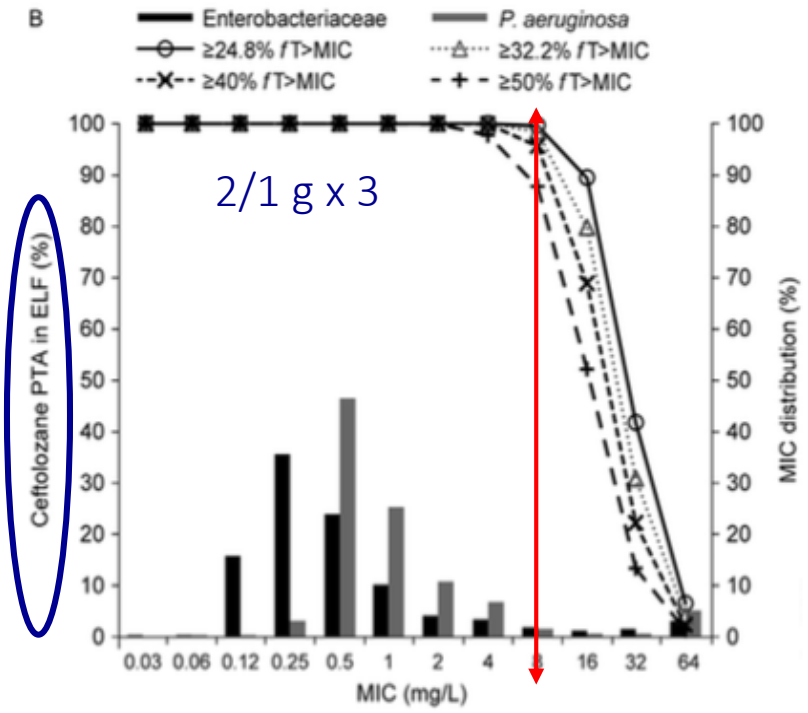

fT > CMI : ≥ 50 %... objectif modeste...

J Clin Pharmacol 2016, 56:56

Ceftolozane/Tazobactam Pharmacokinetic/ Pharmacodynamic-Derived Dose Justification for Phase 3 Studies in Patients With Nosocomial Pneumonia

The Journal of Clinical Pharmacology 2016, 56(1) 56–56

DOI: 10.1002/jcph.566

Alan J. Xiao, PhD[1], Benjamin W. Miller, PharmD[1], Jennifer A. Huntington, PharmD[1], and David P. Nicolau, PharmD, FCCP, FIDSA[2]

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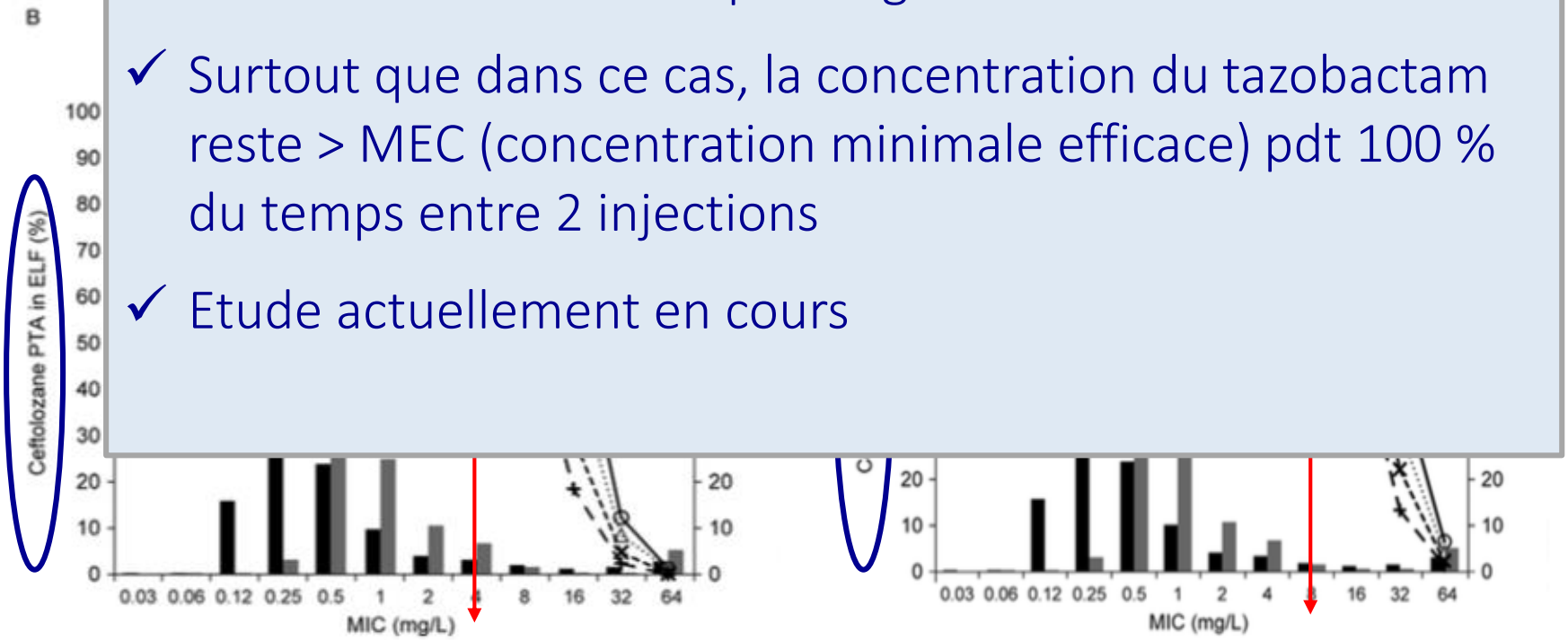
Faculty of Biology and Medicine

- ✓ Rapport concentration ceftolozane plasma/alvéole : 2/1
- ✓ *P. aeruginosa* dans plus de 30 % des PAVM
- ✓ *P. aeruginosa* R si CMI > 4 MG/L

- ✓ Il faut sans doute x 2 la posologie dans les PAVM
- ✓ Surtout que dans ce cas, la concentration du tazobactam reste > MEC (concentration minimale efficace) pdt 100 % du temps entre 2 injections
- ✓ Etude actuellement en cours



fT > CMI : ≥ 50 %... objectif modeste...

J Clin Pharmacol 2016, 56:56

Characteristics and Outcomes of Complicated Intra-abdominal Infections Involving *Pseudomonas aeruginosa* from a Randomized, Double-Blind, Phase 3 Ceftolozane-Tazobactam Study

✓ Ceftolozane-tazobactam + metronidazole vs meropenem

Characteristic	*P. aeruginosa* at baseline ($n = 72$)	No *P. aeruginosa* at baseline ($n = 734$)	Total ($n = 806$)
Baseline APACHE II score category (n [%])[a]			
<10	61 (84.7)	596 (81.2)	657 (81.5)
≥10	11 (15.3)	137 (18.7)	148 (18.4)
Anatomic site of infection (n [%])			
Appendix	43 (59.7)	341 (46.5)	384 (47.6)
Biliary cholecystitis/cholangitis	5 (6.9)	138 (18.8)	143 (17.7)
Stomach/duodenum	4 (5.6)	75 (10.2)	79 (9.8)
Colon	17 (23.6)	101 (13.8)	118 (14.6)
Small bowel	1 (1.4)	41 (5.6)	42 (5.2)
Parenchymal (liver)	1 (1.4)	32 (4.4)	33 (4.1)
Parenchymal (spleen)	0	4 (0.5)	4 (0.5)
Other	1 (1.4)	15 (2.0)	16 (2.0)

Miller et al, AAC 2016, 60:4387

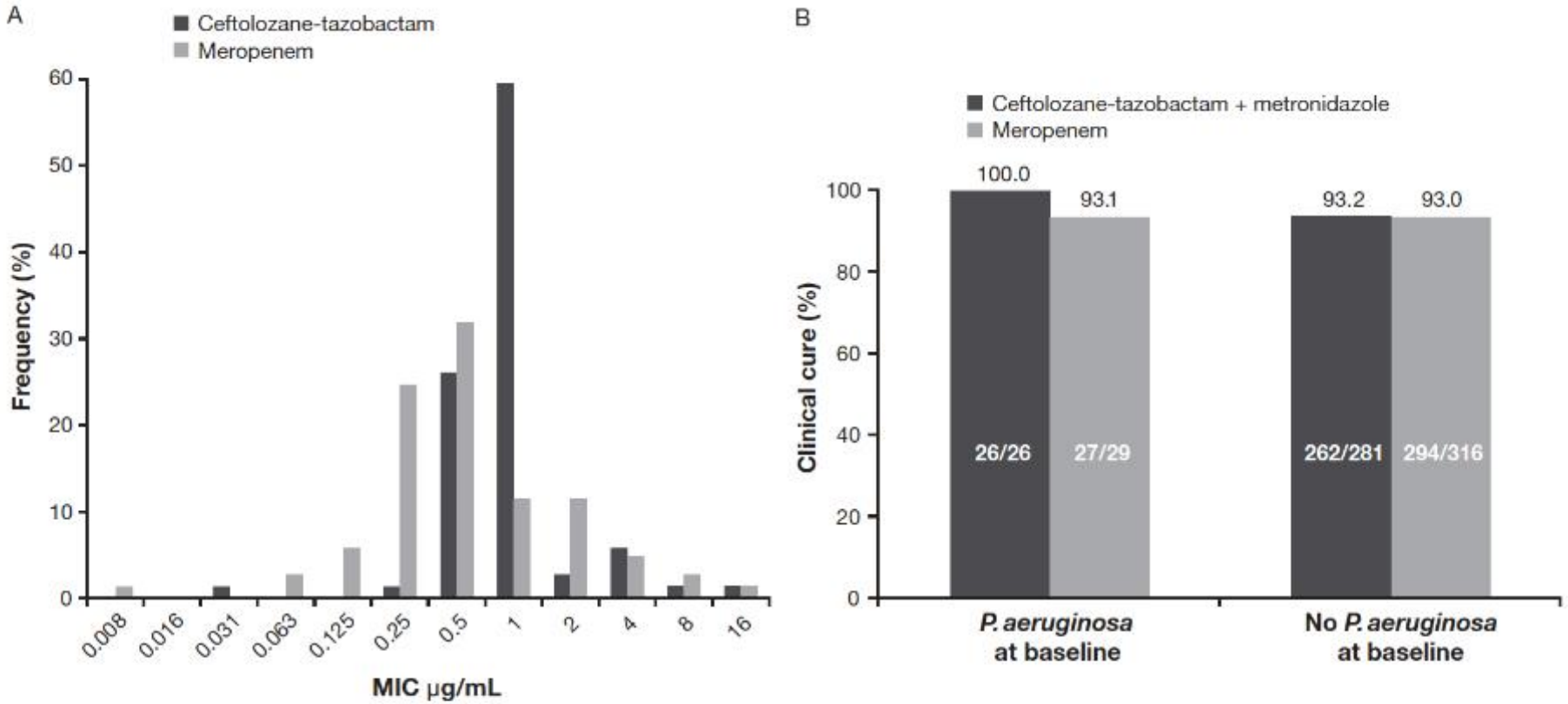
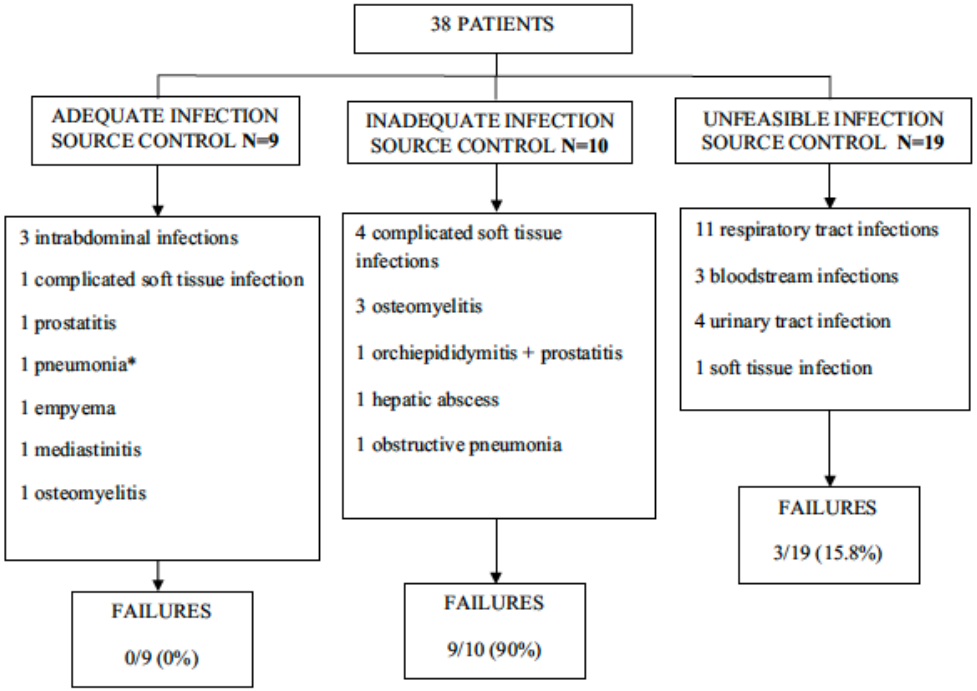


FIG 1 MIC distribution and clinical outcomes with ceftolozane-tazobactam and meropenem. (A) Distribution of ceftolozane-tazobactam and meropenem MICs for 69 *Pseudomonas aeruginosa* isolates identified at the screening visit (microbiological intent-to-treat population). (B) Clinical cure rate at the test-of-cure visit for patients with and without baseline *P. aeruginosa* infection, by treatment group (microbiologically evaluable population, which includes patients with pathogens at baseline who were susceptible or resistant to study drug).

Miller et al, AAC 2016, 60:4387

Ceftolozane/tazobactam for the treatment of XDR *Pseudomonas aeruginosa* infections

- ✓ Retrospective study
- ✓ Consecutive patients treated with C/T for XDR-PA infection at a tertiary referral hospital
- ✓ Thirty-eight patients included
- ✓ At completion of treatment, 33 (86.8%) patients showed clinical response
- ✓ Clinical cure associated to :
  - Lower C/T MIC
  - Adequate source control



*In this patient a lung transplant was performed during the course of pneumonia, so we considered that the focus of infection had been controlled and resolved.

Escola-Vergé et al, Infection 2018, 46:461

Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections: Clinical Effectiveness and Evolution of Resistance

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- ✓ 21 patients treated with ceftolozane-tazobactam for MDR-*P. aeruginosa* infections
- ✓ Eighteen (86%) patients were treated for respiratory tract infections
- ✓ Ceftolozane-tazobactam failure rate was 29% (6/21).
- ✓ Ceftolozane-tazobactam resistance emerged in 3 (14%) patients.
- ✓ Resistance was associated with de novo mutations, rather than acquisition of resistant nosocomial isolates.
- ✓ ampC overexpression and mutations were identified as potential resistance determinants.

canton de vaud

Haidar et al, Clinical Infectious Diseases 2017;65(1):110–20

Ceftolozane-tazobactam resistance induced in vivo during the treatment of MDR Pseudomonas aeruginosa pneumonia.

- ✓ Case report
  - Septic shock on fecal peritonitis: mero/vanco
  - Pneumonia *P. aeruginosa*: Pip-taz and cefta (isolate 1)
  - Isolate 2 following week : cefto-tazo (1,5g/8h)
  - Relapse isolate 3

Table 1. Antibiogram of *P. aeruginosa* isolates.

	Susceptibility [MIC (mg/L)]		
	First isolate (1 January 2017)	Second isolate (5 January 2017)	Third isolate (5 February 2017)
Amikacin	≤0.5 (S)	≤0.5 (S)	8 (S)
Gentamicin	≤0.125 (S)	≤0.125 (S)	4 (S)
Tobramycin	≤0.125 (S)	≤0.125 (S)	1 (S)
Aztreonam	32 (R)	32 (R)	32 (R)
Ceftazidime	8 (S)	16 (R)	64 (R)
Imipenem	32 (R)	32 (R)	4 (S)
Meropenem	16 (R)	>32 (R)	32 (R)
Piperacillin-tazobactam	16 (S)	64 (R)	32 (R)
Carbenicillin	512 (R)	256 (R)	512 (R)
Ceftolozane-tazobactam	0.5 (S)	0.5 (S)	>16 (R)
Colistin	1 (S)	1 (S)	1 (S)
Ciprofloxacin	>8 (R)	>8 (R)	>8 (R)

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY, 2018 VOL. 16, NO. 5, 367

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

- ✓ Adults with nosocomial pneumonia including ventilator-associated pneumonia
- ✓ 136 centres in 23 countries
- ✓ Treatment:
  - 2000 mg ceftazidime and 500 mg avibactam (by 2 h intravenous infusion every 8 h)
  - 1000 mg meropenem (by 30-min intravenous infusion every 8 h) for 7-14 days
- ✓ 879 patients included
  - Klebsiella pneumoniae (37%)
  - Pseudomonas aeruginosa (30%); 28% were ceftazidime-non-susceptible

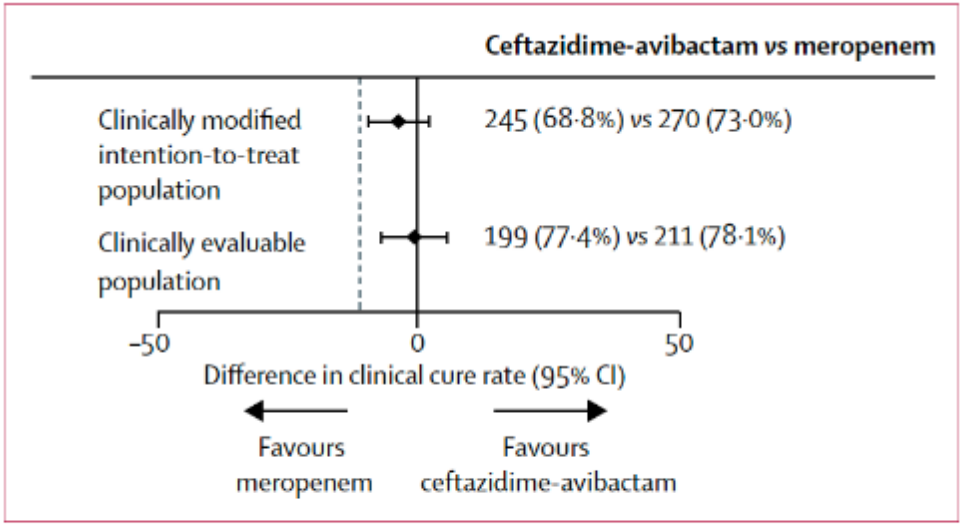


Figure 2: **Clinical cure rates at test-of-cure visit**
Data are number of patients with clinical cure (%). Dashed line indicates non-inferiority margin of −12·5%.

Ceftazidime-avibactam was non-inferior to meropenem in the treatment of nosocomial pneumonia.

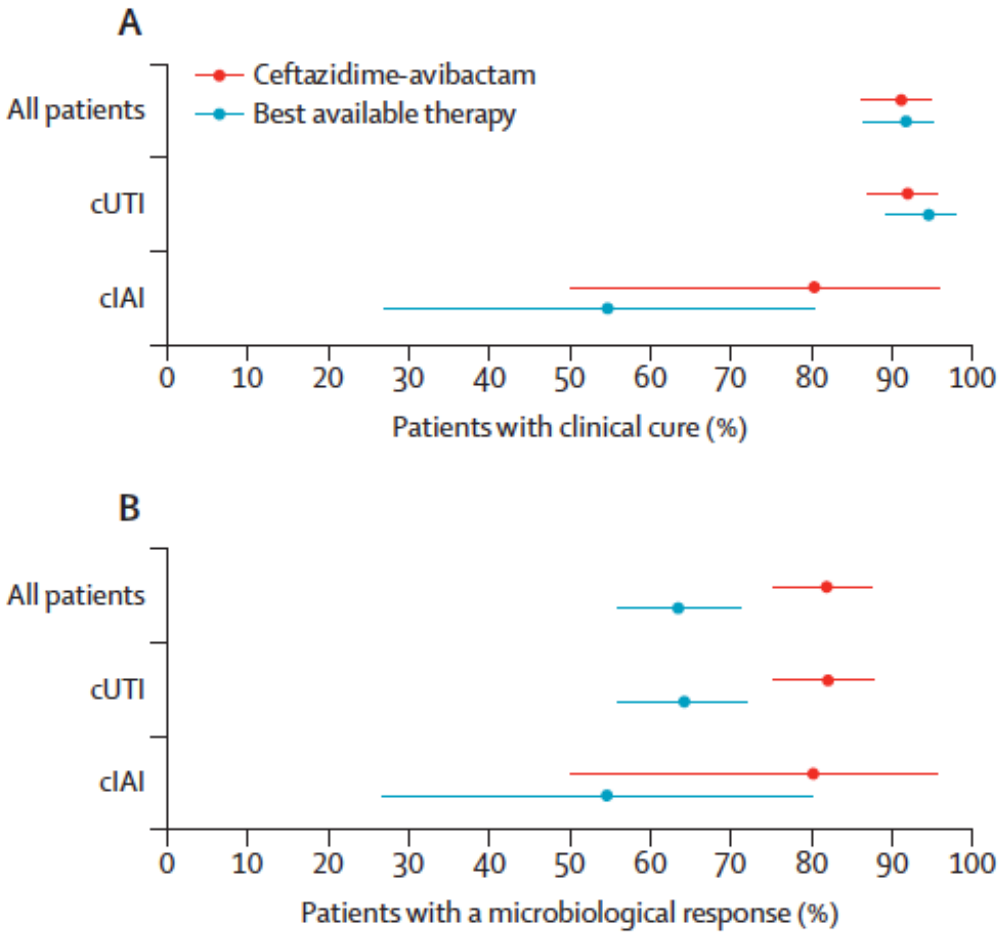
Torres et al, Lancet Infect Dis 2018; 18: 285–95

Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study

- ✓ Pathogen-directed, international, randomised, open-label, phase 3, 16 countries worldwide
- ✓ 18–90 years with complicated urinary tract infection or complicated intra-abdominal infection caused by ceftazidime-resistant Enterobacteriaceae or Pseudomonas aeruginosa
- ✓ Treatment:
  - ceftazidime-avibactam (2000 mg/500 mg), 2-h intravenous infusion every 8 h
  - best available therapy
- ✓ Primary endpoint: clinical response
  - at the test-of-cure visit,
  - 7–10 days after last infusion of study therapy

Carmelli et al, Lancet inf Dis 2016, 16:661-73

- ✓ 163 (97%) of 168 patients in the best available therapy group received a carbapenem, 161 (96%) as monotherapy
- ✓ Conclusion: efficacy of ceftazidime-avibactam as a potential alternative to carbapenems in patients with ceftazidime-resistant Enterobacteriaceae and P aeruginosa



Carmelli et al, Lancet inf Dis 2016, 16:661-73

Efficacy and safety of ceftazidime/avibactam: a systematic review and meta-analysis

Neta Sternbach[1]†, Yaara Leibovici Weissman[1,2]†, Tomer Avni[2,3] and Dafna Yahav[2,3]*

- ✓ Systematic review and meta-analysis including RCTs evaluating ceftazidime/avibactam versus comparator for the treatment of any infection
- ✓ Primary outcome was 30 day all-cause mortality
- ✓ Seven publications (eight trials, 4093 patients) were included

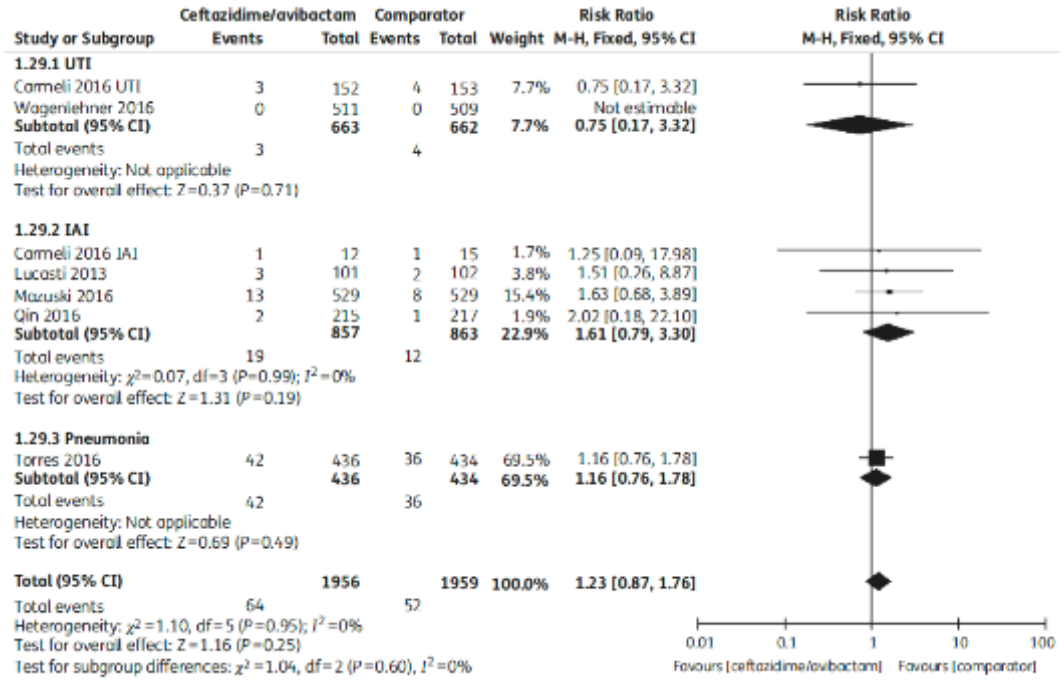


Figure 2. All-cause mortality at late follow-up. M-H, Mantel–Haenszel.

J Antimicrob Chemother 2018; 73: 2021–2029

Cefiderocol

- ✓ Cefiderocol is a siderophore cephalosporin
- ✓ Cefiderocol is administered intravenously, 2 g x 3 daily over 3 hours

Clinical breakpoints for cefiderocol were set by EUCAST as follows:

Organisms	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Enterobacterales	2	2	**30**	22	22
Pseudomonas aeruginosa	2	2	**30**	22	22
Acinetobacter spp.*	IE	IE	–	–	–
*Stenotrophomonas maltophilia**	IE	IE	–	–	–
PK/PD (non-species related) breakpoints	2	2	-	-	-

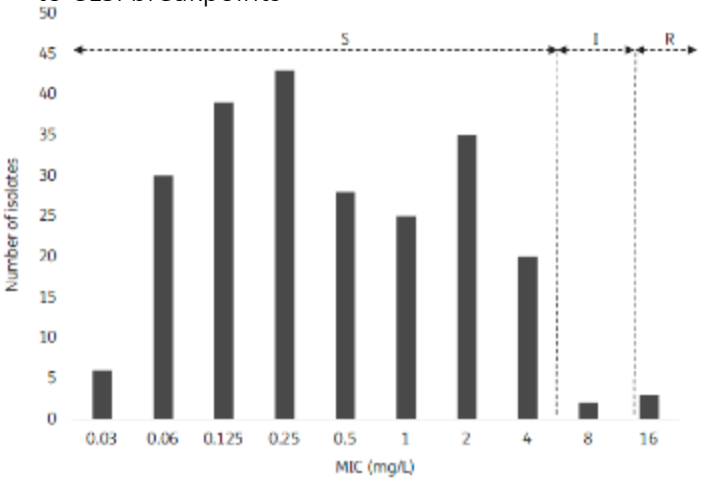
* Clinical data on efficacy are limited, but in vitro and PK-PD activity support the use in difficult-to-treat cases

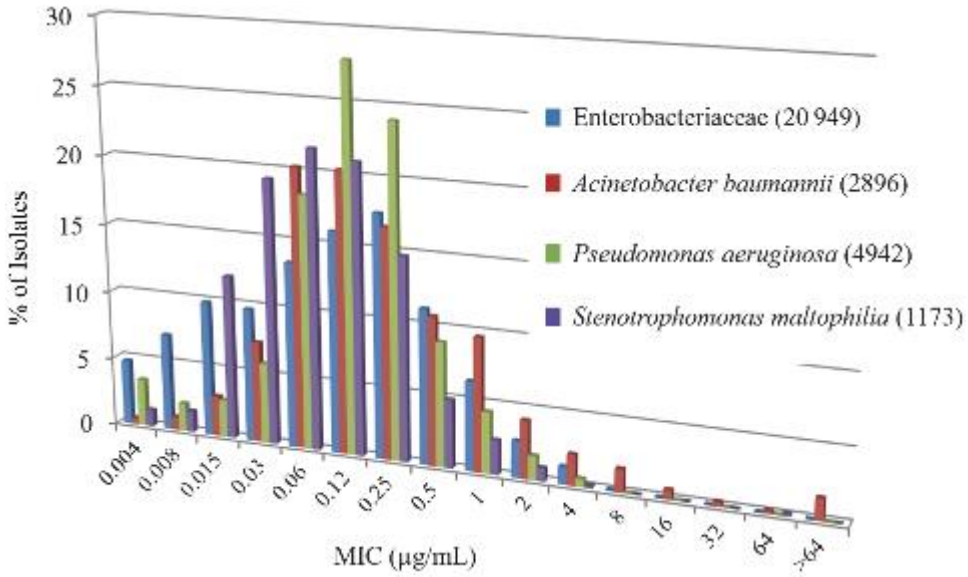
EUCAST May 2020

Cefiderocol

Two hundred and thirty-one isolates : 125 *Enterobacterales*, 80 *Acinetobacter baumannii*, 6 *Pseudomonas aeruginosa* and 20 *Stenotrophomonas maltophilia.*

Distribution of MICs for MDR isolates according to CLSI breakpoints





Delgado-Valverde et al, J Antimicrob Chemother 2020; 75: 1840–1849

Yamano et al, Clinical Infectious Diseases 2019;69(S7):S544–51

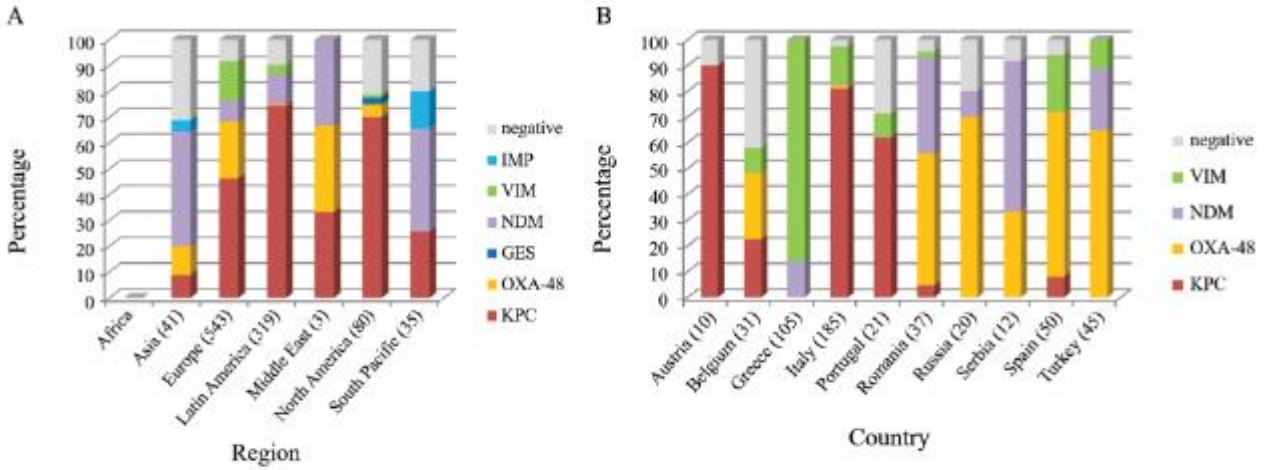


Figure 2. Distribution of carbapenemases produced by carbapenem-resistant Enterobacteriaceae, from the SIDERO-CR study between regions (*A*) and countries (*B*). Adapted from [38, 44]. Abbreviations: GES, Guiana extended-spectrum β-lactamase; IMP, imipenemase metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillin carbapenemase; VIM, Verona integron-encoded metallo-β-lactamase.

Table 2. Susceptibility Ratio to Cefiderocol and Comparators of Carbapenem-resistant Isolates From the SIDERO-CR-2014/2016 Study

	Ratio of Susceptible Strains[a], (%)				
Species (No. of Strains)	Cefiderocol	Ceftazidime-avibactam	Ceftolozane-tazobactam	Ciprofloxacin	Colistin
Carbapenem-nonsusceptible strains[b]					
Enterobacteriaceae (1022)	97.0	77.0	1.7	11.5	77.8[c]
Pseudomonas aeruginosa (262)	99.2	36.3	24.1	1.2	99.6
Acinetobacter baumannii (368)	90.9	NA	NA	0	94.6
Stenotrophomonas maltophilia (217)	100[e]	NA	NA	NA	NA

Yamano et al, Clinical Infectious Diseases 2019;69(S7):S544–51

Intrapulmonary pharmacokinetics of cefiderocol, a novel siderophore cephalosporin, in healthy adult subjects

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- ✓ A single intravenous dose of cefiderocol (2000mg infused over 60 min) in healthy adult males

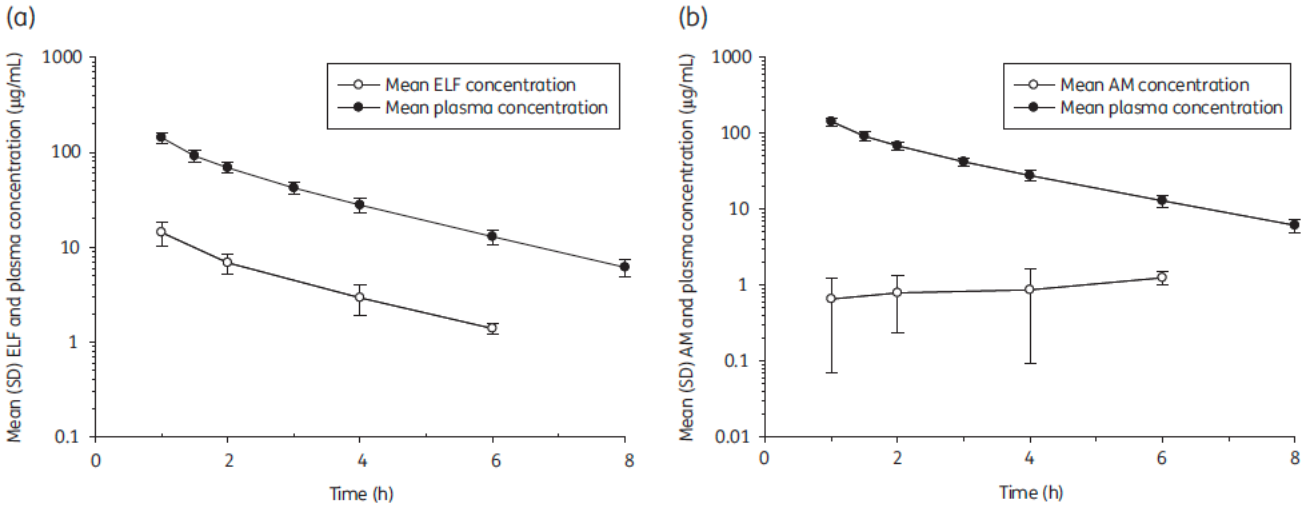


Figure 1. (a) Mean (SD) total plasma and ELF cefiderocol concentration profiles following a single intravenous infusion of 2000 mg of cefiderocol. (b) Mean (SD) total plasma and AM cefiderocol concentration profiles following a single intravenous infusion of 2000 mg of cefiderocol. Arithmetic mean concentrations of cefiderocol in plasma, ELF and AMs were calculated by nominal sampling time. *N*=20 at each timepoint for plasma; *N*=5 at each timepoint for ELF and AMs. Logarithmic *y*-axis.

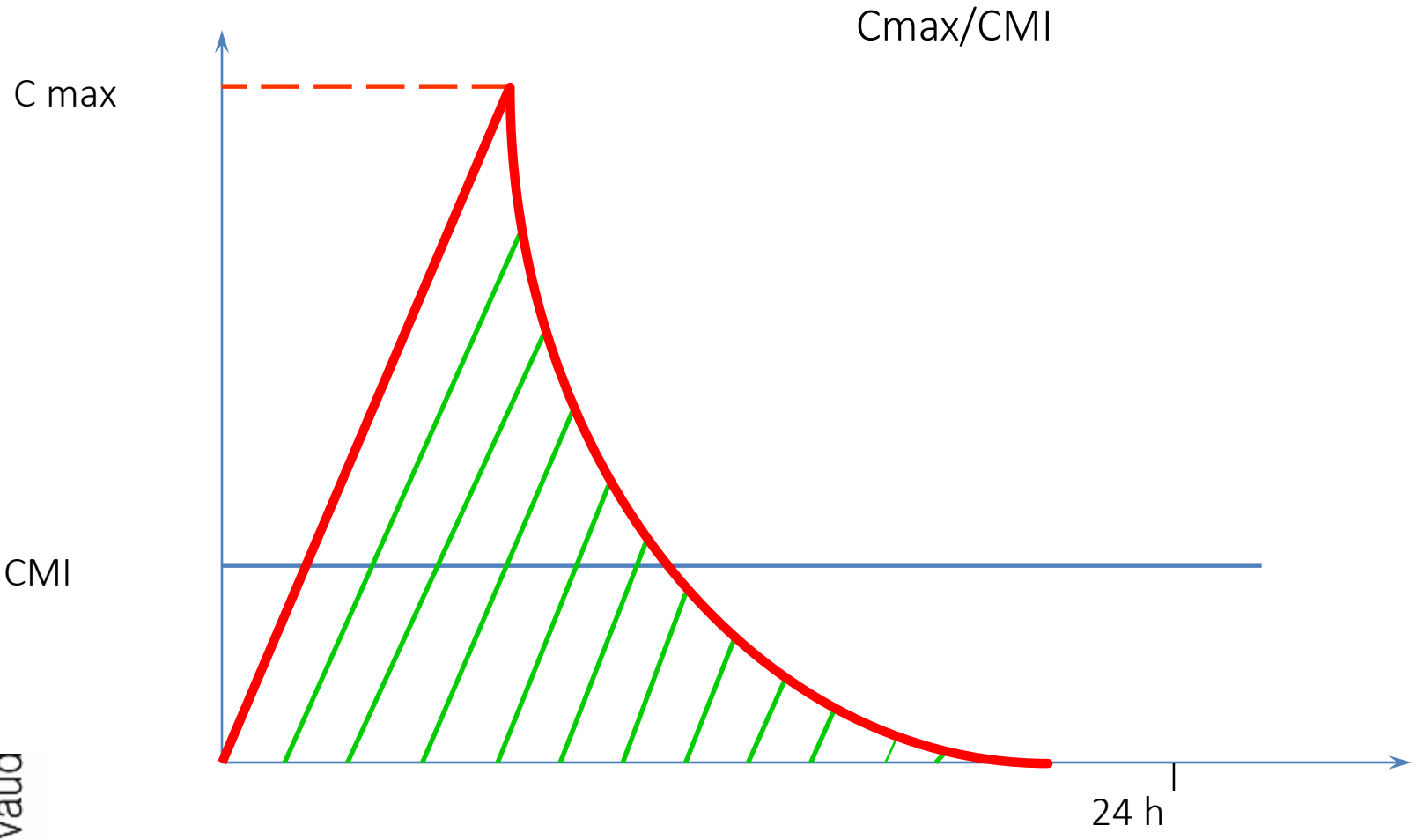
- ✓ Cefiderocol penetrates into ELF, and ELF and plasma concentrations appear to be parallel

Katsube et al, J Antimicrob Chemother 2019; 74: 1971–1974

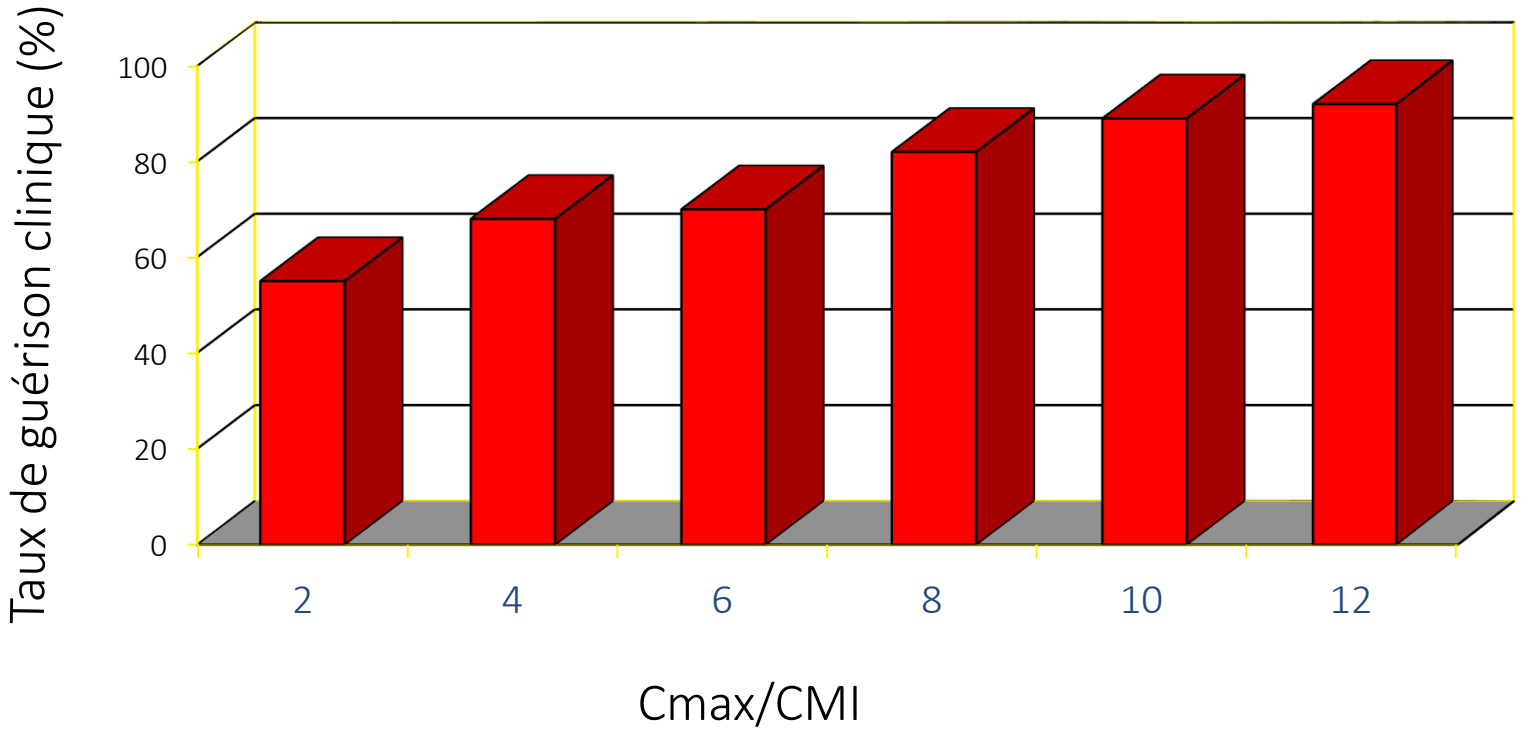
Plan

- ✓ Quelques éléments introductifs….
- ✓ Sensibilité aux principales molécules et nouvelles molécules
- ✓ PK/PD
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives

Aminosides

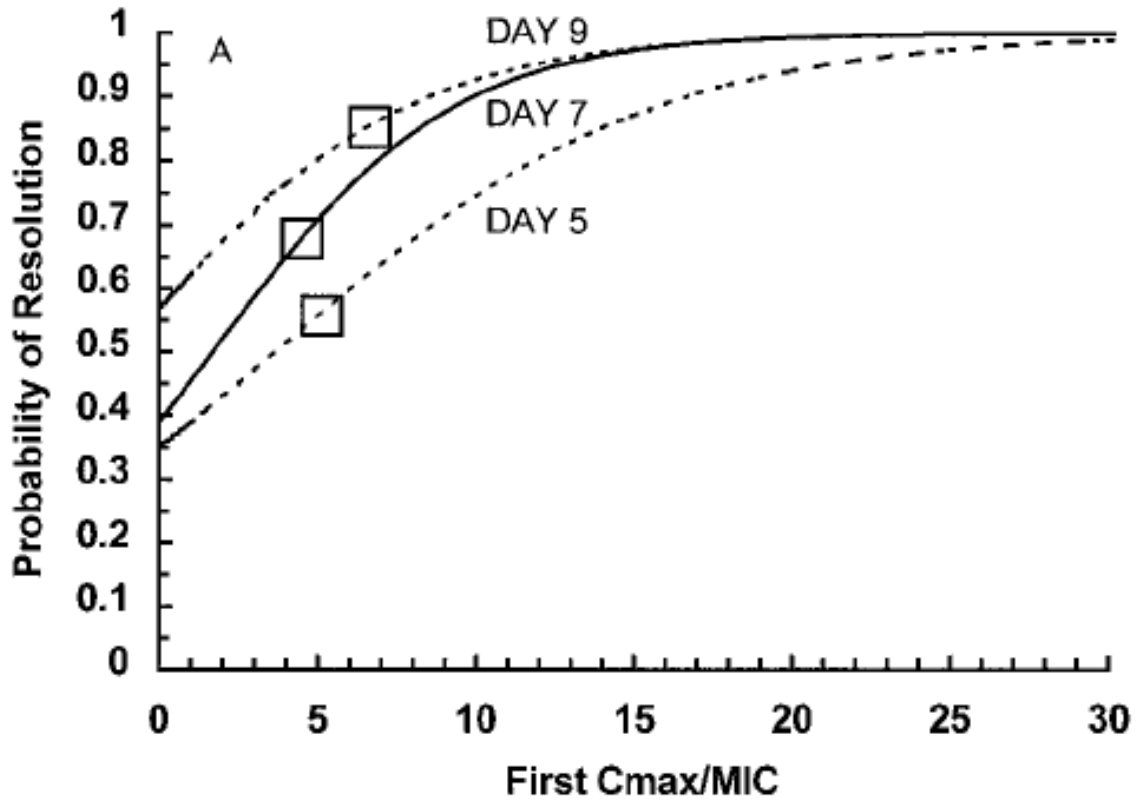


Aminosides
Relation Cmax/CMI - Guérison clinique



Moore, JID 1987

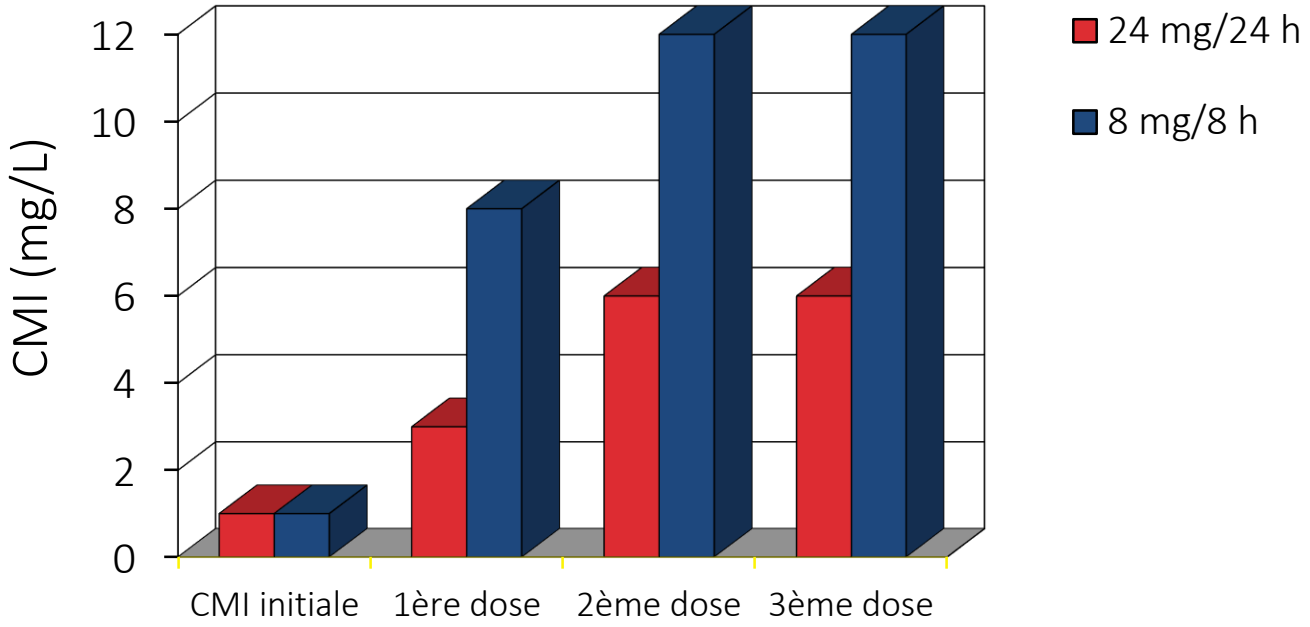
Importance de la première dose d'aminoside sur l'évolution clinique



Kashuba et al, AAC, 1999

Résistance adaptative

CMI; modèle statique *in vitro*



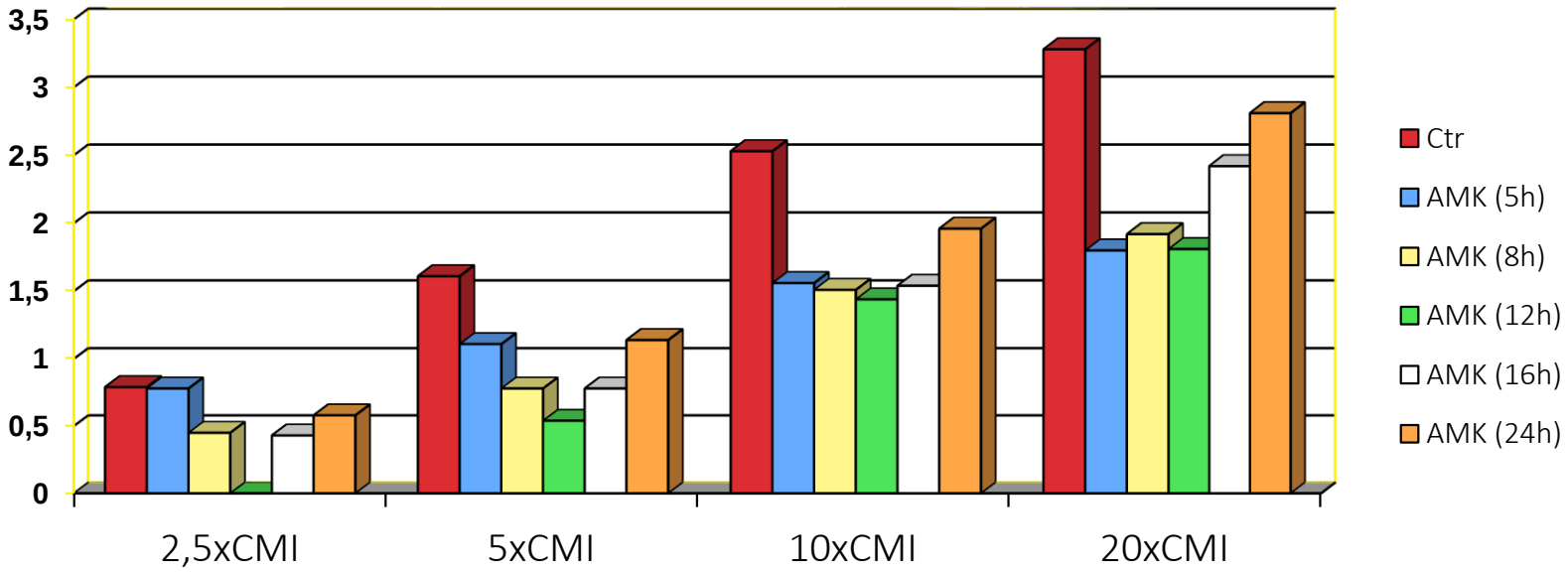
tobramycine

P. aeruginosa

(Karlowsky et al, JAC 1994)

Résistance adaptative

Δlog CFU/ml/90min



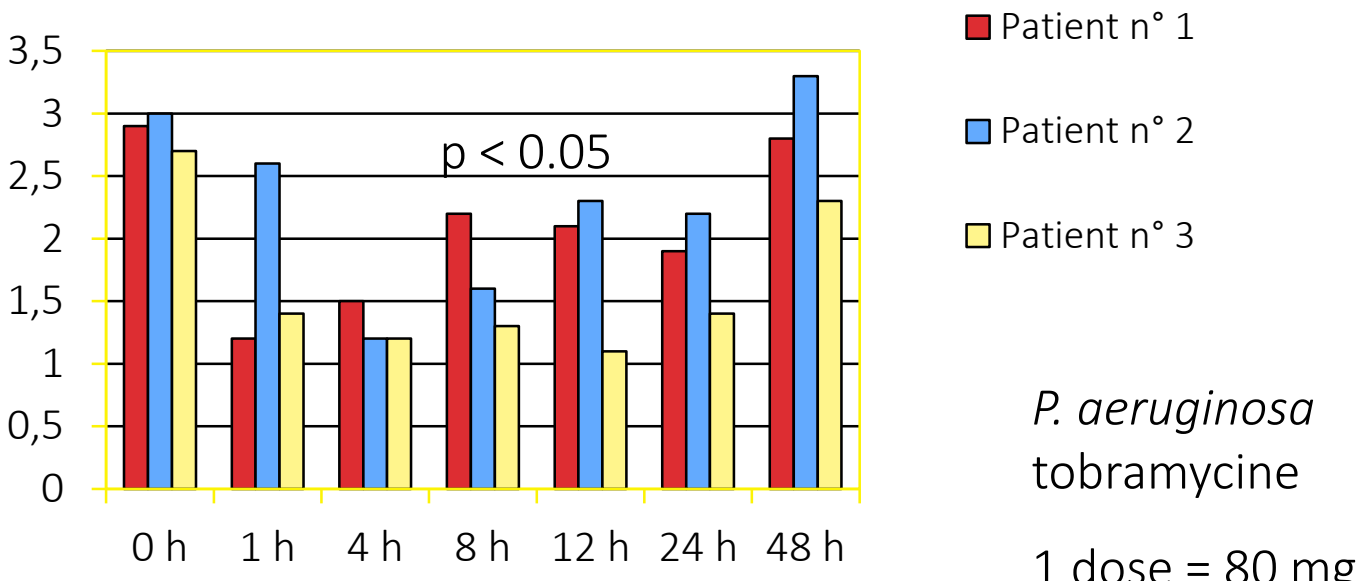
AMK in vivo : 80 mg/kg

Xiong et al, AAC 1997

Résistance adaptative

Mucoviscidose

Bactéricidie (log10 CFU/ml)



P. aeruginosa
tobramycine

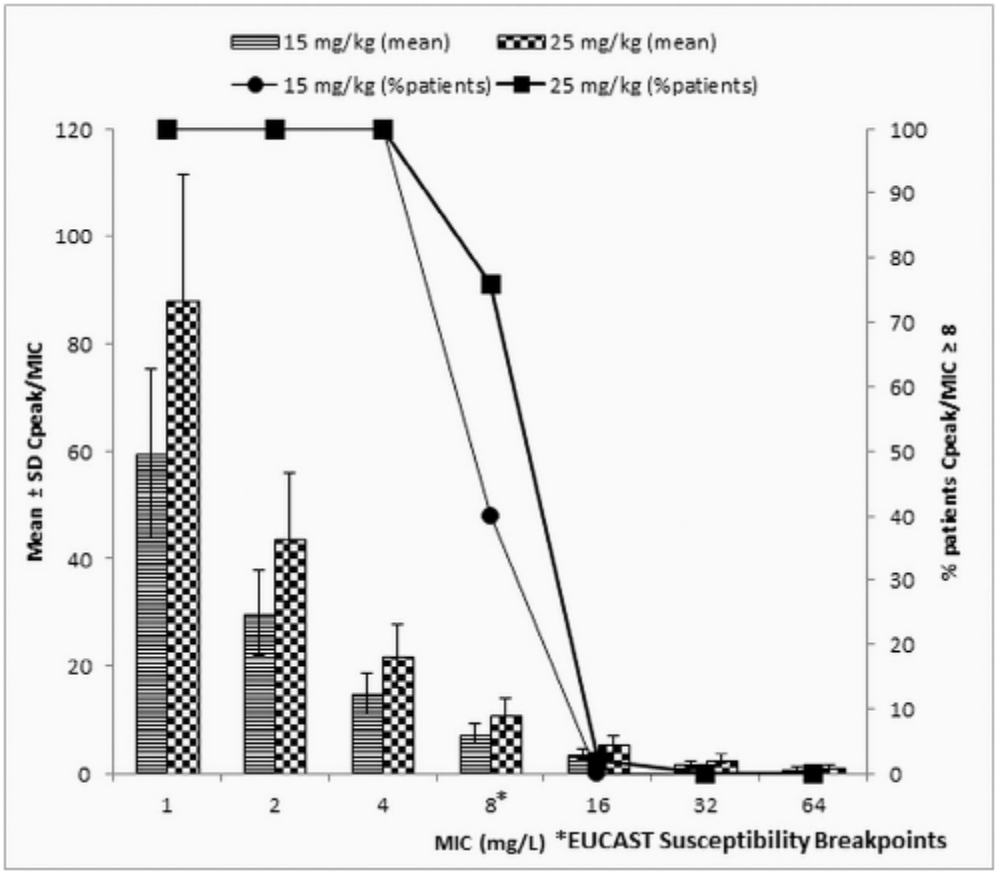
1 dose = 80 mg

Barclay et al, JAC 1996

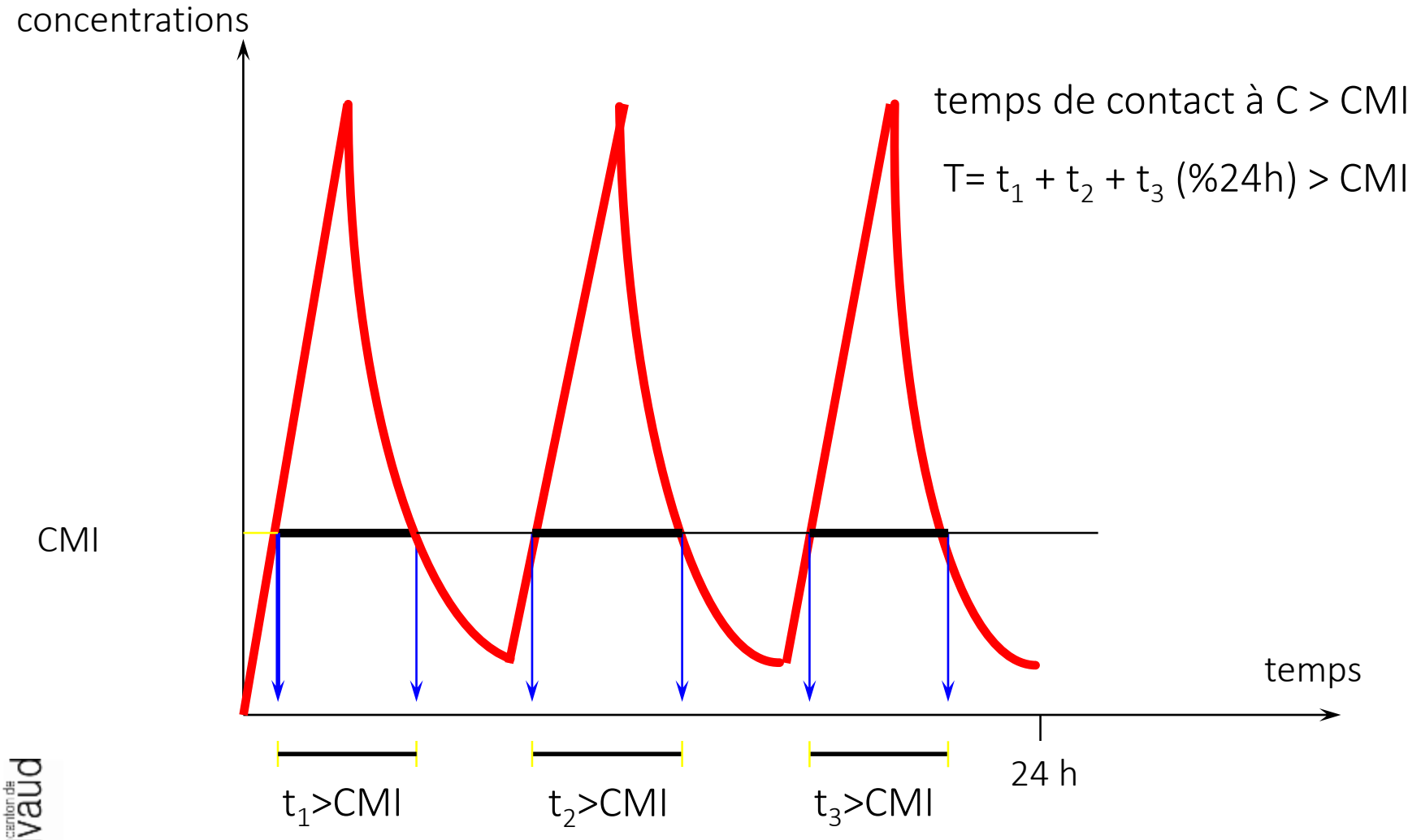
Higher versus standard amikacin single dose in emergency department patients with severe sepsis and septic shock: a randomised controlled trial

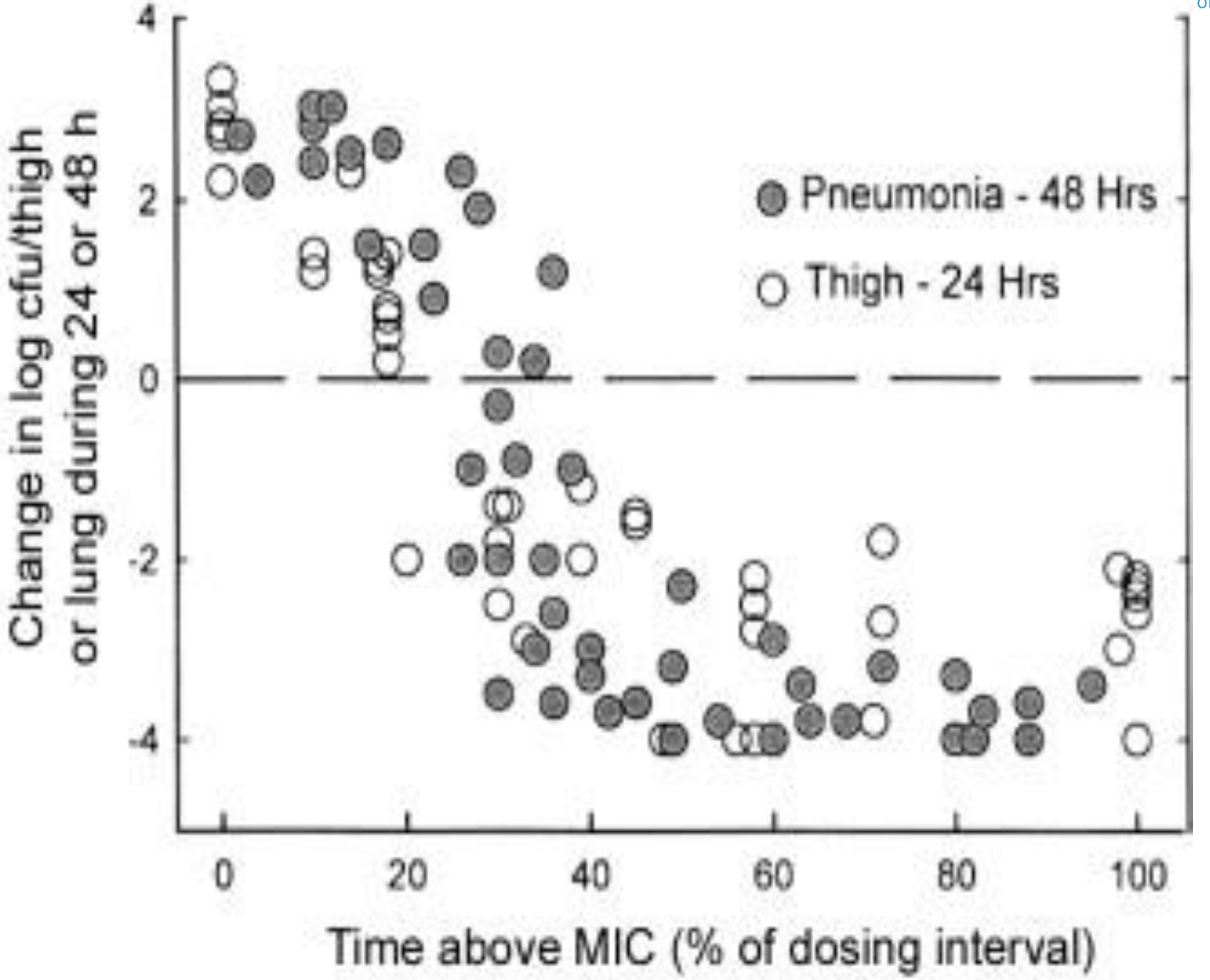
Sabrina De Winter [a,*], Joost Wauters [b], Wouter Meersseman [b], Jan Verhaegen [c], Eric Van Wijngaerden [b], Willy Peetermans [b], Pieter Annaert [d], Sandra Verelst [e], Isabel Spriet [a]

- ✓ Prospective randomised controlled study
- ✓ Severe sepsis or septic shock treated with 15 mg/kg versus 25 mg/kg amikacin.
- ✓ The primary outcome target attainment defined as Cpeak/MIC ≥ 8
- ✓ 104 patients included. The target was attained in 76% vs. 40% of patients assigned to the 25 mg/kg vs. 15 mg/kg dose groups (P < 0.0001).

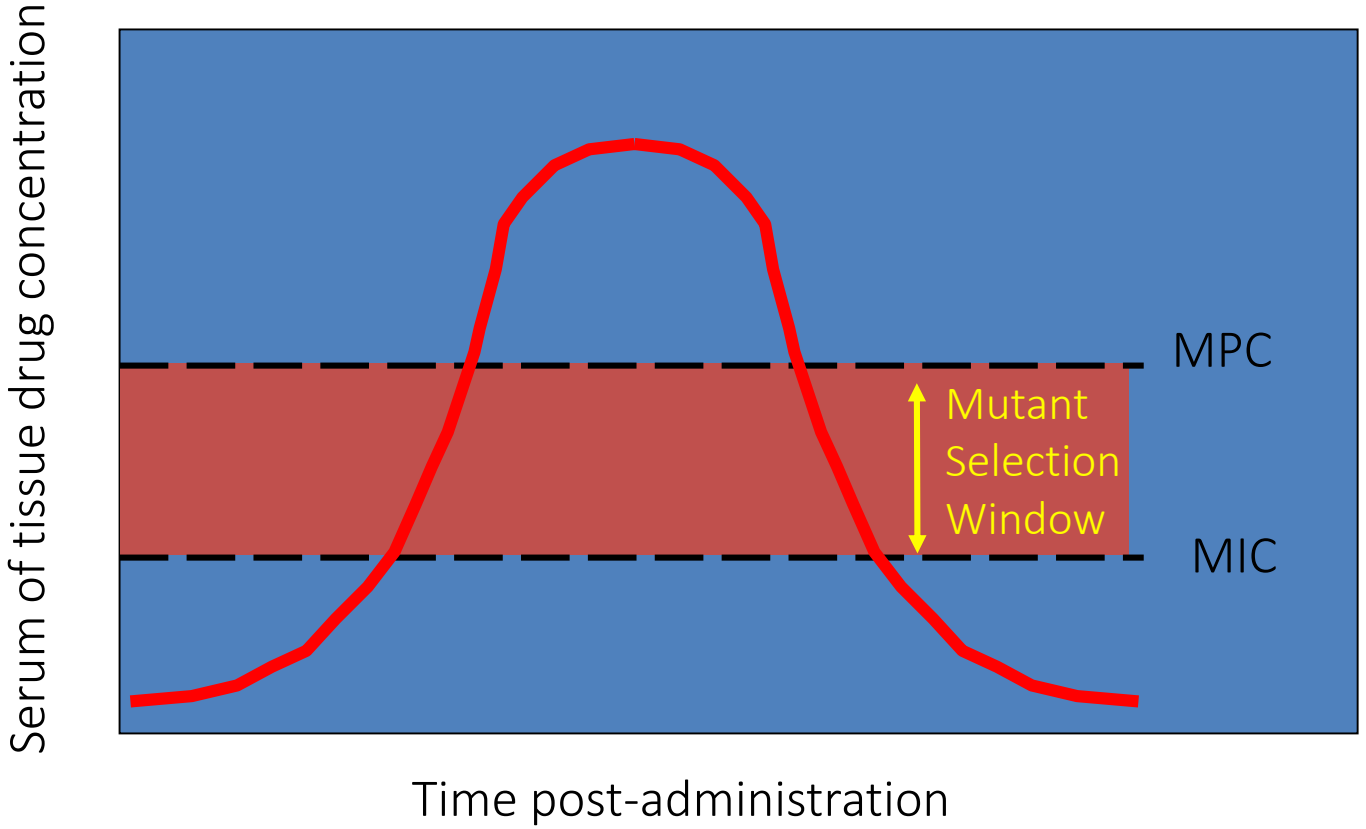


Bêtalactamines:
paramètres pharmacodynamiques





Craig et al, CID 2001



- ✓ Idealized sketch of serum or tissue drug concentration after administration of a single dose of antibiotic to a patient.
  - MIC and mutant prevention concentration (MPC), determined in laboratory studies, are indicated.
  - The area between MPC and MIC (shaded) represents the mutant selection window

Extended-Infusion Cefepime Reduces Mortality in Patients with *Pseudomonas aeruginosa* Infections

Karri A. Bauer,[a] Jessica E. West,[b] James M. O'Brien,[c] Debra A. Goff[a]

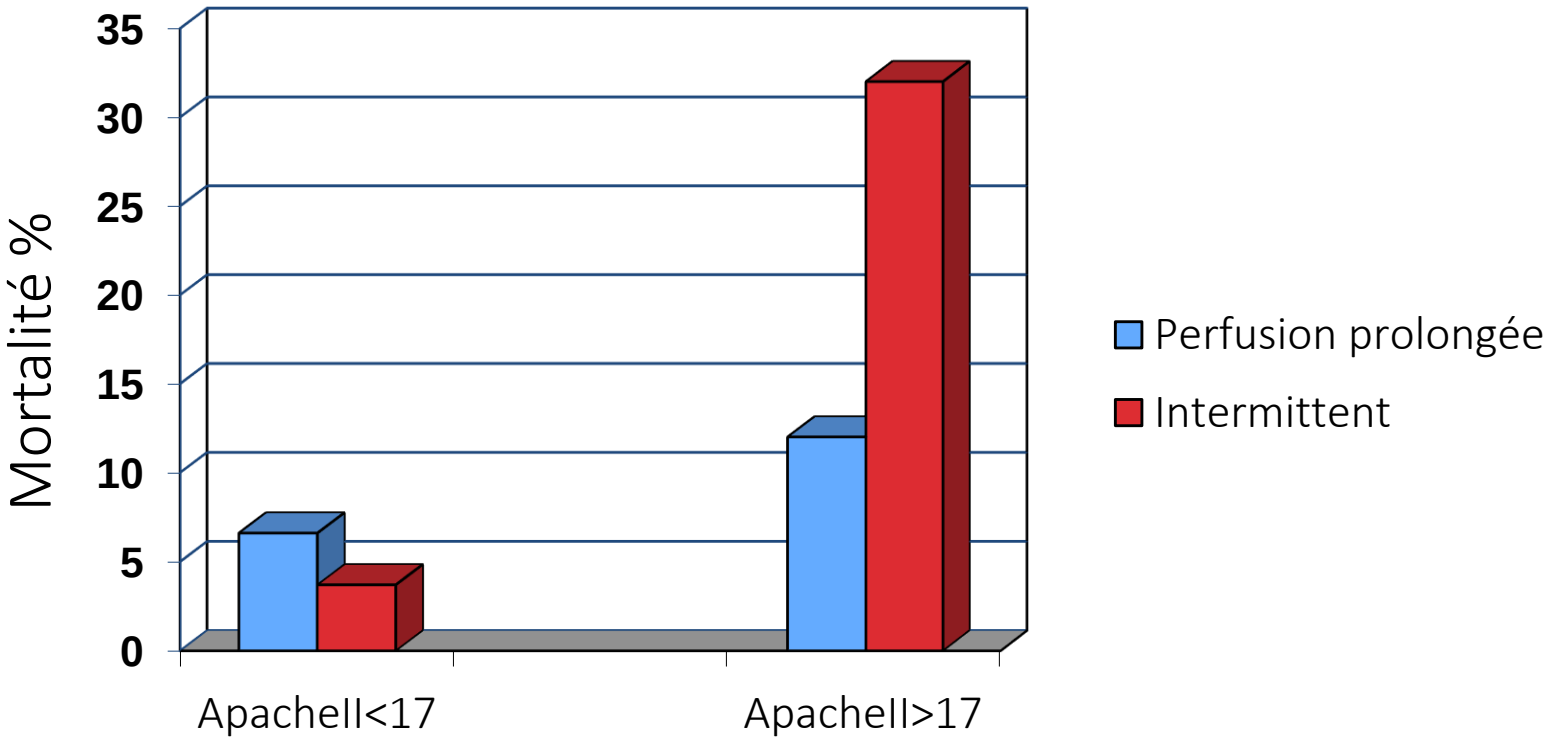
- ✓ Single-center study compared cefepime for bacteremia and/or pneumonia
  - ✓ admitted from 1 January 2008 through 30 June 2010 (a 30-min infusion of 2 g every 8 h)
  - ✓ admitted from 1 July 2010 through 31 May 2011 (a 4-h infusion of 2 g every 8 h).
- ✓ Extended infusion was associated to
  - ✓ **Decreased mortality (20% versus 3%; p=0.03).**
  - ✓ Decreased mean length of stay of 3.5 days less
  - ✓ Decreased mean length of stay was significantly less in the extended-infusion group (18.5 days versus 8 days; P0.04).
  - ✓ Decreased Hospital costs were $23,183 less per patient,
- ✓ Extended-infusion treatment with cefepime provides increased clinical and economic benefits in the treatment of invasive *P. aeruginosa* infections.

July 2013 Volume 57 Number 7 Antimicrobial Agents and Chemotherapy p. 2907–2912

Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

- ✓ Étude sur cohorte de 194 patients
- ✓ Deux modalités d'administration
  - 3.375g en 30 min toutes les 4 à 6 H
  - 3.375g en 4 H toutes les 8 H
- ✓ Analyse de 2 paramètres en fonction du Score Apache II
  - Mortalité
  - Durée d'hospitalisation

Lodise et al , CID, 2007



Lodise et al , CID, 2007

Continuous versus intermittent piperacillin/tazobactam infusion in infection due to or suspected *pseudomonas aeruginosa*

- ✓ Multicenter clinical trial, 11 Spanish hospitals
- ✓ Treatment:
  - continuous infusion of piperacillin–tazobactam
  - 30 % higher dose administered by intermittent infusion
- ✓ Primary efficacy endpoint:
  - percentage of patients having a satisfactory clinical response at completion of treatment, defined as clinical cure or clinical improvement.

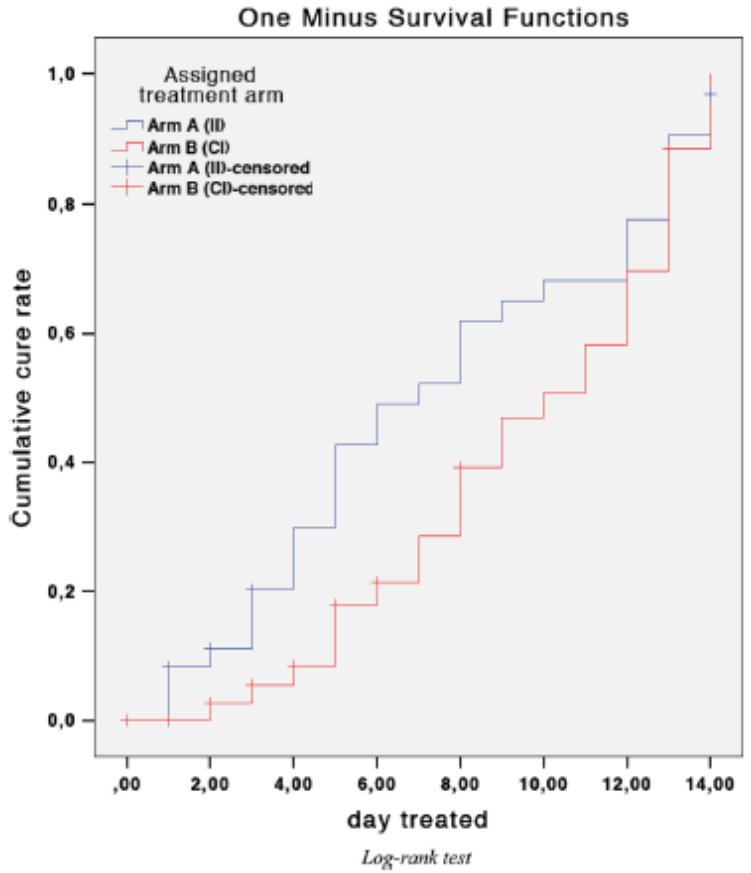


Fig. 2 One minus survival function plot (cure). *CI* Continuous infusion, *II* Intermittent infusion

Cotrina-Luque et al, Int J Clin Pharm 2016,38:70-79

✓ No difference between the 2 groups but…..

	Total		Intermittent		Continuous		*p*
	n	%	n	%	n	%	
Severity of actual infection							
No sepsis	60	76.9	29	76.3	31	77.5	0.992
Sepsis	16	20.5	8	21.1	8	20.0	
Severe sepsis	2	2.6	1	2.6	1	2.5	

✓ No definition of sepsis

Clinical focus of actual infection							
Pneumonia	15	19.2	8	21.1	7	17.5	0.691
Tracheobronchitis	3	3.8	2	5.3	1	2.5	0.610¶
Urological	4	5.1	2	5.3	2	5.0	0.999¶
Abdominal	11	14.1	6	15.8	5	12.5	0.677
Biliary	17	21.8	6	15.8	11	27.5	0.211
Bacteremia with or without focus	3	3.8	1	2.6	2	5.0	0.999¶
Skin and soft tissue	15	19.2	7	18.4	8	20.0	0.860
Unknown	4	5.1	2	5.3	2	5.0	0.999¶
Others	6	7.7	4	10.5	2	5.0	0.425¶

Meropenem Dosing Based on a Population Pharmacokinetic–Pharmacodynamic Model in Elderly Patients with Infection of the Lower Respiratory Tract

- ✓ Prospective single-center open-label randomized controlled trial
- ✓ 79 elderly patients with an LRTI caused by Gram-negative bacilli
- ✓ Treatment
  - Meropenem according to a regimen decided by the attending physician.
  - Individualized meropenem therapy with a dosing strategy based on software developed from a meropenem population PK/PD model (prolonged 3h infusion)
- ✓ Primary endpoint: clinical response

Characteristics	All patients ($n = 79$)	Study group ($n = 39$)	Control group ($n = 40$)	Odds ratio (95% CI)	p value
Daily meropenem dose (g)	1.5 (1.5–3.0)	1.5 (1.5–2.0)	2.0 (1.5–3.0)	–	0.017
Duration of meropenem therapy (days)	9.0 (7.0–13.0)	10.0 (7.0–13.0)	9.0 (7.0–13.0)	–	0.665
Total meropenem dose (g)	18.0 (10.5–26.0)	15.0 (7.5–24.0)	19.0 (12.0–29.5)	–	0.090
$T_{>MIC}$	98.9 (76.3–100.0)	98.9 (77.1–100.0)	79.7 (52.3–100.0)	–	0.105
Clinical success	63 (79.7)	35 (89.7)	28 (70.0)	0.780 (0.620–0.981)	0.029
Bacteriologic success	52 (65.8)	28 (71.8)	24 (60.0)	0.836 (0.607–1.151)	0.269

Zhou et al, Drugs Aging 2017,34:115-21

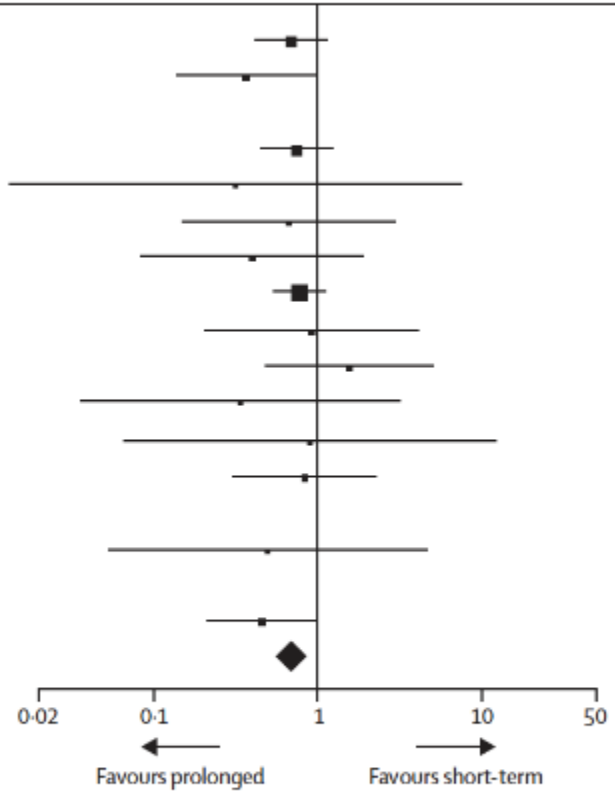
Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials

- ✓ RCT comparing mortality or clinical efficacy of prolonged (continuous or ≥3 h) versus short-term (≤60 min) infusion of antipseudomonal β-lactams for the treatment of patients with sepsis was eligible
- ✓ 2196 articles were identified and screened, and 22 studies (1876 patients) were included in the meta-analysis

Vardakas et al, Lancet Infect Dis 2018, 18:108-20

	Prolonged		Short-term		Weight	Risk ratio (95% CI)	Risk of bias A B C D E
	Events	Total	Events	Total			
Abdul-Aziz (2016)[15]	18	70	26	70	18·5%	0·69 (0·42–1·14)	
Angus (2000)[23]	3	10	9	11	4·8%	0·37 (0·14–0·98)	
Bao (2016)[24]	0	25	0	25	..	Not estimable	
Chytra (2012)[16]	21	120	28	120	18·1%	0·75 (0·45–1·24)	
Cotrina-luque (2016)[26]	0	40	1	38	0·5%	0·32 (0·01–7·55)	
Cousson (2005)[27]	2	8	3	8	2·1%	0·67 (0·15–2·98)	
Dulhunty (2013)[17]	2	30	5	30	1·9%	0·40 (0·08–1·90)	
Dulhunty (2015)[14]	39	212	52	220	33·9%	0·78 (0·54–1·13)	
Georges (2005)[28]	3	26	3	24	2·1%	0·92 (0·21–4·14)	
Lagast (1983)[30]	5	20	4	25	3·4%	1·56 (0·48–5·06)	
Lau (2006)[31]	1	130	3	132	0·9%	0·34 (0·04–3·21)	
Lips (2014)[37]	1	10	1	9	0·7%	0·90 (0·07–12·38)	
Rafati (2006)[35]	5	20	6	20	4·5%	0·83 (0·30–2·29)	
Roberts (2010)[36]	0	8	0	8	..	Not estimable	
Sakka (2007)[37]	1	10	2	10	0·9%	0·50 (0·05–4·67)	
Wang (2009)[38]	0	15	0	15	..	Not estimable	
Wang (2014)[39]	7	38	16	40	7·8%	0·48 (0·21–0·99)	
Total (95% CI)		792		805	100·0%	0·70 (0·56–0·87)	
Total events	108		159				

Heterogeneity: τ^2=0·00; χ^2=6·47, df=13 (p=0·93); I^2=0%
Test for overall effect: Z=3·25 (p=0·001)



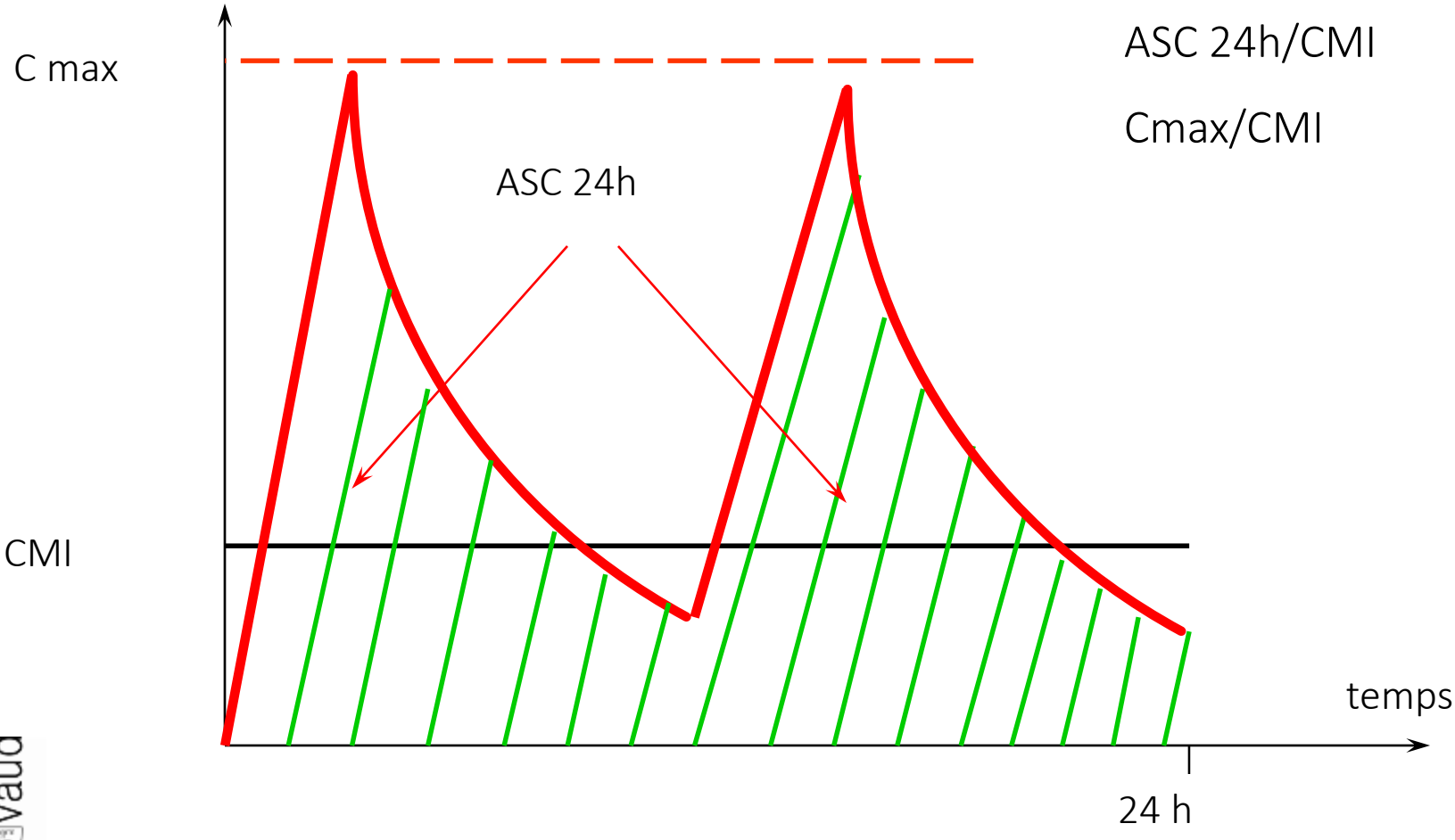
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)

High risk of bias
Low risk of bias
Unclear risk of bias

- ✓ Prolonged infusion of antipseudomonal β-lactams for the treatment of patients with sepsis was associated with significantly lower mortality than short-term infusion

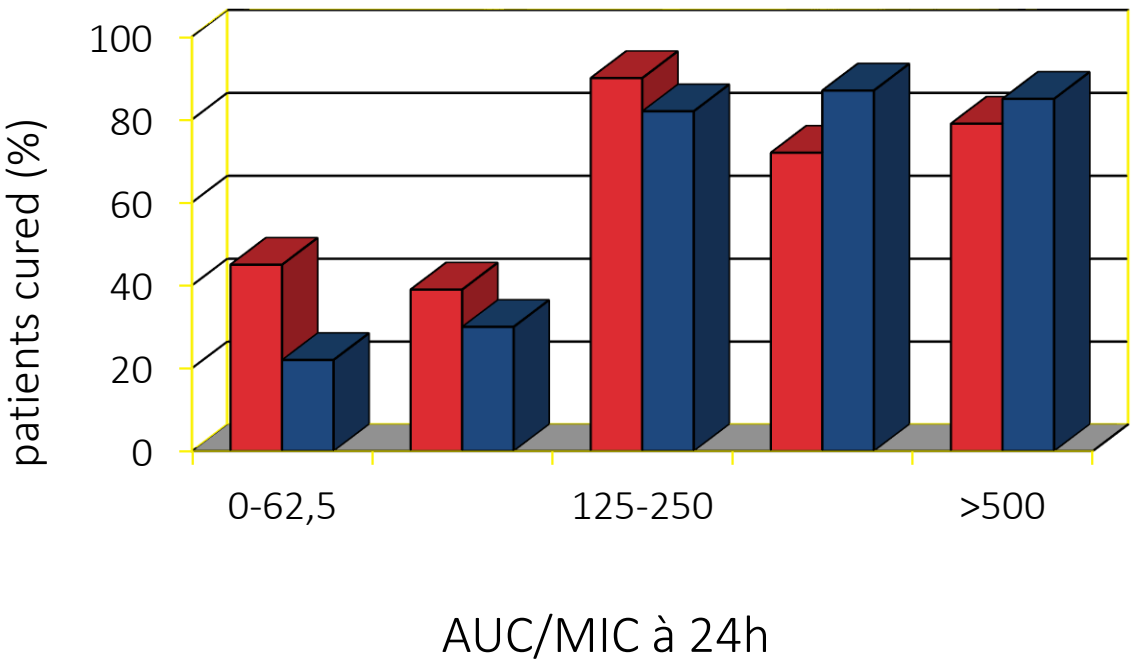
Vardakas et al, Lancet Infect Dis 2018, 18:108-20

Fluoroquinolones



Fluoroquinolones

Relation ASC 24h/CMI et efficacité



64 patients

ciprofloxacine

Clinical

Bacteriologic

Forrest, AAC 1993

Table 1. Relationship of the ratio of 24-h area under the curve to MIC (24-h AUC/MIC ratio) and monotherapy and combination therapy to the emergence of resistant organisms during therapy with β-lactams and ciprofloxacin.

Therapy	24-h AUC/MIC ratio	Patients with resistance/ total patients (%)		
		All patients	Ciprofloxacin treatment	β-Lactam treatment
Monotherapy	<100	14/17 (82)	12/14 (86)	2/3(67)
Monotherapy	⩾100	17/84 (20)	4/44 (9)	13/40 (31)
Combination	⩾100	1/27 (4)	0/16 (0)	1/27 (4)

Craig et al CID 2001

Table 2. Relationship of the 24-h area under the curve to MIC (24-h AUC/MIC ratio) to the emergence of resistant *Pseudomonas* and other gram-negative bacilli (GNB) during monotherapy with ciprofloxacin and β-lactams.

24-h AUC/MIC ratio	Patients with resistance/total patients (%)			
	Ciprofloxacin therapy		β-Lactam therapy	
	Pseudomonas	Other GNB	*Pseudomonas*	Other GNB
<100	10/10 (100)	2/4 (50)	2/3 (67)	
⩾100	2/8 (25)	2/28 (7)	2/3 (67)	10/28 (36)
P	.002	.07	2/3 (67)	

Craig et al CID 2001

Delafloxacin: a novel fluoroquinolone with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*

Eric R. Ocheretyaner[a,b] and Tae Eun Park[c]

Table 2. Susceptibility test interpretive criteria for delafloxacin [4].

	Minimum inhibitory concentrations (μg/mL)			Disk diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Staphylococcus aureus	≤0.25	0.5	≥1	≥23	20–22	≤19
Staphylococcus haemolyticus	≤0.25	0.5	≥1	≥24	21–23	≤20
Streptococcus pyogenes	≤0.06	–	–	≥20	–	–
Streptococcus agalactiae	≤0.06	0.12	≥0.25	–	–	–
Streptococcus anginosus Group	≤0.06	–	–	≥25	–	–
Enterococcus faecalis	≤0.12	0.25	≥0.5	≥21	19–20	≤18
Enterobacteriaceae	≤0.25	0.5	≥1	≥22	19–21	≤18
Pseudomonas aeruginosa	≤0.5	1	≥2	≥23	20–22	≤19

S = susceptible; I = intermediate; R = resistant.

Table 5. Clinical outcomes of delafloxacin for acute bacterial skin and skin-structure infections in Phase III trials [4,19,20,22].

Trial	Delafloxacin	Vancomycin 15 mg/kg + Aztreonam	Treatment difference (2-sided 95% CI)
Trial 1	**300-mg**	**intravenous**	
Total *N*	331	329	
Clinical response, *n* (%)	259 (78.2%)	266 (80.9%)	−2.6 (−8.8 to 3.6)
Success ITT, *n* (%)	270 (81.6%)	274 (83.3%)	−1.7 (−7.6 to 4.1)
Success CE, *n/N* (%)	232/240 (96.7%)	238/244 (97.5%)	−0.9 (−4.3 to 2.4)
Trial 2	**300-mg**	**intravenous and 450-mg oral**	
Total *N*	423	427	
Clinical response, *n* (%)	354 (83.7%)	344 (80.6%)	3.1 (−2 to 8.3)
Success ITT, *n* (%)	369 (87.2%)	362 (84.8%)	2.5 (−2.2 to 7.2)
Success CE, *n/N* (%)	339/353 (96%)	319/329 (97%)	−0.9 (−3.9 to 2)
Trial 3	**300-mg**	**intravenous**	
Total *N*	331	329	
Objective response, *n* (%)	259 (787.2%)	266 (80.9)	−2.6 (−8.78 to 3.57)
Investigator assessed cure, *n* (%)	172 (52%)	166 (50.5%)	1.5 (−6.11 to 9.11)

CI = confidence interval; ITT = intent-to-treat and includes all randomized patients; CE = clinically evaluable consisted of all ITT patients who had a diagnosis of ABSSSI, received at least 80% of expected doses of study drug, did not have any protocol deviations that would affect the assessment of efficacy and had investigator assessment at the follow-up visit.

Is fluoroquinolone monotherapy a useful alternative treatment for *Pseudomonas aeruginosa* bacteraemia?

- ✓ Retrospective study between Nov 2013 and Nov 2014 at Taipei Veterans General Hospital.
- ✓ 105 patients enrolled, 78 patients received beta-lactams and 27 received fluoroquinolones (20 with ciprofloxacin and 7 with levofloxacin)
- ✓ Primary bacteraemia (39.0%) and urinary tract infections (37.1%) were the most common sources of bacteraemia

Outcome	Total ($N=105$)	Fluoroquinolone group ($N=27$)	Beta-lactam group ($N=78$)	P value
28-day mortality	28 (26.7)	3 (11.1)	25 (32.1)	0.062
Bacteraemia-associated mortality	21 (20.0)	3 (11.1)	18 (23.1)	0.289
In-hospital mortality	35 (33.3)	5 (18.5)	30 (38.5)	0.097
Duration of definitive therapy, days[a]	11.5±4.9	11.6±4.6	11.5±5.1	0.731

- ✓ The 28-day mortality rate between the two groups stratified by APACHE II and Pitt bacteraemia scores showed no significant differences in each category
- ✓ Fluoroquinolone might be an alternative to beta-lactam as a definitive monotherapy for *P. aeruginosa* bacteraemia provided they are active in vitro

Wu et al, Infection 2018, 46:365

Table 4. New drugs and usual clinical dosage for new anti-*Pseudomonas* agents.

Drug	Current clinical indications	Usual clinical dosage for serious infections	Other comment
Cephalosporins			
Cefiderocol	Complicated UTI	2 g intravenous every 8 hours	-
Cephalosporin + β-lactamase inhibitor			
Ceftolozane-tazobactam	Complicated UTI and IAI	Loading dose 1.5 g or 3 g intravenous in 1 hour, followed by 1.5 g or 3 g intravenous every 8 hours	Extended infusion (over 3 h) 1.5 g or 3 g every 8 hours is recommended
Ceftazidime-avibactam	Complicated UTI and IAI, HAP and VAP and Gram-negative infections when other treatments might not work	Loading dose 2.5 g intravenous in 1 hour, followed by 2.5 g intravenous every 8 hours	Extended infusion (over 3 h) 2.5 g every 8 hours is recommended
Carbapenem + β-lactamase inhibitor			
Meropenem-vaborbactam	Complicated UTI	2 g/2 g intravenous every 8 hours	Not active against MDR strains
Imipenem-relebactam	Not yet approved by any regulatory authority	500 mg/250 mg intravenous every 6 hours	Not active against MDR strains
Aminoglycoside			
Plazomicin	Not yet approved by any regulatory authority	15 mg/kg every 24 hours	-

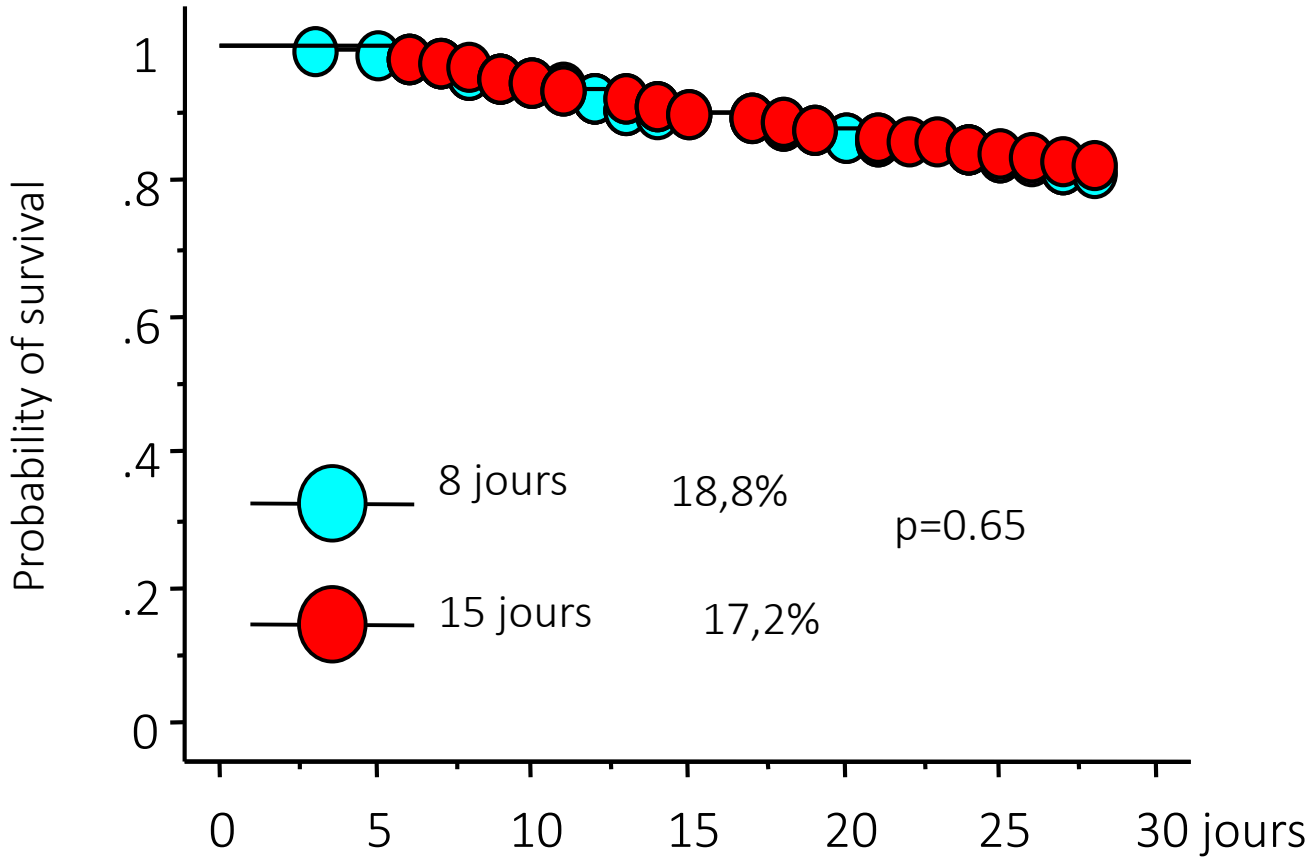
Bassetti M, Vena A, Croxatto A, Righi E, Guery B. Drugs in Context 2018; 7: 212527.

Plan

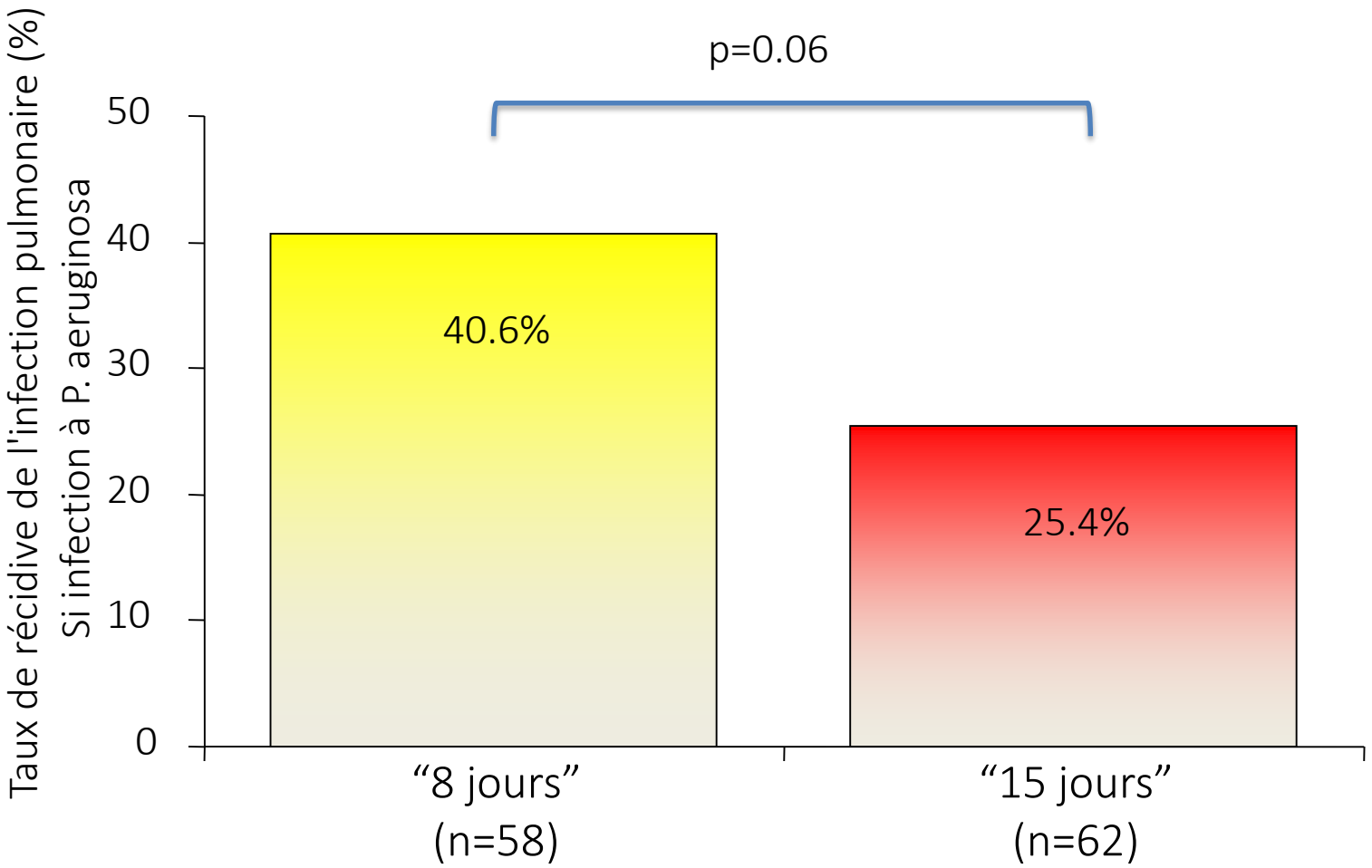
- ✓ Quelques éléments introductifs….
- ✓ Sensibilité aux principales molécules et nouvelles molécules
- ✓ PK/PD
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives

Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults

A Randomized Trial



Chastre et al, JAMA. 2003;290:2588-2598



Chastre et al, JAMA. 2003;290:2588-2598

Impact of the duration of antibiotics on clinical events in patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia: study protocol for a randomized controlled study

Adrien Bouglé[1*], Arnaud Foucrier[2], Hervé Dupont[3,4], Philippe Montravers[5,6], Alexandre Ouattara[7,8], Pierre Kalfon[9], Pierre Squara[10], Tabassome Simon[11,12], Julien Amour[1,12] and for the iDIAPASON study group

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- ✓ The impact of the duration of antibiotics on clinical events in patients with Pseudomonas aeruginosa ventilator-associated pneumonia (iDIAPASON) trial is a randomized, open-labeled non-inferiority controlled trial, conducted in 34 French intensive care units (ICUs), comparing two groups of patients with PA-VAP according to the duration (8 days or 15 days) of effective antibiotic therapy against PA.
- ✓ The primary outcome is a composite endpoint combining day 90 mortality and PA-VAP recurrence rate during hospitalization in the ICU.

- ✓ …..????

Bouglé *et al. Trials* (2017) 18:37

Antibiotic Therapy for *Pseudomonas aeruginosa* Bloodstream Infections: How Long Is Long Enough?

- ✓ Multicenter, observational, propensity-score–weighted cohort
  - 249 adults
  - uncomplicated *Pseudomonas aeruginosa* bacteremia,
- ✓ Treatment duration
  - Short-course: median 9 days (interquartile range [IQR], 8–10)
  - Long course: median 16 days (IQR, 14–17).
- ✓ Results: similar odds of recurrent infection or death within 30 days

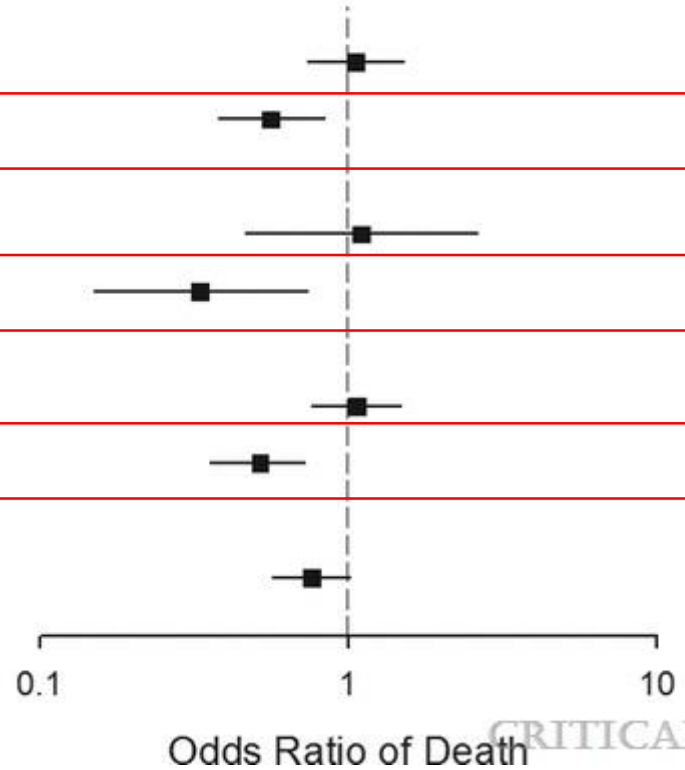
Fabre et al, Clinical Infectious Diseases 2019;69(11):2011–14

Plan

- ✓ Quelques éléments introductifs….
- ✓ Sensibilité aux principales molécules et nouvelles molécules
- ✓ PK/PD
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives

A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: A meta-analytic/meta-regression study

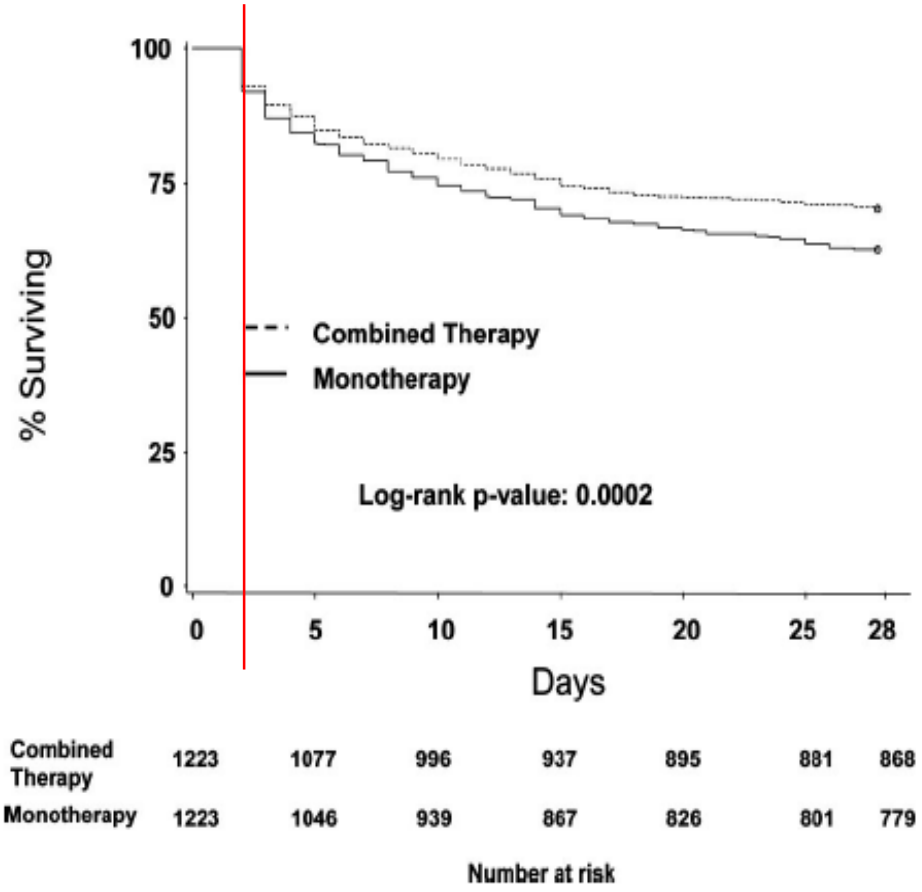
Group	Monotherapy Mortality (%)	Combination Therapy Mortality (%)	Odds Ratio	I^2 (%)	P-value
non-shock	86/680 (12.6)	96/666 (14.4)	1.06 (0.73-1.52)	13.7	.7721
shock	96/188 (51.1)	177/422 (41.9)	0.56 (0.39-0.83)	0.8	.0043
non-critically ill	23/313 (7.3)	35/339 (10.3)	1.10 (0.46-2.60)	45.3	.8321
critically ill	32/64 (50.0)	34/128 (26.6)	0.33 (0.15-0.74)	0	.0067
non-shock/non-critically ill	109/993 (11.0)	131/1005 (13.0)	1.06 (0.76-1.47)	19.1	.7178
shock/critically ill	128/252 (50.1)	211/550 (38.4)	0.51 (0.36-0.72)	0	.0002
overall	237/1245 (19.0)	342/1555 (22.0)	0.76 (0.57-1.02)	33.8	.0622



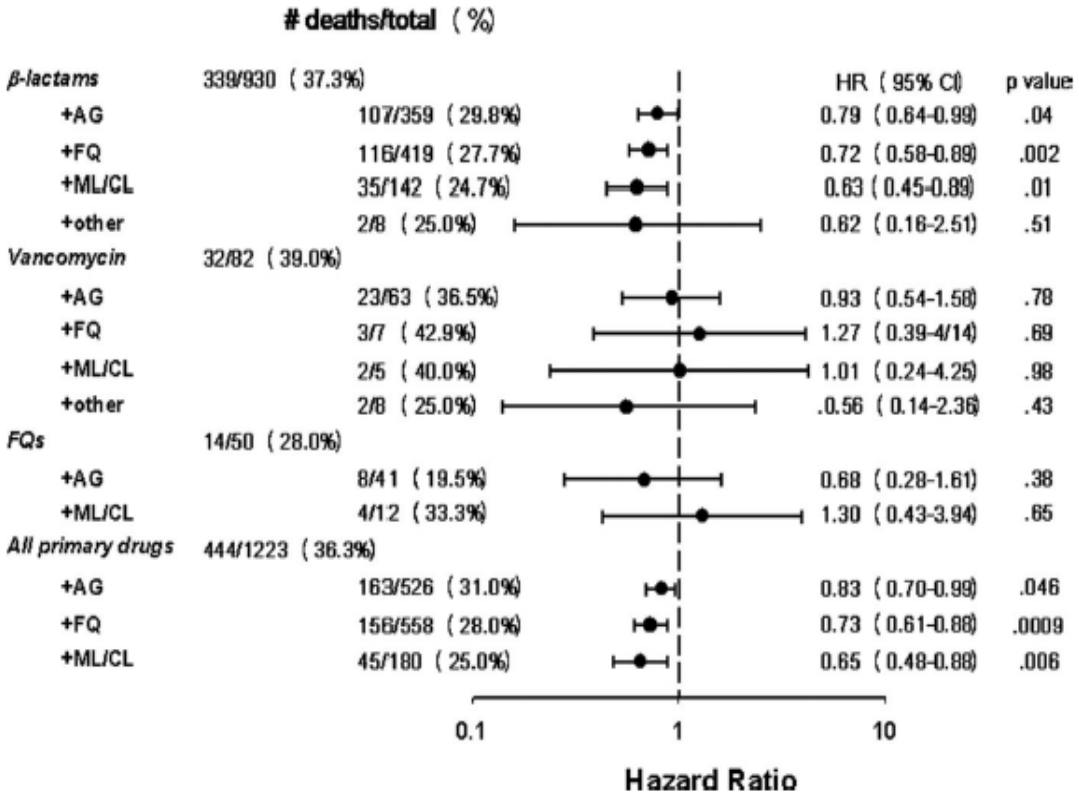
Kumar et al, Critical Care Medicine 38(8): 1651 1664.

Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis*

- ✓ Intensive care units of 28 academic and community hospitals in three countries between 1996 and 2007.
- ✓ A total of 4662 eligible cases of culture-positive, bacterial septic shock treated with combination or monotherapy from which 1223 propensity-matched pairs were generated.



Kumar et al, Critical Care Medicine 38(9): 1773 1785.



- ✓ The use of aminoglycoside (AG), fluoroquinolone (FQ), or a macrolide/clindamycin (ML/CL) in addition to a -lactam was associated with a reduced hazard ratio for death compared to -lactam alone.
- ✓ No other drug combinations demonstrated evidence of significant benefit.

Kumar et al, Critical Care Medicine 38(9): 1773 1785.

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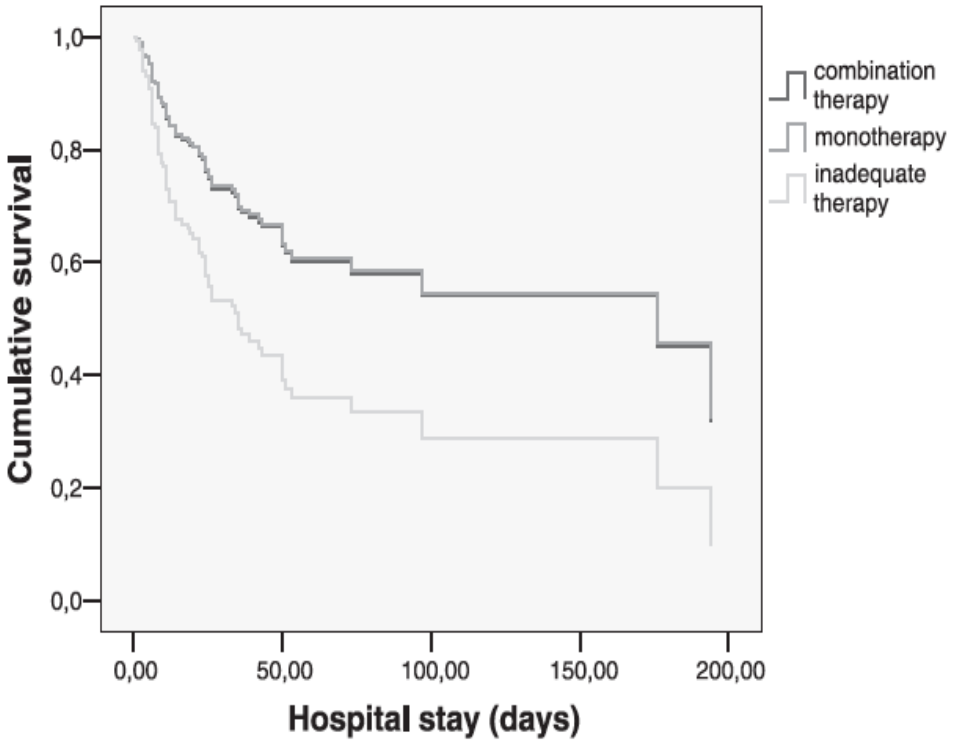
ETUDES CLINIQUES PAVM

canton de vaud

Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy

183 épisodes de VAP à *P. aeruginosa*

Tt final	Survivants n=106	Décédés n=77
APACHE II	18.7	19.8
Choc septique	38 (35.8)	52 (67.5)
Monothérapie	22 (19.9)	12 (15.6)
Association	84 (81.1)	60 (84.4)



Garnacho-Montero et al, Crit Care Med 2007

Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy

Table 5. Variables independently associated with mortality using Cox proportional regression analysis

	aHR	95% CI	*p*
Age	1.02	1.01–1.04	.005
Chronic cardiac failure	1.90	1.04–3.47	.035
Effective empirical therapy			.02
Combined therapy	1		
Monotherapy	0.90	0.50–1.63	.73
Inappropriate therapy	1.85	1.07–3.10	.02

aHR, adjusted hazard ratio; CI, confidence interval.

Garnacho-Montero et al, Crit Care Med 2007

Empiric antibiotic therapy for suspected ventilator-associated pneumonia: A systematic review and meta-analysis of randomized trials

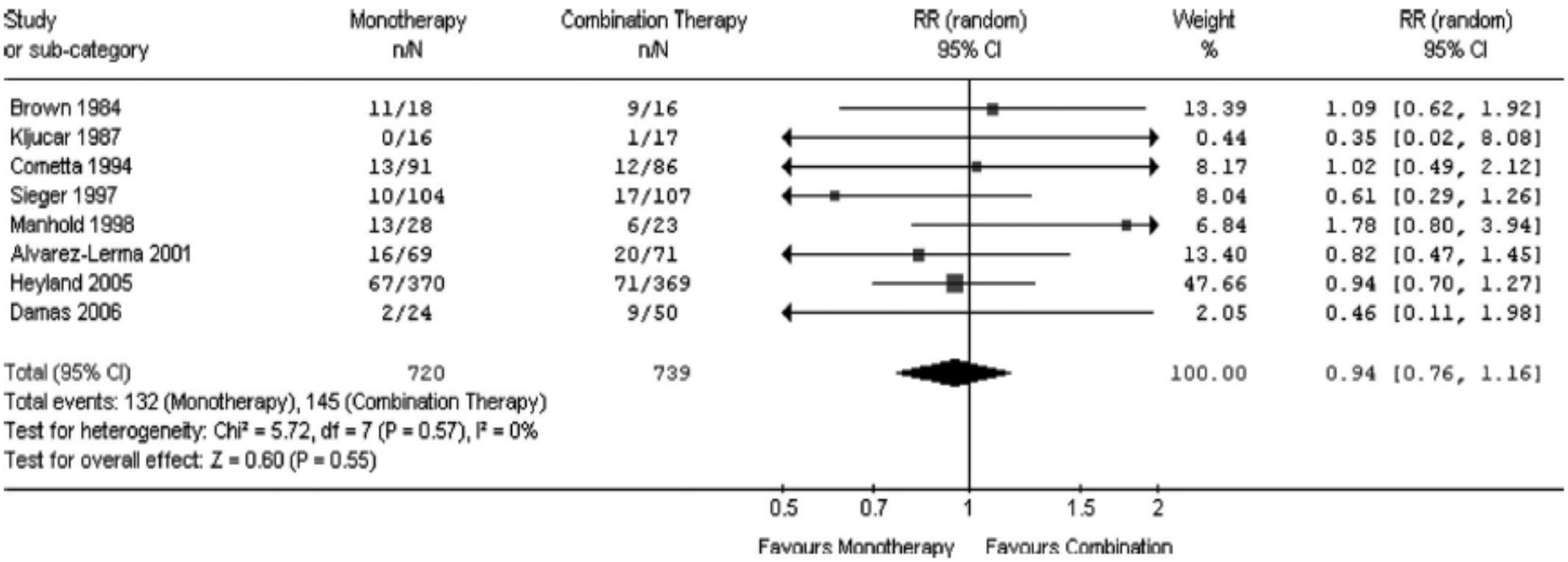


Figure 4. Mortality in pooled trials comparing monotherapy to combination therapy. There is no evidence that combination therapy improves survival when compared with monotherapy. *RR*, relative risk; *CI*, confidence interval.

Aarts et al, Crit Care Med 2008

Impact of combination therapy and early de-escalation on outcome of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*

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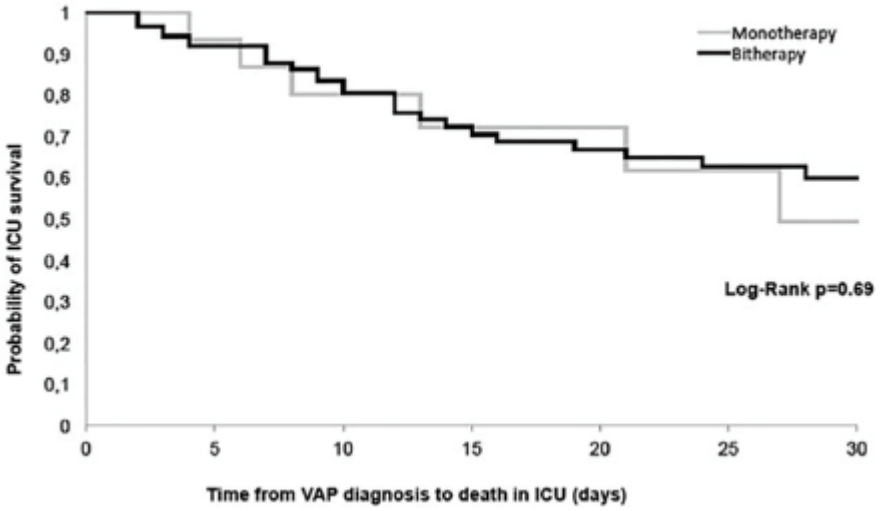
- ✓ Etude rétrospective de cohorte 1994-2014
  - 100 patients: 85 association/15 monothérapie, 9 inadequates
  - SAPS 2: 46, 45% choc, Colonisation 60%, Multi-R 31%
  - Mortalité associée (HR)
    - SAPS>40: 3.08
    - Choc: 4.71



- ✓ L'association augmente la probabilité d'antibiothérapie appropriée sans impact sur la mortalité

Deconinck et al, Infection 2017, 49:396

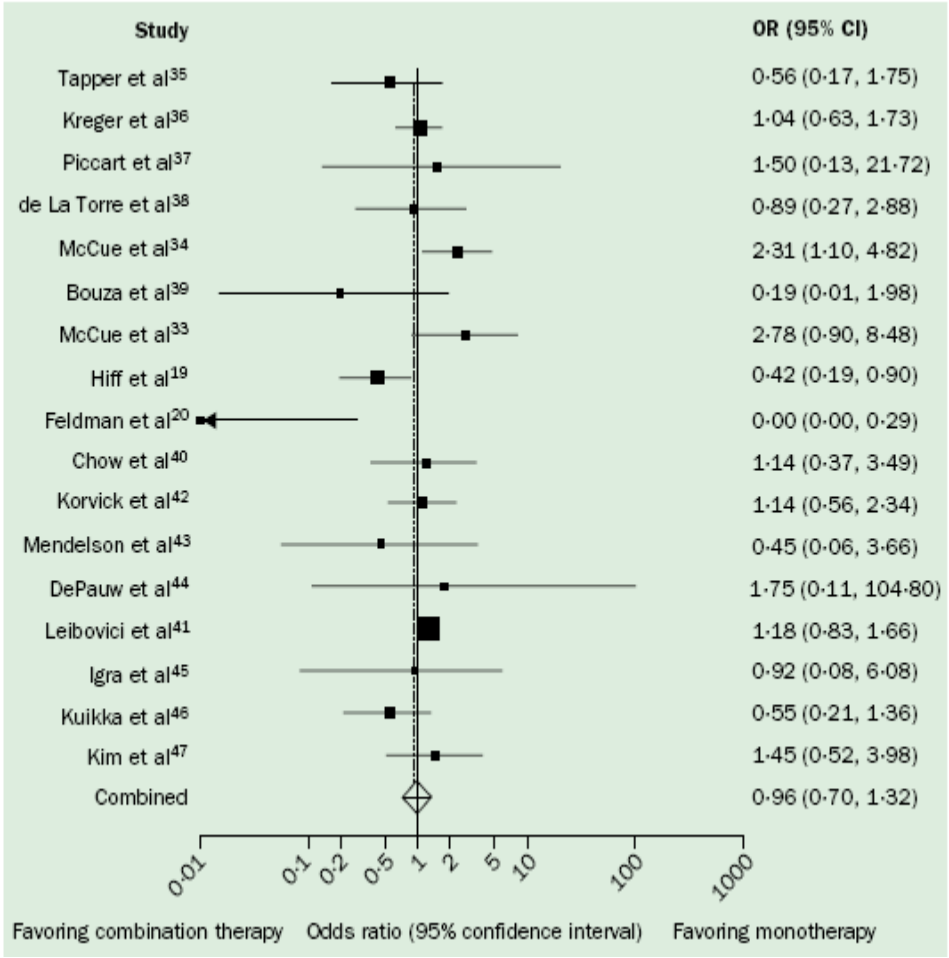
Pseudomonas aeruginosa Ventilator-associated Pneumonia Predictive Factors of Treatment Failure

- ✓ 314 patients avec 393 VAP à P. aeruginosa
- ✓ 112 échec de traitement
- ✓ Facteurs associés avec un échec de traitement
  - Age (P . 0.02);
  - Présence d'au moins une pathologie chronique (P . 0.02);
  - Limitation de soins (P . 0.0004);
  - Score de défaillance d'organe élevé (P , 0.0001);
  - Bacteremie à P. aeruginosa (P .0.003);
  - previous use of FQ before the first PA-VAP (P . 0.0007).
- ✓ Risque d'échec non influencé par le profil de résistance de la souche ou par la prescription d'une association
- ✓ Risque d'échec diminue si le Tt initial inclus une fluoroquinolone
- ✓ Nécessité d'évaluer le potentiel bénéfice des quinolones dans une étude randomisée

Planquette et al, Am J Respir Crit Care Med 2013

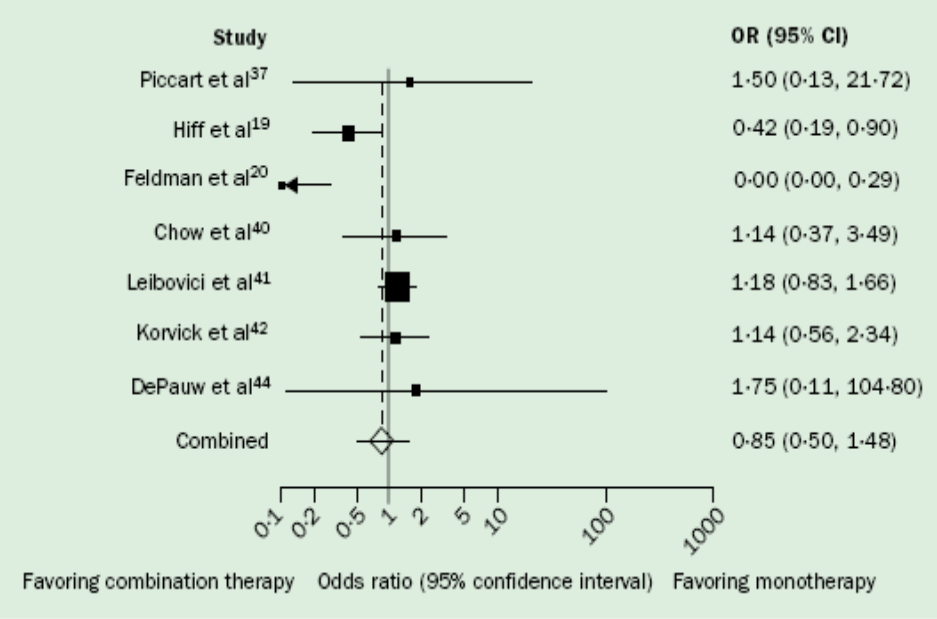
ETUDES CLINIQUES bactériémies

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



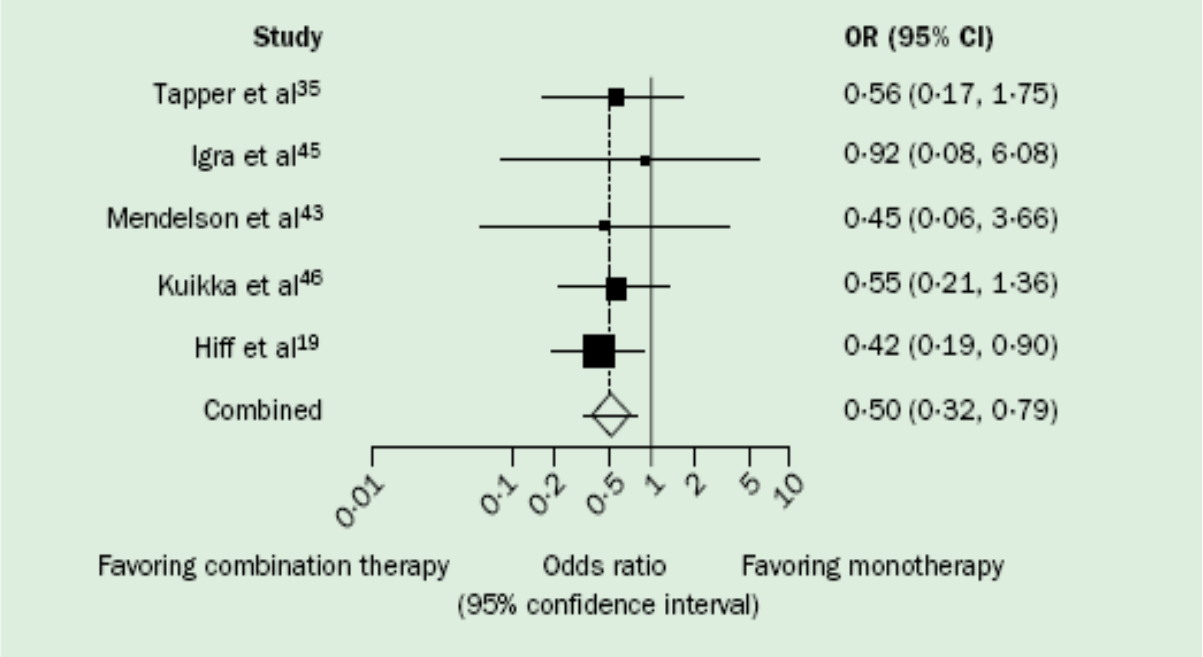
Safdar et al, Lancet Inf Dis 2004

Etudes prospectives uniquement



Safdar et al, Lancet Inf Dis 2004

Bactériémies à *P. aeruginosa*



MAIS
Dans 4 études sur 5 aminosides en monothérapie

Adéquation?

Safdar et al, Lancet Inf Dis 2004

Risk factors associated with unfavorable short-term treatment outcome in patients with documented *Pseudomonas aeruginosa* infection

- ✓ Etude rétrospective monocentrique
  - Bactériémies et pneumonies
  - 117 patients
    - 40 (34%) évolution favorable à J5
    - 77 (66%) évolution défavorable à J5

Monothérapies	Associations
Pip-Tazobactam Ceftazidime Meropenem Cefepime Tobramycine Ciprofloxacine	Pip-Taz+Cipro Mero+Cipro Cefta+Cipro

	OR	p
Vasopresseur	6	0.0003
Admission direct USI	2.9	0.052
≥2 Atb actifs	0.39	0.022

DiMondi et al Int J Clin Pharm 2015

Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia; retrospective study of impact of combination antimicrobial therapy

Youn Jeong Kim[1], Yoon Hee Jun[1], Yang Ree Kim[1], Kang Gyun Park[2], Yeon Joon Park[2], Ji Young Kang[3*] and Sang Il Kim[1]

- ✓ Retrospective study analyzed data of 234 patients with *P. aeruginosa* bacteremia at a 1,200-bed tertiary teaching university hospital in South Korea between January 2010 and December 2012

Table 4 Comparison of outcomes according to adequacy of antibiotics

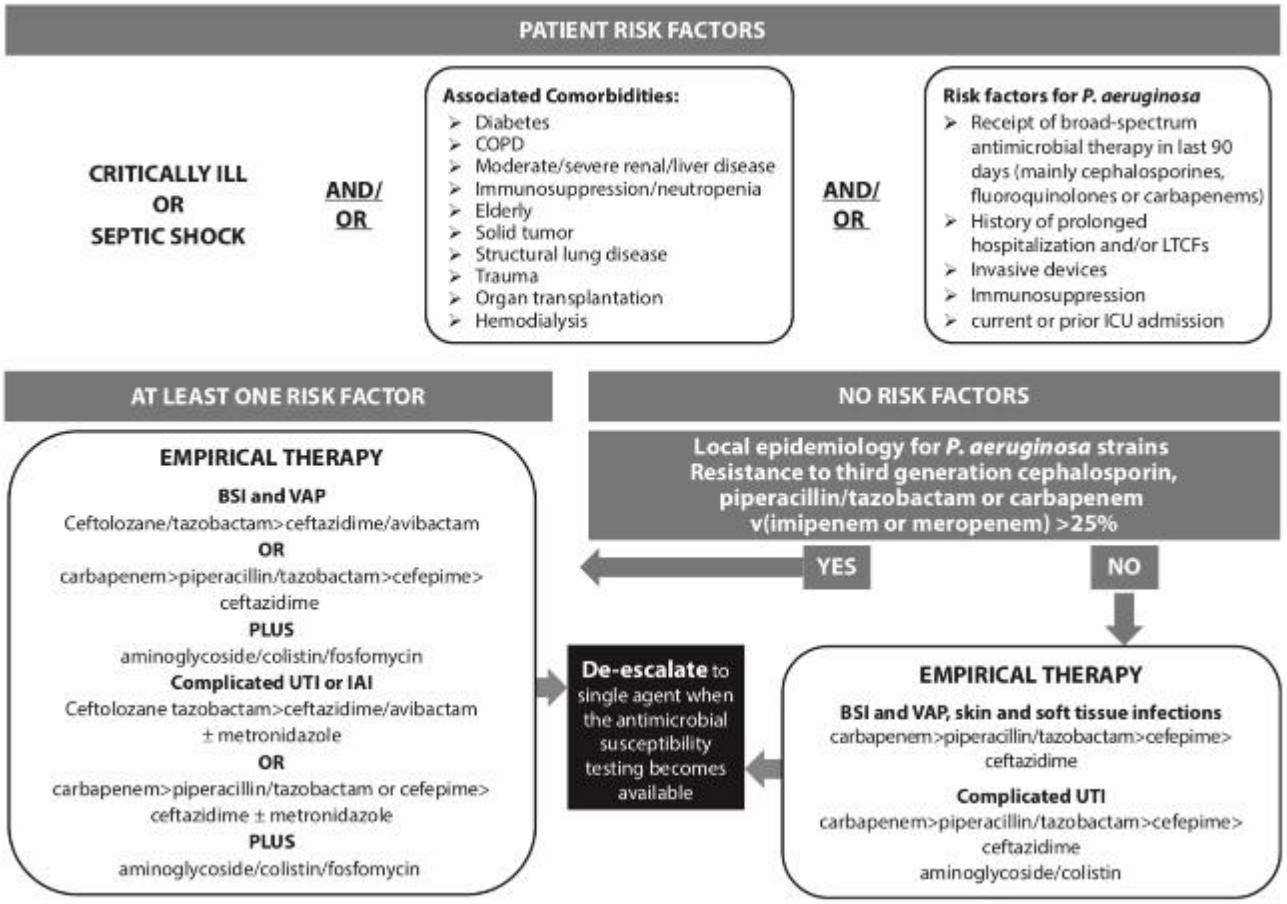
			Survivor (n = 182)	Non survivor (n = 52)	P value
All patients (n = 234)	Empirical	Combination	31 (17.0%)	7 (13.5%)	0.74
		Monotherapy	78 (42.9%)	25 (48.1%)	
		Inappropriate	31 (17.0%)	7 (13.5%)	
	Targeted	Combination	36 (19.8%)	6 (11.5%)	0.31
		Monotherapy	109 (59.9%)	32 (61.5%)	
		Inappropriate	37 (20.3%)	14 (26.9%)	
Patients with neutropenia (n = 54)	Empirical	Combination	19 (52.7%)	4 (22.2%)	0.001
		Monotherapy	16 (44.4%)	7 (38.8%)	
		Inadequate	1 (2.7%)	7 (38.8%)	
	Targeted	Combination	21 (58.3%)	10 (55.5%)	0.01
		Monotherapy	14 (38.8%)	3 (16.7%)	
		Inadequate	1 (2.7%)	5 (27.7%)	

Kim et al, BMC Infectious Diseases 2014,14:161

How to manage *Pseudomonas aeruginosa* infections

Matteo Bassetti MD, PhD[1], Antonio Vena MD[1], Antony Croxatto PhD[2], Elda Righi MD, PhD[1], Benoit Guery MD, PhD[3]

Figure 1. Clinical approach to patients with suspected *P. aeruginosa* infection.



BSI: Bloodstream infection; COPD: Chronic obstructive pulmonary disease; IAI: Intra-abdominal infections; LTCFs: Long term care facilities; UTI: Urinary tract infection; VAP: Ventilator associated pneumonia.

High risk clones

Colistin plus meropenem combination is synergistic in vitro against extensively drug-resistant *Pseudomonas aeruginosa*, including high-risk clones

María M. Montero[a,*], Sandra Domene Ochoa[a], Carla López-Causapé[b], Brian VanScoy[c], Sonia Luque[d], Luisa Sorlí[a], Núria Campillo[d], Eduardo Padilla[e], Núria Prim[e], Concepción Segura[e], Virginia Pomar[f], Alba Rivera[f,g], Santiago Grau[d], Paul G. Ambrose[c], Antonio Oliver[b], Juan P. Horcajada[a,*]

Journal of Global Antimicrobial Resistance 18 (2019) 37–44

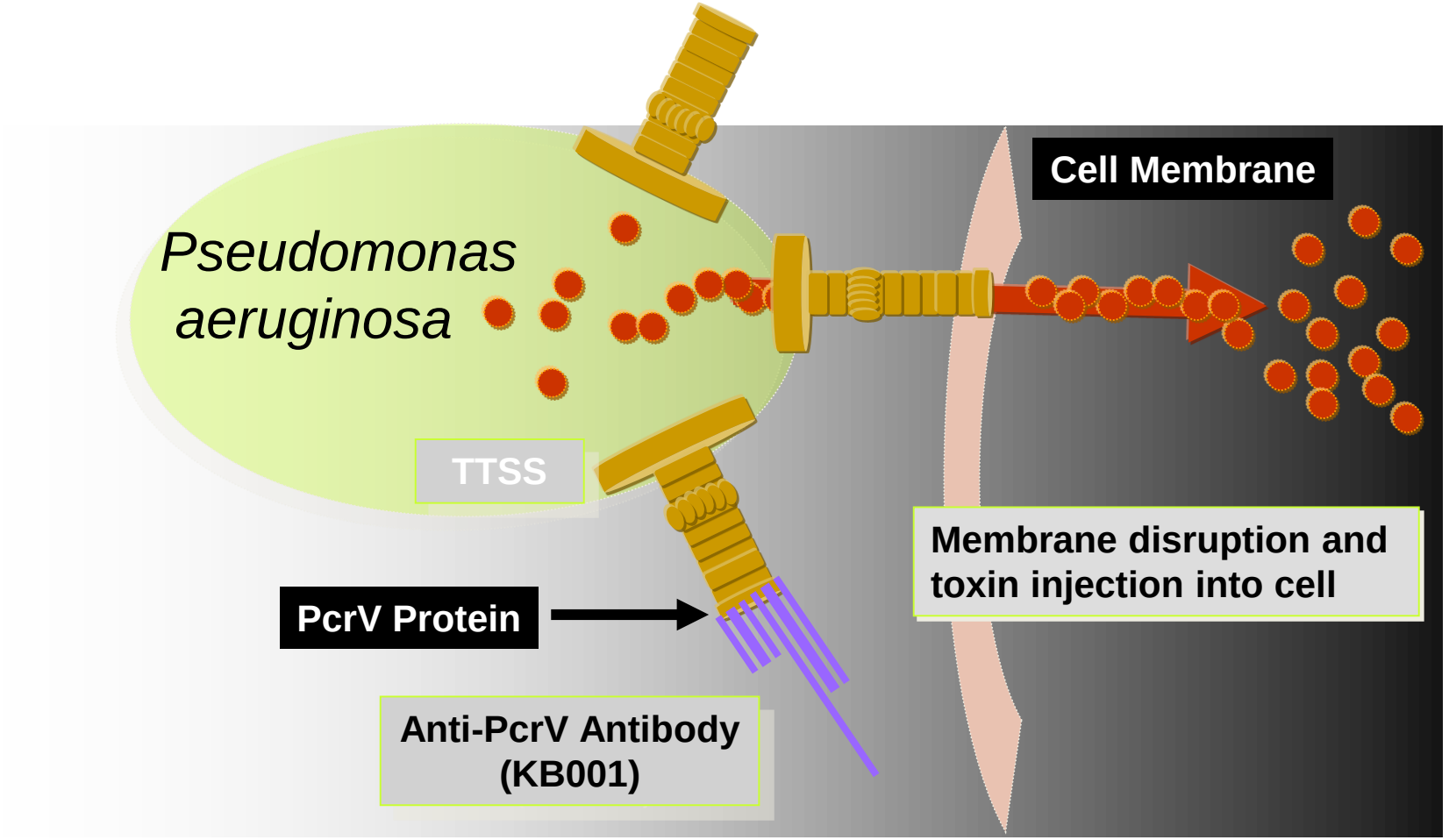
Efficacy of Ceftolozane-Tazobactam in Combination with Colistin against Extensively Drug-Resistant *Pseudomonas aeruginosa*, Including High-Risk Clones, in an *In Vitro* Pharmacodynamic Model

María Montero,[a] Sandra Domene Ochoa,[a] Carla López-Causapé,[b] Brian VanScoy,[c] Sonia Luque,[d] Luisa Sorlí,[a] Núria Campillo,[d] Ariadna Angulo-Brunet,[b] Eduardo Padilla,[e] Núria Prim,[e] Virginia Pomar,[f] Alba Rivera,[g] Santiago Grau,[d] Paul G. Ambrose,[c] Antonio Oliver,[b] Juan P. Horcajada[a]

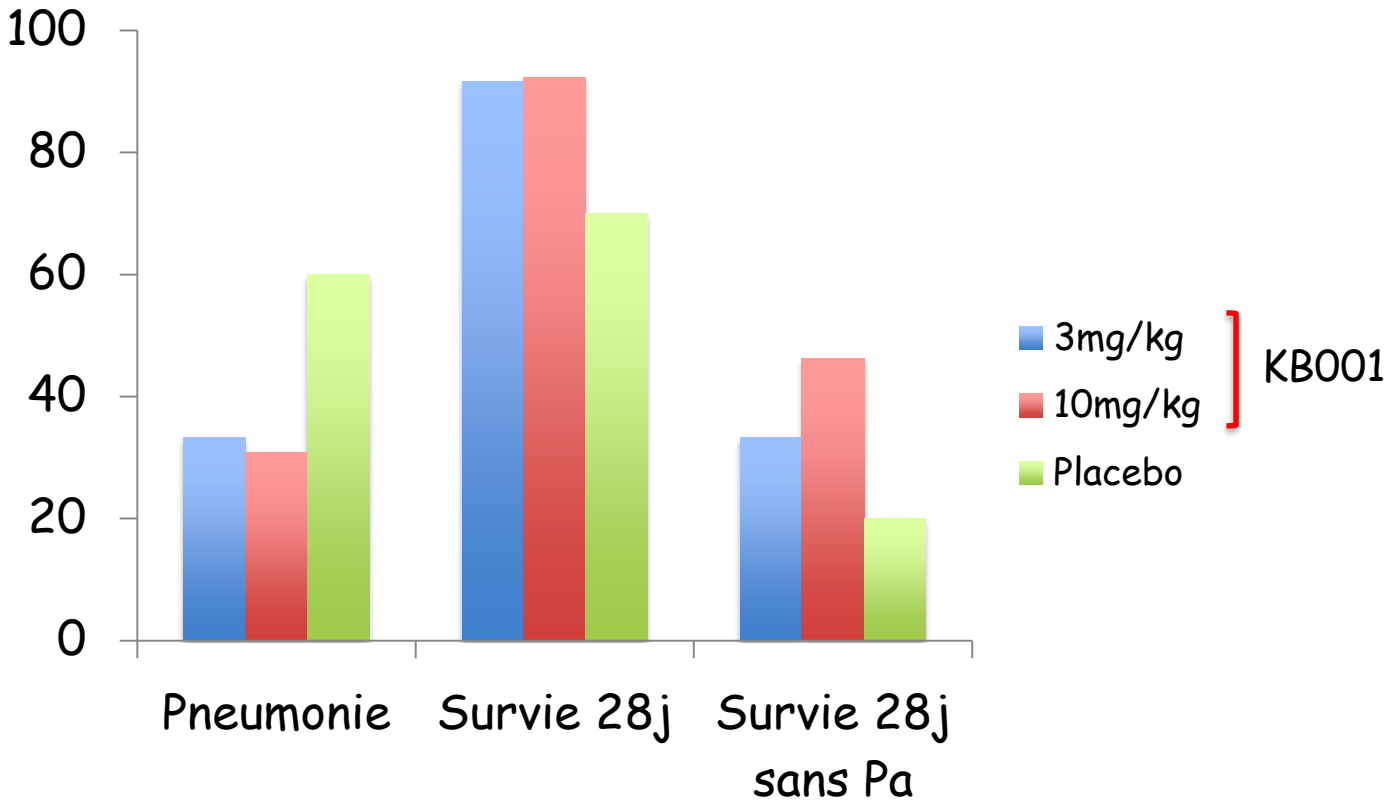
Antimicrobial Agents and Chemotherapy, April 2020 Vol 64 Issue 4 e02542-19

Plan

- ✓ Quelques éléments introductifs….
- ✓ Sensibilité aux principales molécules et nouvelles molécules
- ✓ PK/PD
- ✓ Durée
- ✓ Associations
- ✓ Thérapeutiques alternatives


Cell Membrane
Pseudomonas aeruginosa
TTSS
Membrane disruption and toxin injection into cell
PcrV Protein
Anti-PcrV Antibody (KB001)

Safety and pharmacokinetics of an anti-PcrV PEGylated monoclonal antibody fragment in mechanically ventilated patients colonized with *Pseudomonas aeruginosa:* A randomized, double-blind, placebo-controlled trial*



Francois et al, Crit Care Med 2012; 40: 2320–2326

Anti-PcrV Antibody in Cystic Fibrosis: A Novel Approach Targeting *Pseudomonas aeruginosa* Airway Infection

- ✓ Two cohorts of 12 subjects were planned: each randomized 2:1 to receive a single intravenous (IV) infusion of KB001 or placebo.
- ✓ Subjects randomized to receive KB001 received 3 mg/kg in the first cohort and 10 mg/kg in the second cohort.

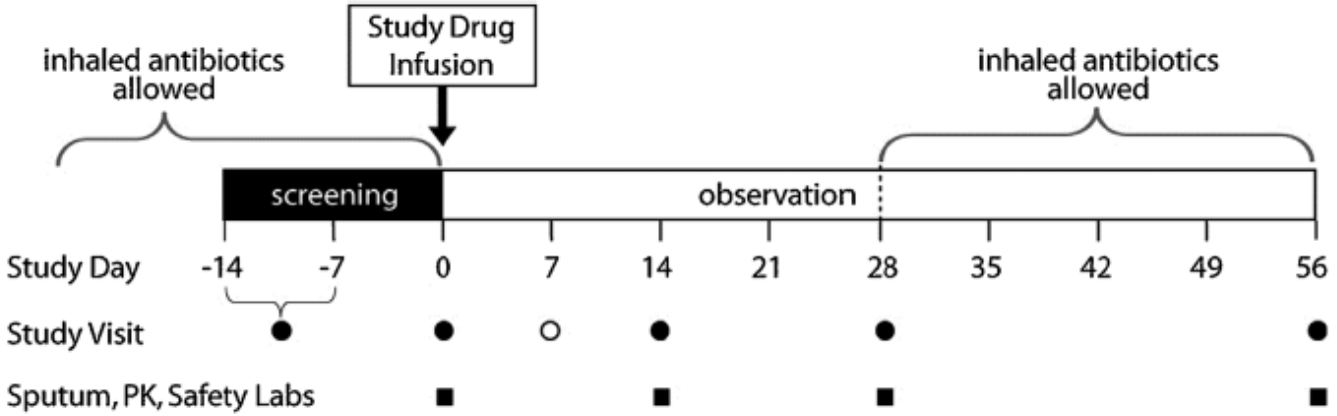
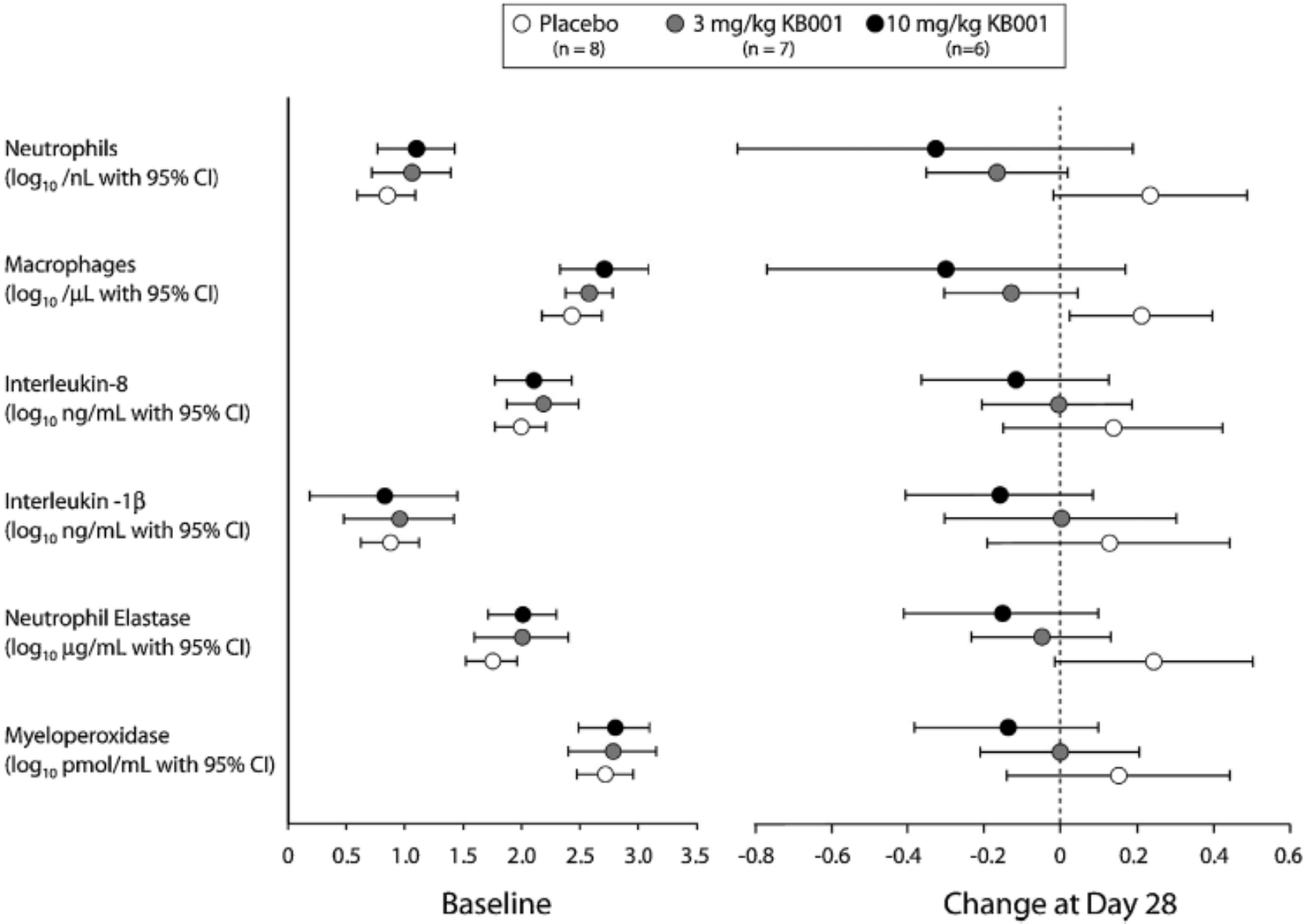


Fig. 1. Schematic of study design. On Day 0 subjects were randomized to receive KB001 or placebo. Filled circles, clinical study visits. Open circle, telephone interview. Filled squares, times of sample collection for safety and efficacy analyses.

Milla et al, Pediatric Pulmonology 2014,49:650-58



Milla et al, Pediatric Pulmonology 2014,49:650-58

Microbiome and Immune system

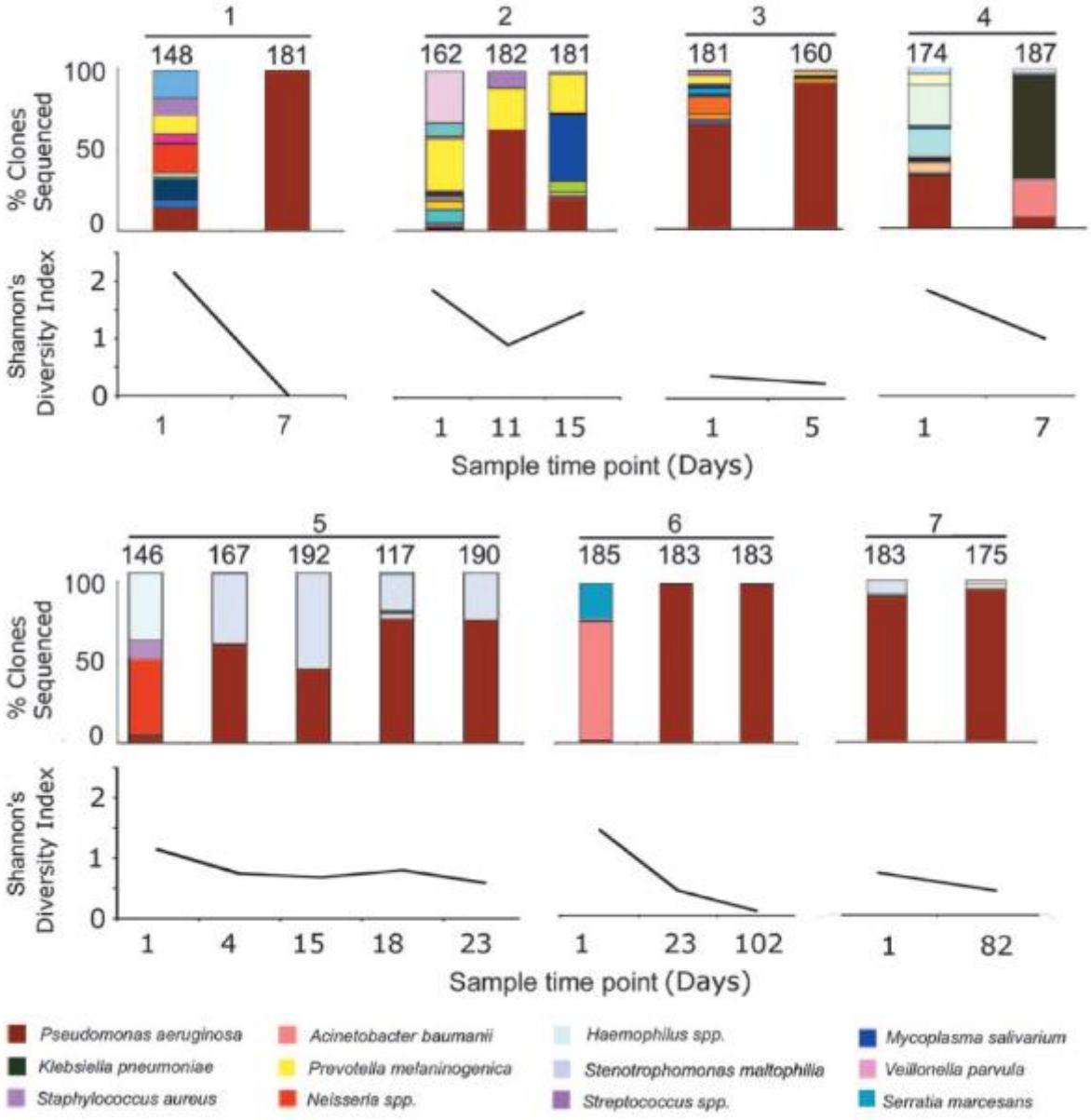
Loss of Bacterial Diversity during Antibiotic Treatment of Intubated Patients Colonized with *Pseudomonas aeruginosa*▽

TABLE 1. Patient information and antimicrobial treatment

Patient	No. of days after enrollment (sample no.)	Sex	Patient age	Antimicrobial treatment	
				Within 24 h before study enrollment	Following sampling (sensitivity[a])
1	1 (1)	Female	57 yr	Cefazolin, piperacillin-tazobactam	Piperacillin-tazobactam (S), fluconazole, cefazolin
	7 (2)				Cefazolin (S), fluconazole (S), levofloxacin (S)
2	1 (1)	Male	79 yr	Cefazolin, ceftazidime	Antifungal, ceftazidime (S), vancomycin
	11 (2)				Ceftazidime (R), vancomycin, piperacillin-tazobactam (S), ciprofloxacin (S)
	15 (3)				Vancomycin, piperacillin-tazobactam, ciprofloxacin
3	1 (1)	Female	54 yr	None	Ciprofloxacin (S)
	5 (2)				Ciprofloxacin
4	1 (1)	Male	55 yr	None	Piperacillin-tazobactam, vancomycin
	7 (2)				Piperacillin-tazobactam
5	1 (1)	Female	85 yr	Clindamycin	Clindamycin, piperacillin-tazobactam (S)
	4 (2)				Piperacillin-tazobactam (S), vancomycin, ciprofloxacin (S)
	15 (3)				None
	18 (4)				None
	23 (5)				None
6	1 (1)	Female	45 yr	None	Meropenem (I), fluconazole, linezolid
	23 (2)				Tobramycin(S), imipenem (I), cefpirome, cefazolin, cefepime (I)
	102 (3)				Timentin, trimethoprim-sulfamethoxazole, imipenem, vancomycin, fluconazole, cefepime, cefpirome, amphotericin B, tobramycin
7	1 (1)	Female	2 mo	Ampicillin, gentamicin, trimethoprim-sulfamethoxazole	Ampicillin (R), gentamicin
	82 (2)				Gentamicin (S)

[a] S, sensitive; R, resistant; I, indeterminate.

Flanagan et al, J Clin Microbiol 2007, 1954-62

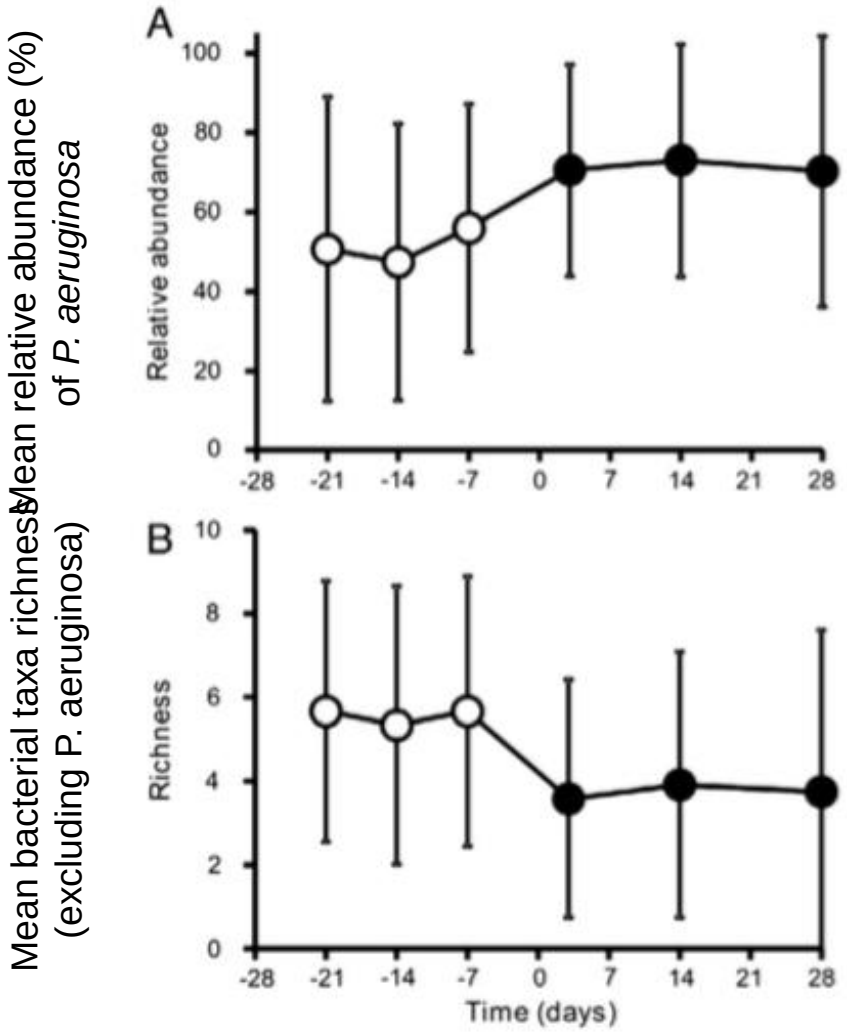


We hypothesize that reduced microbial diversity under antibiotic selection in the airways may contribute directly to pathogen selection through the loss of microbial competition.

Flanagan et al, J Clin Microbiol 2007, 1954-62

Impact of antibiotic treatment for pulmonary exacerbations on bacterial diversity in cystic fibrosis

- ✓ Relative abundance of viable *P. aeruginosa* and non-pseudomonal species in sputa from 12 adult CF subjects
- ✓ Time points:
  - 21, 14, and 7 days prior to antibiotics
  - day 3 of treatment, the final day of treatment
  - 10–14 days afterward

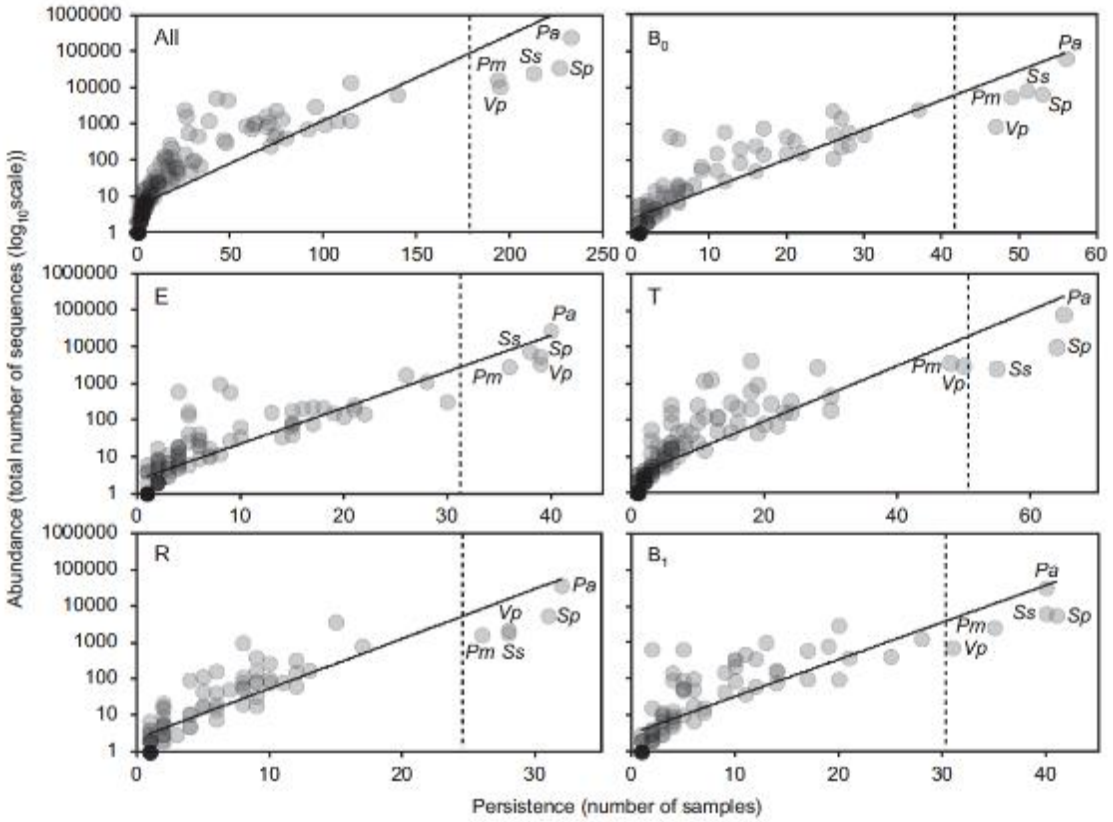


Daniels et al, J of Cystic Fibrosis 2013,12:22-28

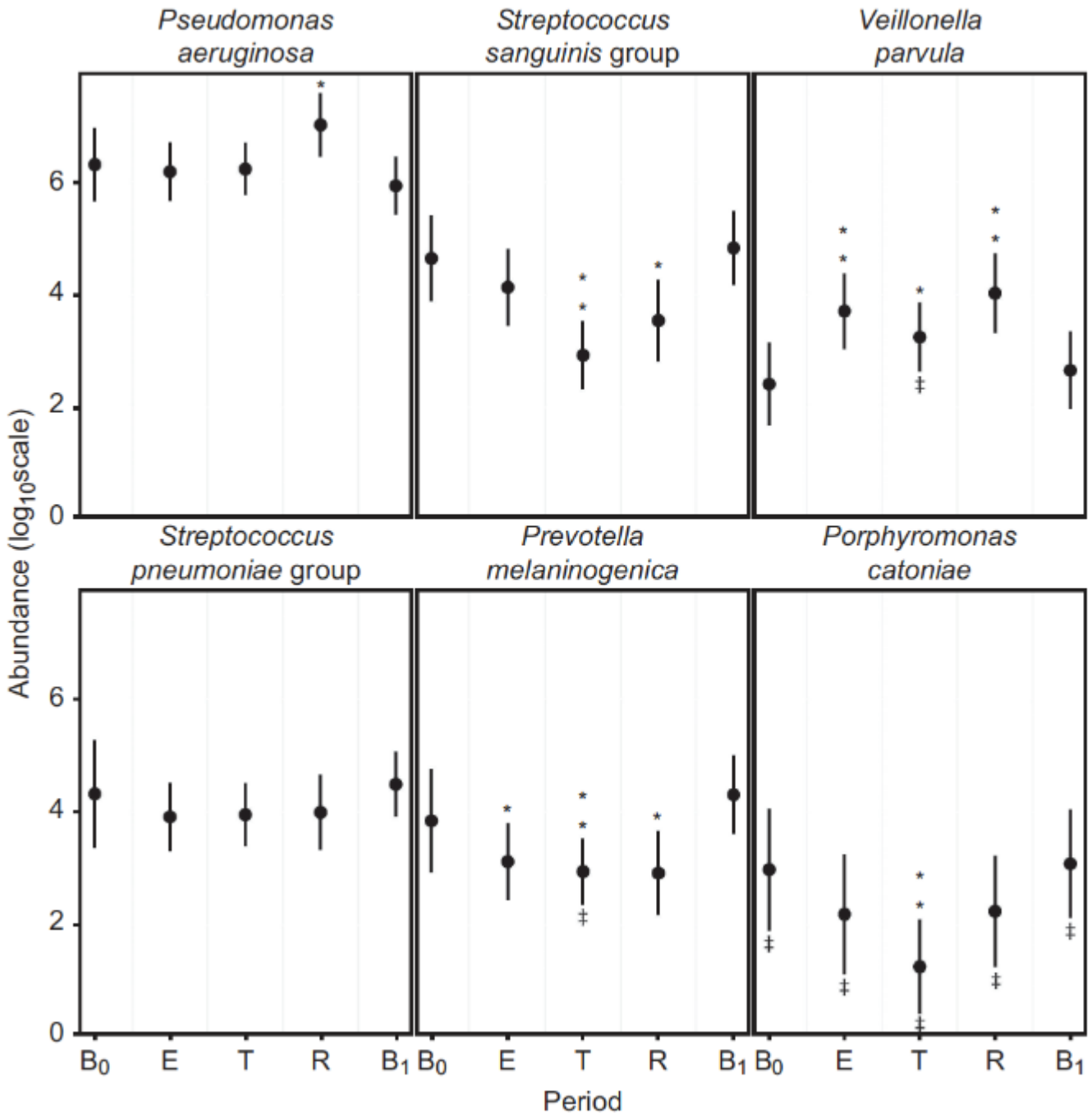
Respiratory microbiota resistance and resilience to pulmonary exacerbation and subsequent antimicrobial intervention

Leah Cuthbertson[1,2], Geraint B Rogers[3], Alan W Walker[4,5], Anna Oliver[1], Laura E Green[6], Thomas WV Daniels[7], Mary P Carroll[7], Julian Parkhill[4], Kenneth D Bruce[2] and Christopher J van der Gast[1]

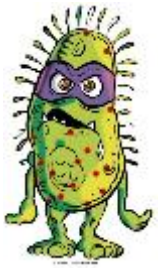
- ✓ (B0) baseline pre-CFPE (n = 56)
- ✓ (E) CFPE, 30 days prior to treatment (n = 41)
- ✓ (T) CFPE treatment period (n = 67)
- ✓ (R) recovery, 30 days post-CFPE treatment (n = 32)
- ✓ (B1) baseline post-CFPE (n = 41)



Cuthbertson et al, ISME Journal 2016,10:1081-91

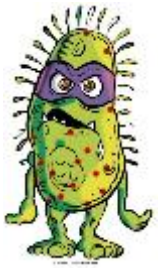


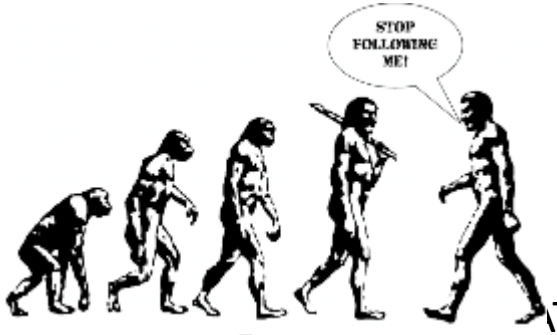
Cuthbertson et al, ISME Journal 2016,10:1081-91



ATB

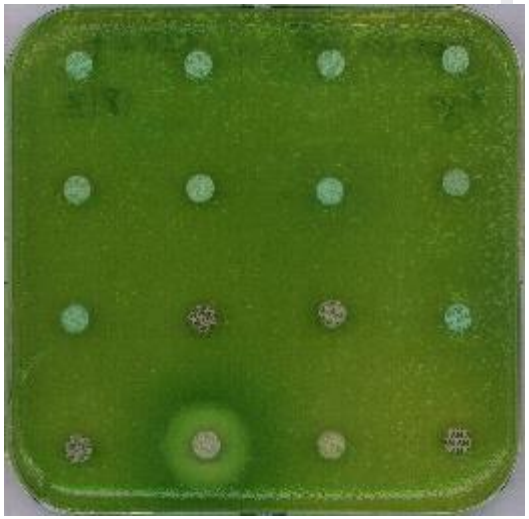
-4,5 Milliards -3,5 Milliards -5 Millions -80

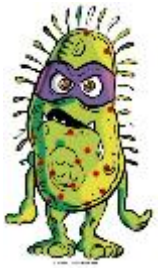


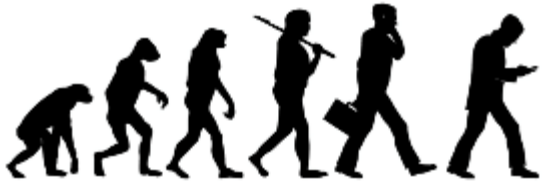


ATB TOTO-R

-4,5 Milliards -3,5 Milliards -5 Millions -80 -15







ATB TOTO-R

-4,5 Milliards -3,5 Milliards -5 Millions -80 -15

CIBLER LA BACTERIE :
NI SUFFISANT
NI POSSIBLE