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Cité des Congrès de Nantes
Nantes
et la région Pays de la Loire

Symposium MSD France

Comment optimiser le bon usage des antibiotiques à l'ère de la multirésistance chez les BGN ?

Dans les infections à *Pseudomonas aeruginosa*

Eric Kipnis

Réanimation Chirurgicale - Pôle d'Anesthésie-Réanimation - CHU Lille

Recherche translationnelle hôte-pathogènes EA 7366 - Univ. Lille

Université de Lille

Centre Hospitalier Régional Universitaire de Lille

HOST PATHOGEN TRANSLATIONAL RESEARCH-EA7366

Déclaration d'intérêts

- 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 à *Pseudomonas aeruginosa*

Infections en réanimation : étude EPIC II (2009)

	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

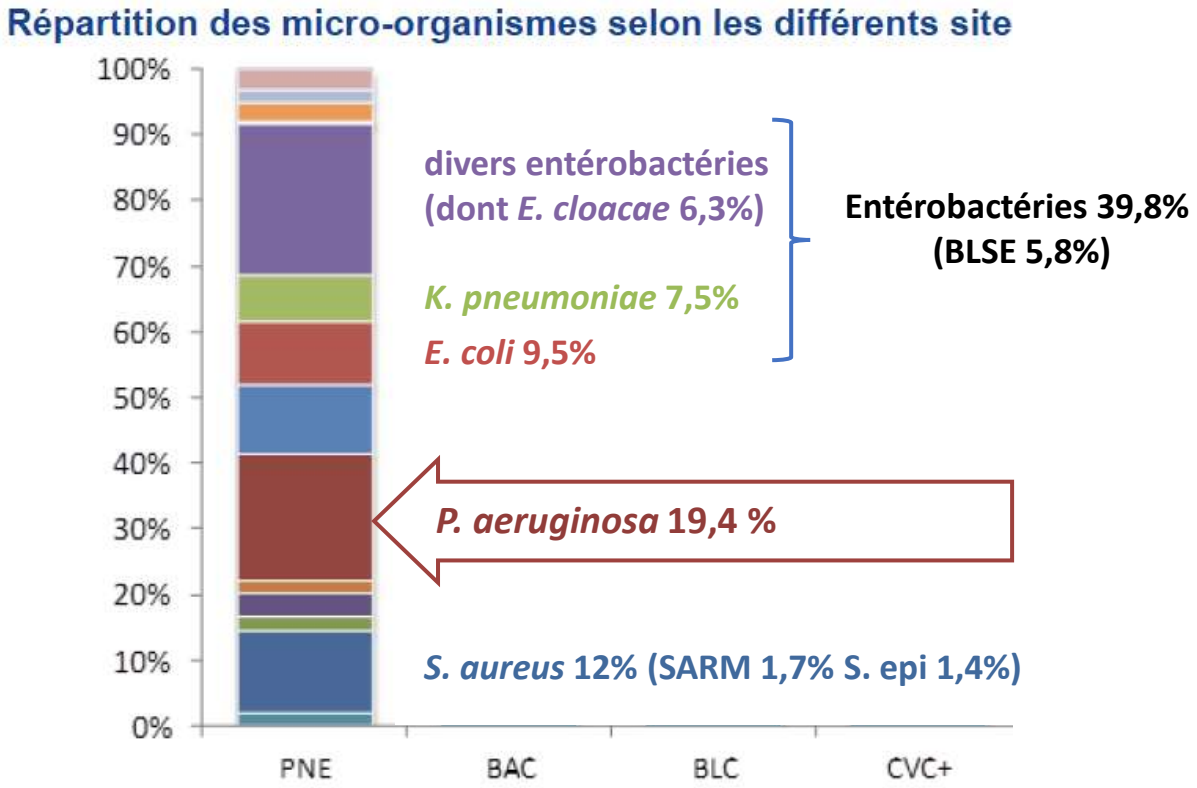
- ***P. aeruginosa 19 %***

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

- *dont BLSE 1.8%*

Vincent JAMA 2009

Pneumonies nosocomiales en réanimation 2015



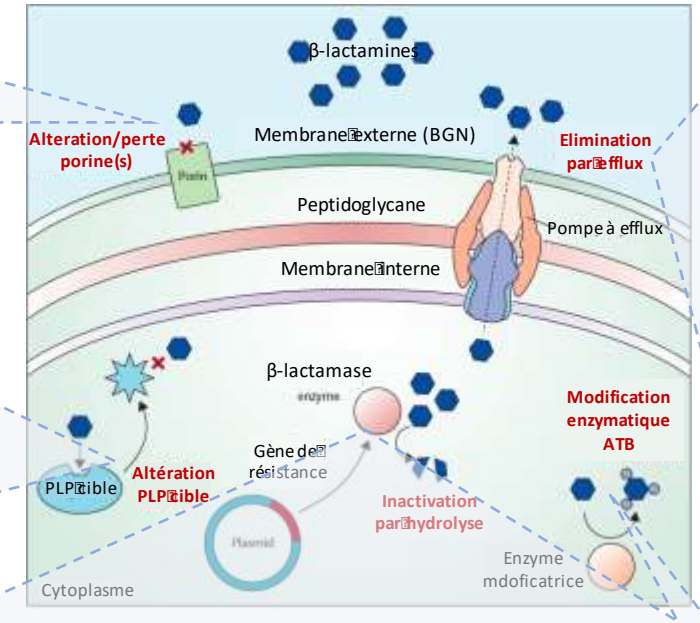
REA-Raisin 2015 – Santé Publique France 2017

“Ere de la multirésistance”

(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

	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

(aminosides)
acetyltransferases
nucleotidyltransferases

d'après Sherrard Lancet 2014

Multirésistance (France) – Réseau microbiologistes N-PdC

souches de *P. aeruginosa* résistantes à :

- Ticarcilline
- Ceftazidime
- et Imipénème I ou R

Tableau 5.27 - *Pseudomonas aeruginosa* : proportion et incidence de souches multi-résistantes.
Table 5.27 - Pseudomonas aeruginosa: percentage and incidence of multi-resistance (réseau microbiologistes du Nord Pas de Calais, 2008-2014)

		2008	2009	2010	2011	2012	2013	2014
Multi-R**	n	548	406	389	406	478	452	358
	%	9,8	8,1	7,0	7,6	8,4	8,0	7,1
	Incidence*/*Incidence**	0,15	0,11	0,09	0,10	0,11	0,11	0,09

(Multi)résistances en réanimation – France, REA-Raisin 2015

Micro-organismes	Marqueur antibiotique	Pourcentage de résistance dans l'espèce										
		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
P. aeruginosa	ceftazidime	22,6	23,3	20,7	22,5	18,2	18,2	28,3	23,6	20,8	17,1	**18,7**
P. aeruginosa	imipénème	-	-	-	-	-	-	22,6	23,4	24,6	19,7	**18,4**

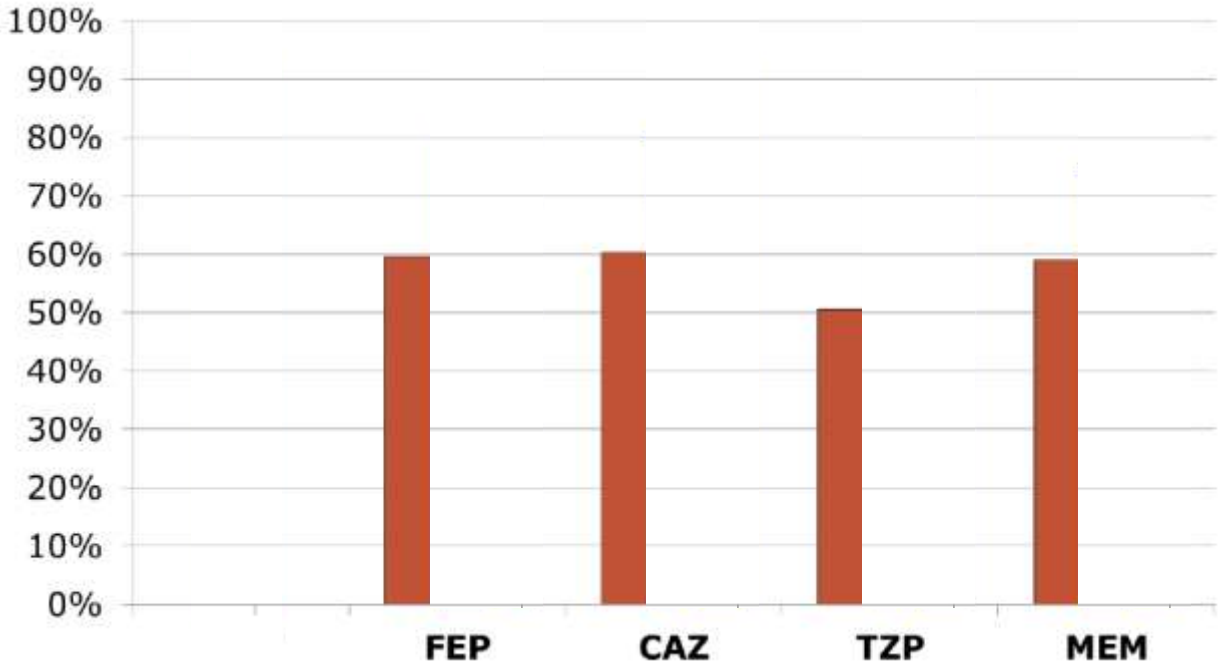
Micro-organisme		Indicateur		n	%
Pseudomonas aeruginosa (+66 profils inconnus)	(2 075)	0. CAZ-S	& IMP-S	1 439	69,3
		1. CAZ-R	& IMP-S	254	12,2
		2. CAZ-S	& IMP-I/R	247	11,9
		3. CAZ-R	& IMP-I/R	135	6,5

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

Réseau REA-Raisin, France. Résultats 2015

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

n=156



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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

R d'un antipseudomonas "socle"
non-récupérées par une alternative seule

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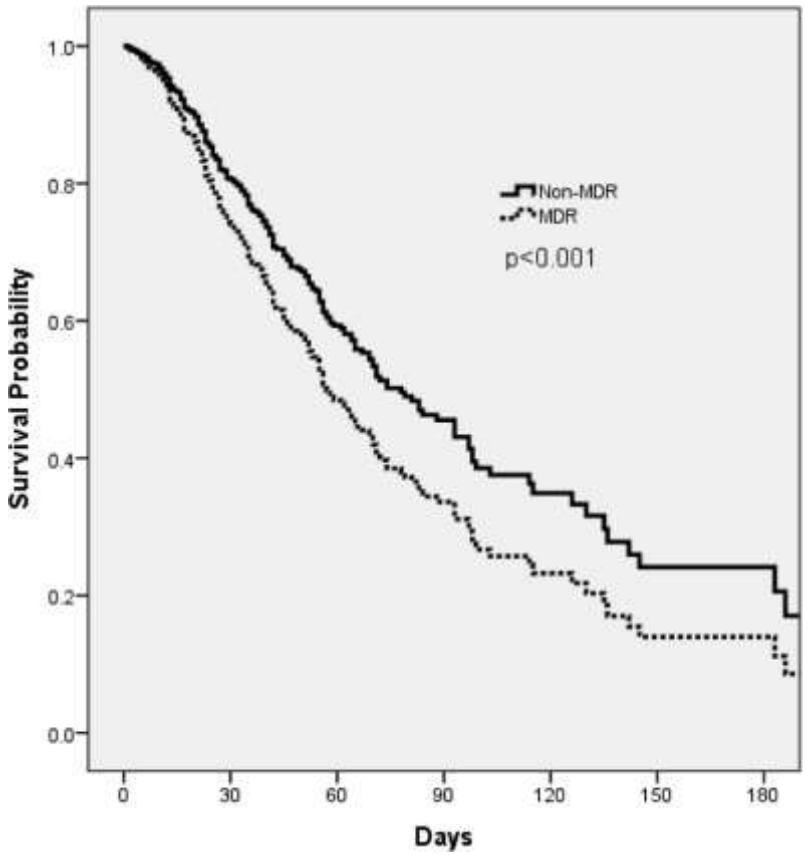
Conséquences de la multirésistance de *P. aeruginosa*

Multirésistance *P. aeruginosa* et surmortalité

- multicentrique
- USA/Europe
- Pneumonies nosocomiales *P. aeruginosa*
- MDR = 30.5%

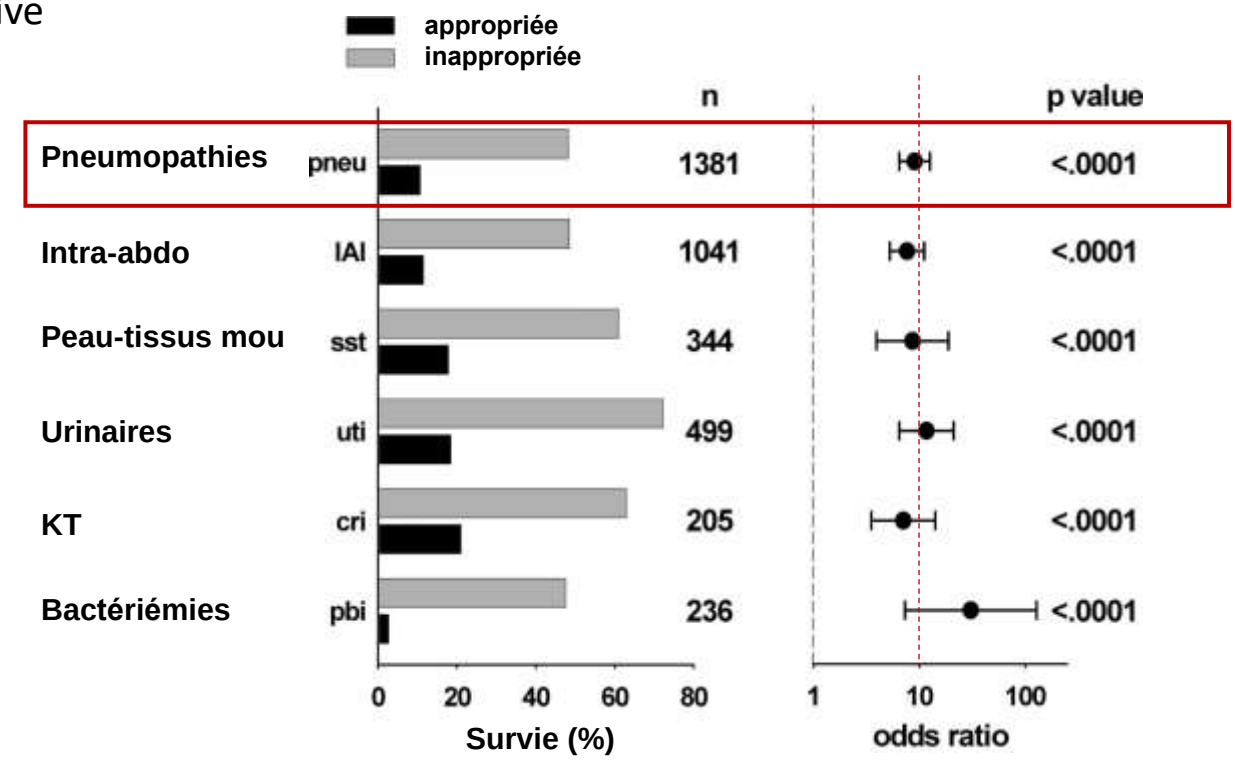


Multirésistance = facteur indépendant de surmortalité

Micek Crit Care 2015

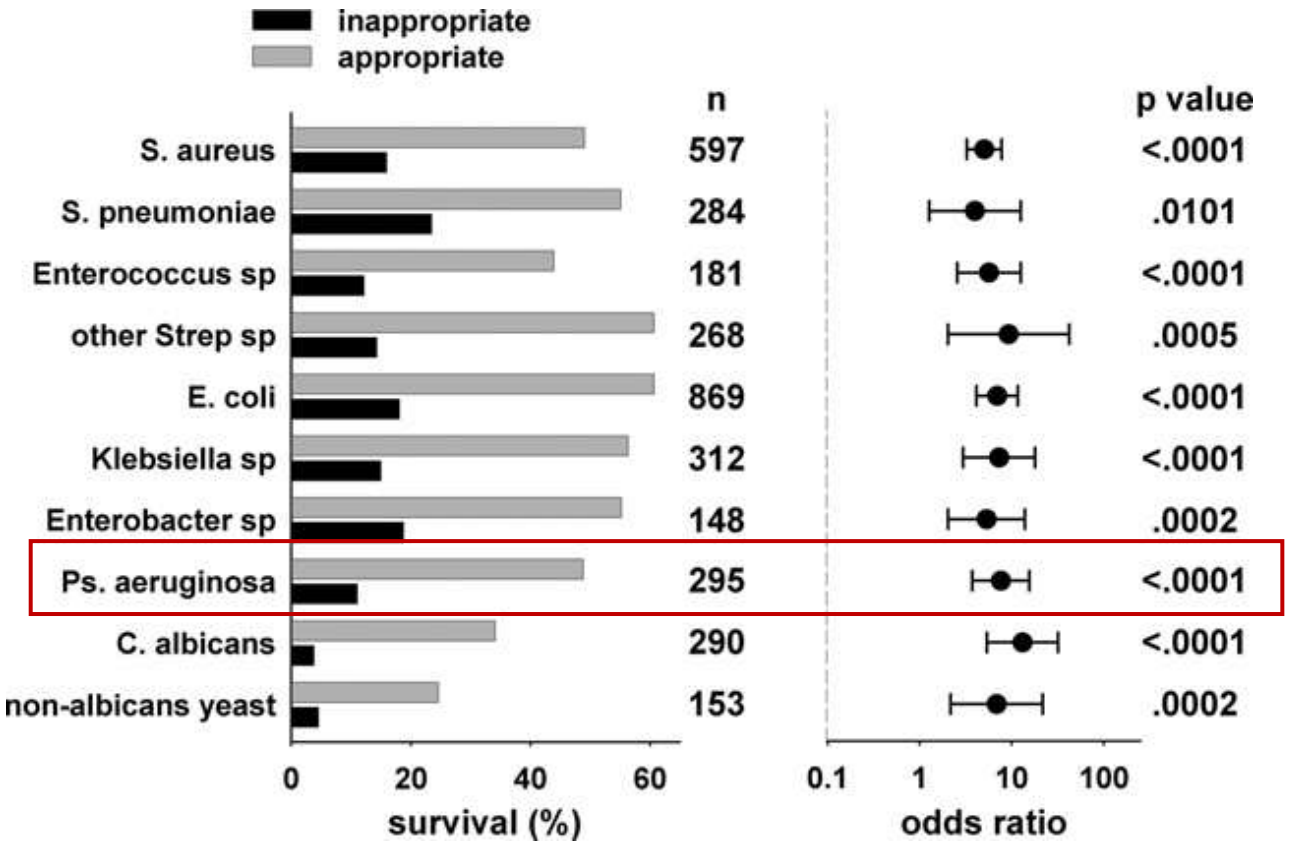
Inadéquation de l'antibiothérapie (probabiliste) initiale

- choc septique
- n= 5715
- rétrospective



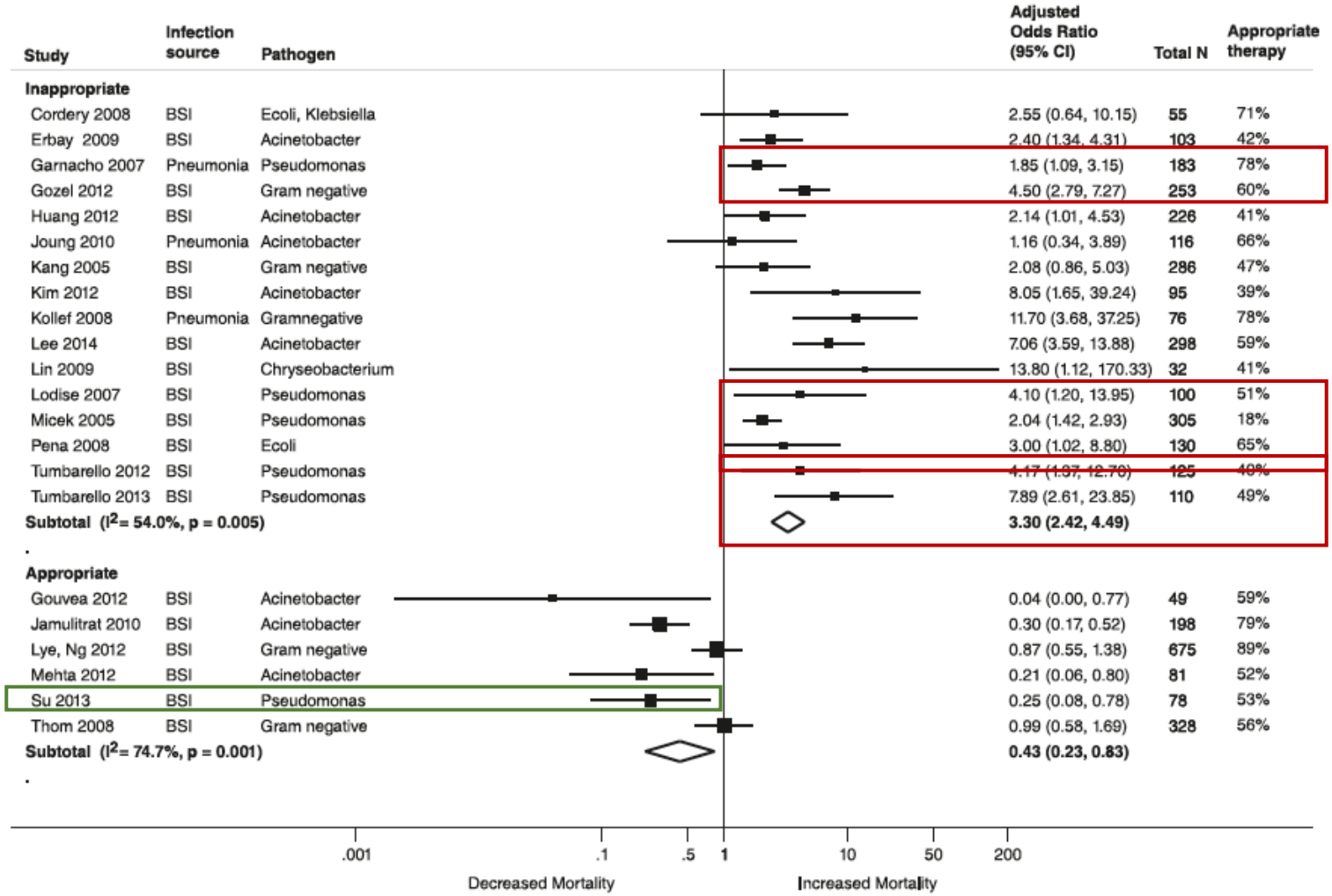
Kumar Chest 2009

Inadéquation et *P. aeruginosa*



Kumar Chest 2009

Inadéquation et *P. aeruginosa*



Raman BMC Infect Dis 2015

Prédire la multi-résistance de *P. aeruginosa* ?

Colonisation préalable et pneumonie à *P. aeruginosa*

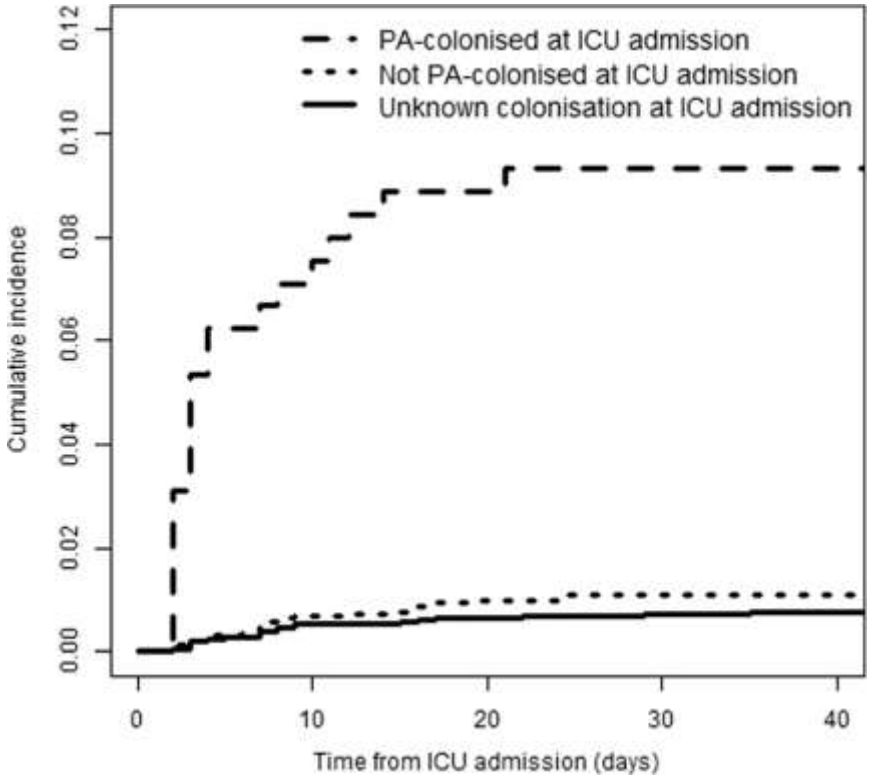
2447
dépistés à l'entrée réa

2221 (90,8%)
non-colonisés

25 (1.1%)
pneumonies PA

226 (9,2%)
colonisés PA

21 (9.3%)
pneumonies PA



Paling Antimicrobial Resistance and Infection Control 2017

FdR *P. aeruginosa avant* entrée en réanimation

Recommandations IDSA Pneumonies associées aux soins/PAVM

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

Kalil Clin Infect Dis 2016

Antibiotiques et émergence résistances *P. aeruginosa*

- Prospective de cohorte
- Prélèvements de dépistage respi réa
- n = 1201 (10 % *P. aeruginosa*)
- suivi microbio /exposition 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

Antibiotiques chez patients colonisés par *P. aeruginosa*

- cohorte prospective (ancillaire DDS)
- Pays-Bas
- *P. aeruginosa n*= 277

TABLE 3. Time-Dependent Cox Regression Analyses on Antibiotic Resistance Development in Patients Colonized With *Pseudomonas aeruginosa*

Antibiotic	Crude HR (95% CI)	AB Adjusted HR (95% CI)	Patient/AB Adjusted HR (95% CI)
Ceftazidime	1.7 (0.7–3.8)	1.7 (0.8–3.9)[a]	1.5 (0.6–3.5)[b]
Ciprofloxacin	2.4 (1.1–5.3)	2.7 (1.2–6.2)[a]	2.3 (0.8–6.0)[c]
Colistin	2.5 (0.6–10.1)	3.3 (0.8–14.1)[a]	2.1 (0.4–10.1)[d]
Aminoglycoside	1.4 (0.5–3.7)	1.7 (0.6–4.5)[a]	1.5 (0.5–4.1)[e]
Carbapenem	2.7 (0.8–9.4)	3.5 (1.0–12.7)[a]	4.2 (1.1–15.6)[f]
Piperacillin-tazobactam	1.6 (0.7–3.7)	1.7 (0.7–2.8)[a]	1.0 (0.1–15.6)[g]

AB = antibiotic, HR = hazard ratio.

Noteboom Crit Care Med 2015

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
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 ba
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

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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

- Éradication microbiologique moindre
  - 7 RCT
  - (OR, 0.50; 95% CI, .24–.89)
- Taux de succès clinique inférieur
  - 6 RCT
  - (OR, 0.42; 95% CI, .22–.82)

Kalil Clin Infect Dis 2016

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

- Éradication microbiologique moindre
  - 7 RCT
  - (OR, 0.50; 95% CI, .24–.89)
- Taux de succès clinique inférieur
  - 6 RCT
  - (OR, 0.42; 95% CI, .22–.82)

SAUF SI PENEME = MEROPENEME
(OR : 1.10; 95% CI, .39–3.14)

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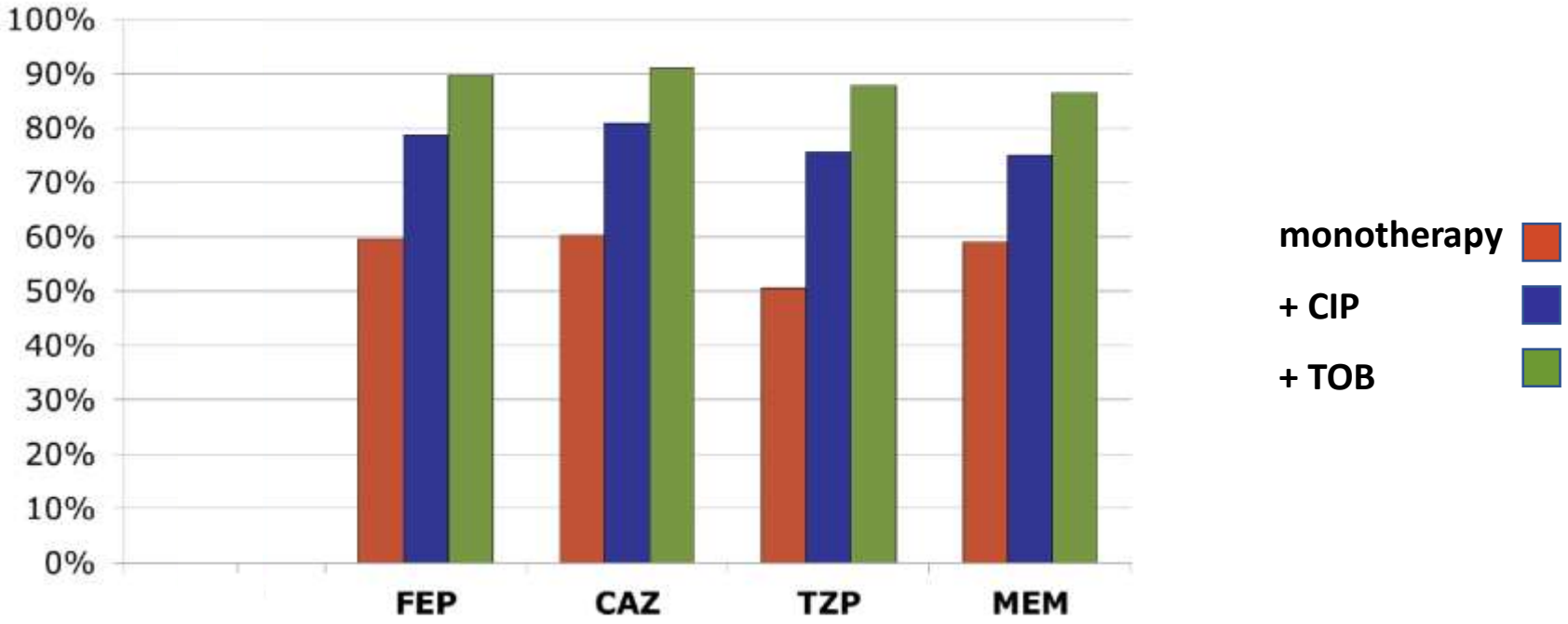
Que faire ?

Associations ?

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

n=156



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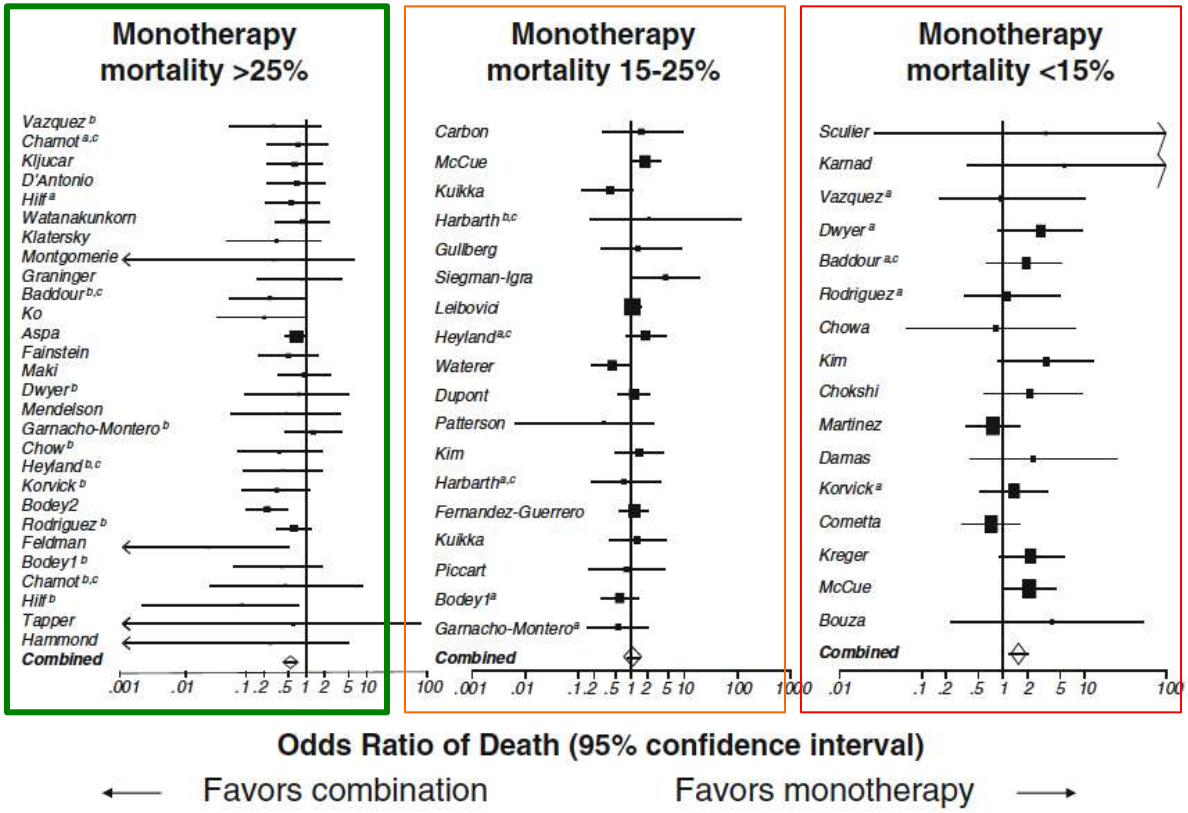
Associations…pour les infections graves



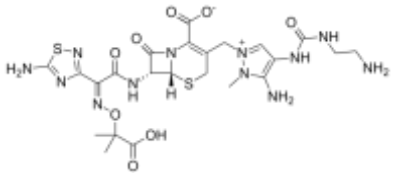
Kumar Curr Infect Dis Rep 2015

Spectres larges ?

Nouvelles Bêta-lactamines/inhibiteurs Blasé (BL/BLI)

Nouvelle céphalosporine à large spectre

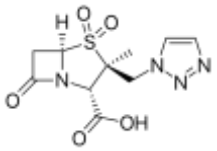
active sur *P. aeruginosa*



ceftolozane

+

Ancien Inhibiteur Blase

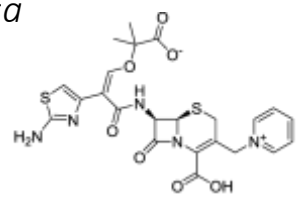


tazobactam

Ancienne céphalosporine à large spectre

active sur *P. aeruginosa*

ceftazidime



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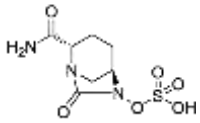
Nouvel Inhibiteur Blase



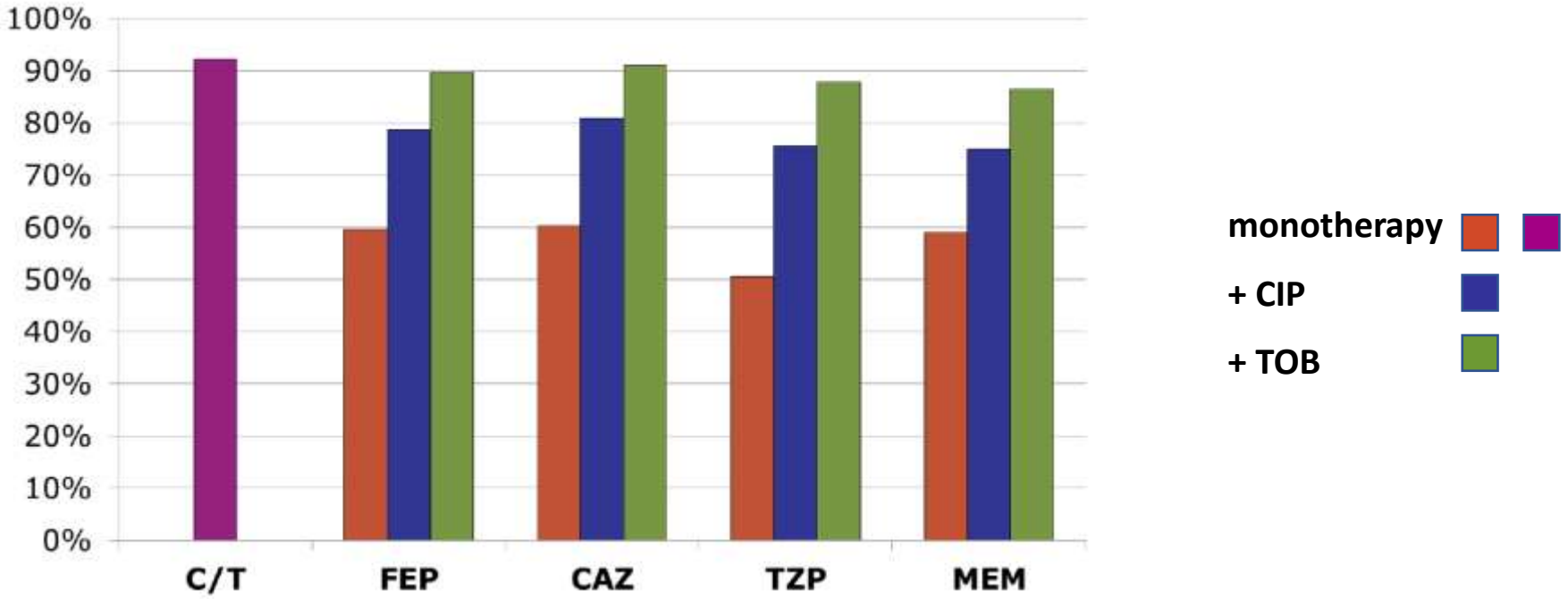
avibactam

- affinité des PLP pour **TOL** > CAZ
- **TOL :**
  - peu sujet à efflux (pour l'instant…)
  - ni autres mécanismes habituels de R de *P. aeruginosa*
  - stabilité // AmpC

- **AVI inihibe Blases +++** (sauf metallo)
  - BLSE, AmpC, OXA-48,
  - KPC
- Entérobactéries > *P. aeruginosa*
  - car reste sujette à d'*autres mécanismes R de P. aeruginosa*

Ceftolozane-tazobactam vs. *P. aeruginosa* (USA, souches respi, réa)

n=156



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Résistances croisées et ceftolozane-tazobactam

β-lactam	% NS	Of NS, % FEP S	Of NS, % CAZ S	Of NS, % TZP S	Of NS, % MEM S	Of NS, % C/T S
All patients						
Cefepime	23.0	N/A	23.9	20.8	39.4	87.5
Ceftazidime	23.0	23.9	N/A	15.2	41.2	86.2
Piperacillin/tazobactam	28.2	35.3	30.8	N/A	45.2	90.1
Meropenem	24.0	42.1	43.7	35.8	N/A	90.1
ICU						
Cefepime	28.4	N/A	16.7	13.7	37.3	84.3
Ceftazidime	31.2	24.1	N/A	11.6	37.5	83.9
Piperacillin/tazobactam	37.0	33.8	25.6	N/A	41.4	88.0
Meropenem	30.1	40.7	35.2	27.8	N/A	87.0

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Ceftazidime-avibactam

Organism	Ceftazidime–avibactam			Ceftazidime		
	$MIC_{50/90}$	MIC range	%S	$MIC_{50/90}$	MIC range	%S
Citrobacter freundii	0.125/0.5	≤0.06–2	100	0.5/>32	≤0.25–>32	78.2
Enterobacter aerogenes	0.25/0.5	≤0.06–16	98.5	0.5/>32	≤0.25–>32	76.9
Enterobacter cloacae	0.25/1	≤0.06–16	99.5	0.5/>32	≤0.25–>32	78.7
Escherichia coli	0.12/0.25	≤0.06–4	100	≤0.25/1	≤0.25–>32	94.9
ESBL-producing	0.12/0.25	≤0.06–1	100	16/>32	1–>32	34.8
AmpC-hyperproducing	0.12/0.5	≤0.06–2	100	16/>32	1–>32	41.4
Klebsiella oxytoca	0.12/2	≤0.06–2	100	≤0.25/0.5	≤0.25–>32	99.3
Klebsiella pneumoniae	0.12/0.5	≤0.06–8	99.9	≤0.25/1	≤0.25–>32	98.5
ESBL-producing	0.5/1	≤0.06–2	100	32/>32	4–64	66.7
OXA-48-producing	0.25/0.5	<0.008–1	100	256/512	≤0.12–512	N/A
KPC-producing	0.25/1	≤0.06–1	100	>256/>256	32–>256	0
Carbapenem-non-susceptible	0.5/2	≤0.03–32	N/A	>32/>32	N/A	N/A
Morganella morganii	≤0.06/0.12	≤0.06–0.5	100	≤0.25/8	≤0.25–16	89.7
Proteus mirabilis	≤0.06/0.12	≤0.06–0.25	100	≤0.25/≤0.25	≤0.25–32	99.6
Proteus vulgaris	0.06/0.25	≤0.03–2	100	0.12/8	N/A	N/A
Salmonella enterica	0.25/0.5	≤0.03–0.5	100	0.25/0.5	N/A	N/A
Serratia marcescens	0.25/0.5	≤0.06–2	100	≤0.25/1	≤0.25–16	99.6
Burkholderia cepacia	8/>128	≤1–>128	N/A	64/>128	8–>128	N/A
Pseudomonas aeruginosa	2/8	≤0.06–>16	94.7	4/32	≤0.25–>32	82.8
Multidrug-resistant	8/>16	4–>16	60.0	>16/>16	4–>16	4.
AmpC-derepressed	4/8	≤1–64	96.2	64/>126	8–>128	3.8
Acinetobacter baumannii	8/>16	0.5–>16	60.3	8/>32	N/A	78.2
Carbapenem-resistant	32/>32	0.25–>32	N/A	>32/>32	N/A	N/A
Haemophilus influenzae	≤0.06/≤0.06	≤0.06–0.1	100	N/A	N/A	N/A

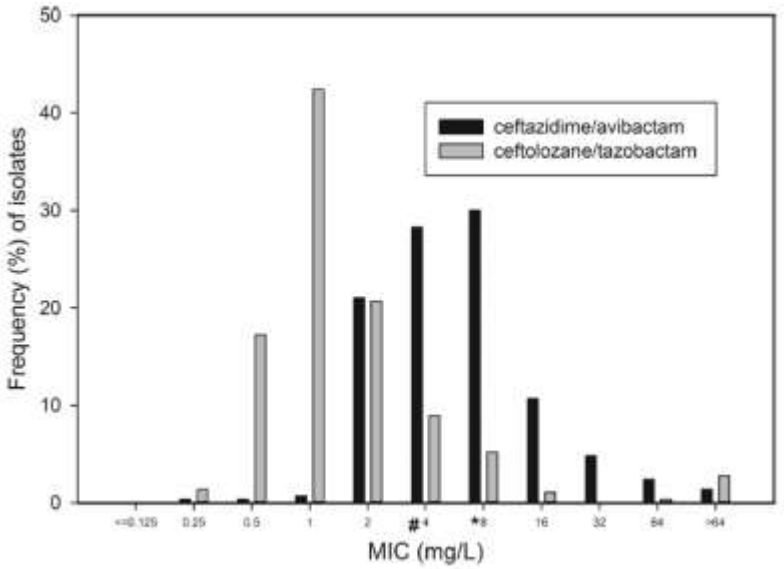
récupération activité contre :

- *Enterobacter spp.*
- *E. coli*
  - BLSE
  - AmpC hyperproducteur
- *K. pneumoniae*
  - BLSE
  - KPC
- ***P. aeruginosa***
  - **(+/- multi-résistant)**
  - **AmpC déréprimé**

Lagacé-Wiens Core Evidence 2014

Comparatif sensibilités aux BL/BLI de souches méropénème-R

USA
n=290



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

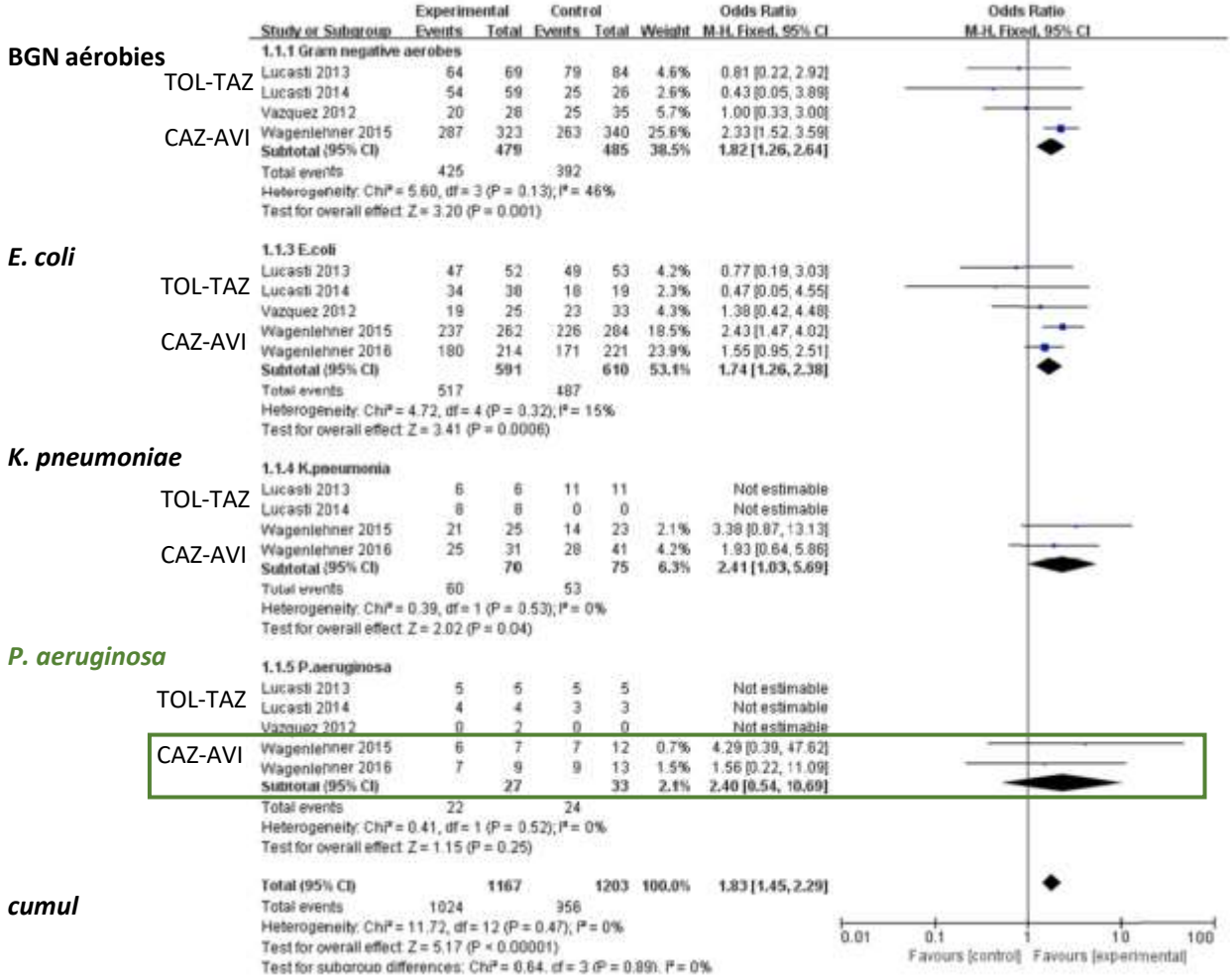
β-Lactam agent(s)[a] to which isolates were NS (no. of isolates/ total, %)	S to CZA (no. of isolates, %)	S to C/T (no. of isolates, %)	P value[b]
FEP (168/290, 58)	114, 68	142, 85	0.0003
CAZ (157/290, 54)	105, 67	132, 84	0.0006
TZP (185/290, 64)	133, 72	159, 86	0.0013
ATM (183/290, 63)	132, 72	159, 87	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

S CAZ-AVI 54-72%

S TOL-TAZ 79-87%

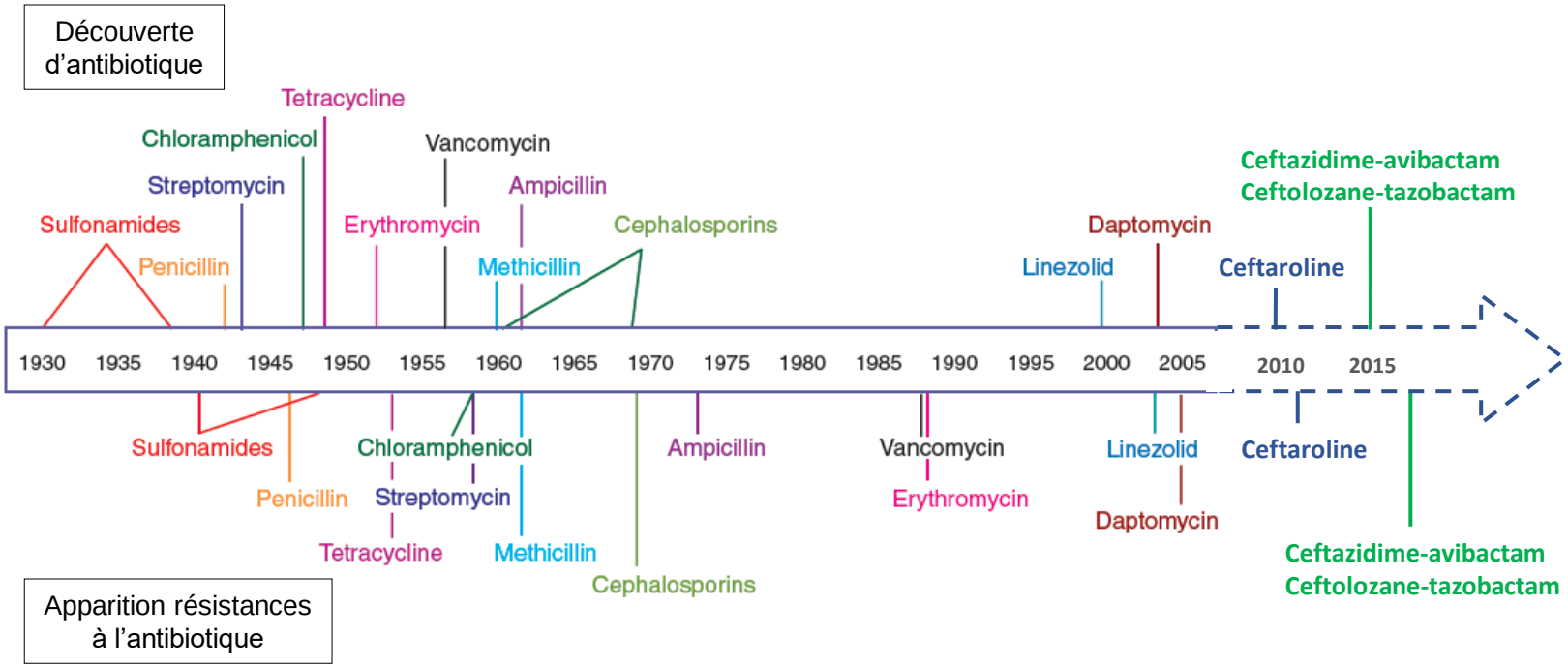
Grupper AAC 2017

Eradication microbiologique nouvelles BL/BLI ~ pathogènes



Chen Expert Rev Anti Infect Ther 2018

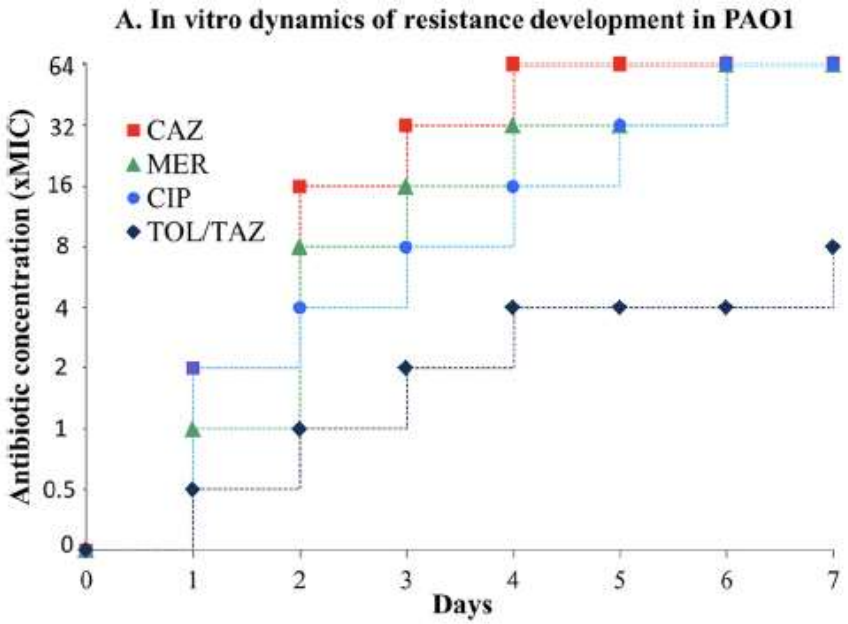
Emergence résistances post-mise sur le marché

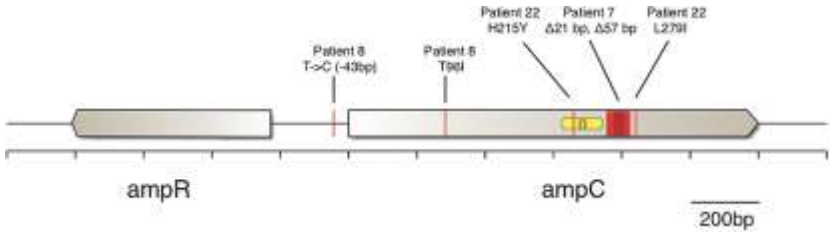


d' après Clatworthy Nat Chem Biol 2007 / Ventola P&T 2015 / Shields AAC 2017

Emergence résistances ceftolozane-tazobactam

Modèle d'émergence in-vitro





TOL-TAZ : émergence lente ?

Mutations de *ampC*
simple?
multiples?
successives?

Haidar CID 2017

ecdc : RAPID RISK ASSESSMENT

Emergence of resistance to ceftazidime-avibactam in carbapenem-resistant Enterobacteriaceae 12 June 2018

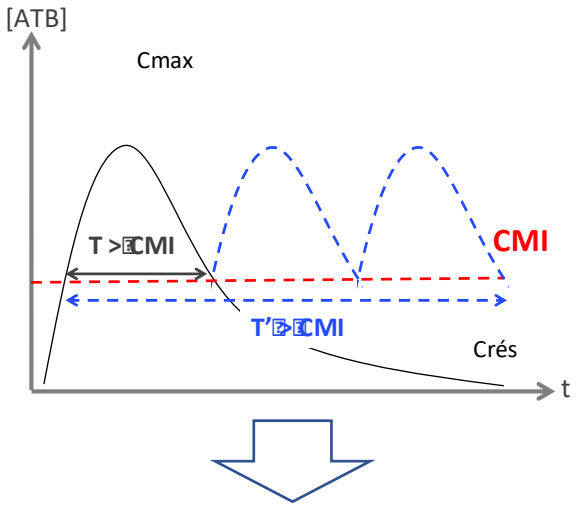
- Reports on the emergence of CAZ-AVI-R CRE soon after its launch represent a public health threat in the EU/EEA and beyond, with the potential for adverse patient outcomes in various settings.
- In the EU/EEA, only sporadic cases (two patients in two different countries) have so far been reported, but CAZ-AVI-R CRE will most probably have the propensity to spread within healthcare settings and across borders, as has been seen for other CRE.

https://ecdc.europa.eu/sites/portal/files/documents/RRA%20-%20Emergence%20of%20resistance%20to%20CAZ-AVI%20in%20CRE%20Enterobacteriaceae%20-%20final.pdf

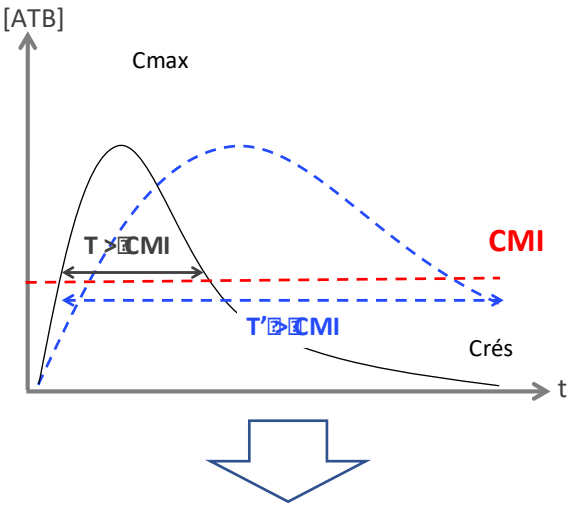
Optimisation PK/PD

PK/PD : paramètre d'optimisation

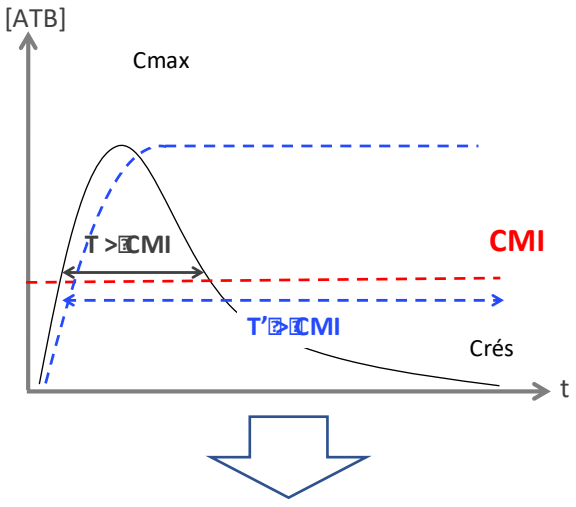
- Paramètre PK/PD d'efficacité = %T > CMI



administrations **pluriquotidiennes**
AUGMENTATION T > CMI



perfusions **prolongées**
AUGMENTATION T > CMI



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

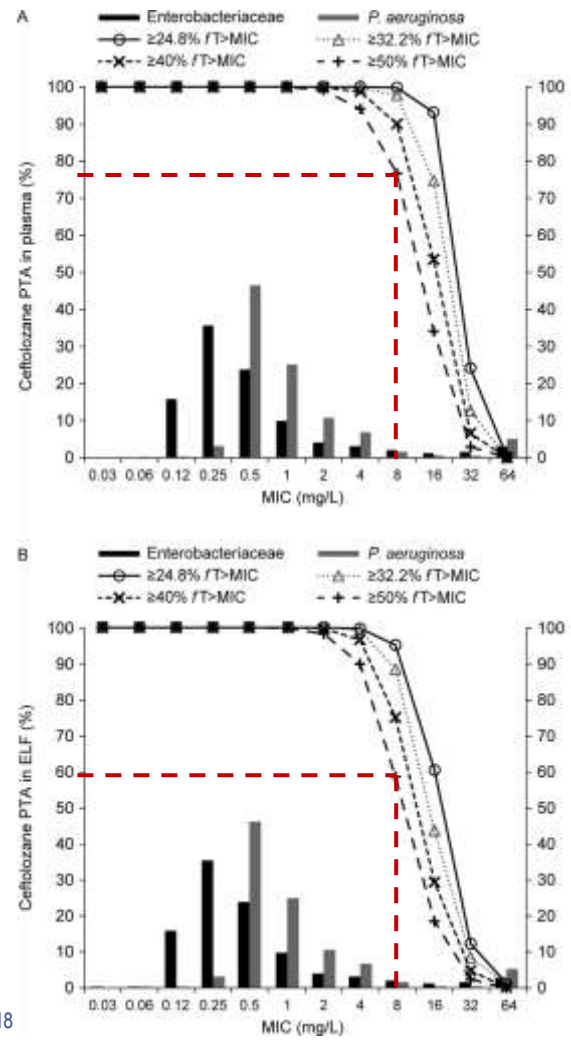
Probabilités d'atteindre la cible PK/PD ~ dose et site

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

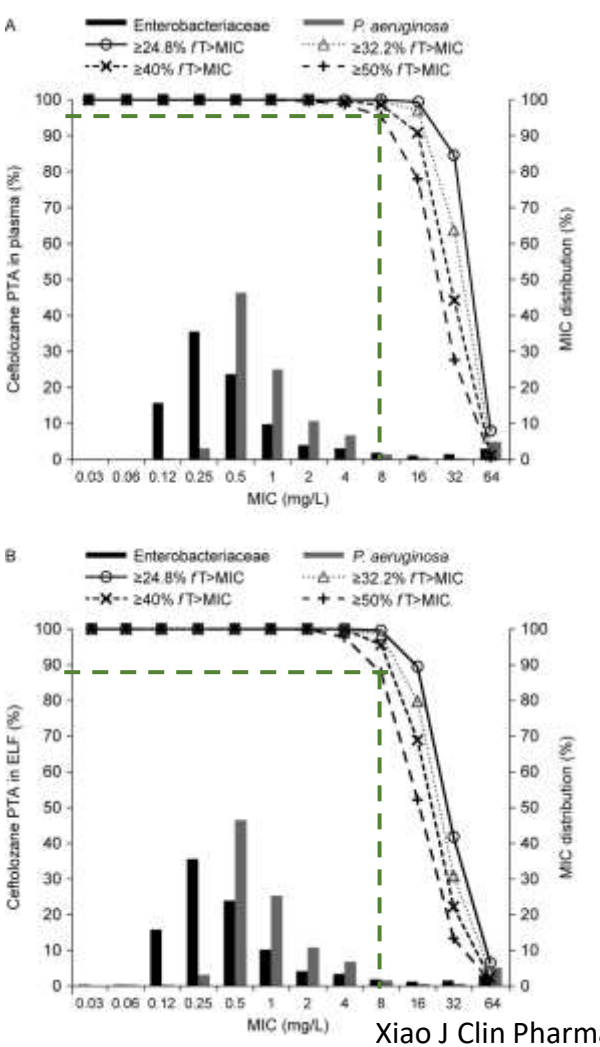
plasmatique

pulmonaire

1,5 g sur 60' / 8h



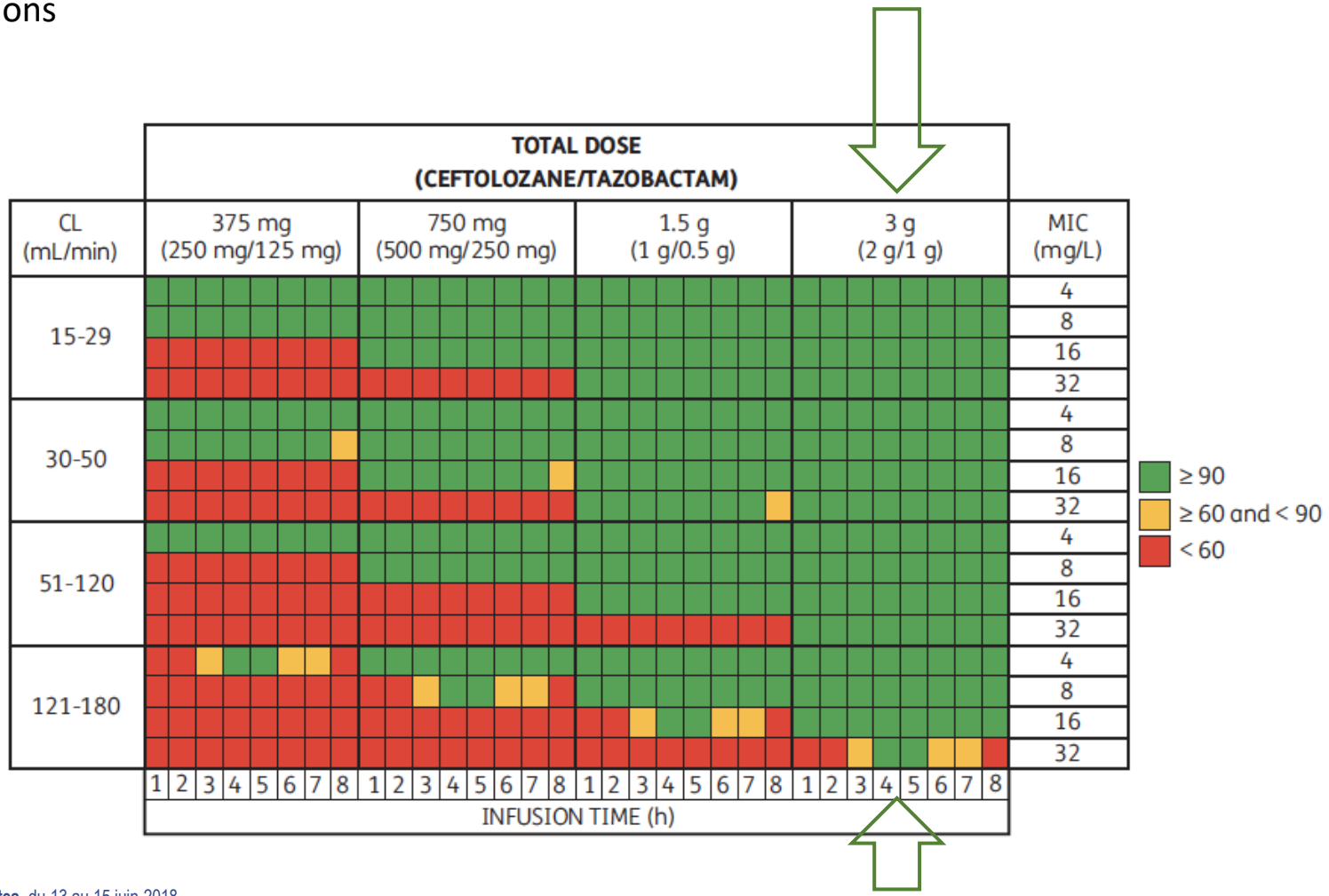
3 g sur 60' / 8h



Xiao J Clin Pharmacol 2016

Perfusions prolongées ceftolozane/tazobactam ?

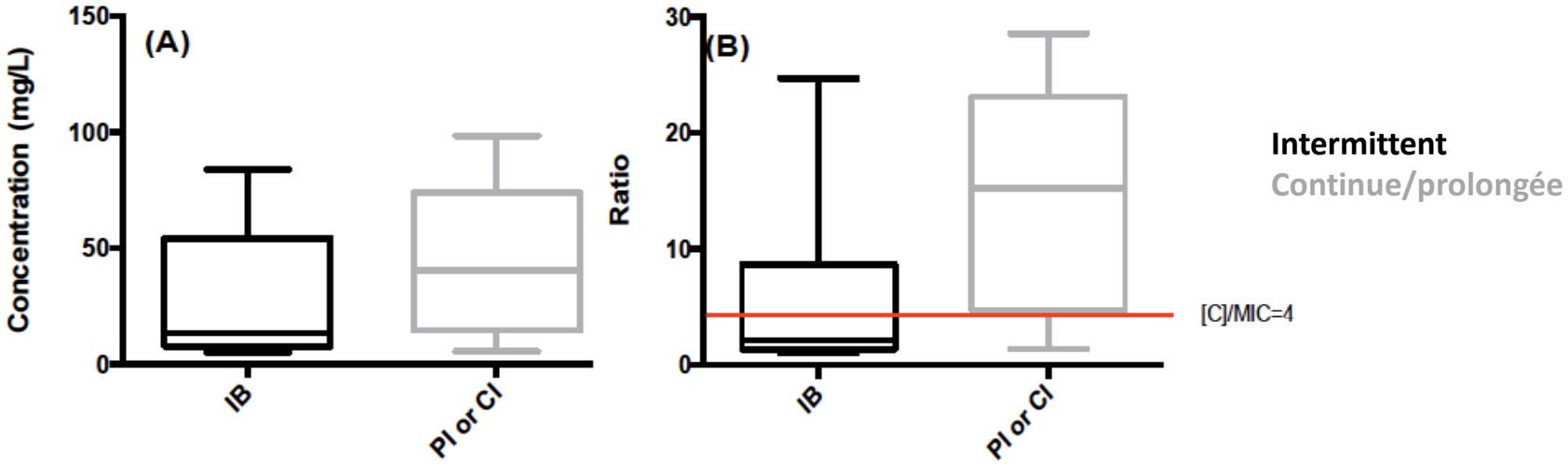
Simulations



Natesan JAC 2017

Perfusions prolongées ceftolozane/tazobactam ?

19 dosages
9 patients
P. aeruginosa MDR



Pilmis RICAI 2017

Inconnues

- Optimisation PK/PD des nouvelles BL/BLI
- Nouvelles BL/BLI en administration optimisée vs. comparateurs optimisés
- Pression de séléction réelle des nouvelles BL/BLI déployées sur le terrain

Conclusions

L'adéquation de l'antibiothérapie initiale des infections graves est l'enjeu

MAIS

- *P. aeruginosa* et entérobactéries
  - pathogènes les plus fréquemment en cause de pneumonies associées aux soins en réa
  - partagent les mêmes facteurs de risque

DONC

- → on ne peut se passer en probabiliste d'associations couvrant

  P. aeruginosa ET entérobactéries ± R /MDR

- l'avantage du spectre anti *P. aeruginosa* MDR de ceftolozane/tazobactam apparaît
  - à l'utilisation de méthodes d'identification rapides de *P. aeruginosa* (+ FdR ou épidémio MDR)
  - à l'utilisation de méthodes de détection rapide de mécanismes de R
  - et sur documentation complète