Diplôme d'Université d'Antibiothérapie et Chimiothérapie Anti-Infectieuse

Traitement des infections à *Pseudomonas aeruginosa*

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Opportunistic Infection, Immunity, Environment & Lung Diseases (OpInfIELD) | Univ. Lille - CNRS - Inserm - IPL - CIIL

Opportunistic Infection
Immunity
Environment
& Lung Diseases

Inserm
La science pour la santé
From science to health

Université de Lille

cnrs

Institut Pasteur de Lille
Vivre mieux, plus longtemps

CHU LILLE

Déclaration d’intérêts

- Comité scientifique : MSD
- Comités de pilotage : MSD, Fresenius
- Investigateur : KaloBios, Biomérieux, Méditor, Fresenius
- Intervenant : Pfizer, MSD
- Congrès : Fresenius, LFB, Pfizer, MSD, Astellas, Gilead
- https://www.transparence.sante.gouv.fr

Infections nosocomiales réanimation : EPIC II 2009 (Monde)

	All	Western Europe
No. (%)	7087 (51.4)	3683 (49)
Site of infection		
Respiratory tract	4503 (63.5)	2332 (63.3)
Abdominal	1392 (19.6)	778 (21.1)
Bloodstream	1071 (15.1)	546 (14.8)
Renal/urinary tract	1011 (14.3)	411 (11.2)
Skin	467 (6.6)	242 (6.6)
Catheter-related	332 (4.7)	171 (4.6)
CNS	208 (2.9)	100 (2.7)
Others	540 (7.6)	289 (7.8)

	All	Western Europe
No. (%)	7087 (51.4)	3683 (49)
Microorganisms		
Positive isolates	4947 (69.8)	2678 (72.7)
Gram-positive	2315 (46.8)	1311 (49.0)
Staphylococcus aureus	1012 (20.5)	525 (19.6)
MRSA	507 (10.2)	233 (8.7)
S epidermidis	535 (10.8)	301 (11.2)
Streptococcus pneumoniae	203 (4.1)	127 (4.7)
VSE	352 (7.1)	250 (9.3)
VRE	186 (3.8)	113 (4.2)
Other	319 (6.4)	184 (6.9)
Gram-negative	3077 (62.2)	1573 (58.7)
Escherichia coli	792 (16.0)	458 (17.1)
Enterobacter	345 (7.0)	184 (6.9)
Klebsiella species	627 (12.7)	261 (9.7)
Pseudomonas species	984 (19.9)	458 (17.1)
Acinetobacter species	435 (8.8)	149 (5.6)
Other	840 (17.0)	487 (18.2)
ESBL-producing	93 (1.9)	47 (1.8)
Anaerobes	222 (4.5)	142 (5.3)
Other bacteria	76 (1.5)	33 (1.2)
Fungi		
Candida	843 (17)	495 (18.5)
Aspergillus	70 (1.4)	44 (1.6)
Other	50 (1)	22 (0.8)
Parasites	34 (0.7)	18 (0.7)
Other organisms	192 (3.9)	122 (4.6)

BGN

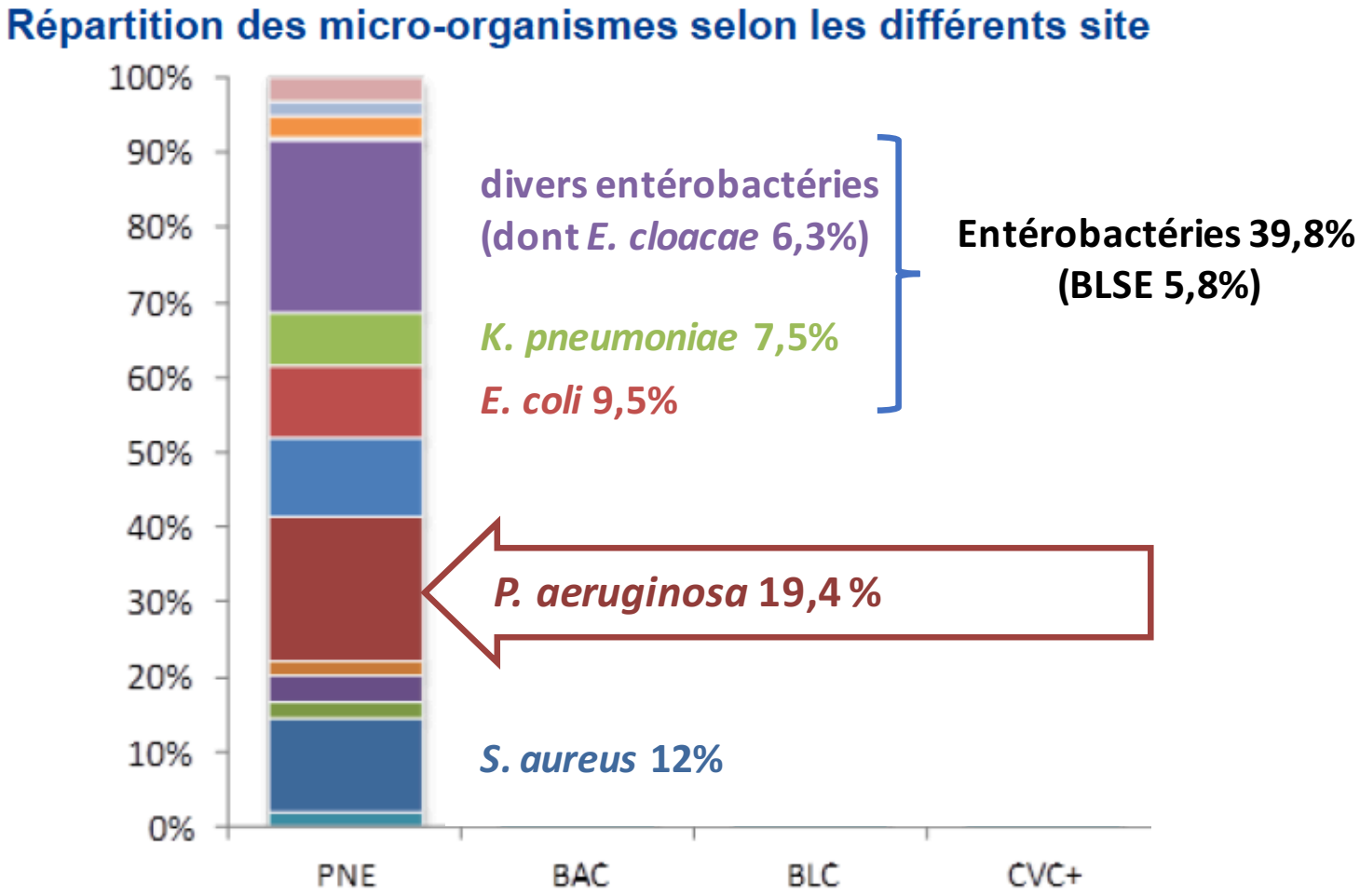
- ***P. aeruginosa 19 %***

- *E. coli* 17 %
- *Klebsiella spp.* 10 %
- *Enterobacter spp. 7 %*

- *dont BLSE 1.8%*

Vincent JAMA 2009

Pneumonies nosocomiales reanimation, Réa-RAISIN 2015 (France)



REA-Raisin 2015 – Santé Publique France 2017

Pneumonies acquises sous ventilation mécanique - PAVM (Europe)

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 Eur J Clin Microbiol Infect Dis 2017

Pneumonies liées aux soins ventilées ou non (USA, monde)

- 1184 patients
- analyse post-hoc d'un ERC international

- 1ère BGN pneumonies :
  - liées aux soins (HCAP)
  - acquises à l'hospital (HAP)
  - acquises sous VM (VAP)

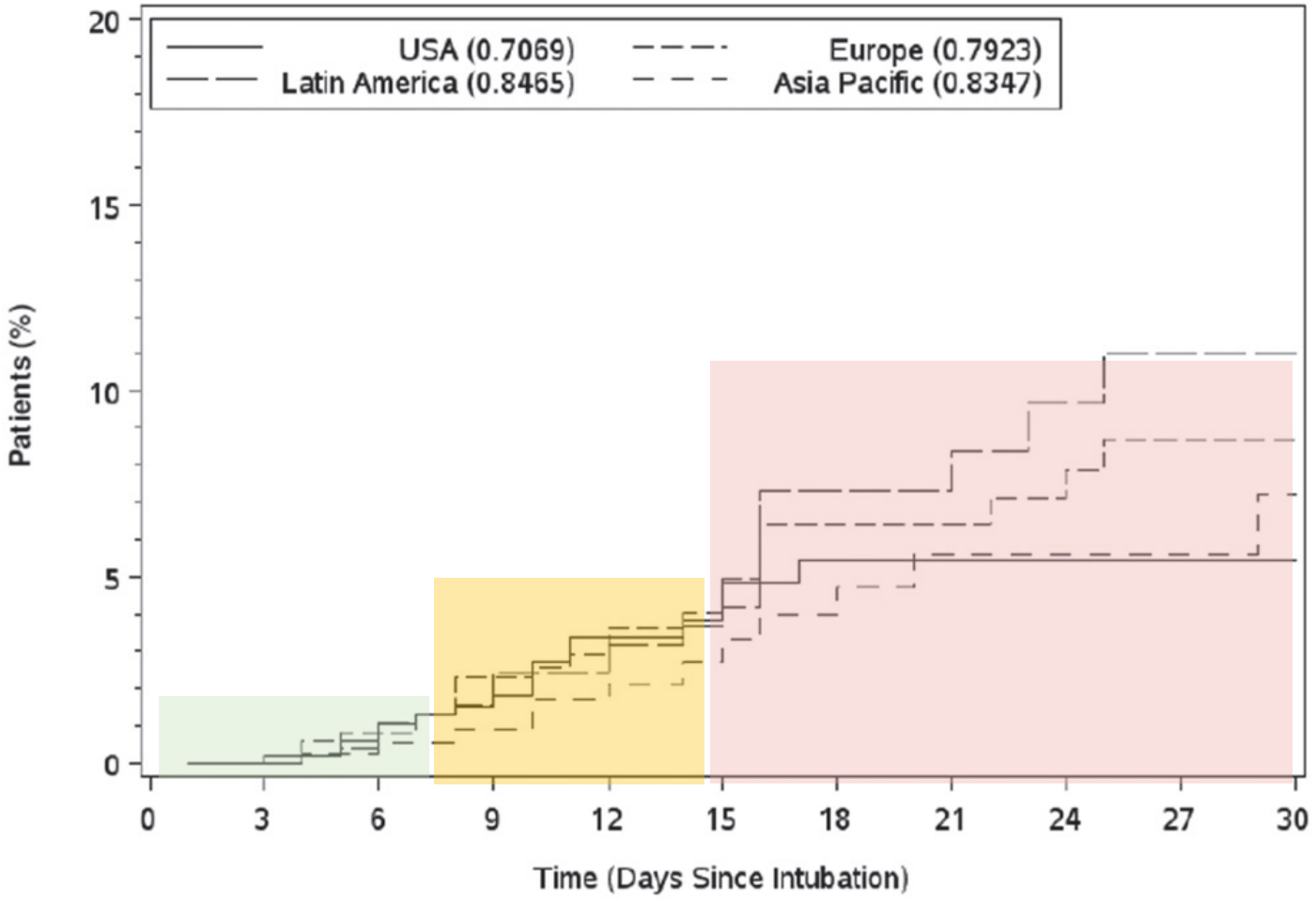
Microbiology	HCAP (n = 199) n (%)	HAP (n = 379) n (%)	VAP (n = 606) n (%)
Gram-positive pathogens	117 (58.8)	226 (59.6)	441 (72.8)
MRSA	82 (41.2)	125 (33.0)	259 (42.7)
MSSA	12 (6.0)	51 (13.5)	107 (17.7)
Pneumococcus	4 (2.0)	10 (2.6)	15 (2.5)
Other *Streptococcus* spp.	7 (3.5)	15 (4.0)	18 (3.0)
Gram-negative 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 BMC Infect Dis 2013

PAVM *P. aeruginosa* : incidence ~ exposition à l'intubation (monde)

> j7 +

> j14 ++



Kollef Crit Care Med 2014

Pendant la pandémie COVID-19…

- Observationelle, multicentrique
- 11 réanimations, Italie, 1ère vague COVID 2020

- 171/586 (29%) PAVM
  - Délai median entrée réa-PAVM = 10j (95% CI 6-17)
  - Incidence 18 PAVM/1000 j ventilés (95% CI 16–21)

- Pathogènes les + frequents
  - ***Pseudomonas aeruginosa* (27/77, 35%)**
  - *Staphylococcus aureus* (18/77, 23%)
  - *Klebsiella pneumoniae* (15/77, 19%)

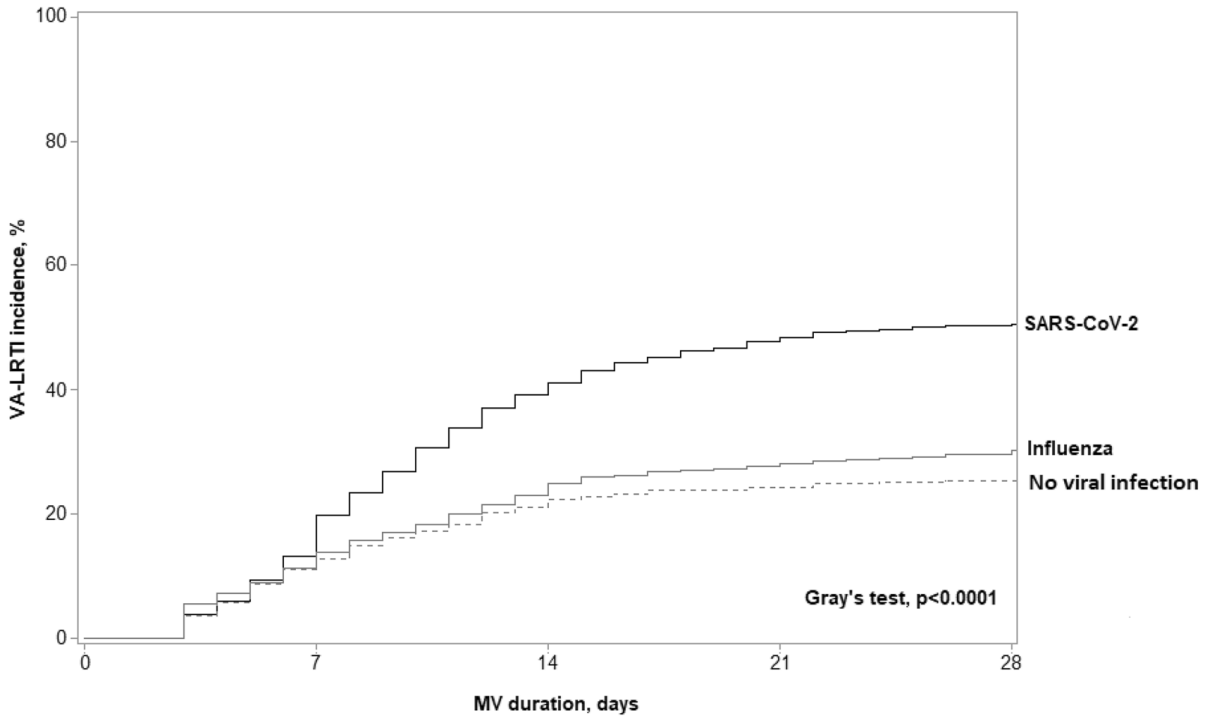
Table S2. Isolates from BALF cultures.

Isolate/s	No. of patients 77 (100)
Pseudomonas aeruginosa	19 (25)
Staphylococcus aureus	13 (17)
Klebsiella pneumoniae	9 (12)
Acinetobacter spp.	6 (8)
Enterobacter aerogenes	4 (5)
Serratia marcescens	3 (4)
Klebsiella oxytoca	2 (3)
tobacter spp. plus *Klebsiella pneumoniae*	2 (3)
Staphylococcus aureus plus *Stenotrophomonas maltophilia*	2 (3)
Staphylococcus aureus plus *Klebsiella pneumoniae*	2 (3)
Pseudomonas aeruginosa plus *Stenotrophomonas maltophilia*	2 (3)
Citrobacter spp.	1 (1)
Chryseobacterium indologenes	1 (1)
Escherichia coli	1 (1)
Haemophilus influenzae	1 (1)
Morganella morganii	1 (1)

Giaccobbe J Clin Med 2021

Pendant la pandémie COVID-19…

- Multicentrique, rétrospective, 36 réanimations, Europe



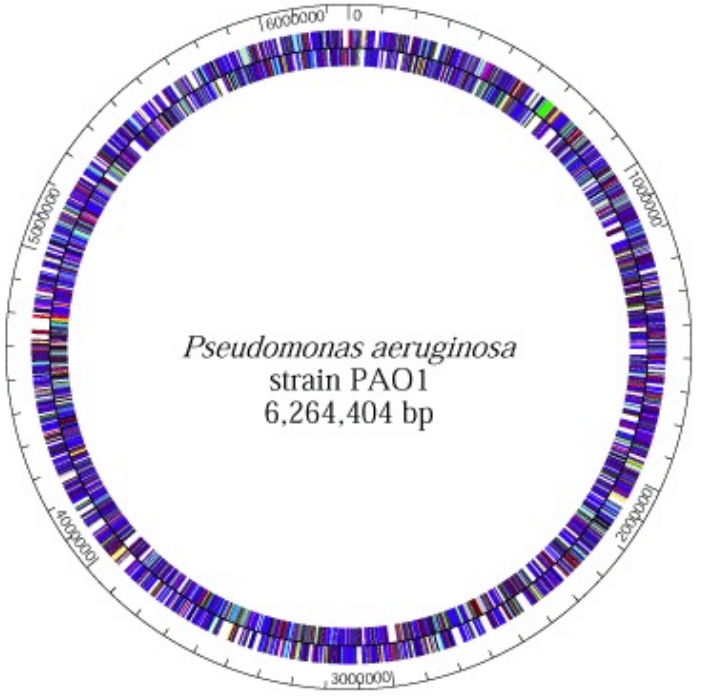
	SARS-CoV-2 pneumonia (*n* = 287)	Influenza pneumonia (*n* = 146)	No viral infection (*n* = 133)
Gram-positive cocci	56 (19.5)	16 (11)	23 (17.3)
MSSA	27 (9.4)	7 (4.8)	13 (9.8)
MRSA	8 (2.8)	5 (3.4)	5 (3.8)
Enterococcus spp.	9 (3.1)	2 (1.4)	2 (1.5)
Streptococcus pneumoniae	8 (2.8)	1 (0.7)	2 (1.5)
Streptococcus spp.	4 (1.4)	1 (0.7)	1 (0.8)
Gram-negative bacilli	240 (83.6)	131 (89.7)	109 (82)
Pseudomonas aeruginosa	64 (22.3)	33 (23.1)	23 (17.3)
Enterobacter spp.	54 (18.8)	23 (15.8)	17 (12.8)
Klebsiella spp.	33 (11.5)	21 (14.4)	21 (15.8)
Escherichia coli	24 (8.4)	12 (8.2)	8 (6.1)
Acinetobacter baumannii	21 (7.3)	22 (15.1)	14 (10.5)
Stenotrophomonas maltophilia	10 (3.5)	3 (2.1)	7 (5.3)
Serratia marcescens	9 (3.1)	2 (1.4)	6 (4.5)
Citrobacter freundii	6 (2.1)	1 (0.7)	1 (0.8)
Citrobacter spp	8 (2.8)	3 (2.1)	4 (3)
Proteus mirabilis	5 (1.7)	1 (0.7)	1 (0.8)
Haemophilus influenza	3 (1)	6 (4.1)	6 (4.5)
Morganella morganii	3 (1)	4 (2.7)	1 (0.8)
Other	15 (5.2)	9 (6.2)	5 (3.8)
Polymicrobial	28 (9.8)	8 (5.5)	10 (7.5)
Multidrug-resistant isolates	67 (23.3)	56 (38.4)	45 (33.8)

Rouze Intens Care Med 2021

Pseudomonas aeruginosa : virulence ET résistances

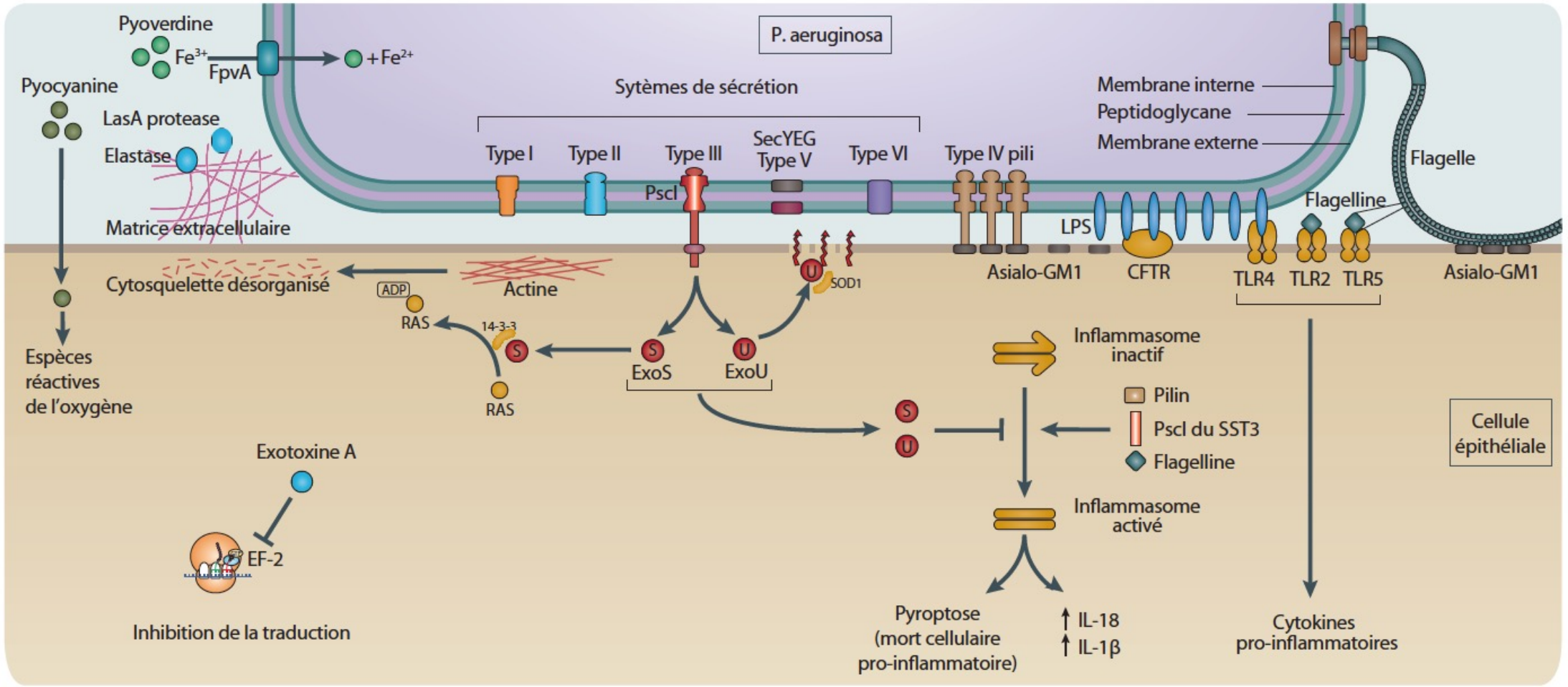
Génome et virulence

- Gros génome > 6.3 M pdb
- Nombreux gènes de virulence
  - Adhésines
  - Transport et de translocation de facteurs de virulence
  - Pompes d'efflux d'antibiotiques
  - Détecteurs de l'environnement



- 260 gènes de virulence conservés
- + gènes de virulence concentrés dans des ilots de pathogénicité

Arsenal de facteurs de virulence



Modifié à partir de Hauser, Nat Rev Microbiol. March 2011; Vol. 9 no. 3

Facteur de virulence (SST3/ExoU) et virulence clinique

Table 2 Associations between the *Pseudomonas aeruginosa* type III secretion system and clinical outcomes

Reference	Year	Country	Target population	Clinical association
Roy-Burman *et al.* [24]	2001	USA	108 isolates from respiratory tract or blood	TTSS-positive phenotype was a predictor of poor clinical outcome.
Hauser *et al.* [80]	2002	USA	35 patients with VAP	In VAP, type III secretory isolates were associated with worse clinical outcomes.
Schulert *et al.* [74]	2003	USA	35 isolates from patients with hospital-acquired pneumonia	ExoU is a marker for highly virulent strains.
Wareham and Curtis [75]	2007	UK	TTSS genotypes and phenotypes of 163 clinical isolates	The *exoS*$^{-}$/*exoU*$^{+}$ genotype was associated with strains isolated from blood.
Garey *et al.* [81]	2008	USA	Hospitalized patients with bacteremia	Mortality did not differ among patients infected with *exoS* or *exoU* isolates.
Wong-Beringer *et al.* [12]	2008	USA	45 isolates susceptible to fluoroquinolones	*exoU*$^{+}$ strains exhibited increased cytotoxicity compared with ExoS-secreting strains.
Bradbury *et al.* [76]	2010	Australia	184 clinical, nosocomial, and environmental isolates	Isolates collected from the environment of intensive therapy units were more likely to possess *exoU*.
Agnello and Wong-Beringer [82]	2012	USA	270 respiratory isolates	Strains with fluoroquinolone resistance correlate with TTSS effector genotype and the more virulent *exoU*$^{+}$ subpopulation.
El-Solh *et al.* [83]	2012	USA	85 cases of bloodstream infection	Expression of TTSS toxins in isolates from bacteremic patients confers poor clinical outcomes.
Jabalameli *et al.* [84]	2012	Iran	96 isolates collected from wound infections of burn patients	*exoU* gene is disseminated among isolates from burn patients.
Sullivan *et al.* [11]	2014	USA	218 adult patients with positive respiratory cultures	Fluoroquinolone-resistant phenotype in *exoU* strains contributes to pneumonia.

TTSS, type III secretion system; VAP, ventilator-associated pneumonia.

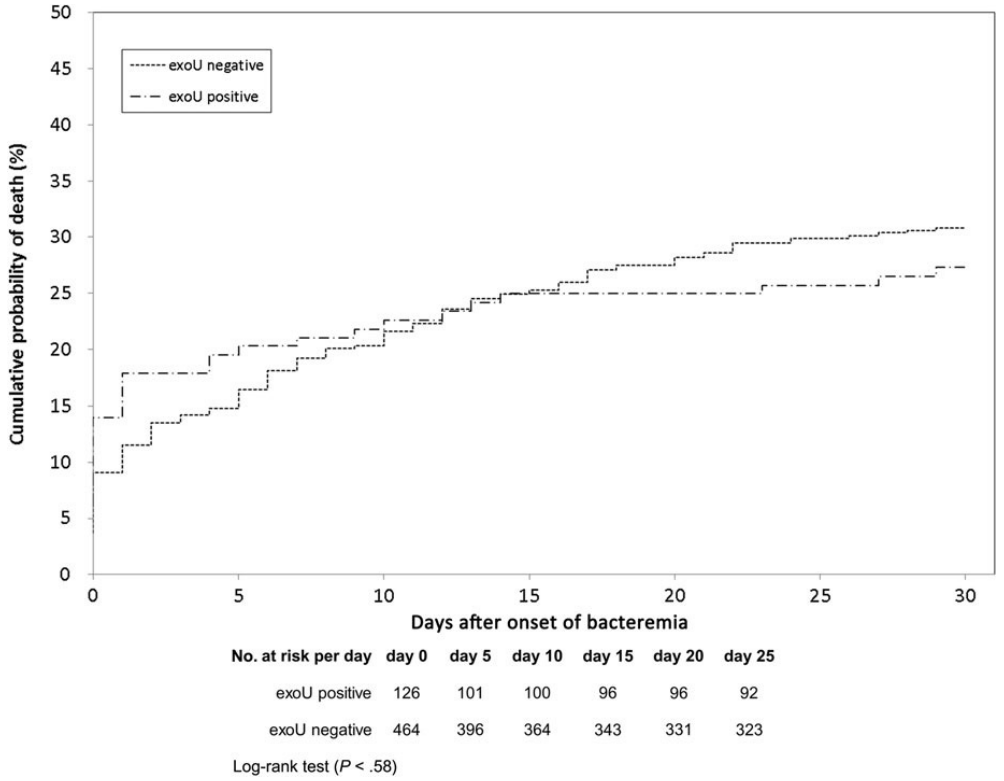
= facteur de *gravité clinique*

Sawa T et al, Crit Care. 2014 Dec 13;18(6):668

Virulence clinique

- Analyse post-hoc multicentrique (Espagne)
- Bactériémies *P. aeruginosa*
- Génotypage
- **exotoxines SST3**

  (*exoU exoS, exoT*)

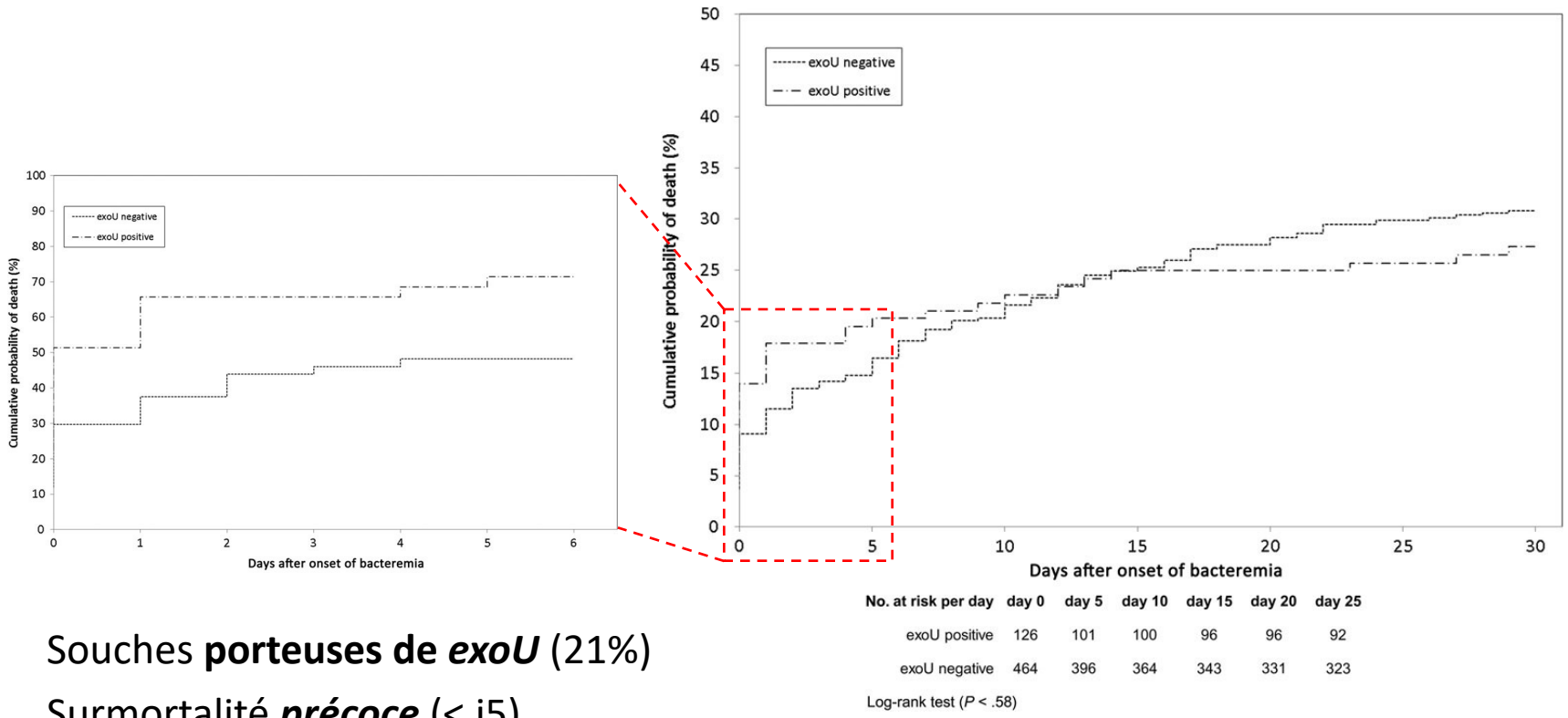


No. at risk per day	day 0	day 5	day 10	day 15	day 20	day 25
exoU positive	126	101	100	96	96	92
exoU negative	464	396	364	343	331	323

Log-rank test ($P < .58$)

Peña C et al, Clin Infect Dis. 2015 Feb 15;60(4):539-48

Virulence clinique



Souches **porteuses de *exoU*** (21%)

Surmortalité ***précoce*** (< j5)

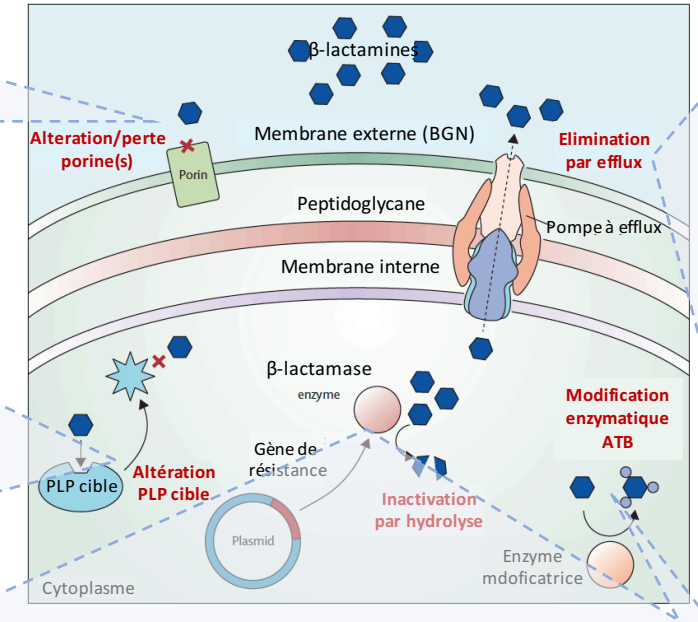
OR ajusté : 1.90 (1.15–3.14) p = 0.01

Peña C et al, Clin Infect Dis. 2015 Feb 15;60(4):539-48

(multi)-résistance de *P. aeruginosa*

OprD⁻ (R-Imipénème)

ribosylmethylation (AG)
Lipide A du LPS (colistine)
DNA gyrase (FQ)
topoisomerase IV (FQ)



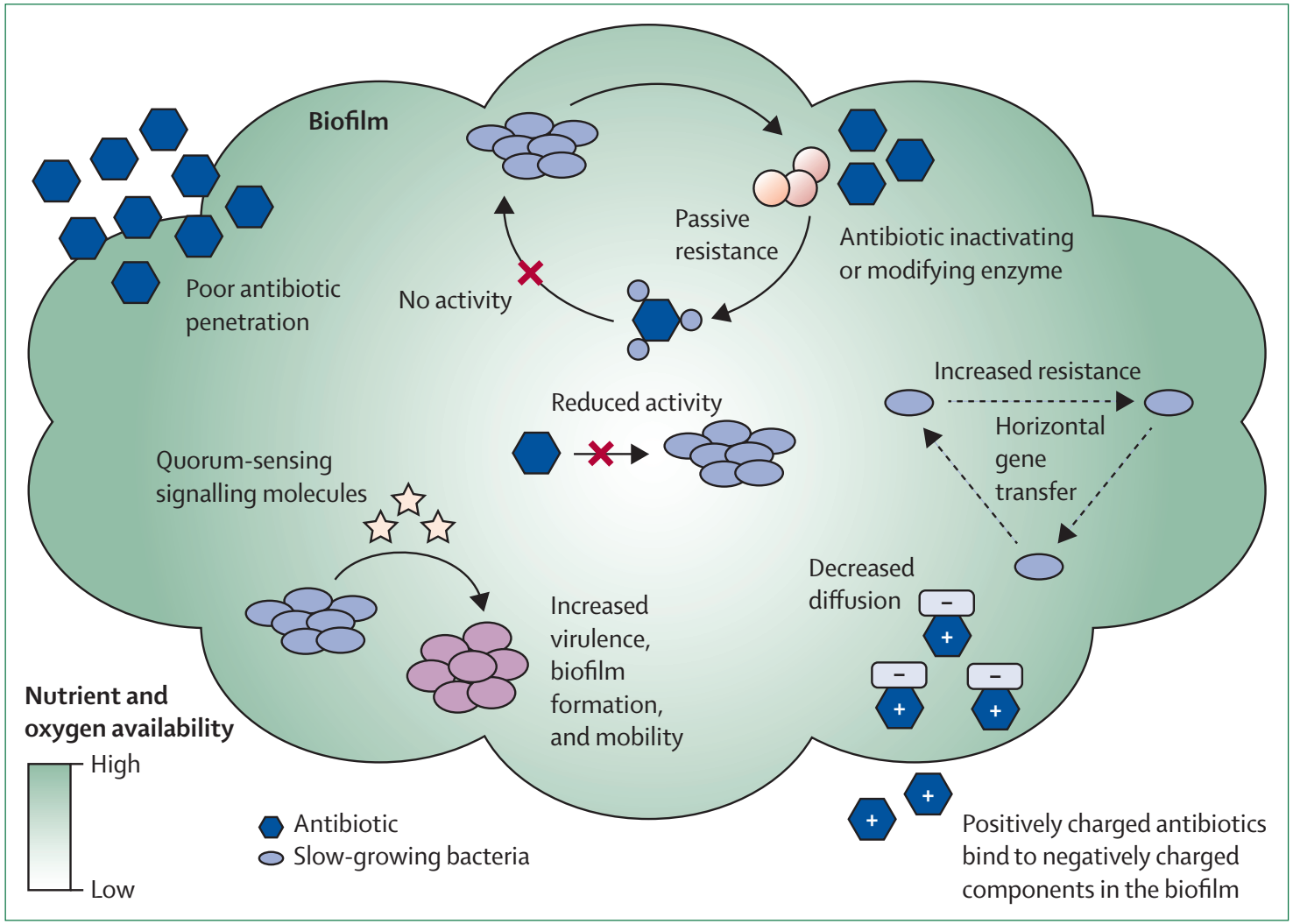
RND system	Substrates
MexAB-OprM	β-lactams except imipenem
	Quinolones
	Macrolides
	Tetracyclines
	Chloramphenicol
MexCD-OprJ	Penicillin, cefepime, cefpirome, meropenem
	Quinolones
	Macrolides
	Tetracyclines
	Chloramphenicol
MexEF-OprN	Carbapenems
	Quinolones
MexXY-OprM	Penicillin, cefepime, cefpirome, meropenem
	Aminoglycosides
	Quinolones
	Macrolides
	Tetracyclines
	Chloramphenicol

(aminosides)
acetyltransferases
nucleotidyltransferases

	WT	PENI		ESBL		CEPH	CARBA
	WT	TEM PSE CARB	OXA	PER VEB TEM SHV CTX-M	OXA	AmpC	IMP VIM NDM KPC
Carboxypenicillins	S	R	R	R	R	R	R
Carboxypenicillins +BLI	S	S/I	I/R	S/I	I/R	R	R
Ureidopenicillins	S	I/R	R	I/R	R	I/R	R
Ureidopenicillins +BLI	S	S/I	I/R	S/I	I/R	I/R	R
Ceftazidime	S	S	S	R	I/R	I/R	R
Cefepime	S	S	I/R	R	I/R	I/R	R
Aztreonam	S	S	S	R	I/R	I/R	S
Imipenem	S	S	S	S	S	S	R

d'après Sherrard LJ et al, Lancet 2014

(multi)-résistance de *P. aeruginosa - biofilm*

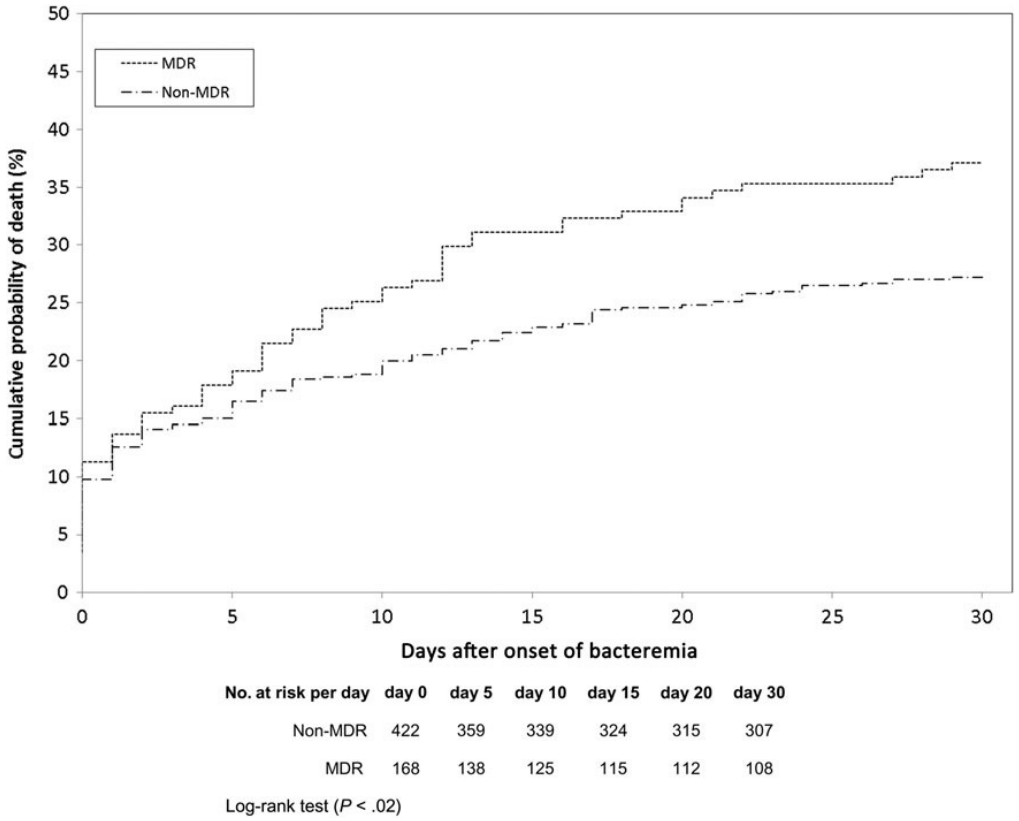


Sherrard Lancet 2014

Multirésistance *P. aeruginosa* et surmortalité

- Analyse post-hoc multicentrique (Espagne)
- Bactériémies *P. aeruginosa*
- Génotypage
- **exotoxines SST3**

  (*exoU exoS, exoT*)



Souches **multirésistantes**

Surmortalité ***globale*** (< j30)

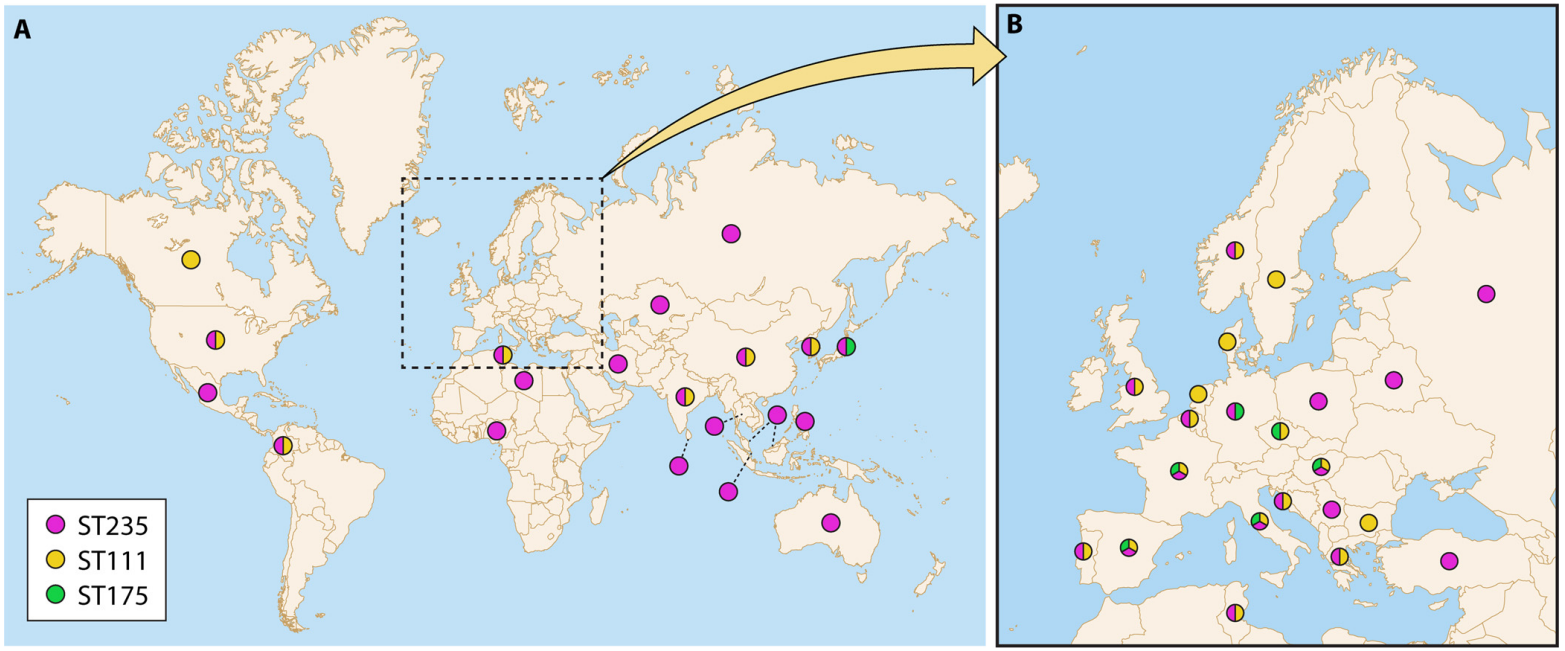
OR ajusté : 1.40 (1.01–1.94) p= 0.04

Peña C et al, Clin Infect Dis. 2015 Feb 15;60(4):539-48

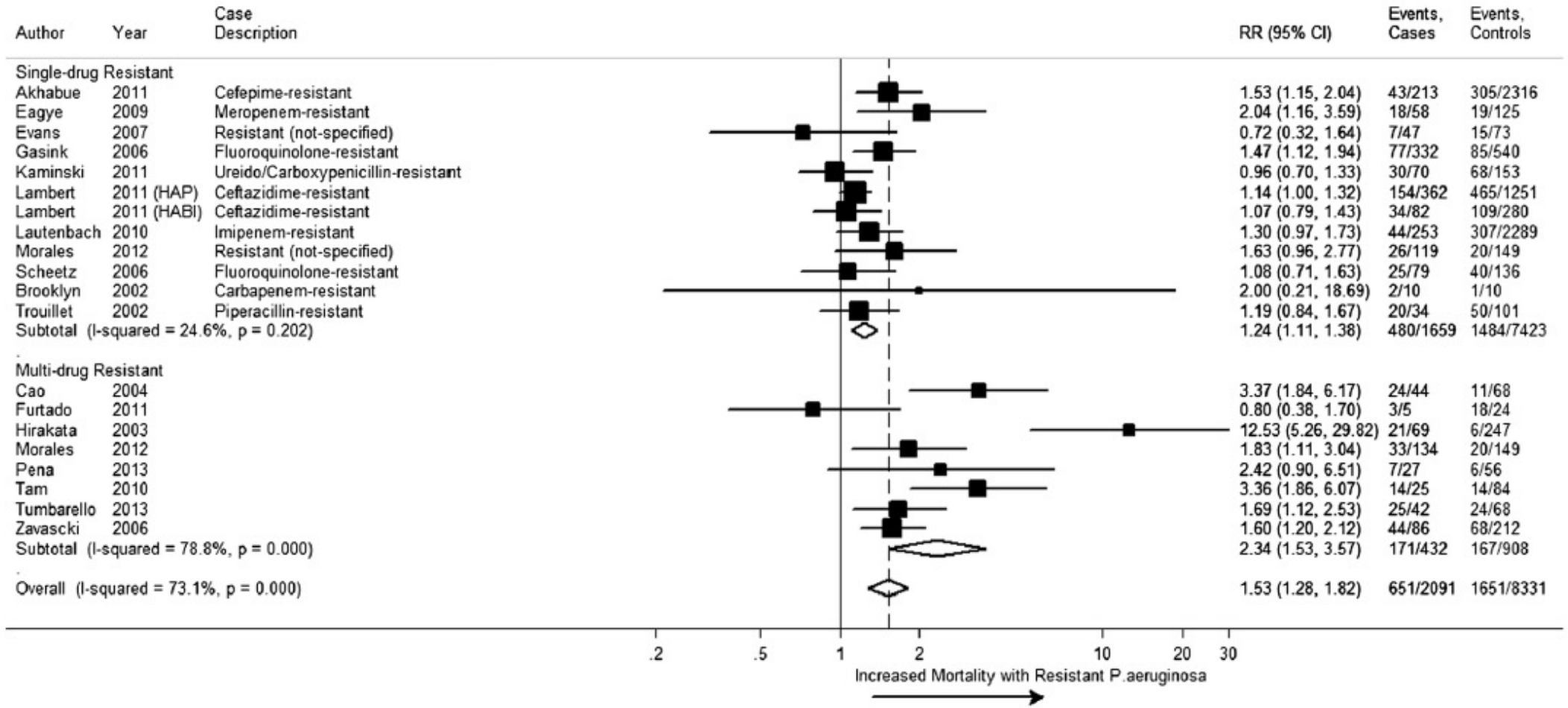
Clones “à risque” : multirésistants et ± virulents

TABLE 2 Characteristics of the three major global *P. aeruginosa* high-risk clones

Characteristic	ST111	ST175	ST235
O-antigen serotype	O12	O4	O11
Type III secretion system	ExoS	ExoS	ExoU
Virulence[a]	++	+	+++
Worldwide distribution	++	+	+++
Transferable resistance	++	+	+++
Mutational resistance	++	+++	++



Surmortalité (toutes) infections *P. aeruginosa* MDR?



Nathwani Antimicrob Resist Infect Control 2014

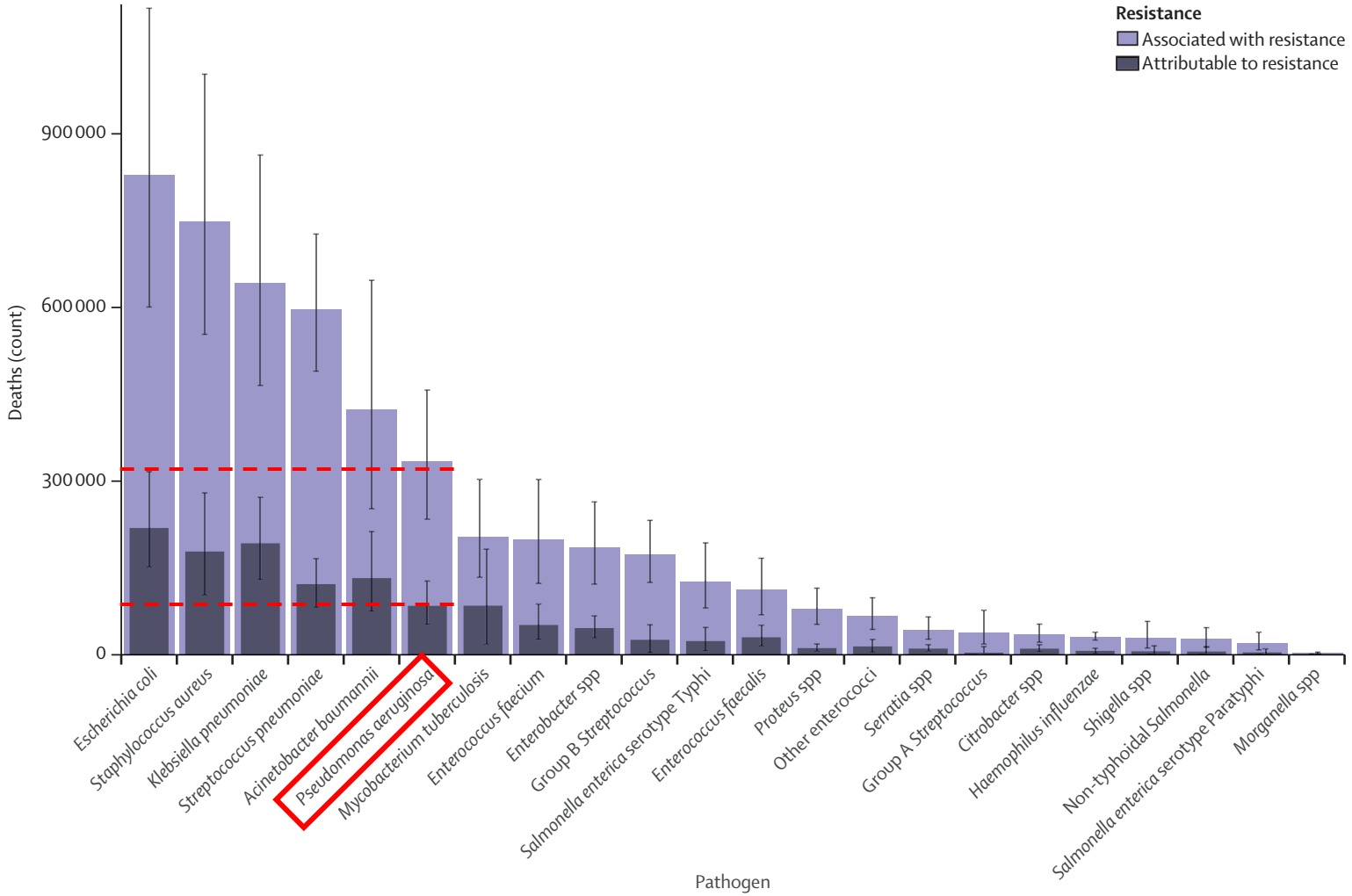
Surmortalité (toutes) infections *P. aeruginosa* MDR?

Global Burden of Disease 2019

- > n = 4 million (big data multi-source)
- Les 6 pathogènes ± ESKAPE
  - *Escherichia coli*
  - *Staphylococcus aureus*
  - *Klebsiella pneumoniae*
  - *Streptococcus pneumoniae*,
    Acinetobacter baumannii
  - ***Pseudomonas aeruginosa***

- Décès ***attribuables*** à la **multi-résistance**
  ~ 929 000 (660 000–1 270 000)

- Décès ***associés*** à la **multi-résistance**
  ~ 3·57 million (2·62–4·78)

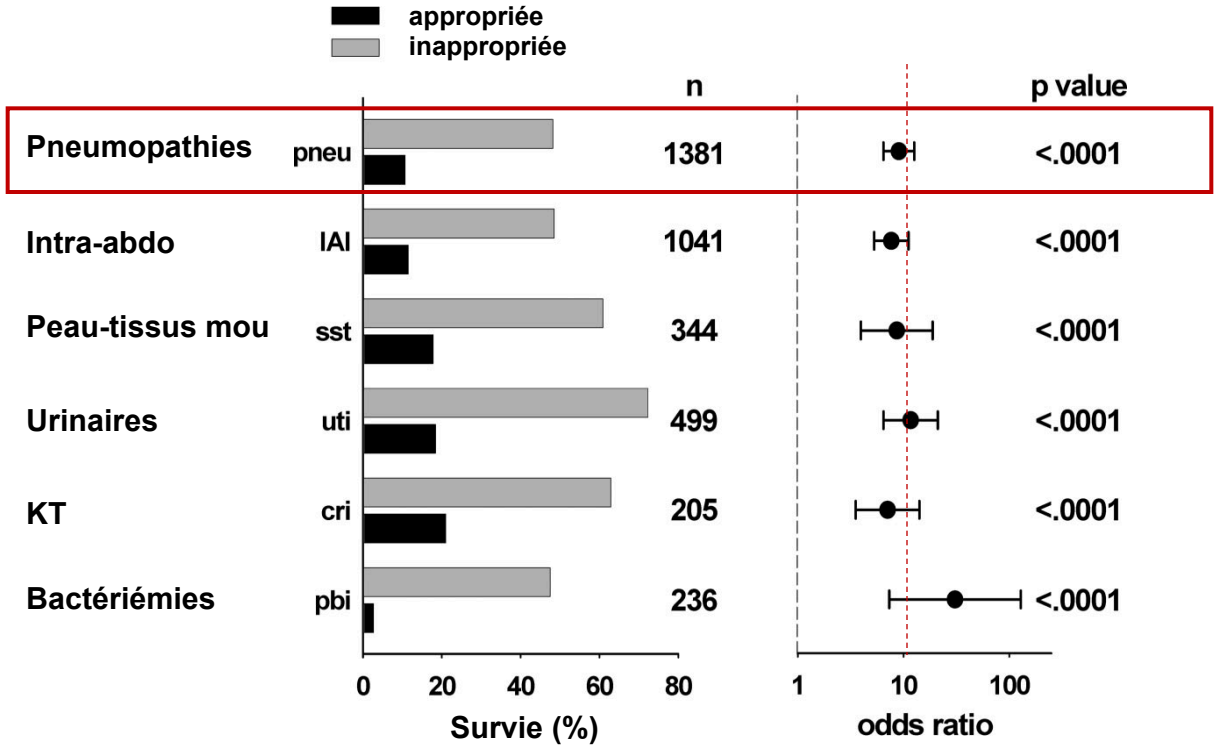


Antimicrobial Resistance Collaborators Lancet 2022

L’enjeu = traitement des infections sévères à *P. aeruginosa*

Enjeu = adéquation de l'antibiothérapie (probabiliste) initiale

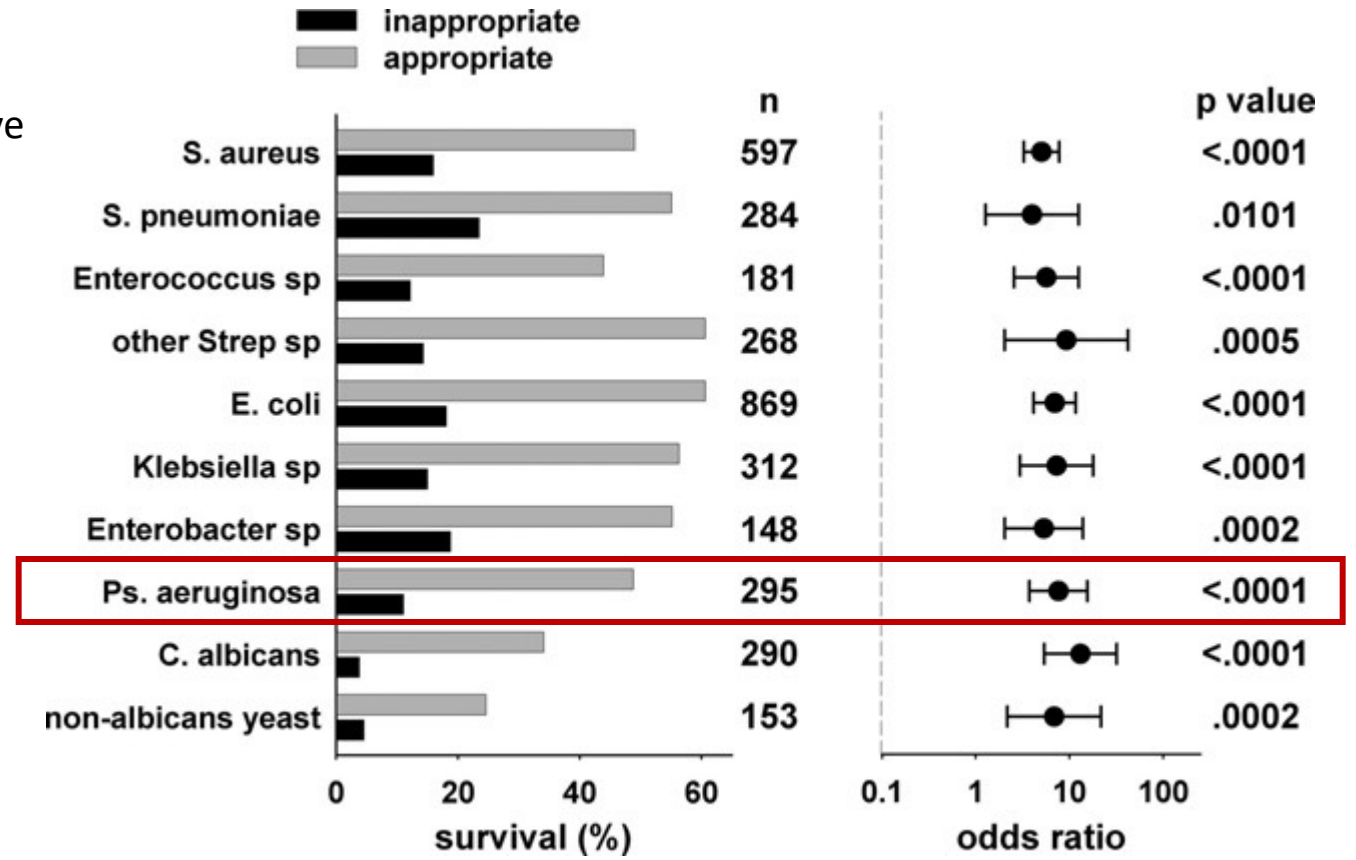
- choc septique
- cohorte rétrospective
- Nord-américaine
- n= 5715



Kumar Chest 2009

Inadéquation et *P. aeruginosa*

- choc septique
- cohorte rétrospective
- Nord-américaine
- n= 5715



Inadéquation et *P. aeruginosa* = surmortalité jusqu'à x 10

Kumar A et al, Chest. 2009 Nov;136(5):1237-1248

P. aeruginosa au cours du choc septique

Species	Adjusted Mortality in Inappropriate Antibiotics Group	Adjusted Mortality in Appropriate Antibiotics Group	NNT (95% CI)	Prevalence (%)	NNT × 1/ Prevalence
Candida	57.4	29.0	3.5 (2.9–4.3)	10.2	34
MDR-all	47.5	29.4	5.5 (4.4–6.9)	27.0	20
MDR-Gram-negative bacteria only	51.4	26.1	4.0 (2.6–6.2)	7.2	56
Methicillin-resistant *Staphylococcus aureus*	45.7	26.5	5.0 (4.1–6.2)	13.2	38
Methicillin-sensitive *S. aureus*	41.2	21.5	5.0 (3.8–6.9)	10.6	47
Vancomycin-resistant enterococci	45.6	33.3	8.1 (5.5–12.2)	6.6	123
Vancomycin-sensitive enterococci	47.6	20.6	4.0 (3.2–5.2)	7.0	57
Pseudomonas aeruginosa	72.9	33.1	2.5 (2.1–3.1)	6.6	38
Enterobacter species	36.9	18.4	5.0 (3.6–7.4)	4.5	111
Acinetobacter species[a]	54.6	26.0	3.0 (2.2–4.2)	2.6	115
Klebsiella species	37.2	17.3	5.0 (3.9–6.6)	8.1	62
Escherichia coli	44.0	21.2	4.0 (3.3–4.9)	10.0	40
Anaerobes[b]	26.2	19.9	16.0 (8.4–28.8)	5.3	302

Vazquez-Guillame Crit Care Med 2014

Que faire ?

Choisir un antibiotique actif contre *P. aeruginosa* ?

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

Facteurs de risque de (multi-) résistance

Pression ATB

	Pseudomonas (n = 121)	
	Crude HR (95% CI)	Adjusted HR (95% CI)
Ciprofloxacin vs. no ciprofloxacin	2.8 (0.7−10.9)	4.1 (1.1−16.2)[a]
Ceftazidime vs. no ceftazidime	2.8 (1.3−6.1)	2.5 (1.1−5.5)[c]
Meropenem vs. no meropenem	8.7 (2.2−33.9)	11.1 (2.4−51.5)[e]
Piperacillin-tazobactam vs. no piperacillin-tazobactam	2.0 (0.7−5.6)	0.8 (0.2−3.2)[f]
Cotrimoxazol vs. no cotrimoxazol	n/a	n/a
Gentamicin vs. no gentamicin	n/a	n/a
Ceftriaxone vs. no ceftriaxone	n/a	n/a
Tobramycin vs. no tobramycin	n/a	n/a

Ong Crit Care Med 2011

Pression ATB : carbapénèmes méta-analyses IDSA HAP/VAP

Méta-analyses restreintes aux pénèmes *vs.* autres ATB :

- Emergences résistances
  - 4 RCT
  - (**OR, 5.17**; 95% CI, 1.96–13.65)

Probability of developing carbapenem resistance with the use of carbapenems vs. non-carbapenems
Carbapenem vs. Other (7 studies: N=1,214 patients)
Outcome: Acquired Resistance
Relative Risk (RR) = 1.40 (0.95, 2.06); P = 0.083; N = 1,214
Number Needed to Harm (NNH) = 50
Real-life Application for the NNH:
NNT adjusted according the patient's expected event rate (PEER) or baseline risk.
If acquired resistance rate in your hospital is 2%: NNH = 125
If acquired resistance rate in your hospital is 3%: NNH = 83
If acquired resistance rate in your hospital is 5%: NNH = 50
If acquired resistance rate in your hospital is 7%: NNH = 36
If acquired resistance rate in your hospital is 10%: NNH = 25

Kalil AC et al, Clin Infect Dis. 2016 Sep 1;63(5):e61-e111

FdR (MDR) *P. aeruginosa* (Recommandations IDSA 2016)

Risk factors for MDR VAP
Prior intravenous antibiotic use within 90 d
Septic shock at time of VAP
ARDS preceding VAP
Five or more days of hospitalization prior to the occurrence of VAP
Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP
Prior intravenous antibiotic use within 90 d
Risk factors for MRSA VAP/HAP
Prior intravenous antibiotic use within 90 d
Risk factors for MDR *Pseudomonas* VAP/HAP
Prior intravenous antibiotic use within 90 d

ATB I.V. dans les 90 j

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Quel traitement(s) ?

choix ATB anti-pseudomonaux ? (Recommandations IDSA 2016)

SUMMARY OF RANDOMIZED CONTROLLED STUDIES EVALUATING EMPIRIC ANTIBIOTIC TREATMENTS FOR HAP AND VAP WITH PSEUDOMONAS COHORT														
	Rx A	Rx B	N	Mech Vent	Pseudomonas patients	All Patient and Pseudomonas (PA) Clinical Response			Pseudomonas Patient Mortality			All-patient Mortality		
						A	B	Diff	A	B	Diff	A	B	Diff
Alvarez-Lerma 2001 [24]	Meropenem	Ceftaz-Amikacin	140	100%	27/140 (19%)	47/69 (68%)	39/71 (55%)	.04	NR	--	--	16/69 (23%)	20/71 (28%)	NS
Sieger 1997 [25]	Meropenem	Ceftaz-Tobra	211	70%	12/211 (6%)	76/106 (72%)	62/105 (59%)	.10	NR	--	--	13/104 (13%)	23/107 (21%)	.06
Brown 1984 [26]	Moxalactam	Carbenicillin-Tobra	48	85%[a]	7/34 (21%)	11/18 (61%)[a]	7/16 (44%)[a]	NS	NR		--	11/18 (61%)	9/16 (56%)	NS
Kljucar 1987 [27]	Ceftazidime	Ceftaz-Tobra	33	100%	18/33 (55%)	12/16 (75%)	12/17 (71%)	NS	NR	--	--	0/16 (0%)	1/17 (5.9%)	NS
Kljucar 1987 [27]	Ceftazidime	Azlocillin-Tobra	33	100%	23/33 (70%)	12/16 (75%)	8/17 (47%)	NS	NR	--	--	0/16 (0%)	2/17 (12%)	NS
Chastre 2008 [28]	Doripenem	Imipenem	531	100%	56/409 (14%)	147/249 (59%)[c] PA 16/20 (80%)	146/252 (58%)[c] PA 6/14 (43%)	NS	7/20 (35%)	6/14 (43%)	NS	27/249 (11%)	24/252 (10%)	NS
Kollef 2012 [79]	Doripenem x 7 days	Imipenem x 10 days	274	100%	27/167 (16%)	36/79 (46%) PA (41%)	50/88 (57%) PA (60%)	NS	6/17 (35.3%)	0/10 (0%)	95% CI 12.6-58	26/115 (23%)	18/112 (16%)	NS
Hartenauer 1990 [29]	Ceftazidime	Imipenem	45	100%	7/45 (16%)	17/21 (81%)[c]	16/24 (67%)[c]	NS	NR	--	--	--	--	--
Torres 2000 [30]	Ciprofloxacin	Imipenem	149	100%	26/75 (35%)	40/57 (70%)[c]	34/52 (65%)[c]	NS	NR	--	--	8/41 (20%)[d]	4/34 (12%)[d]	NS
Fink 1994 [31]	Ciprofloxacin	Imipenem	405[b]	79%	91/402 (22%)	74/121 (61%)[e]	71/130 (55%)[e]	NS	NR	--	--	43/202 (21%)	38/200 (19%)	NS
Shorr 2005 [32]	Levofloxacin	Imipenem	222	100%	34/222 (15%)	65/111 (59%)	70/111 (63%)	NS	NR	--	--	--	--	--
Réa Neto 2008 [33]	Doripenem (+ Aminoglycoside if Pseudomonas)	Piperacillin-tazobactam (+ Aminoglycoside if Pseudomonas)	448	22%[c]	54/285 (19%)	20/29 (69%)[f]	15/26 (58%)[f]	NS	6/32 (19%)	8/44 (18%)	NS	30/217 (14%)	31/212 (15%)	NS
Beaucaire 1995 [35]	Isepamicin	Amikacin	113[d]	100%	35/130 (27%)	23/44 (52%)	25/41 (61%)	NS	NR	--	--	17/56 (30%)	15/57 (26%)	NS
Ahmed 2007 [36]	Cefepime-levofloxacin	Pip-tazo + Amikacin	93	100%	37/93 (40%)	--	--	--	--	--	--	13/38 (35%)	15/38 (40%)	NS
Beaucaire 1999 [37]	Cefipime/ Amikacin	Ceftazidime/ Amikacin	275	100%	16/275 (6%)	68/141 (48%)	60/134 (45%)	NS	NR			29/141 (20%)	21/134 (16%)	--

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choix ATB anti-pseudomonaux ? (Recommandations IDSA 2016)

SUMMARY OF RANDOMIZED CONTROLLED STUDIES EVALUATING EMPIRIC ANTIBIOTIC TREATMENTS FOR HAP AND VAP WITH PSEUDOMONAS COHORT														
	Rx A	Rx B	N	Mech Vent	Pseudomonas patients	All Patient and Pseudomonas (PA) Clinical Response			Pseudomonas Patient Mortality			All-patient Mortality		
						A	B	Diff	A	B	Diff	A	B	Diff
Croce 1993 [80]	Cefoperazone	Ceftazidime	39	100%	6/59 (10%)	10/19 (53%)	12/20 (60%)	--	NR	--	--	--	--	--
Croce 1993 [80]	Cefoperazone/ Gentamicin	Ceftazidime/ Gentamicin	70	100%	13/137 (10%)	10/35 (29%)	12/35 (34%)	--	NR	--	--	--	--	--
Reeves 1989 [38]	Ceftriaxone	Cefotaxime	51	90%	2/51 (4%)	12/25 (48%)	19/26 (73%)	--	NR	--	--	2/25 (8%)	4/26 (15%)	--
Saginur[h] 1997 [39]	Ceftazidime	Ciprofloxacin	149	52%	4/149 (3%)	14/34 (41%)	17/30 (57%)	--	NR	--	--	6/77[i] (8%)	8/62[i] (13%)	--
Alvarez-Lerma 2001[40]	Pip/Tazo + Amikacin	Ceftazidime + Amikacin	124	85%	13/124 (10%)	44/88 (50%)	16/36 (28%)	--	NR	--	--	27/88 (31%)	8/36 (22%)	
Bruin-Bruisson 1998[41]	Pip/Tazo + Amikacin	Ceftazidime + Amikacin	197	100%	42/190 (22%)	28/58 (48%)	23/69 (33%)	--	NR	--	--	8/51 (15%)	12/61 (20%)	--
Freire 2010 [42]	Tigecycline +/- Ceftazidime	Imipenen +/- Vancomycin	934	34%	18/253 VAP (7%) 24/626 Non-VAP (4%)	59/127 (46%) VAP 217/313 (69%) Non-VAP PA 7/11 (63.6%) Non-VAP PA 3/11 (27.3%) VAP	67/116 (58%) VAP 223/313 (71%) Non-VAP PA 8/13 (69.2%) Non-VAP PA 6/7 (85.7%) VAP	--	NR	--	--	Overall 66/467 (14.1%) 25/131 (19%) VAP 41/336 (12.2%) Non-VAP	Overall 57/467 (12.2%) 15/122 (12%) VAP 43/345 (12.5%) Non-VAP	NS
Giamarellos-Bourboulis 2008 [43]	Clarithro + usual therapy	Usual therapy	200	100%	29/200 (15%)	61/100 (61%)	54/100 (54%)	--	NR	--	--	28/100 (28%)	31/100 (31%)	NS
Damas (A) 2006 [48]	Cefepime	Cefepime - Amikacin	39	100%	7/39 (18%)	37/53 (70%)	26/40 (65%)	NS	NR	--	--	2/20 (10%)	4/19 (21%)	
Damas (B) 2006 [48]	Cefepime	Cefepime - Levofloxacin	40	100%	9/40 (23%)	--	--	--	NR	--	--	2/20 (10%)	4/20 (16%)	
Heyland 2008 [44]	Meropenem	Meropenem-cipro	739	100%	47/739 (6%)	203/369 (55%)	220/369 (60%)	NS	NR	--	--	67/370 (18%)	71/369 (19%)	NS
Manhold 1998 [49]	Cipro	Ceftazidime - Gentamicin	18[d]	100%	2/18 (11%)	2/10 (20%)	4/8 (50%)	--	NR	--	--	8/10 (80%)	4/8 (50%)	--
Awad SS 2014 [81]	Ceftobiprole	Ceftazidime-Linezolid	781	38%	101/781 (13%)	195/391 (49.9%)	206/390 (52.8%)	NS	NR			HAP 16.7%	HAP 18.0%	NS

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choix ATB anti-pseudomonaux ? (Recommandations IDSA 2016)

SUMMARY OF RANDOMIZED CONTROLLED STUDIES EVALUATING EMPIRIC ANTIBIOTIC TREATMENTS FOR HAP AND VAP WITH PSEUDOMONAS COHORT														
	Rx A	Rx B	N	Mech Vent	Pseudomonas patients	All Patient and Pseudomonas (PA) Clinical Response			Pseudomonas Patient Mortality			All-patient Mortality		
						A	B	Diff	A	B	Diff	A	B	Diff
(HAP, including 210 VAP)						HAP 171/287 (59.6%) VAP 24/104 (23.1%) PA 17/27 (63%)	HAP 167/284 (58.8%) VAP 19/70 (27.1%) PA 24/34 (71%)					VAP 26.9%	VAP 19.8%	
Kim 2012 [82] (HAP)	Imipenem + Vancomycin with De-escalation	Non-carbapenem + Non-vancomycin, No de-escalation	109	50%	13/108 (12%)	NR	NR		NR	--	--	21/53 (39.6%)	14/55 (25.9%)	NS
Joshi 2006 [50](NP)	Pip/Tazo + Tobramycin	Imipenem + Tobramycin	437	69%	35/437 (8%)	121/222 (54.5%)	111/215 (51.6%)	NS	NR	--	--	23/222 (10%)	17/215 (8%)	NS
West 2003 [83] (NP)	Levofloxacin (+ Ceftazidime for Pseudomonas)	Imipenem + Amikacin or other AG for Pseudomonas)	438	71%	34/438 (8%)	135/204 (66.2%) PA 11/17 (64.7%)	143/206 (69.4%) PA 7/17 (41.2%)	NS	NR	--	--	38/220 (17.3%)	32/218 (14.7%)	NS
Zanetti 2003 [84] (NP)	Cefipime	Imipenem	281	66%	59/148 (40%)	76/108 (70%) PA 23/27 (75%)	75/101 (74%) PA 23/32 (72%)	NS	NR	--	--	28/108 (26%)	19/101 (19%)	NS
Jaccard 1998 [85] (NP or peritonitis)	Imipenem	Pip/Tazo	154 NP		45/154 (29%)	23/79 (29%) PA 12/24 (50%)[g]	13/75 (17%) PA19/21 (90%)[g]		NR			6/79 (8%)	7/75 (9%)	NS
Thomas 1994 [45]	Cefotaxime	Ceftriaxone	93	--	--	--	--	--	--	--	--	12/40 (30%)	13/53 (25%)	NS
Cometta 1994 [86]	Imipenem	Imipenem + netilmicin	177[h]	55%	34/177 (19%)	16/91 (17.6%)	14/86 (16.3%)		NR	--	--	13/91 (14%)	12/86 (14%)	NS
Giamarellou 1990 [87]	Pefloxacin	Imipenem	71	72%	25 of 88 pathogens	23/35 (65.7%)	19/35 (52.8%)		NR			1/25 (4%)	4/29 (14%)	NS

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choix ATB anti-pseudomonaux ? (Recommandations IDSA 2016)

Aucune molécule *parmi les antipseudomonaux*
n'est retenue comme supérieure à une autre

(sauf échecs et néphrotoxicité des monothérapies par aminosides)

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(Multi)résistances en réanimation – France (2015 et 2016)

Micro-organisme		Indicateur		n	n'	%
Pseudomonas aeruginosa	(2 233)	Pipéracilline/tazobactam		2 187	619	28,3
		Ceftazidime		2 191	426	19,4
		Carbapénème		2 169	505	23,3
		Colistine		1 510	40	2,6
		PanR	probable	2 158	27	1,3
			confirmé		7	0,3

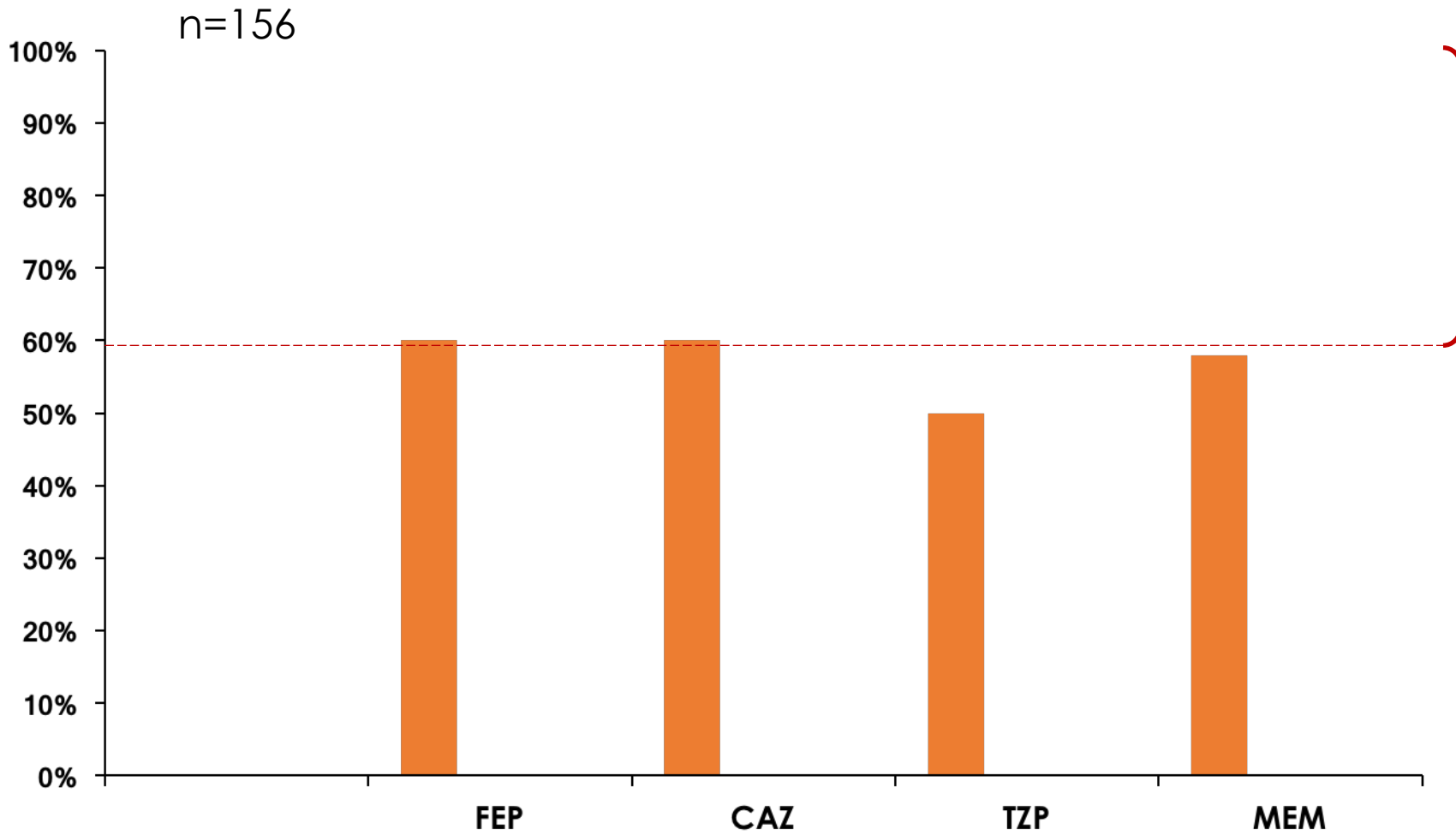
Réseau REA-Raisin, France. Résultats 2016. Saint-Maurice : Santé publique France, 2018

Micro-organisme		Indicateur		n	%
Pseudomonas aeruginosa (+66 profils inconnus)	(2 075)	0. CAZ-S	& IMP-S	1 439	69,3
		1. CAZ-R	& IMP-S	254	12,2
		2. CAZ-S	& IMP-I/R	247	11,9
		3. CAZ-R	& IMP-I/R	135	6,5

- **~ 30 % non-multisensibles**
- **1 chance sur 2 de perdre le pari entre CAZ et IMP**
- **~ 7% multirésistantes**

Réseau REA-Raisin, France. Résultats 2015. Saint-Maurice : Santé publique France, 2017

Sensibilités *in-vitro P. aeruginosa* (USA, souches respi, réanimation)



30-40 % Résistances aux β-lactamines anti-pseudomonas "socles"

= pari probabiliste *difficile* entre :

- ***Céfépime***
- ***Ceftazidime***
- ***Meropénème (Imipénème)***

Goodlet Antimicrob Agents Chemother 2017

Résistances croisées *in-vitro* (USA, toutes souches ou respi réa)

β-lactam	% NS	Of NS, % FEP S	Of NS, % CAZ S	Of NS, % TZP S	Of NS, % MEM S
All patients					
Cefepime	23.0	N/A	23.9	20.8	39.4
Ceftazidime	23.0	23.9	N/A	15.2	41.2
Piperacillin/tazobactam	28.2	35.3	30.8	N/A	45.2
Meropenem	24.0	42.1	43.7	35.8	N/A
ICU					
Cefepime	28.4	N/A	16.7	13.7	37.3
Ceftazidime	31.2	24.1	N/A	11.6	37.5
Piperacillin/tazobactam	37.0	33.8	25.6	N/A	41.4
Meropenem	30.1	40.7	35.2	27.8	N/A

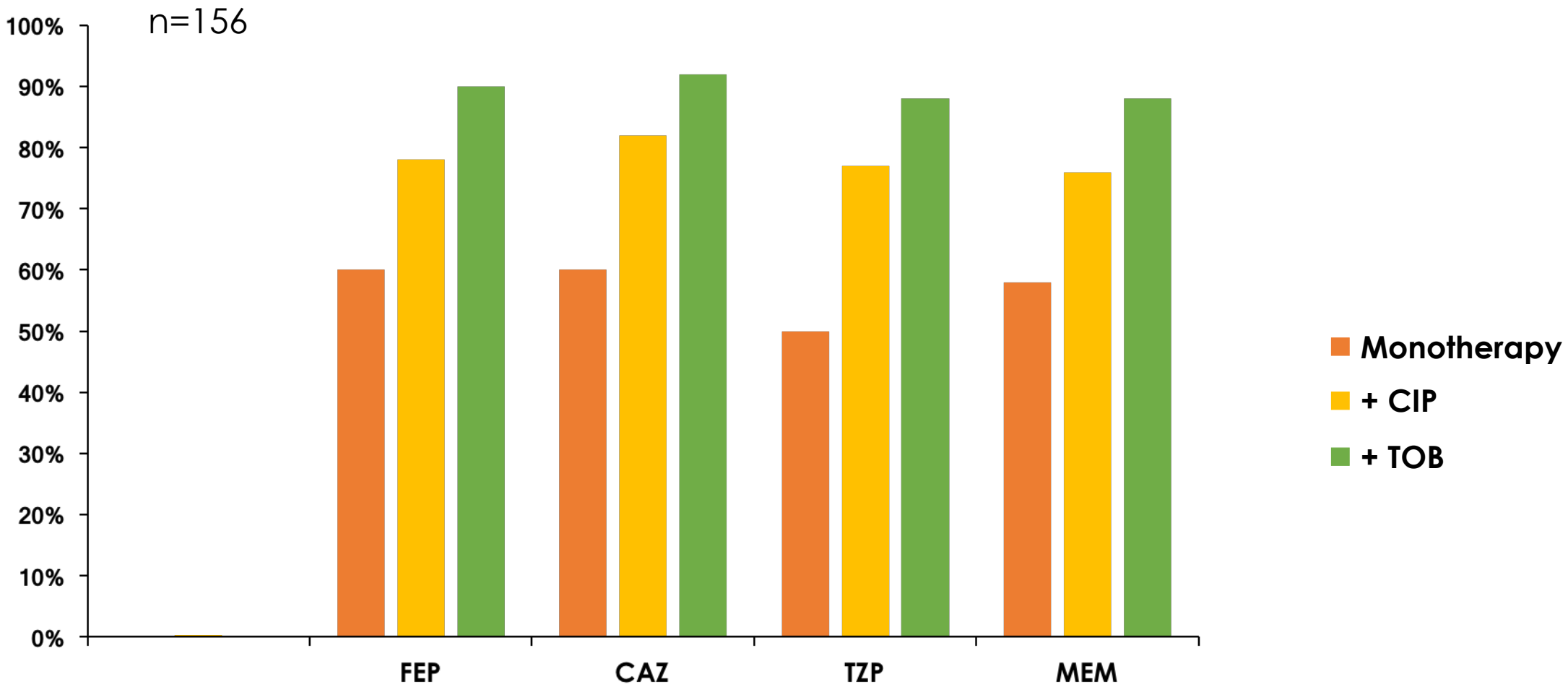
Résistance(s) à un antipseudomonas “socle”

non-récupérée(s) par un autre choix

Goodlet Antimicrob Agents Chemother 2017

Associations ?

Associations *in-vitro vs. P. aeruginosa* (US, souches respi, réa)



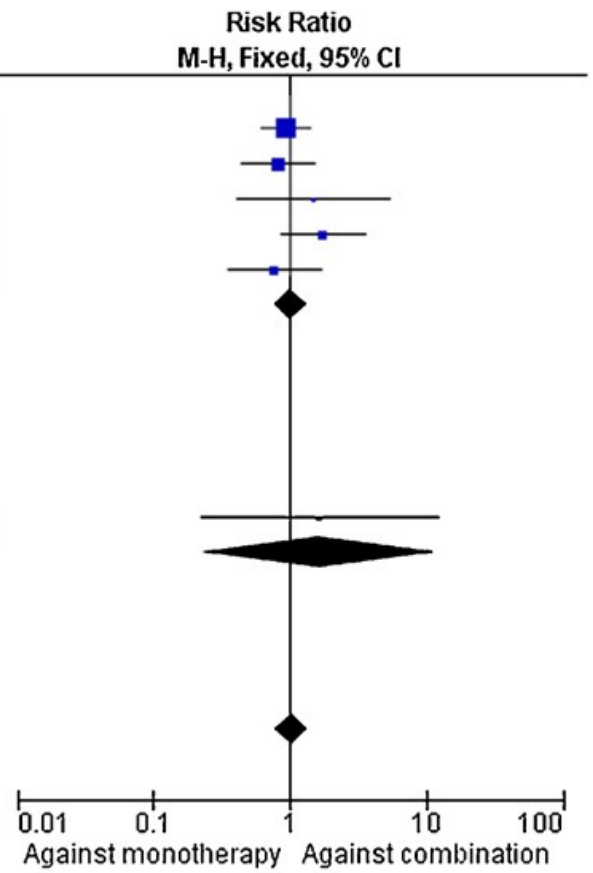
Goodlet KJ et al, Antimicrob Agents Chemother. 2017 Nov 22;61(12). pii: e01350-17

Mono vs. bithérapie *P. aeruginosa*

β-lact vs. même β-lact + FQ ou aminoside

ttt probabiliste mortalité

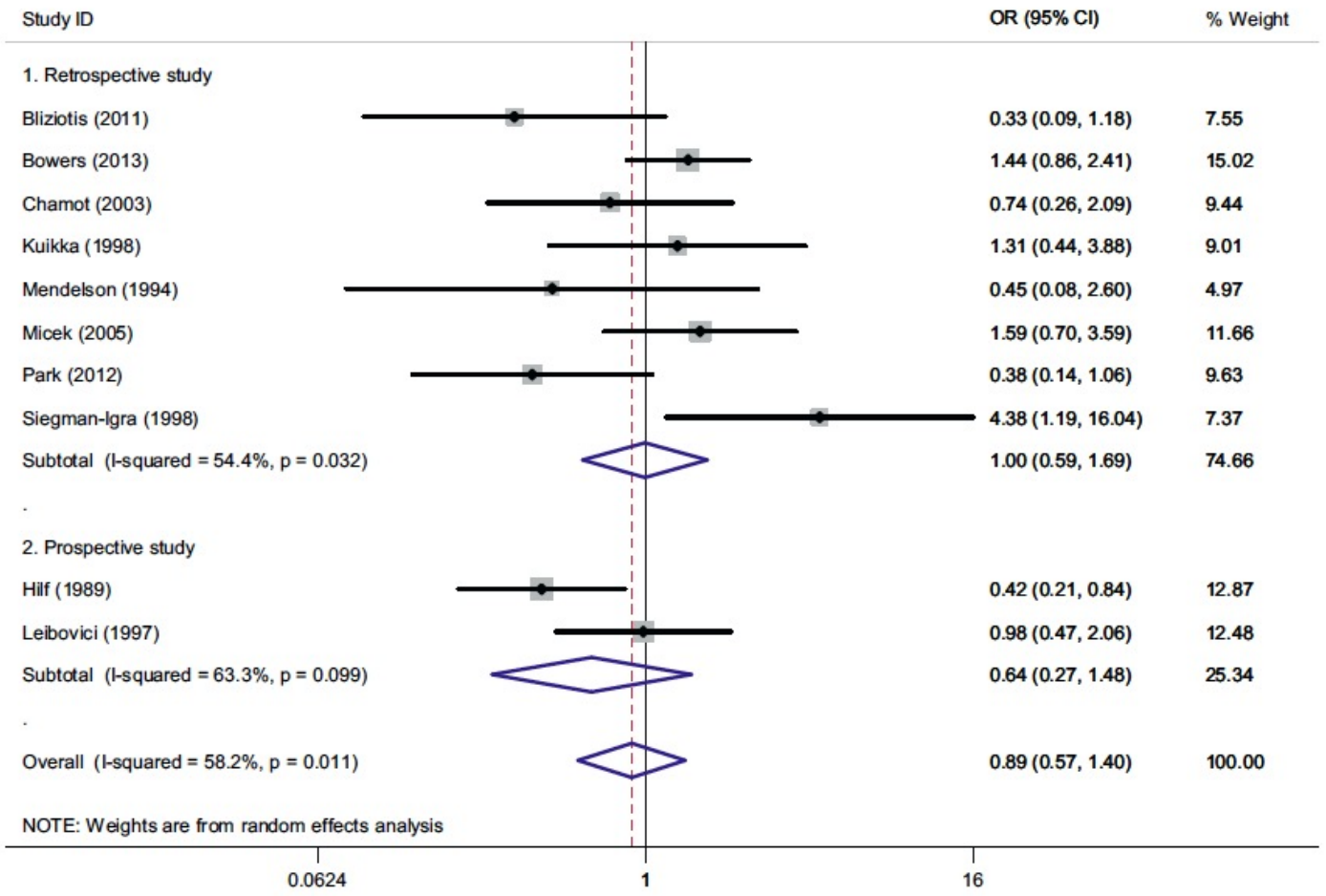
Study or Subgroup	Combination Events	Total	Monotherapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Non-RCTs						
Garnacho-Montero 2007	41	104	22	52	43.4%	0.93 [0.63, 1.39]
Leibovici 1997	11	39	21	61	24.2%	0.82 [0.45, 1.51]
Mendelson 1994	3	5	2	5	3.0%	1.50 [0.41, 5.45]
Micek 2005	13	59	12	95	13.6%	1.74 [0.85, 3.56]
Todeschini 1999	16	66	6	19	13.8%	0.77 [0.35, 1.69]
Subtotal (95% CI)		**273**		**232**	**97.9%**	**1.01 [0.77, 1.33]**
Total events	84		63			
Heterogeneity: Chi² = 3.69, df = 4 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.94)						
1.5.2 RCTs						
Del Favero 2001	4	17	1	7	2.1%	1.65 [0.22, 12.25]
Subtotal (95% CI)		**17**		**7**	**2.1%**	**1.65 [0.22, 12.25]**
Total events	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.63)						
Total (95% CI)		**290**		**239**	**100.0%**	**1.02 [0.78, 1.34]**
Total events	88		64			
Heterogeneity: Chi² = 3.94, df = 5 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.86)						
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%						



Vardaka Int J of Antimicrob Agents 2013

Mono vs. bithérapie *P. aeruginosa* (bactériémies)

β-lact vs. même β-lact + FQ ou aminoside



Hu Int J of Antimicrob Agents 2013

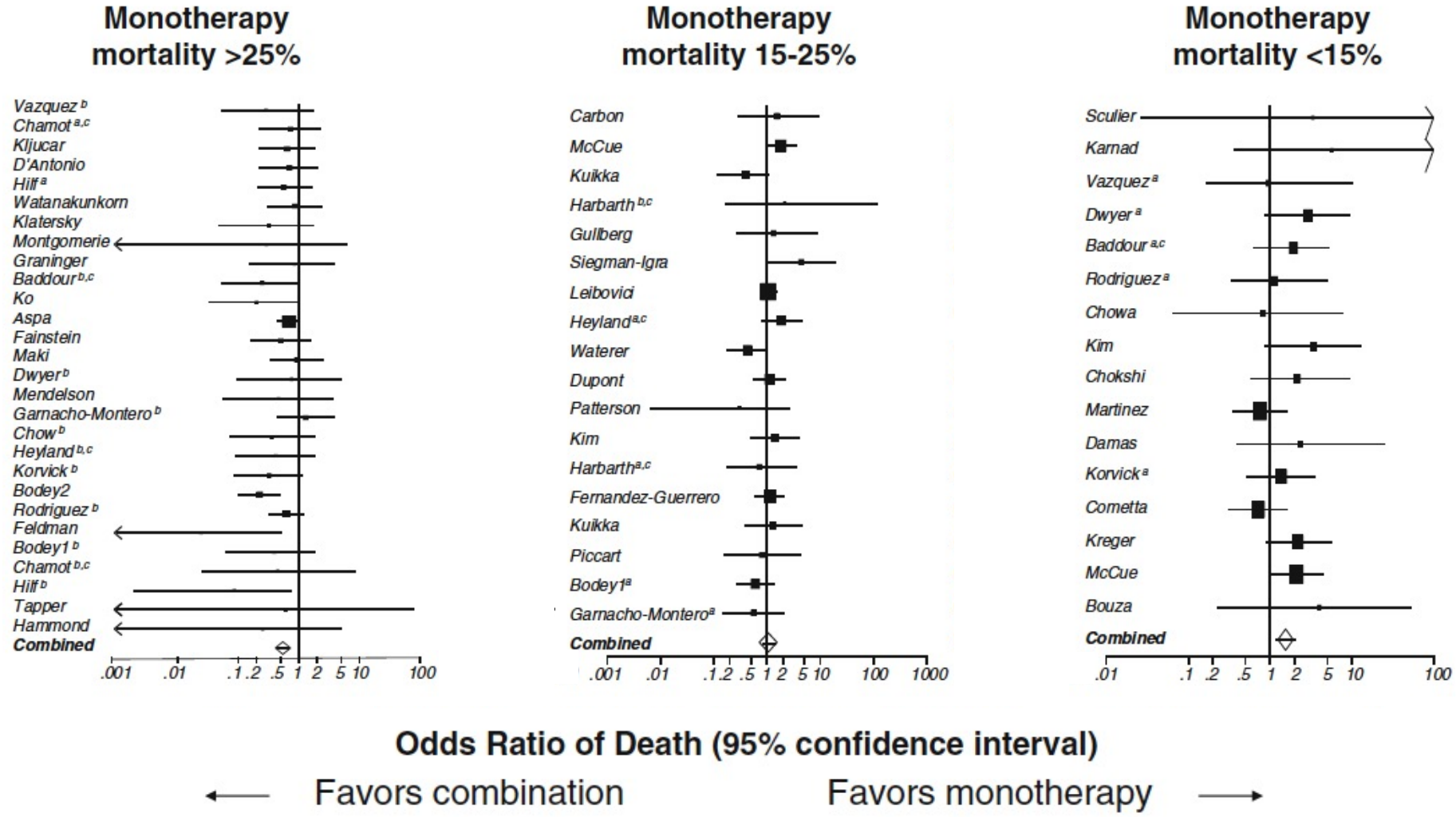
Controverse des associations antibiotiques…et *P. aeruginosa*

- Aucune méta-analyse ne met en évidence un avantage sur la mortalité
- MAIS :
  - beaucoup d'études rétrospectives
  - de cohortes non randomisées
  - patients peu graves
  - majorité de "bactériemies" (uro-sepsis drainés ou sur KT retirés)
  - peu de foyers à haut inoculum non-éradicables type pneumonie grave
  - souvent association avec aminosides à une époque de doses non optimisées

Nécessité RCT monotherapie versus associations,

infections sévères à *P. aeruginosa*

Associations… pour les infections graves uniquement?



Liang SY and Kumar A, l Curr Infect Dis Rep. 2015 Jul;17(7):493

Associations (méta-analyse recommandations IDSA 2016)

MORTALITY OUTCOMES					
		Mortality Rate by Therapy n of Deaths/Total n of Patients (%)			
	Sample Size, n	Monotherapy	Combination Rx	Odds Ratio (95% Confidence Interval)	*P*
Intensive care unit mortality	2446	437/1223 (35.7%)	352/1223 (28.8%)	0.75 (0.63-0.88)	.0006
Hospital mortality	2446	584/1223 (47.8%)	457/1223 (37.4%)	0.69 (0.59-0.81)	<.0001
Death from:					
Refractory shock	2446	311/1223 (25.4%)	258/1223 (21.1%)	0.78 (0.65-0.95)	.01
Sepsis-related organ failure	2446	184/1223 (15%)	137/1223 (11.2%)	0.71 (0.56-0.90)	.005
Nonsepsis-related organ failure	2446	89/1223 (7.3%)	62/1223 (5.1%)	0.68 (0.49-0.95)	.02

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ATB anti- *P. aeruginosa* (Recommandations IDSA 2016)

B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR
Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
OR	OR
Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
OR	
Monobactams[f] Aztreonam 2 g IV q8h	

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Recommandations formalisées d'experts

PNEUMONIES ASSOCIÉES AUX SOINS DE RÉANIMATION

RFE commune SFAR – SRLF

Société Française d'Anesthésie et de Réanimation

Société de Réanimation de Langue Française

En collaboration avec les Sociétés ADARPEF et GFRUP

Association des Anesthésistes Réanimateurs Pédiatriques d'Expression Française,

Groupe Francophone de Réanimation et Urgences Pédiatriques

HEALTHCARE ASSOCIATED PNEUMONIA IN INTENSIVE CARE UNIT

http://sfar.org/pneumonies-associees-aux-soins-de-reanimation/

Leone Anaesth Crit Care Pain Med 2018

Traitement PASR : antibiothérapie probabiliste / associations

R3.2 **– Il faut traiter par monothérapie en probabiliste les pneumonies associées aux soins du patient immunocompétent** sous ventilation mécanique,

en dehors de la présence de

facteurs de risque de bactéries multirésistantes, de bacilles à Gram négatif non fermentants,*

facteurs de risque élevé de mortalité (choc septique, défaillances d'organes)

GRADE 1+, ACCORD FORT

*** FdR non-fermentants (*Pseudomonas aeruginosa*…)**

- **antibiothérapie dans les 90 jours** précédant l'épisode de pneumonie
- **hospitalisation de plus de 5 jours précédant l'épisode** de pneumonie
- séance d'épuration extra-rénale lors du diagnostic de pneumonie
- **choc septique, SDRA**

http://sfar.org/pneumonies-associees-aux-soins-de-reanimation/

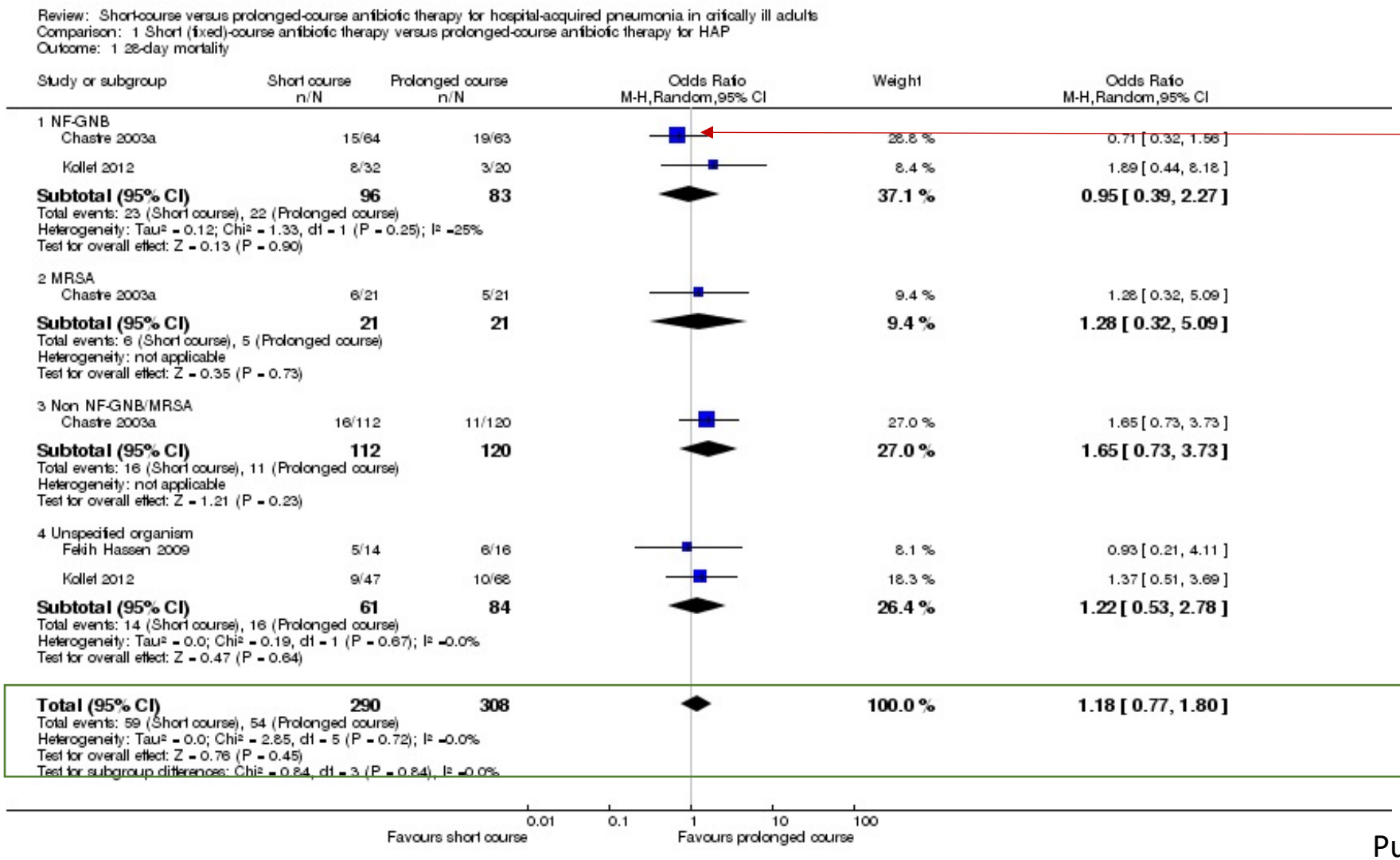
Leone Anaesth Crit Care Pain Med 2018

Traitement PASR : propositions thérapeutiques (Avis d'experts)

Pneumonie tardive **≥ 5 jours** ***Ou autre facteur de risque de bacille à Gram négatif non fermentant***	Béta-lactamine active contre *P. aeruginosa* + Aminoside [b] ou Fluoroquinolone	Ceftazidime ou Céfépime ou Pipéracilline-tazobactam ou si portage de BLSE [c] Imipenem-cilastatine ou Méropénème + Amikacine [d] ou Ciprofloxacine Si allergie aux Béta-lactamines Aztréonam + Clindamycine	6 g/j 4 à 6 g/j 16 g/j 3 g/j 3 à 6 g/j 30 mg/kg/j 400 mg x 3/j 3 à 6 g/j 600 mg x 3 à 4/j

http://sfar.org/pneumonies-associees-aux-soins-de-reanimation/ Leone Anaesth Crit Care Pain Med 2018

Traitement PASR : durée courte ≤ 8j vs. > 8j



plus de récidives (microbiologiques surtout) de PAVM à *P. aeruginosa* sans différence de mortalité

aucune différence de mortalité

Pugh Cochrane Database Syst Rev 2015

Traitement PASR : durée

R3.5 – **Il ne faut pas prolonger plus de 7 jours la durée du traitement antibiotique** pour les pneumonies associées aux soins, **y compris pour les pneumonies à bacille à Gram négatif non fermentant**

en dehors de certaines situations
(immunodépression, empyème, pneumonie nécrosante ou abcédée)

GRADE 1-, ACCORD FORT

http://sfar.org/pneumonies-associees-aux-soins-de-reanimation/

Leone Anaesth Crit Care Pain Med 2018

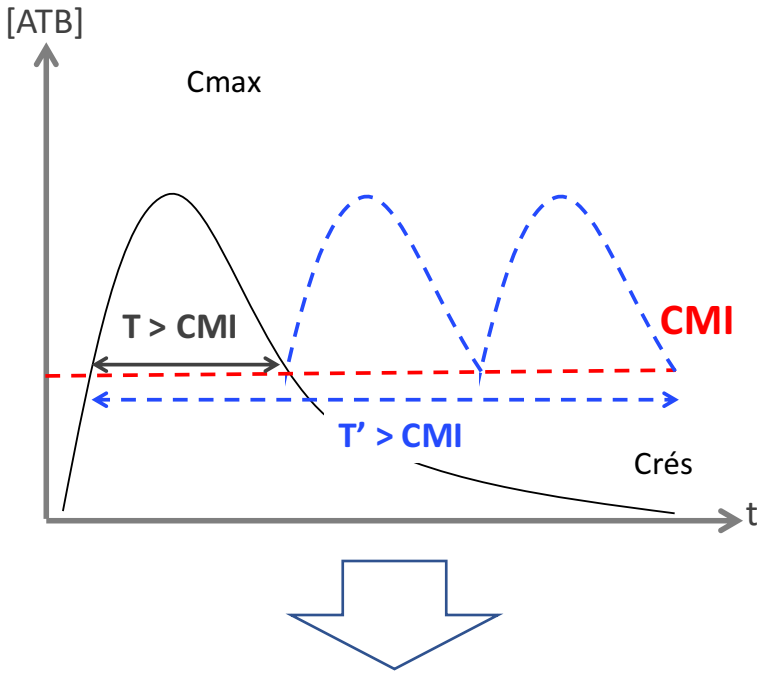
Cibles PK/PD

STUDIES DESCRIBING PK/PD TARGETS ASSOCIATED WITH IMPROVED PATIENT OUTCOMES	
Drug	**PK/PD target associated with improved outcome of HAP/VAP**
Aminoglycosides	Cmax/MIC 8-10 AUC/MIC 100
Levofloxacin	AUC/MIC > 87
Vancomycin	AUC/MIC > 400
Tigecycline (not approved for HAP/VAP)	AUC/MIC > 0.9
Cefoperazone (Discontinued in the US, EU, and Australia)	50% T>MIC
Ceftazidime	45% T>MIC
Ceftazidime and Cefepime	100% T>MIC
Meropenem	54% T>MIC for microbiological response C_{min}:MIC > 5 for clinical response
Meropenem	75% T>MIC

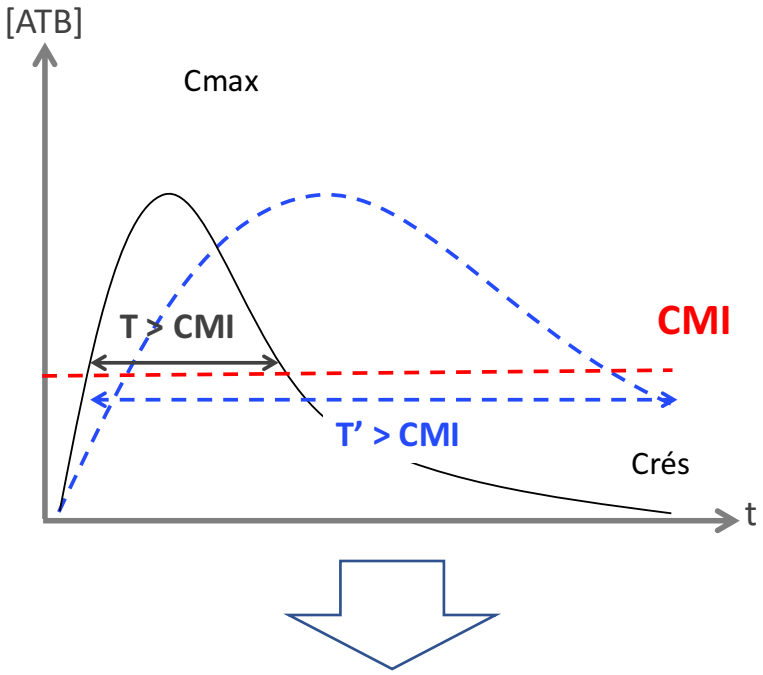
Kalil Clin Infect Dis 2016

Optimisation β-lactamines : modes d'administration

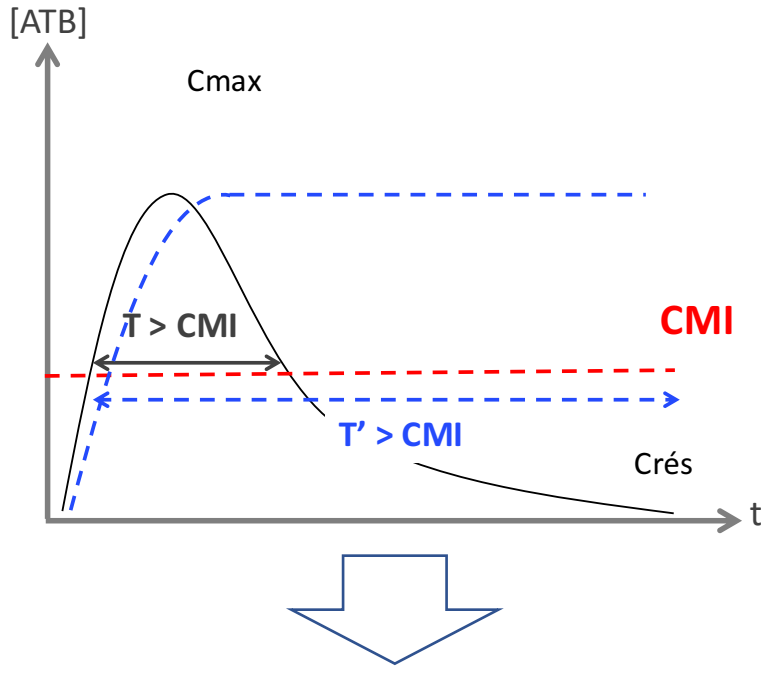
- Paramètre PK/PD d'efficacité = T > CMI



administrations **pluriquotidiennes**
AUGMENTATION T > CMI

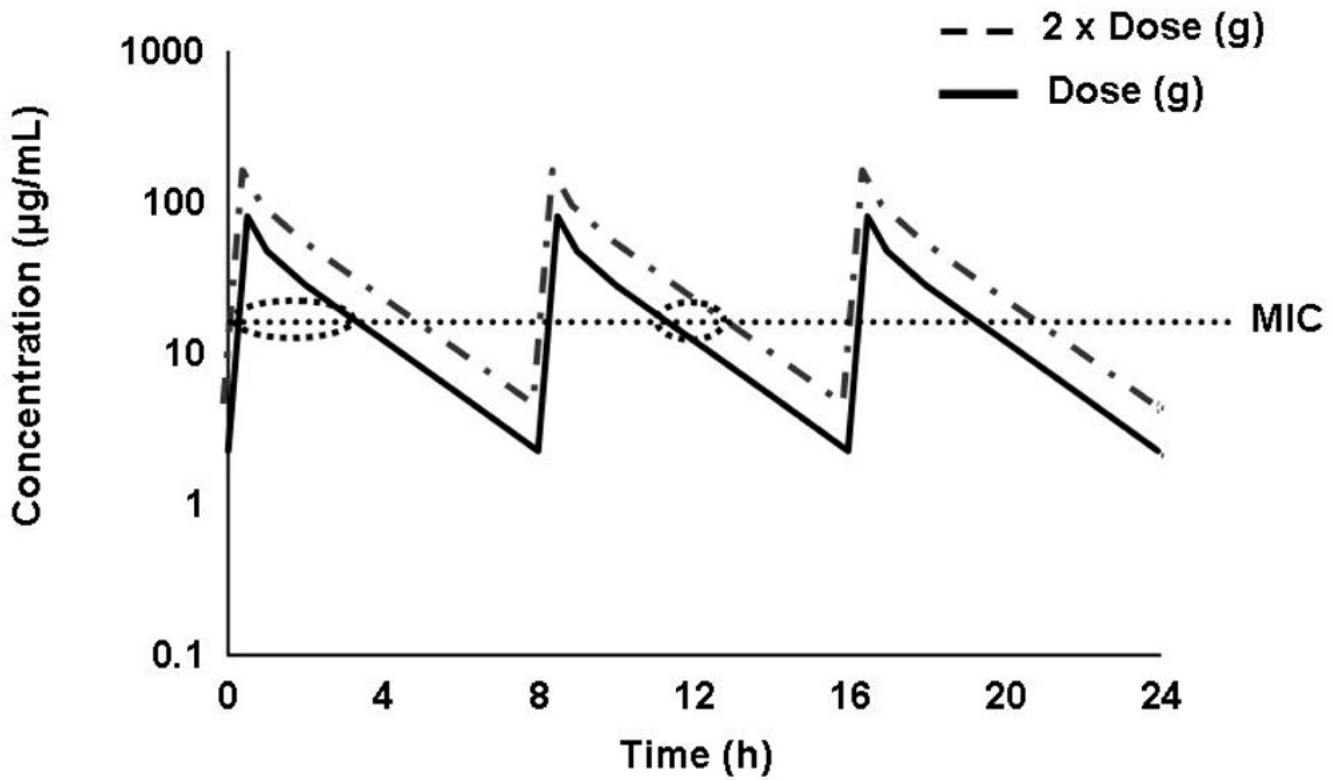


perfusions **prolongées**
AUGMENTATION T > CMI



perfusions **continues après charge**
AUGMENTATION T > CMI

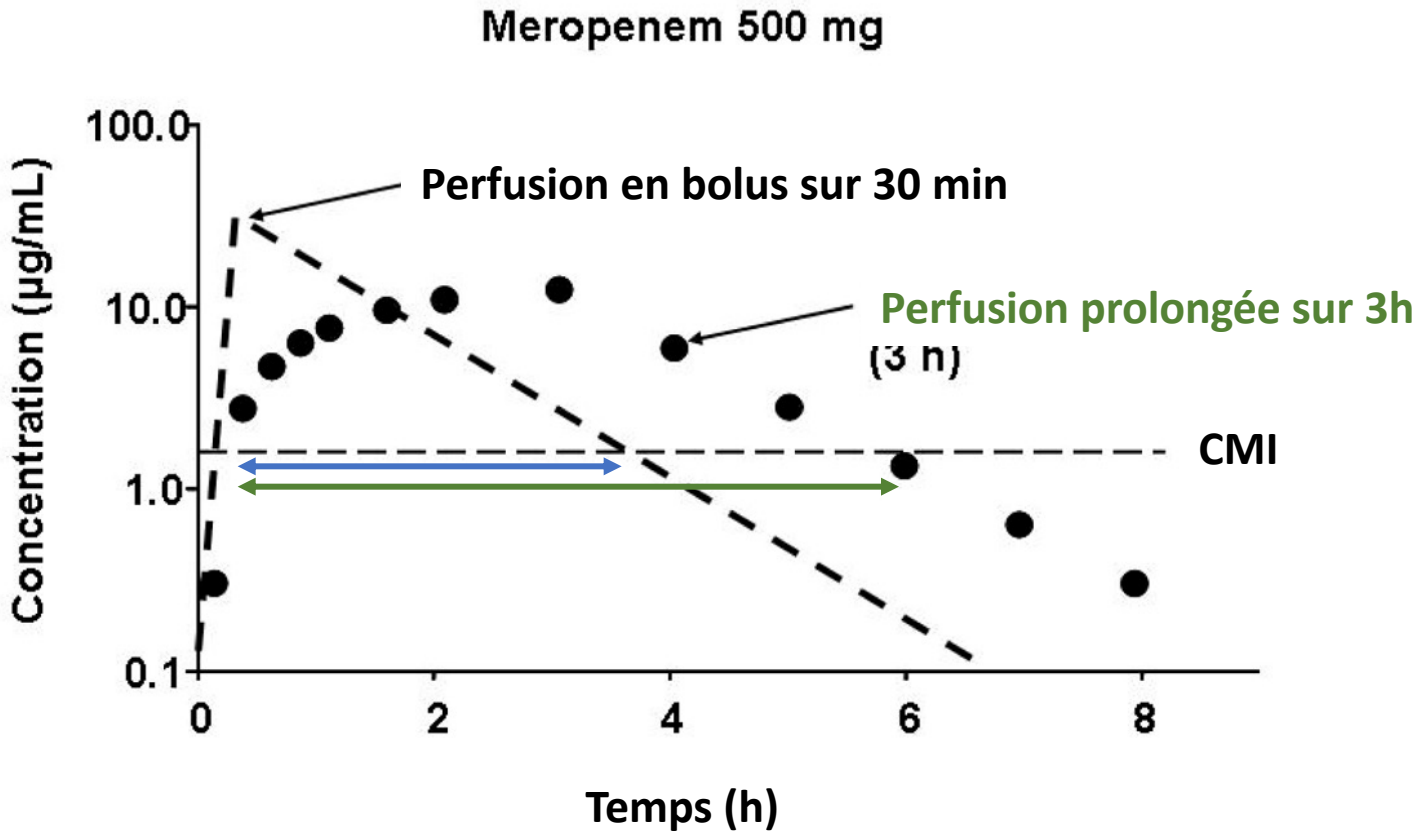
Optimisation β-lactamines : augmentation de doses ?



Augmente le pic **ET le temps** > CMI

Nicolau Crit Care 2008

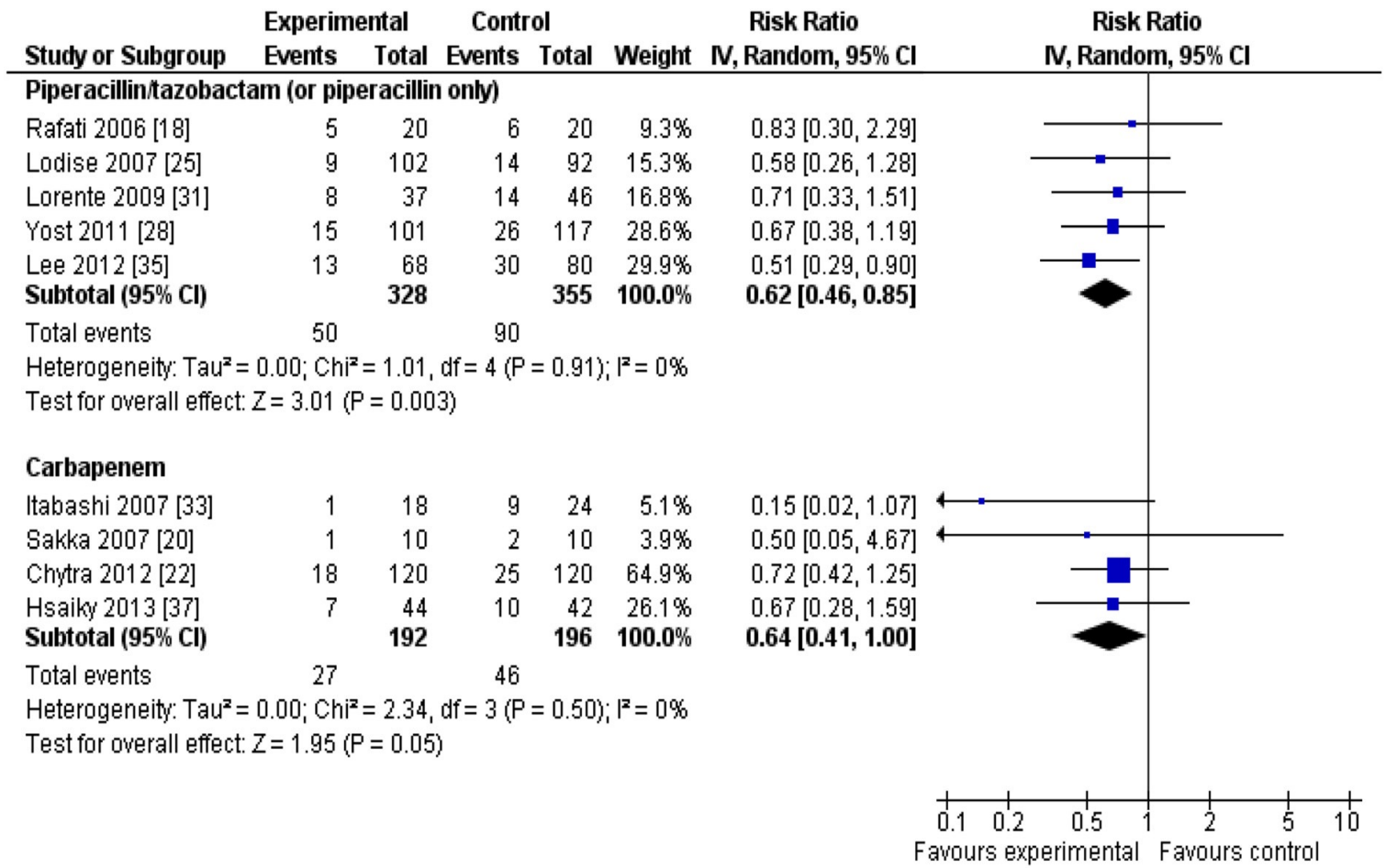
Optimisation β-lactamines : perfusions prolongées



Augmente le **le temps** > CMI

Nicolau Crit Care 2008

Continue/prolongée vs. intermittente : PIP/TAZ, carbapénèmes

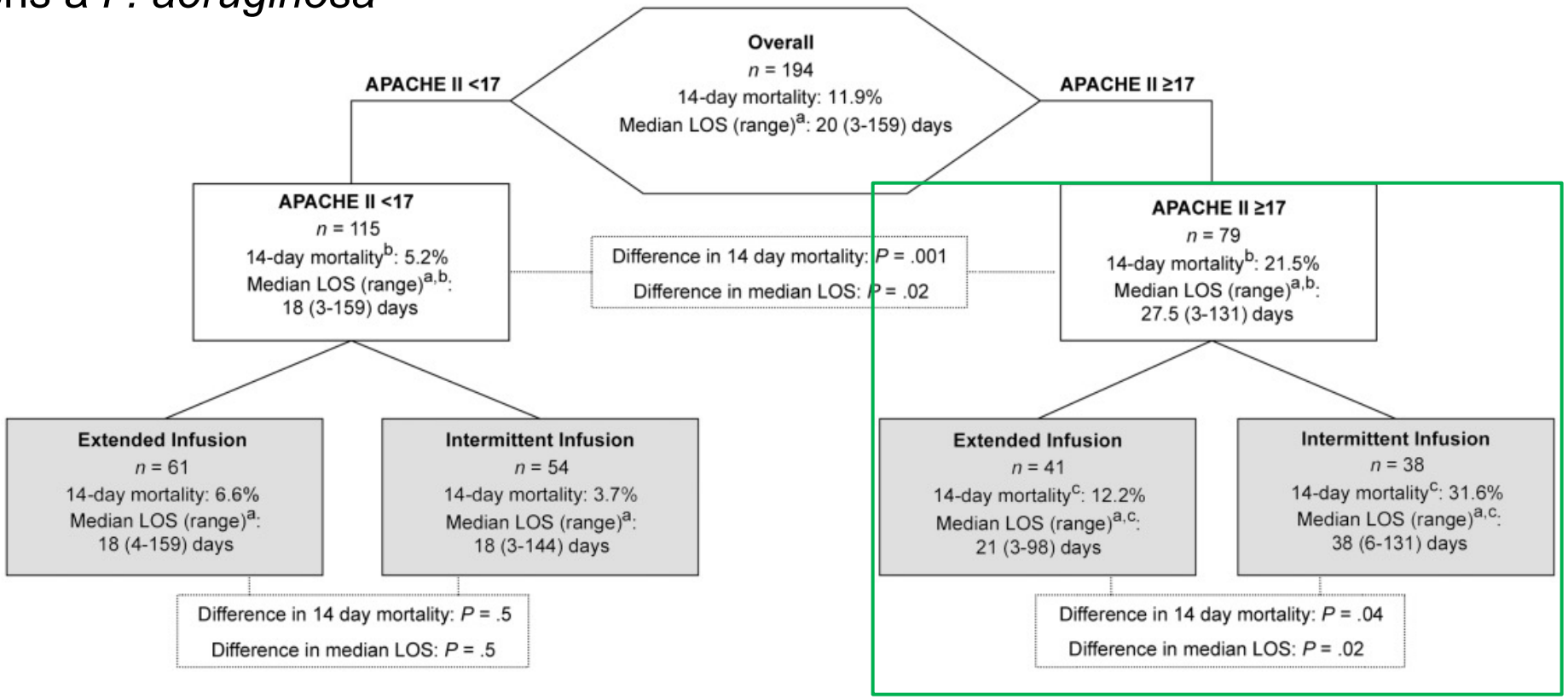


Chant Crit Care 2013

Optimisation β-lactamine : PIP/TAZ (Tazocilline®) prolongée

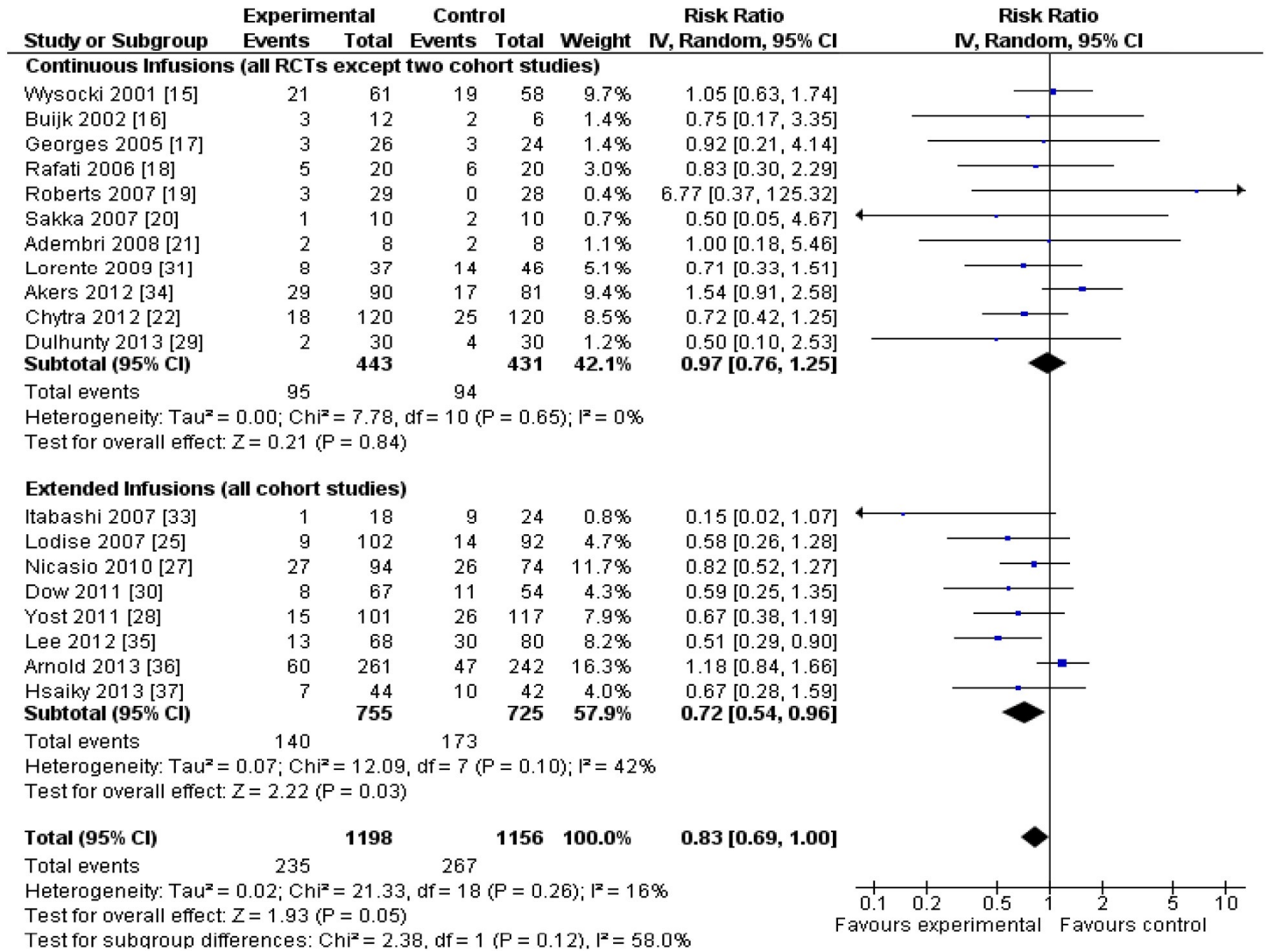
perfusions prolongées 4g sur 4h / 8h

infections à *P. aeruginosa*



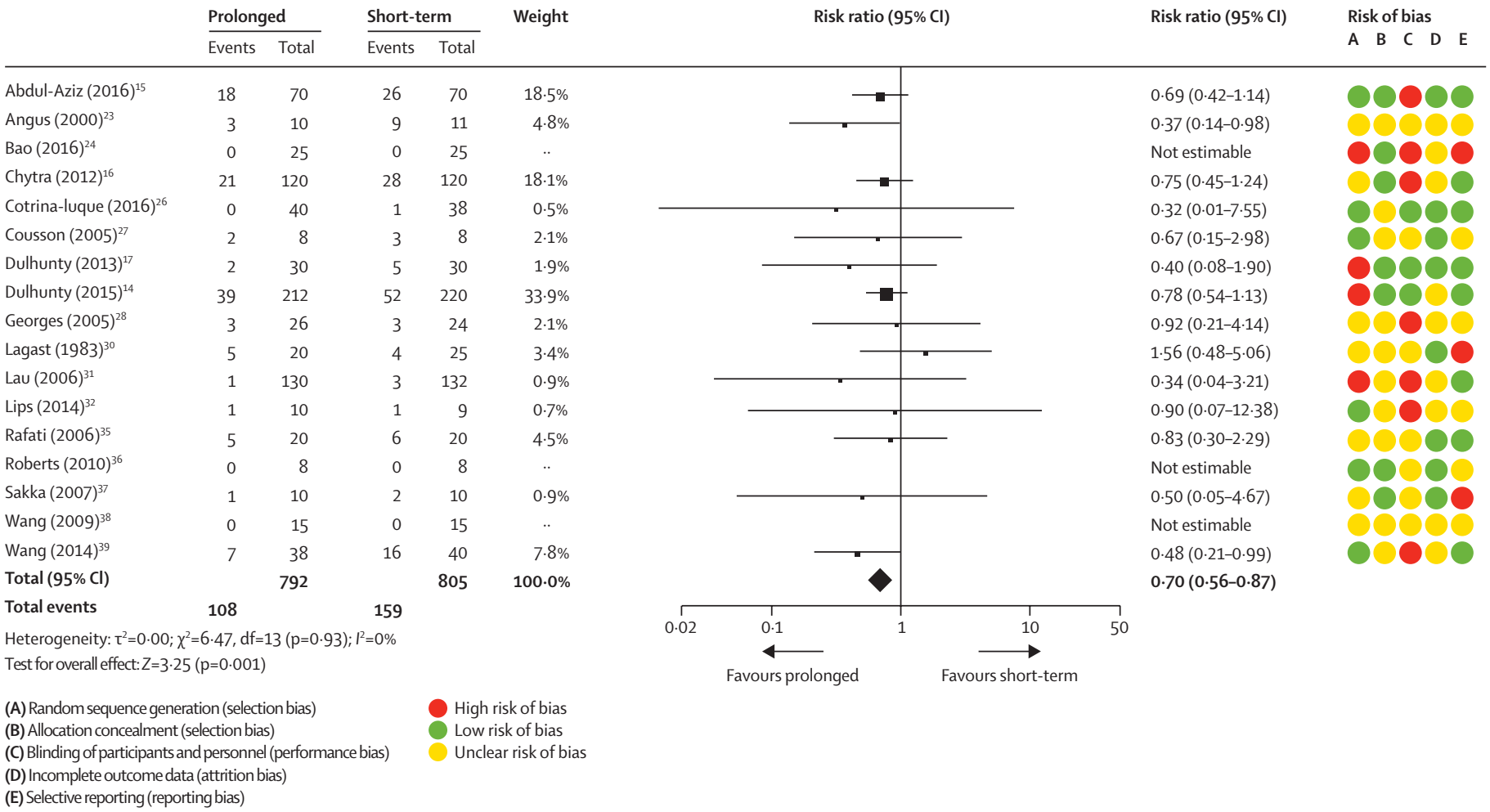
Lodise CID 2007

β-lactamine ~~Continue~~ **Prolongée !** vs. intermittente



Chant Crit Care 2013

β-lactamines Prolongées vs. intermittentes (sepsis)



	Prolonged		Short-term		Weight	Risk ratio (95% CI)	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)[32]	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

Vardakas Lancet Infect Dis 2018

Optimisation β-lactamine : Cefépime prolongée

2 g sur 4h / 8 h vs. 2g sur 30' /8h

infections à *P. aeruginosa*

	Infusion treatment[a]		
Clinical or economic outcome	Intermittent (n = 54)	Extended (n = 33)	P^b
Mortality	11 (20)	1 (3)	0.03
LOS			
Hospital	14.5 (6–30)	11 (7–20)	0.36
Infection related	12 (6–21)	10 (6–16)	0.45
ICU	18.5 (5.5–32.5)	8 (4–20)	0.04
Duration (days) of mechanical ventilation	14.5 (5–30)	10.5 (8–18)	0.42
Cost (US$)			
Total hospital costs	51,231 (17,558–107,031)	28,048 (13,866–68,991)	0.13
Infection-related hospital costs	15,322 (8,343–27,337)	13,736 (10,800–23,312)	0.78

Variable	OR (95% CI)	P
Infusion type	0.06 (0.001–0.64)	0.01
ICU admission at time of culture collection	8.88 (1.45–100.85)	0.01
APACHE II score	1.13 (1.03–1.27)	0.01

Bauer AAC 2013

CA-SFM Pseudomonas aeruginosa (quel que soit l'ATB)

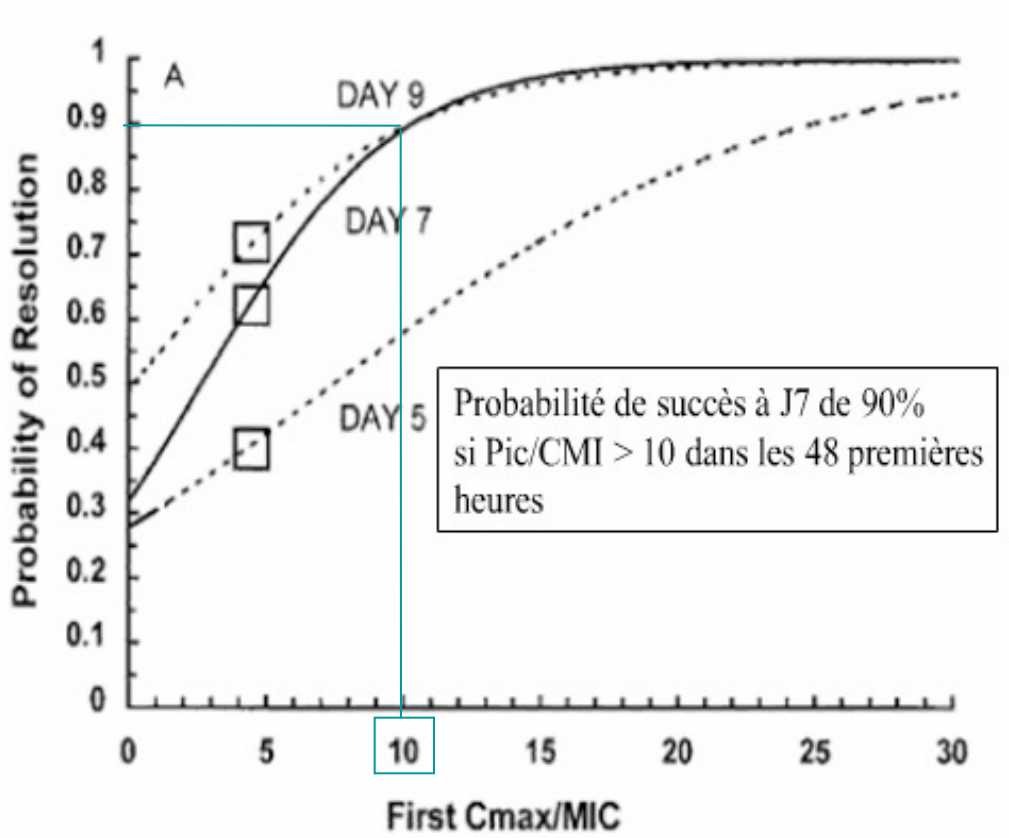
Pénicillines	Concentrations critiques (mg/L) S ≤	R >	Charge du disque (µg)	Diamètres critiques (mm) S ≥	R <	Notes Chiffres arabes pour les commentaires portant sur les concentrations critiques (CMI) Lettres pour les commentaires portant sur les diamètres critiques d'inhibition
Pipéracilline[1]	16	16	**30**	18	18	1. Concentrations critiques valables uniquement pour des fortes posologies (avec ou sans tazobactam, 4 g x 4). 2. Concentration fixe de tazobactam (4 mg/L). 3. Concentrations critiques valables uniquement pour des fortes posologies (avec ou sans clavulanate, 3g x 6). A. Un résultat «sensible» à la ticarcilline et «intermédiaire» ou «résistant» pour l'association ticarcilline-acide clavulanique est dû à l'induction de la céphalosporinase par l'acide clavulanique (antagonisme). Il n'y a pas lieu de changer la catégorisation de la ticarcilline ni de l'association ticarcilline-acide clavulanique. 4. Concentration fixe d'acide clavulanique (2 mg/L).
Pipéracilline-tazobactam[2]	16[2]	16[2]	**30-6**	18	18	
Ticarcilline[3/A]	16	16	**75**	18	18	
Ticarcilline-acide clavulanique[3]	16[4]	16[4]	**75-10**	18	18	

Céphalosporines	Concentrations critiques (mg/L) S ≤	R >	Charge du disque (µg)	Diamètres critiques (mm) S ≥	R <	Notes Chiffres arabes pour les commentaires portant sur les concentrations critiques (CMI) Lettres pour les commentaires portant sur les diamètres critiques d'inhibition
Une synergie entre un disque contenant de l'acide clavulanique et un disque de ceftazidime, d'aztréonam ou de céfépime permet la détection de certaines bêta-lactamases à spectre étendu (BLSE).						
Céfépime	8[1]	8	**30**	21	21	1. Concentrations critiques valables uniquement pour des fortes posologies (2 g x 3). 2. Concentrations critiques valables uniquement pour des fortes posologies (2g x 3) ou 4 g en perfusion continue. 3. Pour la mesure de la CMI, la concentration d'avibactam est de 4 mg/L. Pour évaluer la sensibilité, la concentration du tazobactam est fixée à 4 mg/L. Une diminution de sensibilité à l'imipénème (diamètre < 20 mm) et une résistance à l'association ceftolozane-tazobactam (< 24 mm) est évocatrice de la production de carbapénèmase.
Ceftazidime	8[2]	8	**10**	17	17	
Ceftazidime-avibactam	8[3]	8[3]	**10-4**	17	17	
Ceftolozane-tazobactam	4	4	**30-10**	24	24	

Optimisation aminosides : premier pic élevé

(1er Pic > 10 x CMI de la bactérie)

Pneumopathie BGN sous aminosides

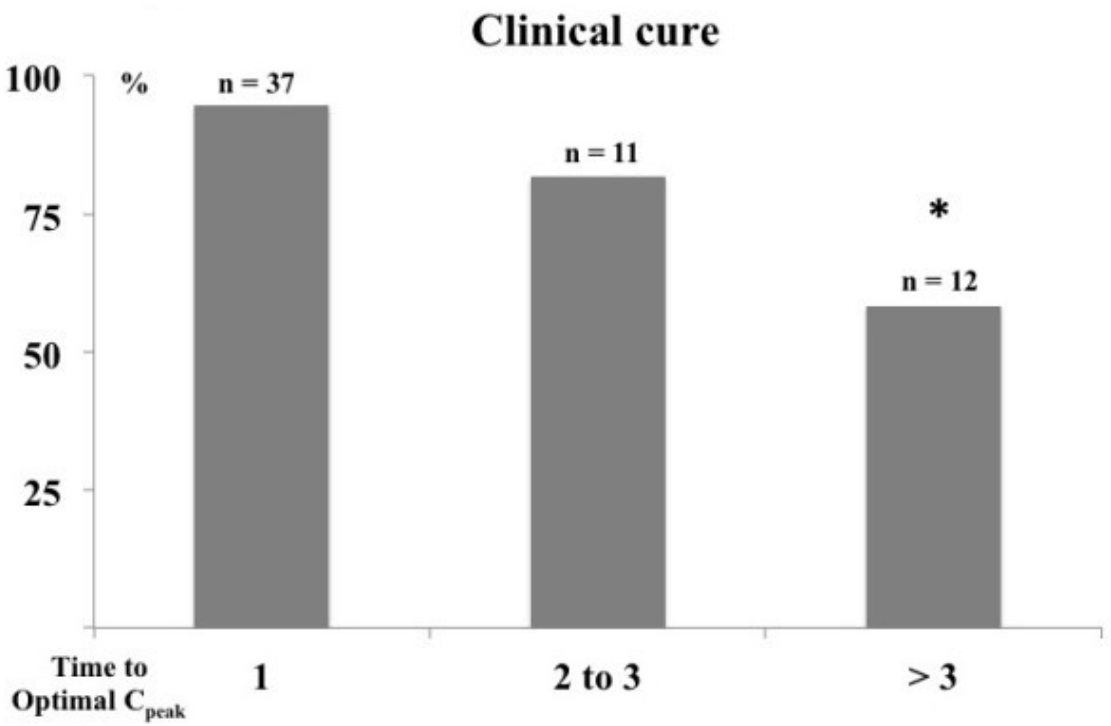


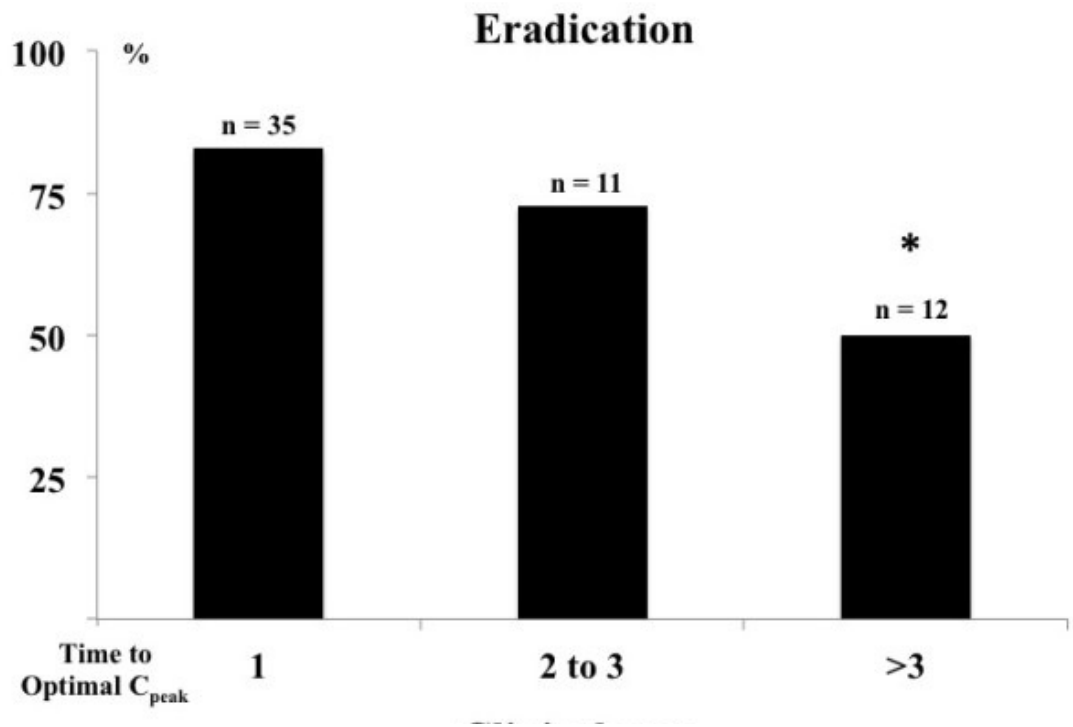
Kashuba *AAC* 1999

Amikacine : premier pic

Délai (j) du pic optimal (> 10x CMI)

PAVM (30% *P. aeruginosa*)





Duszynska Crit Care 2013

Optimisation aminosides : premier pic élevé et dose/poids

Regimen	Peak >64 µg/ml n (%)	C_{min} >5 µg/ml n (%)
15 mg/kg TBW	7 (9)	29 (39)
25 mg/kg TBW	50 (72)	39 (52)
30 mg/kg TBW	59 (79)	43 (58)
25 mg/kg IBW	35 (47)	39 (52)
25 mg/kg DW	42 (56)	39 (52)

Doses were calculated by using total body weight (TBW), ideal body weight (IBW), or IBW with correction factors (DW) for extreme body mass indexes.

25-30 mg/kg…poids REEL !

Taccone Crit Care 2010

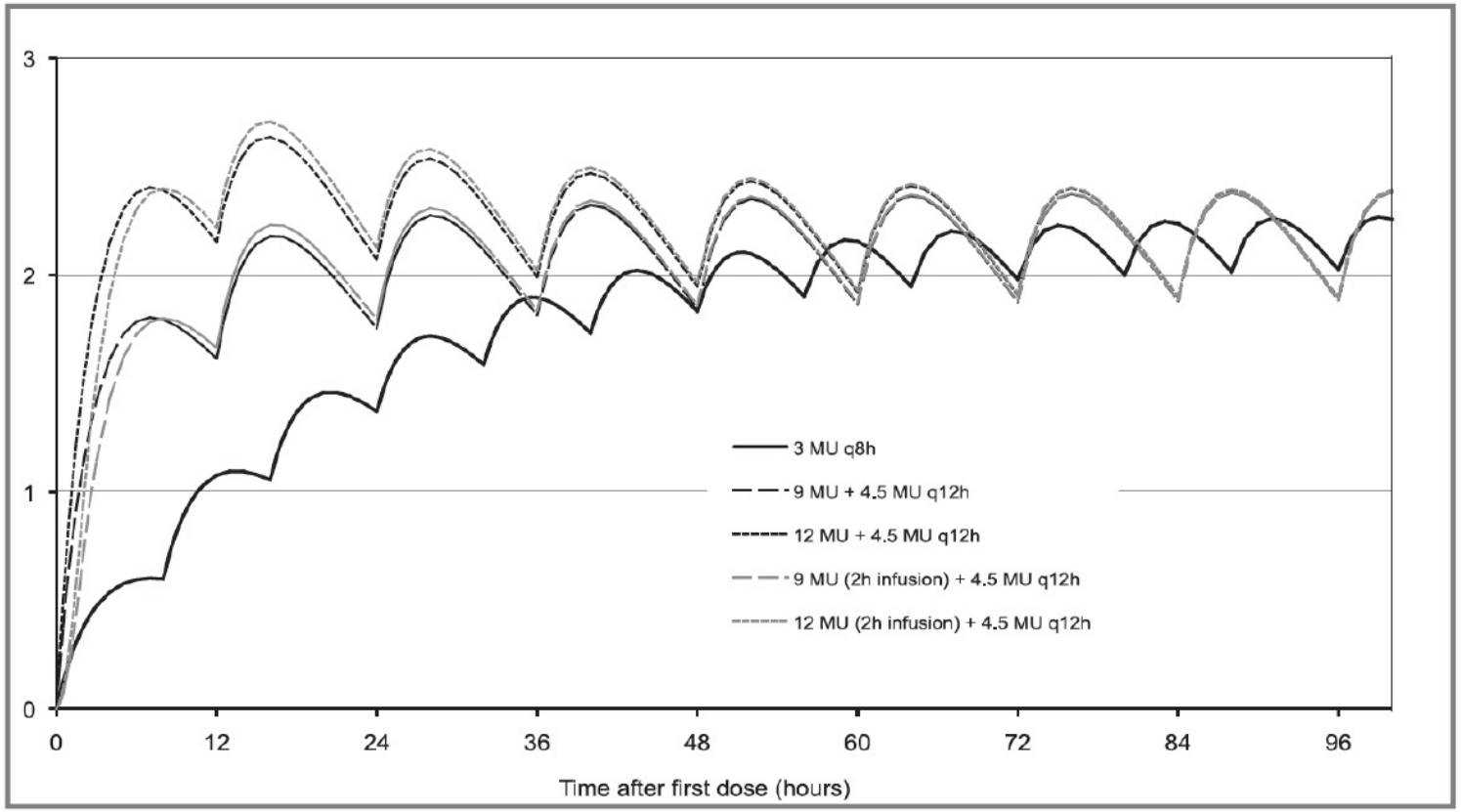
Optimisation colimycine : modélisation

9 MUI qq soit fonction rénale (Cmax 8)

Puis posologie 2 x 4,5 MUI/j normoR (10 MUI/j max)

Cl<50: 7 MUI/j

Cl<10: 3 MUI/j



Pachouras AAC 2009

Optimisaiton colimycine : clinique

High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

Lidia Dalfino,[1] Filomena Puntillo,[1] Adriana Mosca,[2] Rosa Monno,[2] Maria Luigia Spada,[1] Sara Coppolecchia,[1] Giuseppe Miragliotta,[2] Francesco Bruno,[1] and Nicola Brienza[1]

- **38 VAP ou septicémies à *A. Baumannii*, *K. pneumoniae* et *P. aeruginosa***
- **Colistine : 9 MUI dose de charge**
  4,5 MUI x 2/j

- **Guérison clinique : 82,1%**
- **Ins rénale : 17,8 % (aucune nécessitant EER)**
  Régression en 10 j après l'arrêt de la colistine

Dalfino L CID 2012 March 15

Dalfino Clin Infect Dis 2012

Molécules à spectre élargi (…contre les souches résistantes) ?

Nouvelles β-lactamines/inhibiteurs β-lactamase (BL/BLI)

	nouveaux BLI			anciens BLI		
	Relebactam	Vaborbactam	Avibactam	Clavulanic acid	Sulbactam	Tazobactam
Class A						
TEM	+	+	+	+	+	+
SHV	+	+	+	+	+	+
CTX-M	+	+	+	+	+	+
KPC	+	+	+	−	−	−
Class B						
MBL (VIM, IMP)	−	−	−	−	−	−
Class C						
AmpC	+	+	+	−	±[a]	−
Class D						
OXA	±	−[b]	±	−	−	−

Zhanel Drugs 2018

Nouvelles β-lactamines/inhibiteurs β-lactamase (BL/BLI)

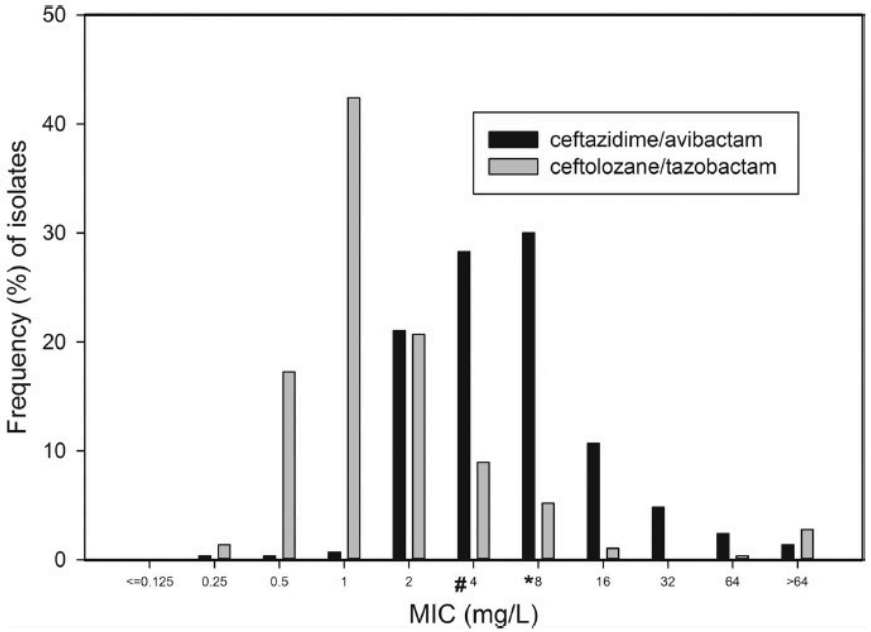
nouveaux BLI | anciens BLI | **+ nouvelle BL ceftolozane**

	Imipenem	meropenem	ceftazidime			
	Relebactam	Vaborbactam	Avibactam	Clavulanic acid	Sulbactam	Tazobactam
Class A						
TEM	+	+	+	+	+	+
SHV	+	+	+	+	+	+
CTX-M	+	+	+	+	+	+
KPC	+	+	+	−	−	−
Class B						
MBL (VIM, IMP)	−	−	−	−	−	−
Class C						
AmpC	+	+	+	−	±[a]	−
Class D						
OXA	±	−[b]	±	−	−	−

Zhanel Drugs 2018

Comparatif sensibilités aux BL/BLI de souches méropénème-R

USA
n=290



%R aux autres Blact anti-PA (en + de R-MEM)

β-Lactam agent(s)[a] to which isolates were NS (no. of isolates/ total, %)	S to CZA (no. of isolates, %)	S to C/T (no. of isolates, %)	P value[b]
FEP (168/290, 58)	114, 68	142, 85	0.0003
CAZ (157/290, 54)	105, 67	132, 84	0.0006
TZP (185/290, 64)	133, 72	159, 86	0.0013
ATM (183/290, 63)	132, 72	159, 87	0.0007
FEP and CAZ (133/290, 46)	82, 62	108, 81	0.0006
FEP and TZP (147/290, 51)	97, 66	122, 83	0.0012
FEP and ATM (131/290, 45)	82, 63	108, 82	0.0005
CAZ and TZP (145/290, 50)	95, 66	121, 83	0.0007
CAZ and ATM (121/290, 42)	73, 60	99, 82	0.0004
TZP and ATM (148/290, 51)	99, 67	125, 85	0.0006
FEP, CAZ, and TZP (127/290, 44)	78/127, 61	103/127, 81	0.0008
FEP, CAZ, and ATM (106/290, 37)	59/106, 56	84/106, 79	0.0004
FEP, TZP, and ATM (121/290, 42)	73/121, 60	98/121, 81	0.0006
CAZ, TZP, and ATM (118/290, 41)	70/118, 59	96/118, 81	0.0003
All 4 β-lactam agents (103/290, 36)	56/103, 54	81/103, 79	0.0004

ceftazidime-avibactam (CAZ/AVI)

S CAZ-AVI 54-72%

S TOL-TAZ 79-87%

Ceftolozane/tazobactam (TOL/TAZ)

Grupper AAC 2017

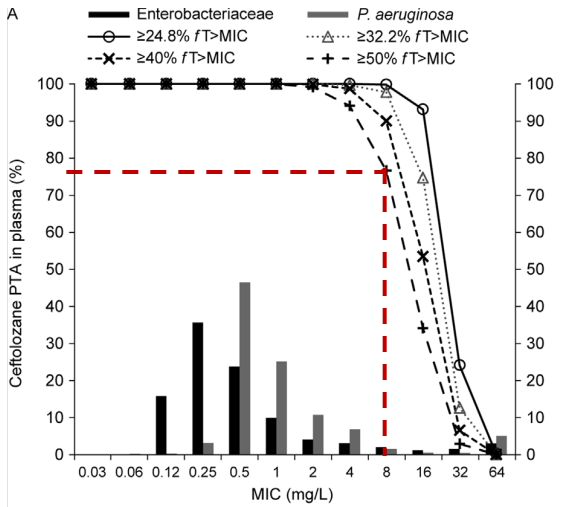
TOL/TAZ probabilités d'atteindre la cible PK/PD ~ dose et site

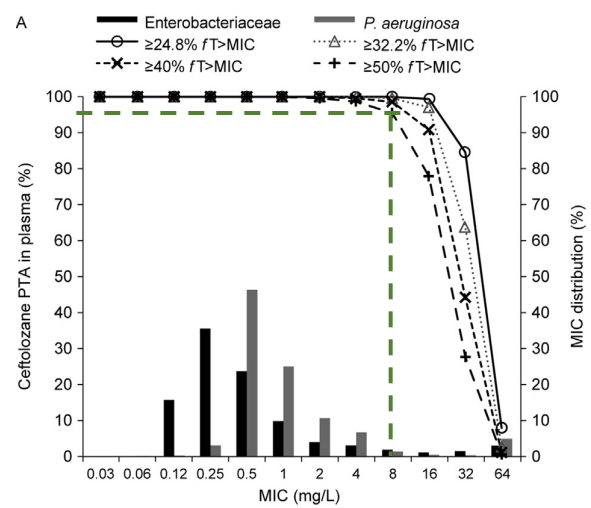
Simulations
Monte-Carlo
Cible Optimale **≥50%T>CMI**

1:0,5 g sur 60' / 8h

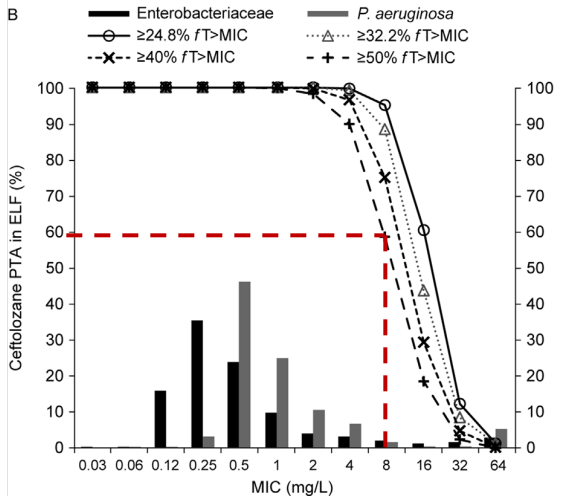
2:1 g sur 60' / 8h

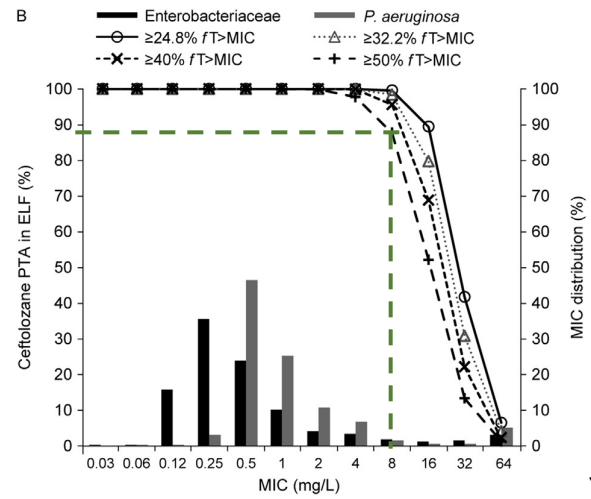
plasmatique





pulmonaire

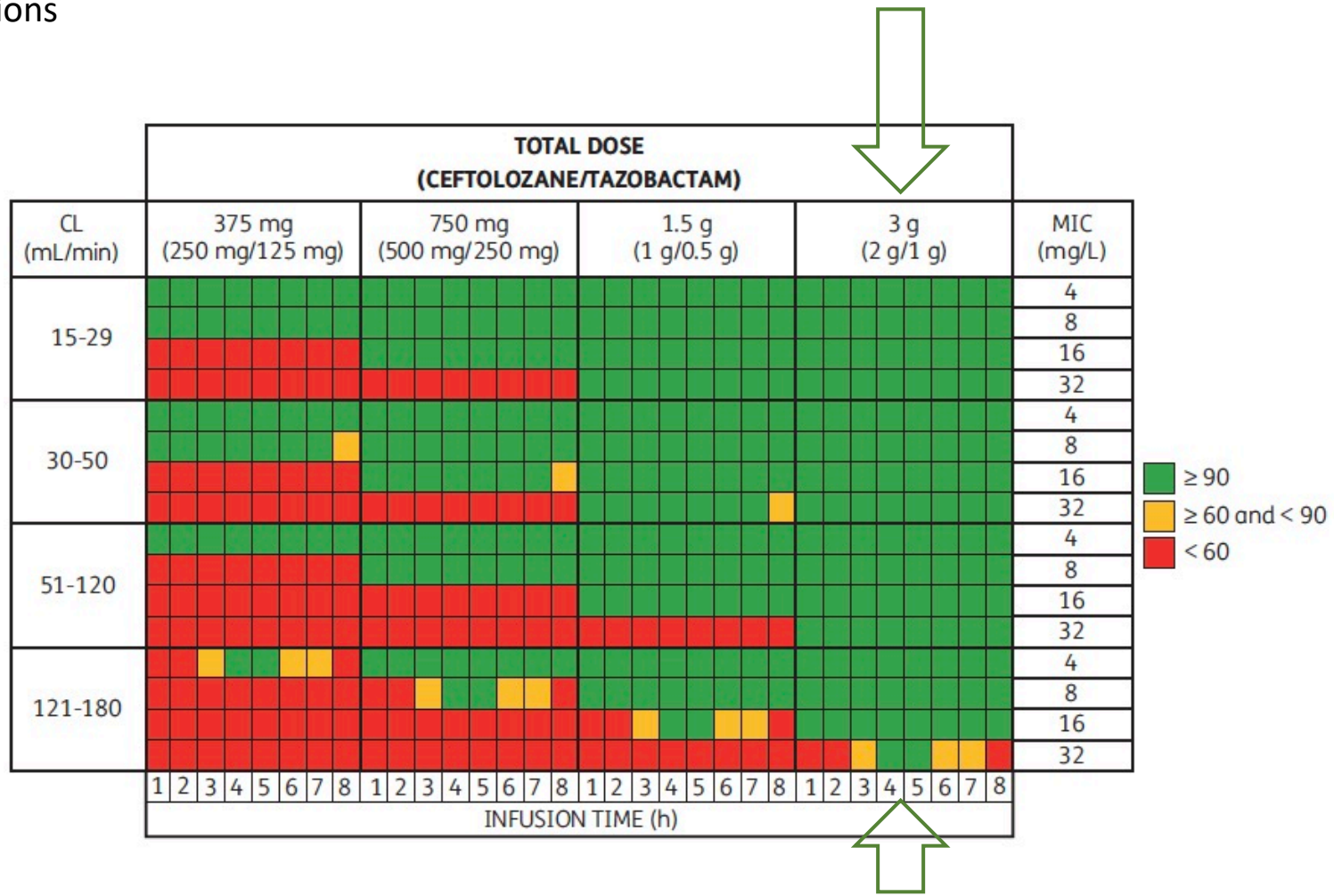




Xiao J Clin Pharmacol 2016

Perfusions prolongées hautes doses ceftolozane/tazobactam ?

Simulations



Natesan JAC 2017

Limites des données des essais randomisés d'antibiothérapie

Les essais randomisés contrôlés d'AMM de nouveaux ATB sont des essais

- fréquemment peu-graves (ou **moins graves**) afin de recruter en nombre
- concernant des infections à tous **BGN confondus**
  - ***P. aeruginosa* en proportion variable souvent faible**
  - *P. aeruginosa* multirésistants en nombre encore plus faible

Le reste =petites séries, case-reports…registres ?

= aucune conclusion forte spécifique à *P. aeruginosa*

Essais randomisés contrôlés de VAP ?

- plus grande proportion de *P. aeruginosa*
- patients de réanimation : infections plus graves
- comparateurs robustes

ceftolozane/tazobactam vs. mero PAVM PASR-V (ASPECT-NP)

- ERC double aveugle, 263 hôpitaux, 34 pays
- Patients de réanimation, ventilés (PAVM ou PASR-ventilée), 726 patients
- 3 g ceftolozane-tazobactam or 1 g meropenem I.V. / 8 h, 8-14j

	Ceftolozane–tazobactam group	Meropenem group	% difference (95% CI)*
28-day all-cause mortality (ITT population)†			
Overall	87/362 (24·0%)	92/364 (25·3%)	1·1 (–5·1 to 7·4)‡
Ventilator-associated pneumonia	63/263 (24·0%)	52/256 (20·3%)	–3·6 (–10·7 to 3·5)§
Ventilated hospital-acquired pneumonia	24/99 (24·2%)	40/108 (37·0%)	12·8 (0·2 to 24·8)§
28-day all-cause mortality (microbiological ITT population)†	53/264 (20·1%)	63/247 (25·5%)	4·4 (–2·8 to 11·8)‡
Clinical cure at test of cure (ITT population)†			
Overall	197/362 (54·4%)	194/364 (53·3%)	1·1 (–6·2 to 8·3)‡
Ventilator-associated pneumonia	147/263 (55·9%)	146/256 (57·0%)	–1·1 (–9·6 to 7·4)§
Ventilated hospital-acquired pneumonia	50/99 (50·5%)	48/108 (44·4%)	6·1 (–7·4 to 19·3)§
Clinical cure at test of cure (clinically evaluable population)¶			
Overall	139/218 (63·8%)	143/221 (64·7%)	–1·3 (–10·2 to 7·7)‡
Ventilator-associated pneumonia	105/159 (66·0%)	111/172 (64·5%)	1·5 (–8·7 to 11·6)§
Ventilated hospital-acquired pneumonia	34/59 (57·6%)	32/49 (65·3%)	–7·7 (–25·0 to 10·6)§
Microbiological eradication at test of cure (microbiological ITT population)†	193/264 (73·1%)	168/247 (68·0%)	4·5 (–3·4 to 12·5)‡

graves
Mortalité 20-25%

Non-inferiorité

Kolleff Lancet ID 2019

ceftolozane/tazobactam vs. mero PAVM PASR-V (ASPECT-NP)

- ERC double aveugle, 263 hôpitaux, 34 pays
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25%
P. aeruginosa

	Ceftolozane–tazobactam group	Meropenem group	% difference (95% CI)*
Gram-negative pathogens	157/259 (60·6%)	137/240 (57·1%)	3·5 (–5·1 to 12·1)
Enterobacteriaceae	120/195 (61·5%)	105/185 (56·8%)	4·8 (–5·1 to 14·5)
ESBL-producing Enterobacteriaceae	48/84 (57·1%)	45/73 (61·6%)	–4·5 (–19·3 to 10·7)
Pseudomonas aeruginosa	36/63 (57·1%)	39/65 (60·0%)	–2·9 (–19·4 to 13·8)
Multidrug-resistant *P aeruginosa*	13/24 (54·2%)	6/11 (54·5%)	–0·4 (–31·2 to 31·7)
Extensively drug-resistant *P aeruginosa*	4/10 (40·0%)	2/5 (40·0%)	0·0 (–43·6 to 40·3)

Data are n/N (%). *Unstratified Newcombe CIs; inferences drawn from these intervals might therefore not be reproducible.

Table 3: **Per-pathogen clinical cure at test-of-cure visit in the microbiological intention-to-treat population**

Non-infériorité en cure microbiologique, y compris P. aeruginosa

Kolleff Lancet ID 2019

ceftazidime/avibactam vs. meropenem PAS±PAVM (REPROVE)

- ERC, double aveugle, 136 centres, 23 pays
- Pneumonies nosocomiales (dont PAVM)
- CAZ (2g)/AVI (0,5g) sur 2h vs.MEM 1g sur 30 min /8h, 7-14j

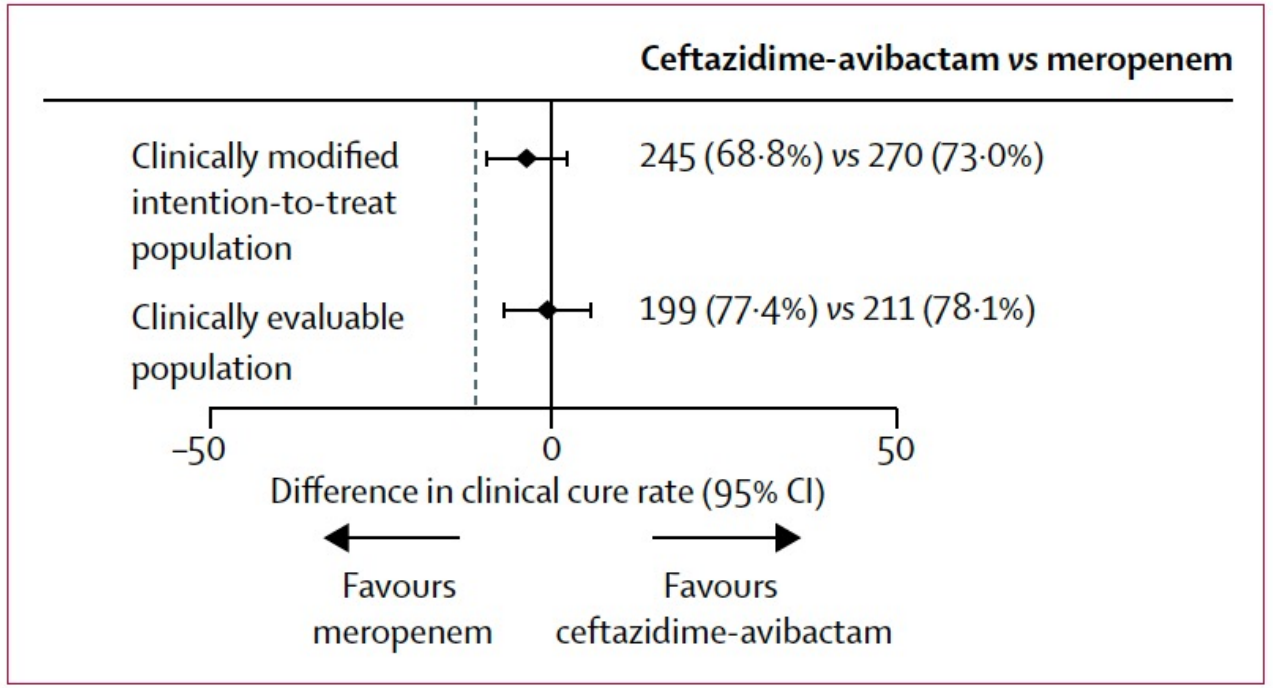


Figure 2: **Clinical cure rates at test-of-cure visit**
Data are number of patients with clinical cure (%). Dashed line indicates non-inferiority margin of −12·5%.

Torres Lancet ID 2018

ceftazidime/avibactam vs. meropenem PAS±PAVM (REPROVE)

- ERC, double aveugle, 136 centres, 23 pays
- Pneumonies nosocomiales (dont PAVM)
- CAZ (2g)/AVI (0,5g) sur 2h vs.MEM 1g sur 30 min /8h, 7-14j

P. aeruginosa (30%)

	Patients with clinical cure (clinically evaluable population)			Patients with favourable microbiological response* (extended microbiologically evaluable population)		
	Ceftazidime-avibactam (n=257)	Meropenem (n=270)	% difference (95% CI)	Ceftazidime-avibactam (n=125)	Meropenem (n=131)	% difference (95% CI)
Enterobacteriaceae						
Klebsiella pneumoniae	31/37 (83·8%)	39/49 (79·6%)	4·2 (–13·49 to 20·50)	29/37 (78·4%)	39/49 (79·6%)	–1·2 (–19·60 to 15·96)
Enterobacter cloacae	20/21 (95·2%)	7/11 (63·6%)	31·6 (4·79 to 61·30)	18/21 (85·7%)	7/11 (63·6%)	22·1 (–8·07 to 53·69)
Escherichia coli	8/11 (72·7%)	14/18 (77·8%)	–5·1 (–39·26 to 25·79)	10/11 (90·9%)	16/18 (88·9%)	2·0 (–29·11 to 26·44)
Proteus mirabilis	11/11 (100·0%)	7/8 (87·5%)	12·5 (–16·54 to 48·07)	9/11 (81·8%)	6/8 (75·0%)	6·8 (–30·73 to 46·51)
Serratia marcescens	10/12 (83·3%)	8/8 (100·0%)	–16·7 (–45·58 to 19·48)	9/12 (75·0%)	5/8 (62·5%)	12·5 (–27·47 to 51·82)
Enterobacter aerogenes	4/6 (66·7%)	2/5 (40·0%)	26·7 (–31·92 to 70·73)	5/6 (83·3%)	3/5 (60·0%)	23·3 (–31·30 to 68·33)
Gram-negative pathogens other than Enterobacteriaceae						
Pseudomonas aeruginosa	27/42 (64·3%)	27/35 (77·1%)	–12·8 (–32·25 to 8·01)	18/42 (42·9%)	14/35 (40·0%)	2·9 (–19·13 to 24·32)
Haemophilus influenzae	10/11 (90·9%)	11/13 (84·6%)	6·3 (–26·19 to 36·09)	11/11 (100·0%)	12/13 (92·3%)	7·7 (–20·08 to 34·00)
Gram-positive aerobes						
Staphylococcus aureus	11/14 (78·6%)	16/22 (72·7%)	5·8 (–25·24 to 32·67)	5/14 (35·7%)	17/22 (77·3%)	–41·6 (–67·04 to –8·36)

*Eradication or presumed eradication of the baseline pathogens.

Table 2: **Per-pathogen clinical cure rates and favourable microbiological response rates at test-of-cure visit**

Torres Lancet ID 2018

ceftazidime/avibactam vs. penem (pool des phases III)

Phase III clinical trials in patients with

- complicated **intra-abdominal infection (cIAI),**
- complicated **urinary tract infection (cUTI)**
- **nosocomial pneumonia (NP) including ventilator-associated pneumonia (VAP).**

Table 1. Ceftazidime/avibactam MIC range, MIC_{50} and MIC_{90} for MDR pathogens of key interest isolated in the ceftazidime/avibactam treatment arms of the Phase III trials (pooled mMITT population)

Pathogen	Number of isolates	Number of patients	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Susceptibility (%)
Enterobacteriaceae (all)	509	509	≤0.008 to >256	0.12	1	99.2
E. coli	323	323	≤0.008 to 8	0.12	0.5	100
K. pneumoniae	123	123	≤0.008 to >256	0.5	1	98.4
E. cloacae	29	29	0.25 to >256	1	32	89.7
Proteus mirabilis	17	17	≤0.008 to 1	0.06	0.5	100
P. aeruginosa	56	56	1 to >256	8	64	66.1

Stone JAC 2018

ceftazidime/avibactam vs. penem (pool des phases III)

Phase III clinical trials in patients with

- complicated **intra-abdominal infection (cIAI),**
- complicated **urinary tract infection (cUTI)**
- nosocomial **pneumonia (NP) including ventilator-associated pneumonia (VAP).**

Table 2. Favourable per-pathogen microbiological response rates at TOC for ceftazidime/avibactam and comparators against MDR pathogens of key interest across the Phase III trials (pooled mMITT population)

Indication	Patients with favourable response, *n/N* (%)													
	all Enterobacteriaceae		*E. coli*		*K. pneumoniae*		*E. cloacae*		*P. mirabilis*		other Enterobacteriaceae		*P. aeruginosa*	
	CAZ/AVI	comparator	CAZ/AVI	comparator	CAZ/AVI	comparator	CAZ/AVI	comparator	CAZ/AVI	comparator	CAZ/AVI	comparator	CAZ/AVI	comparator
All (pooled)	399/509 (78.4)	388/542 (71.6)	256/323 (79.3)	247/329 (75.1)	97/123 (78.9)	95/153 (62.1)	20/29 (69.0)	24/29 (82.8)	12/17 (70.6)	11/14 (78.6)	22/31 (71.0)	19/28 (67.9)	32/56 (57.1)	21/39 (53.8)
cIAI	144/176 (81.8)	175/200 (87.5)	115/141 (81.6)	141/160 (88.1)	18/22 (81.8)	14/19 (73.7)	5/7 (71.4)	7/9 (77.8)	3/3 (100)	3/3 (100)	5/9 (55.6)	11/11 (100)	5/5 (100)	7/7 (100)
cUTI	218/285 (76.5)	174/287 (60.6)	134/173 (77.5)	97/159 (61.0)	61/77 (79.2)	61/101 (60.4)	8/14 (57.1)	11/14 (78.6)	7/11 (63.6)	5/8 (62.5)	10/13 (76.9)	4/10 (40.0)	19/28 (67.9)	10/14 (71.4)
NP/VAP	37/48 (77.1)	39/55 (70.9)	7/9 (77.8)	9/10 (90.0)	18/24 (75.0)	20/33 (60.6)	7/8 (87.5)	6/6 (100)	2/3 (66.7)	3/3 (100)	7/9 (77.8)	4/7 (57.1)	8/23 (34.8)	4/18 (22.2)

CAZ/AVI, ceftazidime/avibactam.
Patients could have >1 pathogen. A patient was only counted once for a specific pathogen if that patient had multiple isolates of the same species. The 'all Enterobacteriaceae' count included patients with at least one of the listed Enterobacteriaceae. A patient was only counted once in this category even if they had more than one species of Enterobacteriaceae; for this reason, the 'all Enterobacteriaceae' count may not match the sums of the isolates for each individual species.

Stone JAC 2018

imipenem/relebactam vs. imipenem+coli, sur imipenem-R

- **hospital- acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)**
- **complicated urinary tract infections (cUTIs)**
- **complicated intraabdominal infections (cIAIs)**
- **imipenem-R**, imipenem/relebactam-S, and colistin-S

	IMI/REL (n = 21)		Colistin + IMI (n = 10)		Unadjusted Difference	Adjusted Difference[a]	
Endpoint	n	% (95% CI)[b]	n	% (95% CI)[a]	%	%	90% CI
Primary endpoint							
Favorable overall response[c]	15	71.4 (49.8, 86.4)	7	70.0 (39.2, 89.7)	1.4	–7.3	(–27.5, 21.4)
Hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia	7/8	87.5 (50.8, 99.9)	2/3	66.7		20.8	
Complicated intraabdominal infection	0/2[d]	0.0	0/2[e]	0.0		0.0	
Complicated urinary tract infection	8/11	72.7 (42.9, 90.8)	5/5	100.0 (51.1, 100.0)		–27.3 (–52.8, 12.8)	
Secondary endpoints							
Favorable clinical response (day 28)	15[f]	71.4 (49.8, 86.4)	4[g]	40.0 (16.7, 68.8)	31.4	26.3	(1.3, 51.5)
28-day all-cause mortality	2	9.5 (1.4, 30.1)	3	30.0 (10.3, 60.8)	–20.5	–17.3	(–46.4, 6.7)
Treatment-emergent nephrotoxicity[h]	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)		–45.9 (–69.1, –18.4)	

Motsch CID 2020

imipenem/relebactam vs. imipenem+coli, sur imipenem-R

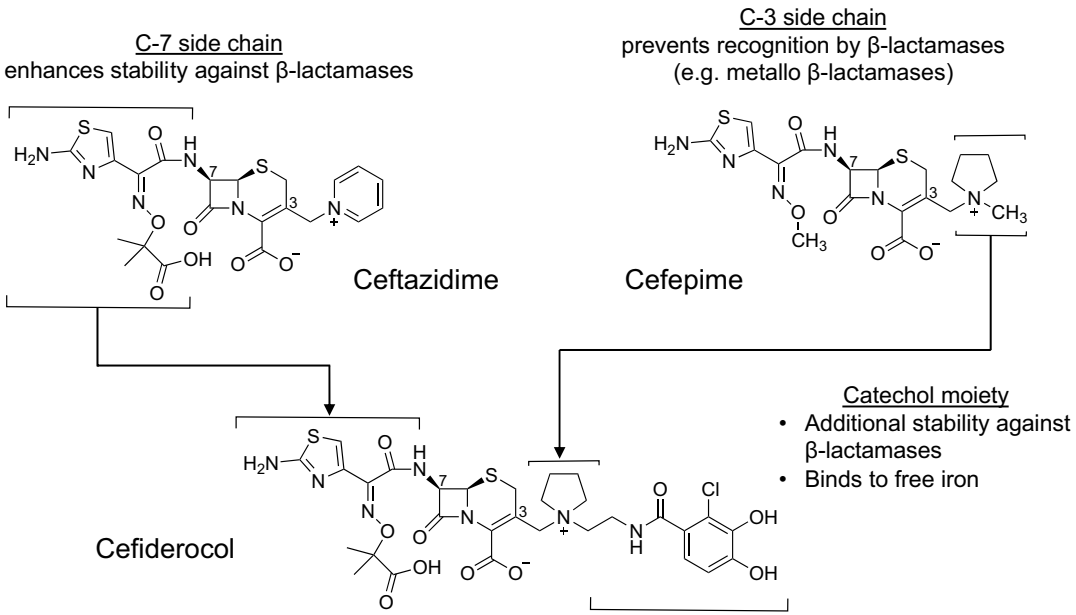
- **hospital- acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)**
- **complicated urinary tract infections (cUTIs)**
- **complicated intraabdominal infections (cIAIs)**
- **imipenem-R**, imipenem/relebactam-S, and colistin-S

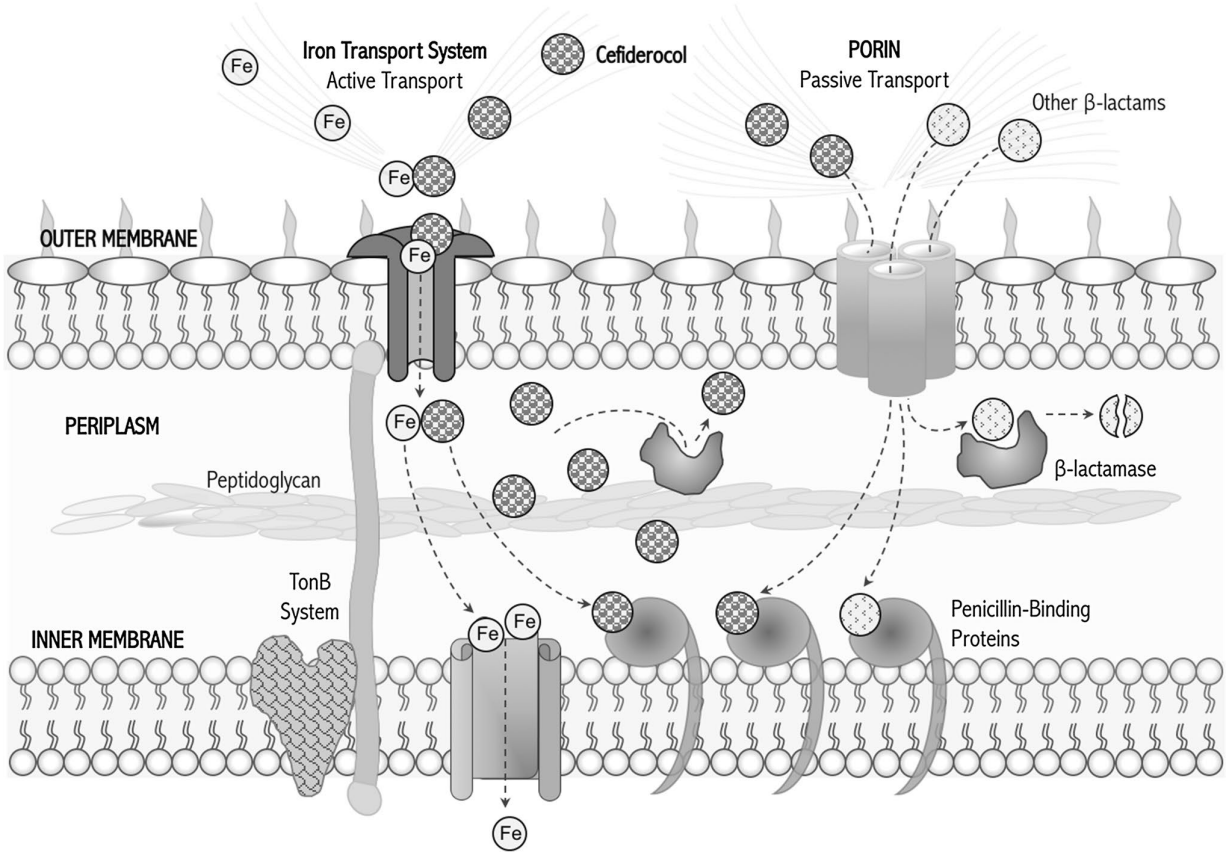
	IMI/REL (N=21)		Colistin + IMI (N=10)		Unadjusted difference	Adjusted difference[b]	
	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	%	%	90% CI
Citrobacter freundii	0/1	0.0	0/0	-	NC	NC	NC
Enterobacter cloacae	1/1	100.0	0/0	-	NC	NC	NC
Klebsiella oxytoca	0/0	-	1/1	100.0	NC	NC	NC
Klebsiella pneumoniae	1/3	33.3	1/1	100.0	-66.7	-66.7	NC
KPC-positive Enterobacteriaceae[c]	1/4[d]	25.0[d] (3.4, 71.1)	1/1	100.0	-75.0	-66.7	NC
Pseudomonas aeruginosa	13/16	81.3 (56.2, 94.2)	5/8	62.5 (30.4, 86.5)	18.8	3.1	-19.8, 38.2

Favorable overall response against *P. aeruginosa* was observed in 13/16 (81%) of IMI/REL and 5/8 (63%) of colistin+IMI patients

Motsch CID 2020

cefiderocol : nouvelle cephalosporine chélateur du fer





Zhanel Drugs 2019

cefiderocol vs. comparateurs (penems et +)

Study, year published	Study design	Study duration	Study site	Study population	No. of patients (ITT population)		Dose regimen	
					Cefiderocol	Comparator	Cefiderocol	Comparator
Portsmouth et al., 2018 [25]	Double-blind, non-inferiority, phase 2 trial	2015–2016	65 hospitals in 15 countries	Adults with Gram-negative cUTI	300	148	1-h infusion of cefiderocol (2 g) every 8 h for 7–14 days	1-h infusion of imipenem/ cilastatin (1 g each) every 8 h for 7–14 days
Wunderink et al., 2021 (APEKS-NP trial) [26]	Randomised, double-blind, non-inferiority, phase 3 trial	2017–2019	76 hospitals in 17 countries	Adults with Gram-negative NP	148	150	3-h infusion of cefiderocol (2 g) every 8 h for 7–14 days	3-h infusion of meropenem (2 g) every 8 h for 7–14 days
Bassetti et al., 2021 (CREDIBLE-CR trial) [27]	Randomised, open-label, pathogen-focused, descriptive, phase 3 study	2016–2019	95 hospital in 16 countries	Adults with NP, BSI or sepsis, or cUTI and a CR-Gram-negative pathogen	101	49	3-h infusion of cefiderocol (2 g) every 8 h for 7–14 days	Best available therapy for 7–14 days

Hsueh J Glob Antimicrob Resist 2021

cefiderocol vs. comparateurs (penems et +)

Pathogen	No. (%) of indicated pathogen isolated					
	Portsmouth et al., 2018 [25]		Wunderink et al., 2021 (APEKS-NP trial) [26]		Bassetti et al., 2021 (CREDIBLE-CR trial) [27]	
	Cefiderocol ($n = 252$)	Comparator ($n = 119$)	Cefiderocol ($n = 145$)	Comparator ($n = 147$)	Cefiderocol ($n = 87$)	Comparator ($n = 40$)
Escherichia coli	152 (60.3)	79 (66.4)	19 (13.1)	22 (15.0)	2 (2.3)	1 (2.5)
Klebsiella pneumoniae	48 (19.0)	25 (21.0)	48 (33.1)	44 (29.9)	27 (31.0)	12 (30.0)
Acinetobacter baumannii	0 (0)	0 (0)	23 (15.9)	24 (16.3)	37 (42.5)	17 (42.5)
Pseudomonas aeruginosa	18 (7.1)	5 (4.2)	24 (16.6)	24 (16.3)	12 (13.8)	10 (25.0)
Stenotrophomonas maltophilia	0 (0)	0 (0)	1 (0.7)	3 (2.0)	5 (5.7)	0 (0)
Enterobacter cloacae	9 (3.6)	1 (0.8)	7 (4.8)	8 (5.4)	2 (2.3)	0 (0)
Proteus mirabilis	17 (6.7)	2 (1.7)	NA	NA	0 (0)	0 (0)
Others	8 (3.2)	7 (5.9)	38 (26.2)	42 (28.6)	*A. nosocomialis*: 2 (2.3), *E. cloacae*: 2 (2.3)	0 (0)

Hsueh J Glob Antimicrob Resist 2021

cefiderocol vs. comparateurs (penems et +)

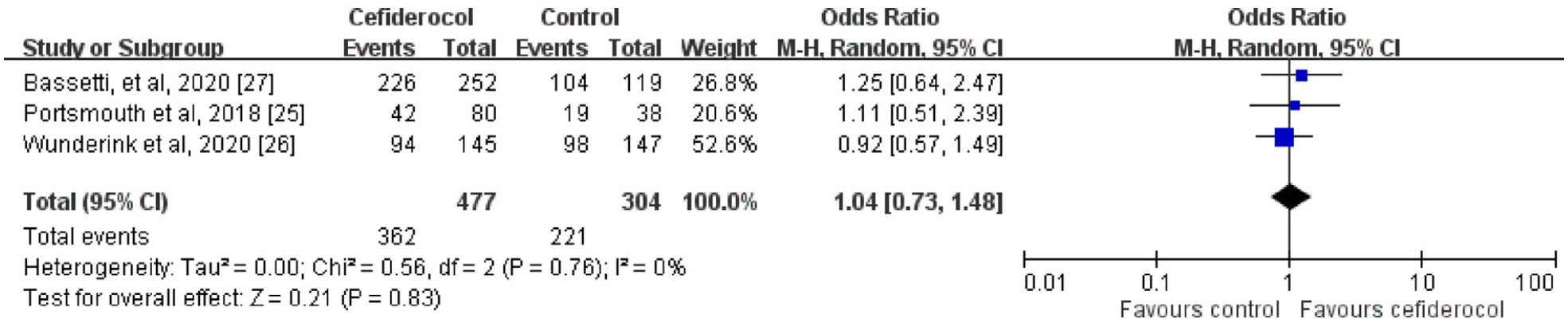
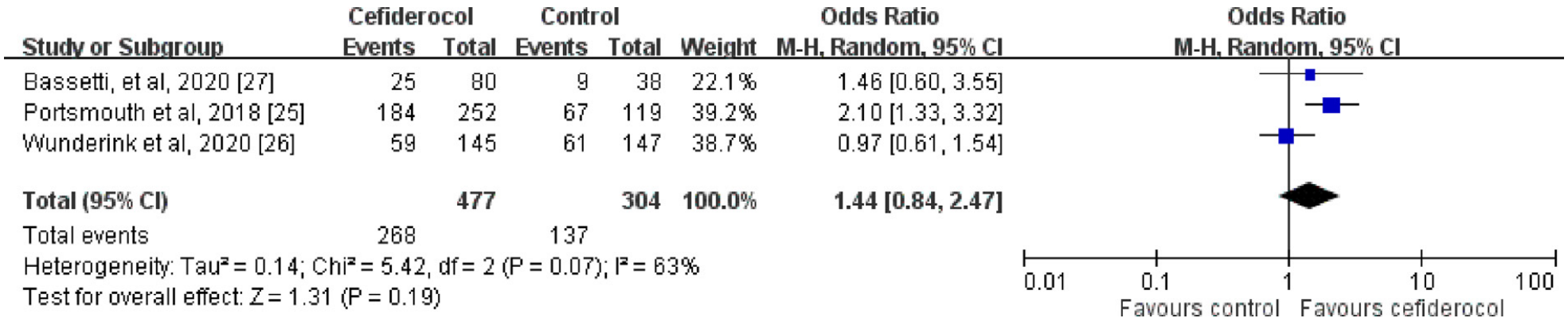


Fig. 3. Forest plot of clinical response rate between cefiderocol and comparators.



Hsueh J Glob Antimicrob Resist 2021

“Nouveaux” antibiotiques disponibles contre *P. aeruginosa*

Table 5. Possible applications of new antibiotics against Gram-negative bacteria based on resistant mechanisms.

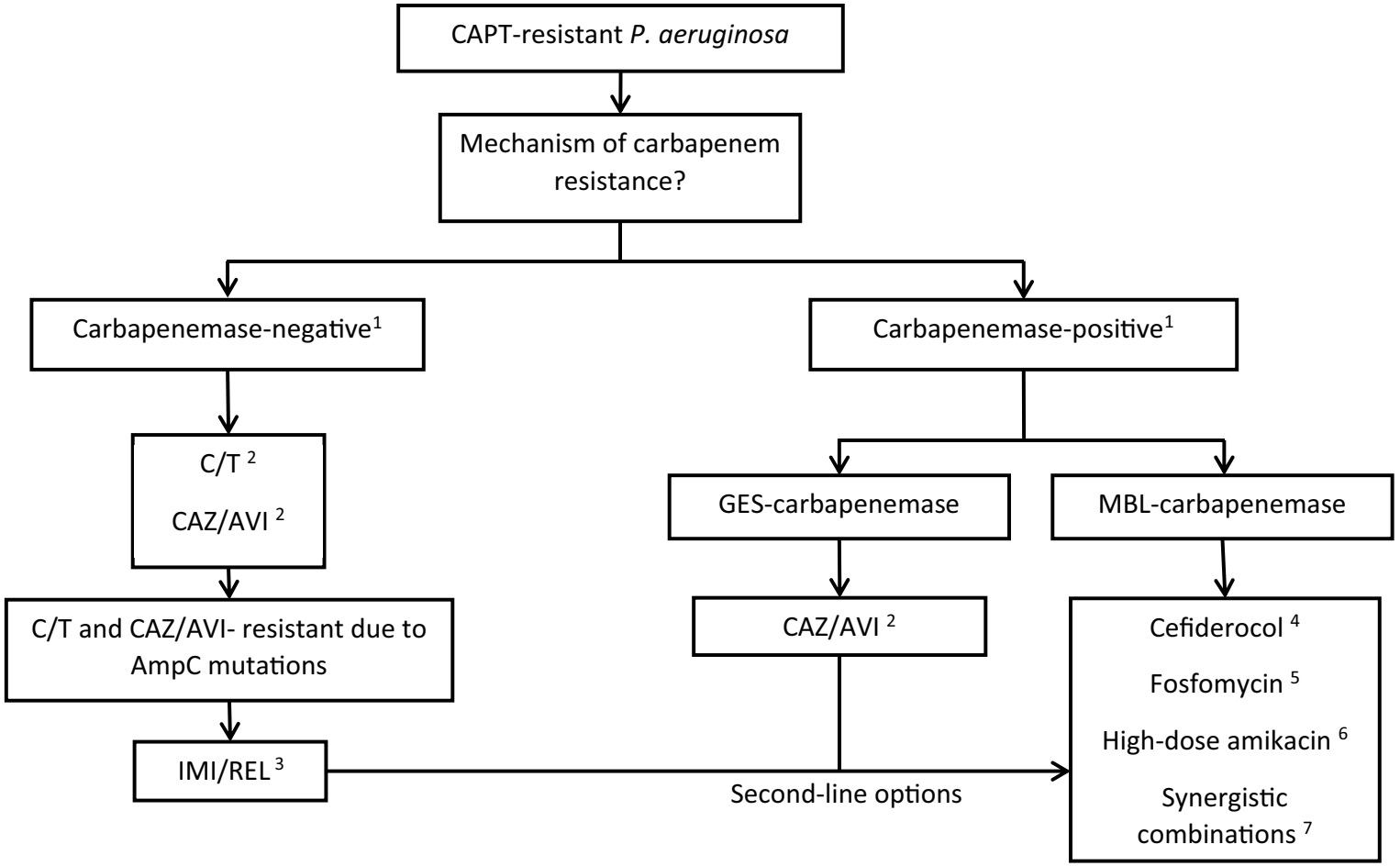
	ESBL and AmpC	KPC	OXA-48	MBL	Carbapenem Nonsusceptible *A. baumanii*	Carbapenem Nonsusceptible *P. aeruginosa*
Plazomicin	++	++	++	+/− [a]	−	−
Eravacycline	++	++	++	+ [b]	++	−
Temocillin	++ (urine breakpoint only)	++ (urine breakpoint only)	−	−	−	−
Cefiderocol	++	++	++	++	++	++
Ceftazidime/avibactam	++	++	++	−	−	+/−
Ceftolozane/tazobactam	++	−	−	−	−	+/− [c]
Meropenem/vaborbactam	++	++	−	−	?	?
Imipenem/relebactam	++	++	−	−	−	+/− [d]

++: Activity (>90% of the isolates); +: activity in 70 to 90% of the isolates; +/−: activity in around the half of the; −: no activity; ?: no surveillance data available. [a] 42.1% susceptible isolates [12]; [b] 70% susceptible isolates [32]; [c] good activity against isolates with elevated efflux, derepressed AmpC or loss of OprD, but not when the underlying mechanism is MBL production [82]; [d] not for isolates with class B or D carbapenemase activity [83].

Yusuf J Clin Med 2021

Souches ”Pan-résistantes”

- co-resistant to
- carbapenems,
- aminoglycosides,
- Polymyxins
- and tigecycline



Karakonstantis infection 2020

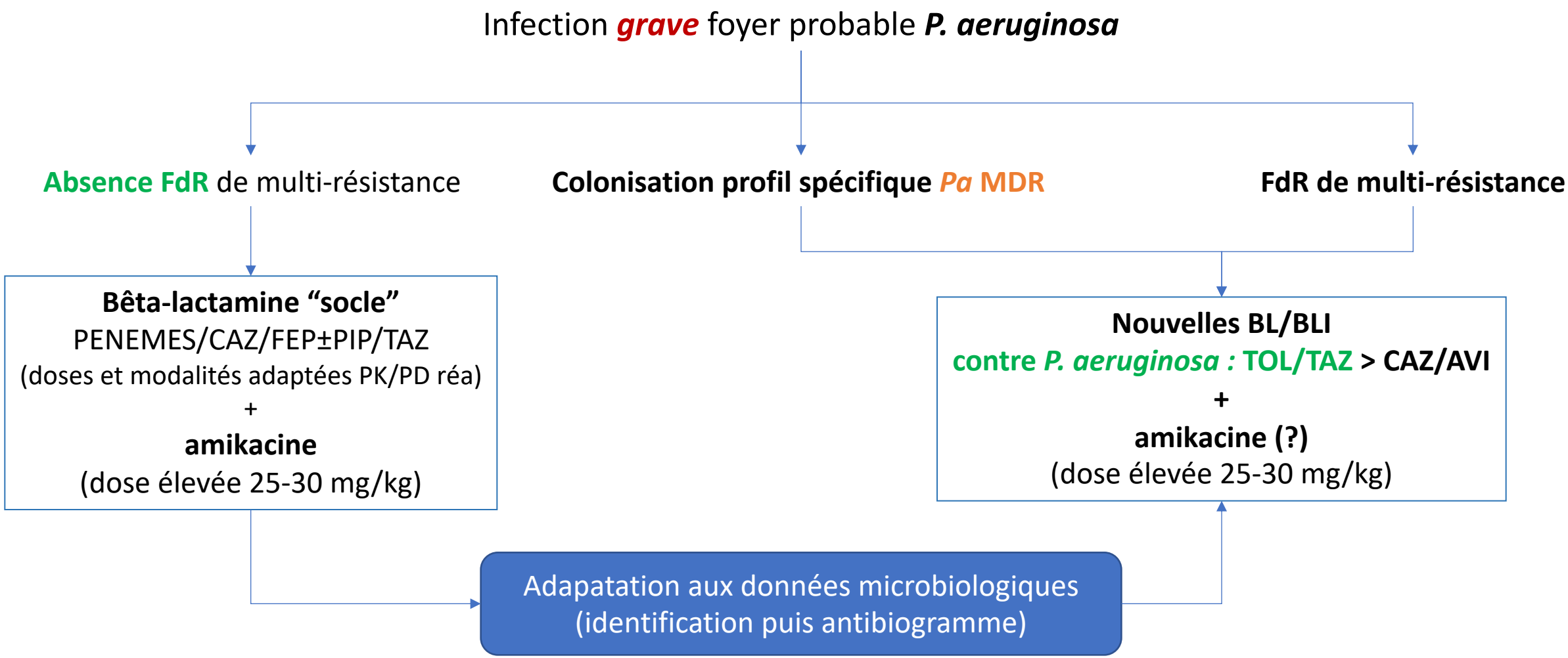
Nouveaux ATB

à venir…

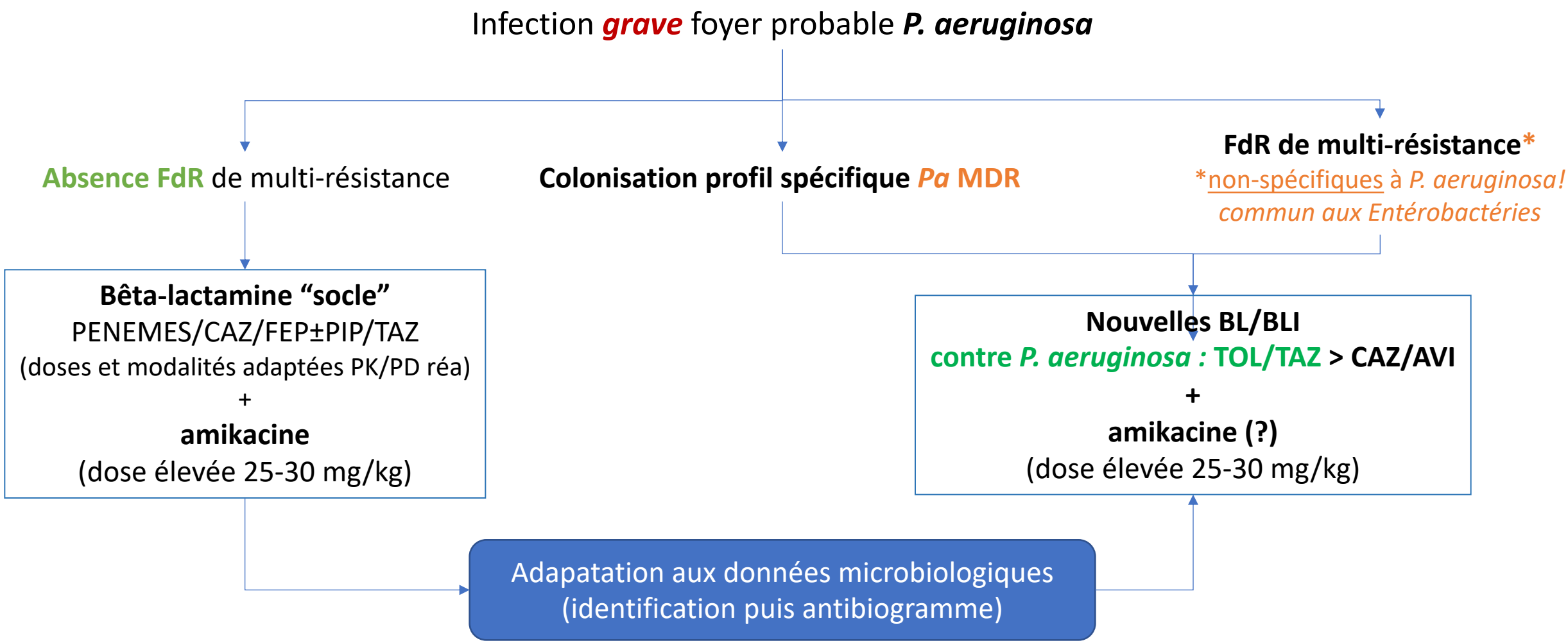
Drug	Spectrum of activity (references)	Limitations in spectrum (reference[s])[b]
Cefepime-tazobactam	*Enterobacterales*, including those with β-lactamases: class A, ESBL, K1; class B, VIM (~75%); class C, AmpC; class D, OXA-48 (232, 233)	No activity against class B except VIM; KPC mostly R; For *P. aeruginosa*, same activity as meropenem (232, 233)
Cefepime-enmetazobactam	*Enterobacterales*, including those with β-lactamases: class A, ESBL, some KPC (limited evidence); class C, AmpC; class D, OXA-48 (limited evidence) (239, 323)	No activity against class B; no additional coverage for *P. aeruginosa* over cefepime (239, 323)
Cefepime-zidebactam	*Enterobacterales*, including those with β-lactamases: class A, ESBL, KPC; class B, MBLs (IMP, VIM, NDM); class C, AmpC; class D, OXA-48; highly active against *P. aeruginosa*, including carbapenem R (243, 244, 324)	Activity against *Acinetobacter* spp. probably limited (244)
Aztreonam-avibactam	*Enterobacterales*, including those with β-lactamases: class A, ESBL, KPC; class B, any MBL; class C, AmpC; class D, OXA-48 (248–250)	No enhanced activity over aztreonam alone for *P. aeruginosa*; no *in vitro* activity against *A. baumannii* (248–250)
Sulbactam-durlobactam	*Acinetobacter baumannii*, including carbapenem R (256)	Limited data on potential activity against *Enterobacterales* (255)
Meropenem-nacubactam	Potential activity against *Enterobacterales*, including those with β-lactamases: class A, ESBL, KPC; class B, NDM; class C, AmpC; class D, OXA-48 (259, 262, 264)	For *Pseudomonas* and *Acinetobacter* spp., similar activity to meropenem (264)
Cefpodoxime proxetil-ETX0282	Potential activity against *Enterobacterales*, including those with β-lactamases: class A, ESBL, KPC; class C, AmpC; class D, OXA-48 (265–267)	No activity described for *P. aeruginosa* or *A. baumannii* (265–267)
Cefepime-taniborbactam (VNRX-5133)	Potential activity against *Enterobacterales*, including those with β-lactamases: class A, ESBL, KPC; class B, VIM, NDM, SPM-1, and GIM-1 (but not IMP-1); class C, AmpC; class D, OXA-48; *P. aeruginosa*, cefepime and carbapenem R (268–270)	

Clinical Microbiology Reviews January 2021

Utilisation *probabiliste* nouvelles BL/BLI ?



Utilisation *probabiliste* nouvelles BL/BLI ?



Utilisation *conservatrice*, traitement de certitude ?

Infection ***grave*** foyer probable ***P. aeruginosa***

Bêta-lactamine "socle"
PENEMES/CAZ/FEP±PIP/TAZ
(doses et modalités adaptées PK/PD réa)
+
amikacine
(dose élevée 25-30 mg/kg)

Nouvelles molécules *selon ATBgramme*
TOL/TAZ
CAZ/AVI
IMP/REL
MEM/VAB
cefiderocol

Adapatation aux données microbiologiques
(identification puis antibiogramme)

Perspective : *identification rapide des résistances*

Infection ***grave*** foyer avec ***mécanismes de resistance identifié***

Adapatation aux tests rapides

Bêta-lactamine "socle"
PENEMES/CAZ/FEP±PIP/TAZ
(doses et modalités adaptées PK/PD réa)
+
amikacine
(dose élevée 25-30 mg/kg)

Nouvelles molécules *selon ATBgramme*
TOL/TAZ
CAZ/AVI
IMP/REL
MEM/VAB
cefiderocol

Merci !