Traitement des infections liées à *P. aeruginosa*… et un peu *Acinetobacter*….

B Guery

Maladies Infectieuses

CHRU Lille-EA7366

Cas clinique

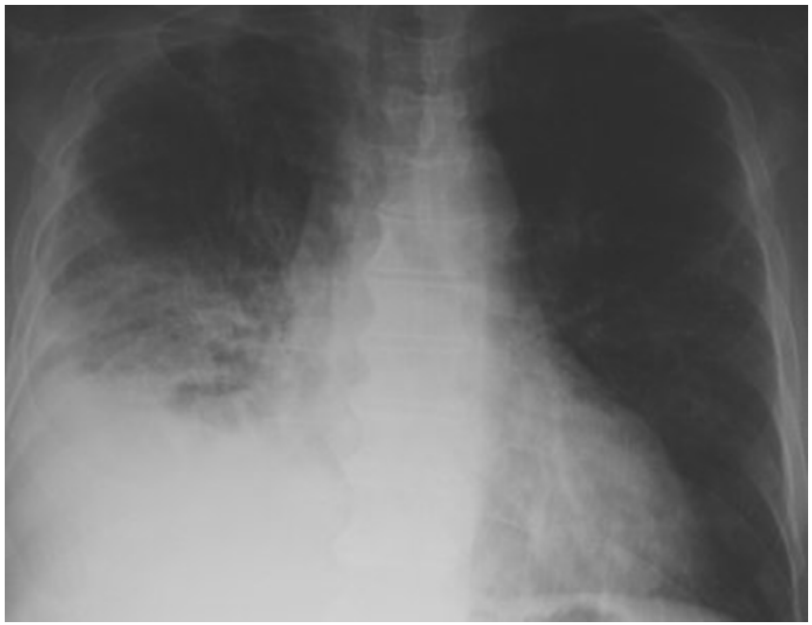
- ✓ Mr D
  - Insuffisant respiratoire chronique
  - Intoxication mixte

Admis en réanimation pour une nouvelle décompensation respiratoire sur exacerbation de sa BPCO.

L'antibiothérapie de première ligne en l'absence d'arguments en faveur d'une pneumonie repose sur une monothérapie par ceftriaxone seule.

- ✓ L'évolution initiale est favorable
- ✓ A J7 de son hospitalisation, il présente
  - Température à 39°C
  - Dégradation de son état respiratoire avec augmentation des besoins en oxygène
  - Image de pneumonie à la radiographie de thorax
  - Au niveau clinique, Mr D a présenté une hypotension qui a répondue au remplissage (2L sur 1h).

  Quel est votre prise en charge anti-infectieuse?



Résistance naturelle de *P. aeruginosa*

Amoxicilline
C1g, c2g
Céfotaxime...

Kanamycine
Néomycine
Spectinomycine

Glycopeptides

Chloramphénicol

Nitroimidazoles

Tétracyclines

Triméthoprime
Sulfamides

Nitrofuranes

Anciennes quinolones
Péfloxacine...

Macrolides
Lincosamides
Synergistines

Antibiotiques anti-pyocyanique

ß-lactamines

- ticarcilline ± clavu
- pipéracilline ± tazo
- aztréonam
- cefsulodine
- céfopérazone
- ceftazidime
- cefpirome
- céfépime
- imipénème
- méropénème
- doripénème

Aminosides

- gentamicine
- nétilmicine
- tobramycine
- amikacine
- isépamicine

Fluoroquinolones

- ofloxacine
- ciprofloxacine
- Lévofloxacine

Autres

- colistine
- polymyxine B
- rifampicine
- fosfomycine

Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: Results from the SENTRY Antimicrobial Surveillance Program, 2009–2012

Helio S. Sader*, David J. Farrell, Robert K. Flamm, Ronald N. Jones

- ✓ Frequency of occurrence and antimicrobial susceptibility patterns of Gram-negative bacteria pneumonia in USA (n = 28) and Europe and the Mediterranean region (EMR) (n = 25) in 2009 2012.
- ✓ 12851 isolates collected (6873/5978 in USA/EMR).

Organism/antimicrobial agent	%S/%R (no. tested)			
	CLSI[a]		EUCAST[a]	
	USA	EMR	USA	EMR
Pseudomonas aeruginosa	(1439)	(1250)	(1439)	(1250)
TZP	72.9/15.6	63.9/21.3	72.9/27.1	63.9/36.1
Ceftazidime	79.6/16.1	68.7/24.0	79.6/20.4	68.7/31.3
Cefepime	80.4/9.5	72.1/13.1	80.4/19.6	72.1/27.9
Meropenem	76.3/16.1	65.8/25.9	76.3/9.0	65.8/14.4
Amikacin	96.2/1.7	88.8/9.0	92.2/3.8	82.8/11.2
Gentamicin	87.0/9.2	75.2/21.2	87.0/13.0	75.2/24.8
Tobramycin	91.7/7.1	76.9/22.0	91.7/8.3	76.9/23.1
Levofloxacin	70.5/21.3	63.4/29.1	59.1/29.5	53.8/36.6
Colistin	98.9/0.3	99.0/0.3	98.9/1.1	99.0/1.0

International Journal of Antimicrobial Agents 43 (2014) 328–334

- ✓ La sélection de mutant est –elle comparable quelque soit la molécule utilisée?

Émergence de résistants

Modèle de péritonite expérimentale à *P. aeruginosa* (10^8 CFU)

Molécule	% d'émergence
Ceftazidime	25
Céfépime	<10
Imipénème	<5
Ciprofloxacine	>60
Amikacine	<5

(Pechere et al, JAC 198

271 patients/ Emergence de résistance chez 28 (10,2%)

TABLE 2. Multivariable Cox hazard models for the emergence of resistance to any of the four study drugs[a]

Antibiotic	Events (no./total Rx)	Multivariable model	
		HR (95% CI)	*P* value
Culturing score	NI	2.5 (1.1–6.0)	0.04
Aminoglycosides	13/77	0.8 (0.4–2.0)	0.8
Ceftazidime	10/125	0.7 (0.3–1.7)	0.4
Ciprofloxacin	12/98	0.8 (0.3–2.0)	0.6
Imipenem	11/37	2.8 (1.2–6.6)	0.02
Piperacillin	9/91	1.7 (0.7–4.1)	0.3

[a] Rx, treatment; CI, confidence interval; NI, not included.

Carmeli et al AAC 199

267 bactériémies, 25% avec une exposition à un anti-pyo

Table 2. Univariate analysis of therapies, including ceftazidime, piperacillin, imipenem, ciprofloxacin, and aminoglycosides, as risk factors for antibiotic-specific resistance in 267 bacteremic strains of *Pseudomonas aeruginosa*.

Antipseudomonal agent, included in previous therapy	P
Ceftazidime	
Yes	
No	
Piperacillin[a]	
Yes	
No	
Imipenem[a]	
Yes	
No	
Ciprofloxacin	
Yes	
No	
Aminoglycoside	
Yes	
No	

[a] One isolate was not against imipenem.

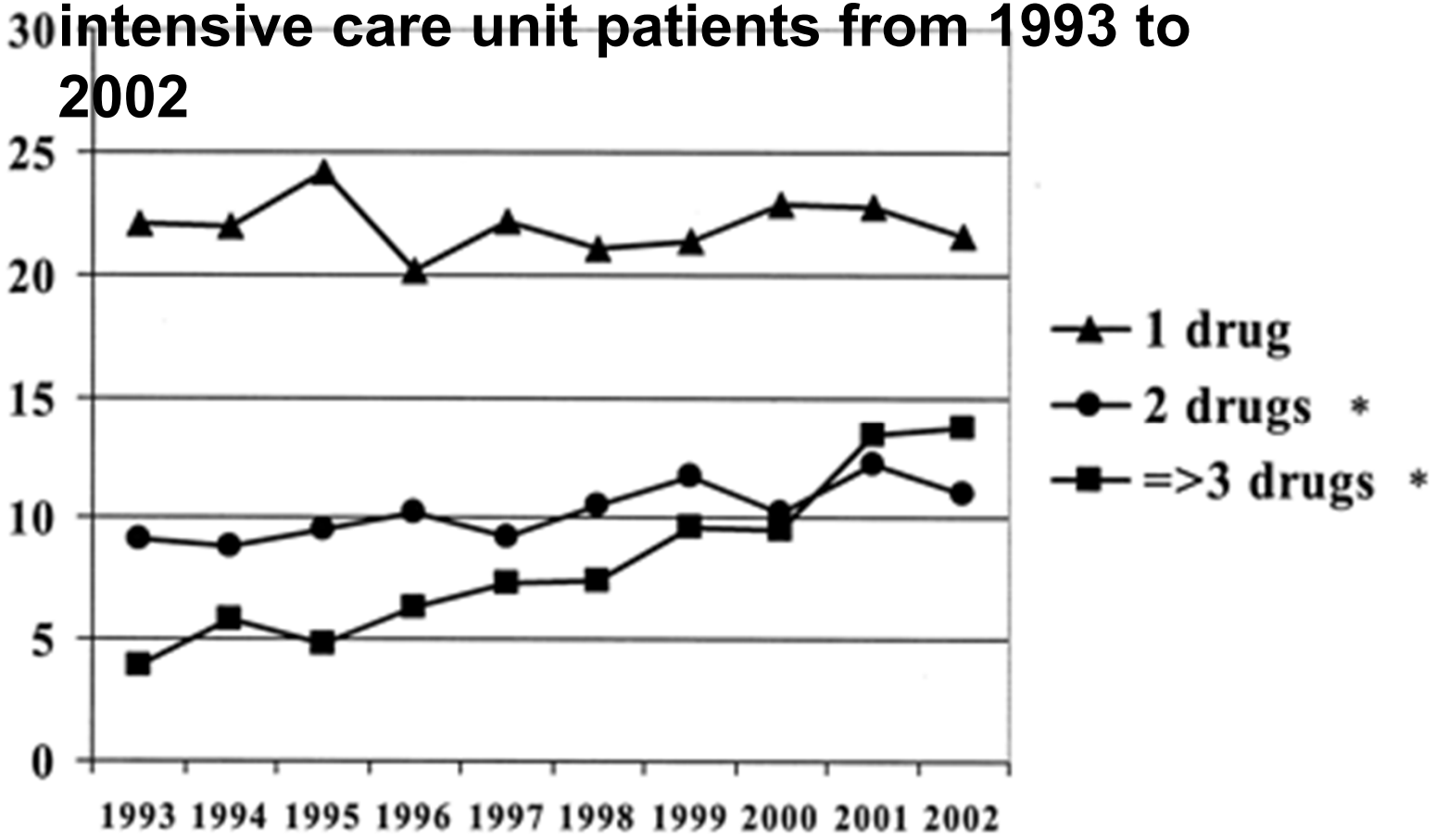
Table 3. Multivariate association, averaged across antipseudomonal agents, of previous exposure to an agent, and resistance to that same agent in 267 bacteremic strains of *Pseudomonas aeruginosa*.

Characteristic	Adjusted OR (95% CI)	*P*
Previous monotherapy with the agent	2.5 (1.3–4.8)	.006
Previous combination therapy including the agent	1.8 (0.55–5.6)	.34
Severe sepsis or septic shock	1.6 (0.94–2.6)	.08

NOTE. Stratified logistic regression analysis in which each episode of bacteremia contributed 5 times to the model (i.e., once per antipseudomonal agent). Variance estimates were adjusted for the resulting dependence among observations.

Boffi El Amari et al, CID 2001

National surveillance of antimicrobial resistance in *Pseudomonas aeruginosa* isolates obtained from intensive care unit patients from 1993 to 2002



13999 souches

Obritsch et al, AAC 2004

TABLE 3. Resistance of P. aeruginosa isolates to both agents in potential combination regimens[a]

Yr	Cefepime			Imipenem			Piperacillin-tazobactam			Aztreonam		
	CIP	TOB	AK	CIP	TOB	AK	CIP	TOB	AK	CIP	TOB	AK
1993	NA	NA	NA	5	3	2	NA	NA	NA	7	4	4
1994	NA	NA	NA	6	5	6	NA	NA	NA	11	8	8
1995	NA	NA	NA	6	3	3	NA	NA	NA	10	5	5
1996	NA	NA	NA	6	4	3	NA	NA	NA	10	6	6
1997	NA	NA	NA	9	4	3	5	2	2	11	5	5
1998	10	5	4	8	5	2	7	4	3	14	6	5
1999	15	10	6	10	6	4	8	6	3	16	9	6
2000	16	8	6	10	6	3	8	4	3	17	7	6
2001	19	11	9	13	8	5	9	5	4	20	10	8
2002	17	11	6	16	9	5	7	4	4	17	11	7
P value[b]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0002	0.013	<0.0001	<0.0001	<0.0001

[a] AK, amikacin; CIP, ciprofloxacin; TOB, tobramycin; NA, not available. Data presented as percentages.

[b] P values representative of available resistance data over the 10-year period.

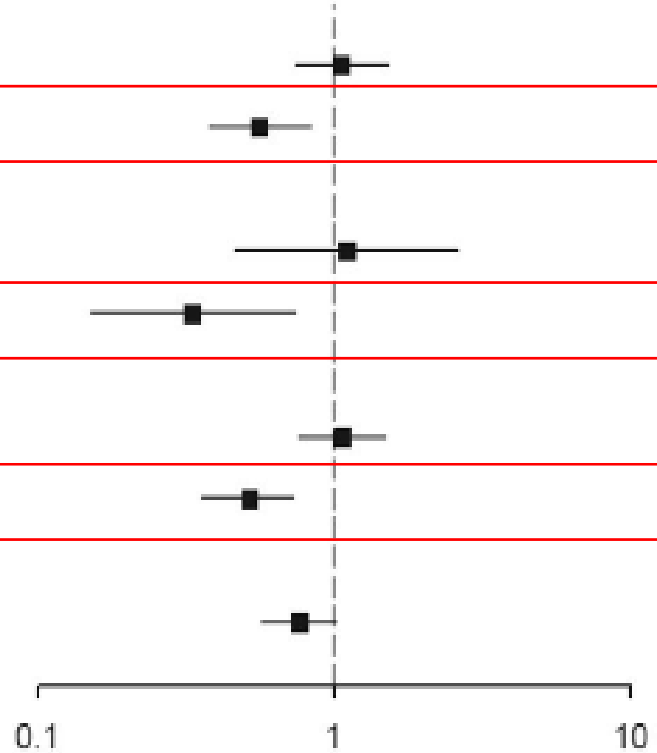
Obritsch et al, AAC 2004

- ✓ Vous mettez en place
  - Une monothérapie?
  - Une association?

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

Anand Kumar, MD; Nasia Safdar, MD; Shravan Kethireddy, MD; Dan Chateau, PhD

Group	Monotherapy Mortality (%)	Combination Therapy Mortality (%)	Odds Ratio	I^2 (%)	P-value
non-shock	86/680 (12.6)	96/668 (14.4)	1.06 (0.73-1.52)	13.7	.7721
shock	96/188 (51.1)	177/422 (41.9)	0.56 (0.39-0.83)	0.8	.0043
non-critically ill	23/313 (7.3)	35/339 (10.3)	1.10 (0.46-2.60)	45.3	.8321
critically ill	32/64 (50.0)	34/128 (26.6)	0.33 (0.15-0.74)	0	.0067
non-shock/non-critically ill	109/993 (11.0)	131/1005 (13.0)	1.06 (0.76-1.47)	19.1	.7178
shock/critically ill	128/252 (50.1)	211/550 (38.4)	0.51 (0.36-0.72)	0	.0002
overall	237/1245 (19.0)	342/1555 (22.0)	0.76 (0.57-1.02)	33.8	.0622



Crit Care Med 2010 Vol. 38, No. 8

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

Anand Kumar, MD; Ryan Zarychanski, MD; Bruce Light, MD; Joseph Parrillo, MD; Dennis Maki, MD; Dave Simon, MD; Denny Laporta, MD; Steve Lapinsky, MD; Paul Ellis, MD; Yazdan Mirzanejad, MD; Greg Martinka, MD; Sean Keenan, MD; Gordon Wood, MD; Yaseen Arabi, MD; Daniel Feinstein, MD; Aseem Kumar, PhD; Peter Dodek, MD; Laura Kravetsky, BSc; Steve Doucette, MSc; the Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group

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

	Unmatched Cohort			Propensity Matched Cohort		
	Monotherapy, n = 2948	Combined Therapy, n = 1714	*p*	Monotherapy, n = 1223	Combined Therapy, n = 1223	*p*
Site of Infection, n (%)						
Primary bloodstream infection	152 (5.2%)	113 (6.6%)	<.0001	68 (5.6%)	70 (5.7%)	1.00
Catheter-related infection	124 (4.2%)	72 (4.2%)		50 (4.1%)	52 (4.3%)	
Respiratory infection	1214 (41.2%)	639 (37.3%)		449 (36.7%)	439 (35.9%)	
Urinary tract infection	379 (12.9%)	304 (17.7%)		224 (18.3%)	229 (18.7%)	
Intra-abdominal infection	681 (23.1%)	332 (19.4%)		272 (22.2%)	275 (22.5%)	
Central nervous system infection	41 (1.4%)	13 (0.8%)		13 (1.1%)	12 (1%)	
Soft tissue infection	281 (9.5%)	201 (11.7%)		119 (9.7%)	116 (9.5%)	
Surgical site infection	48 (1.6%)	21 (1.2%)		16 (1.3%)	16 (1.3%)	
Nonrespiratory intrathoracic infection	17 (0.6%)	8 (0.5%)		7 (0.6%)	8 (0.7%)	
Other infection	11 (0.4%)	11 (0.6%)		5 (0.4%)	6 (0.5%)	

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	Unmatched Cohort			Propensity Matched Cohort		
	Monotherapy, n = 2948	Combined Therapy, n = 1714	*p*	Monotherapy, n = 1223	Combined Therapy, n = 1223	*p*
Primary pathogen, n (%)						
Streptococcus pyogenes (group A streptococci)	47 (1.6%)	141 (8.2%)	<.0001	45 (3.7%)	49 (4%)	1.00
Non-group A b-hemolytic streptococci	50 (1.7%)	57 (3.3%)		33 (2.7%)	30 (2.5%)	
Viridans streptococci	56 (1.9%)	39 (2.3%)		30 (2.5%)	30 (2.5%)	
Streptococcus pneumoniae	170 (5.8%)	281 (16.4%)		141 (11.5%)	141 (11.5%)	
Staphylococcus aureus	803 (27.2%)	129 (7.5%)		139 (11.4%)	128 (10.5%)	
Enterococcus species	179 (6.1%)	33 (1.9%)		29 (2.4%)	30 (2.5%)	
Other Gram-positives[g]	4 (0.1%)	3 (0.2%)		2 (0.2%)	2 (0.2%)	
Escherichia coli	681 (23.1%)	490 (28.6%)		373 (30.5%)	386 (31.6%)	
Klebsiella species	269 (9.1%)	179 (10.4%)		144 (11.8%)	139 (11.4%)	
Enterobacter species	118 (4%)	68 (4%)		55 (4.5%)	51 (4.2%)	
Other Enterobacteriaceae[h]	150 (5.1%)	97 (5.7%)		67 (5.5%)	71 (5.8%)	
Pseudomonas aeruginosa	226 (7.7%)	125 (7.3%)		102 (8.3%)	98 (8%)	
Haemophilus species	76 (2.6%)	32 (1.9%)		32 (2.6%)	31 (2.5%)	
Other non-Enterobacteriaceae[i]	81 (2.7%)	28 (1.6%)		22 (1.8%)	25 (2%)	
Neisseria meningitidis	27 (0.9%)	6 (0.4%)		4 (0.3%)	6 (0.5%)	
Moraxella catarrhalis	11 (0.4%)	6 (0.4%)		5 (0.4%)	6 (0.5%)	

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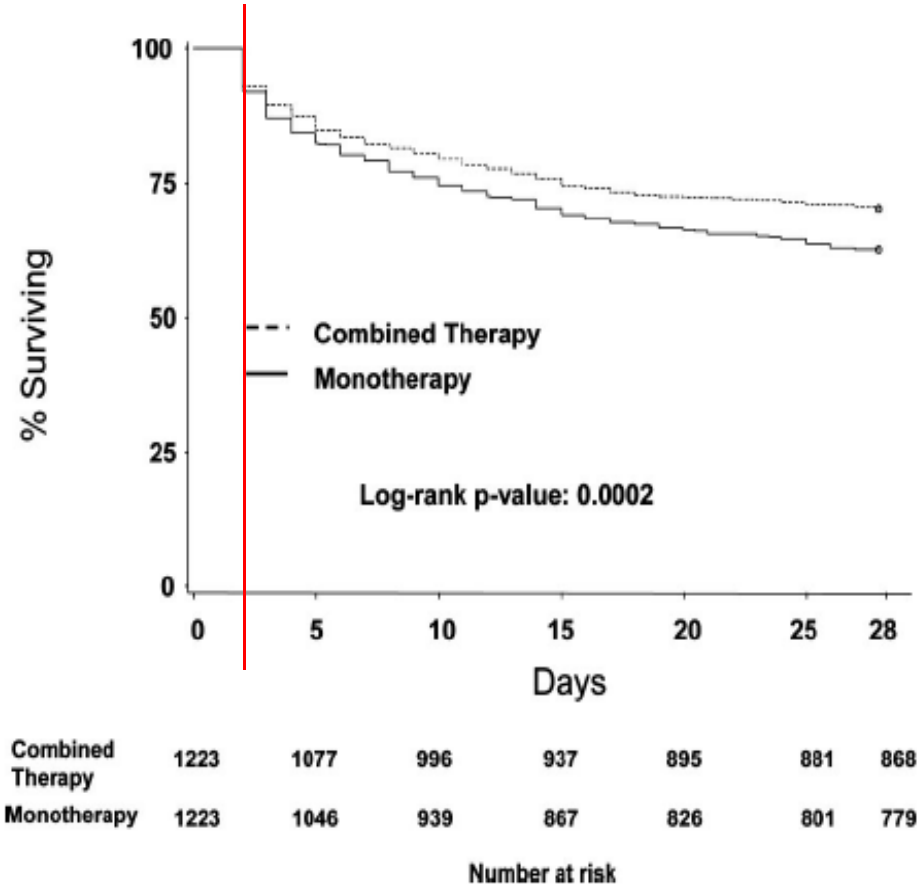

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	Sample Size, n	Mortality Rate by Therapy n of Deaths/Total n of Patients (%)		Odds Ratio (95% Confidence Interval)	*p*
		Monotherapy	Combination Rx		
Intensive care unit mortality	2446	437/1223 (35.7%)	352/1223 (28.8%)	0.75 (0.63–0.88)	.0006
Hospital 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 (15.0%)	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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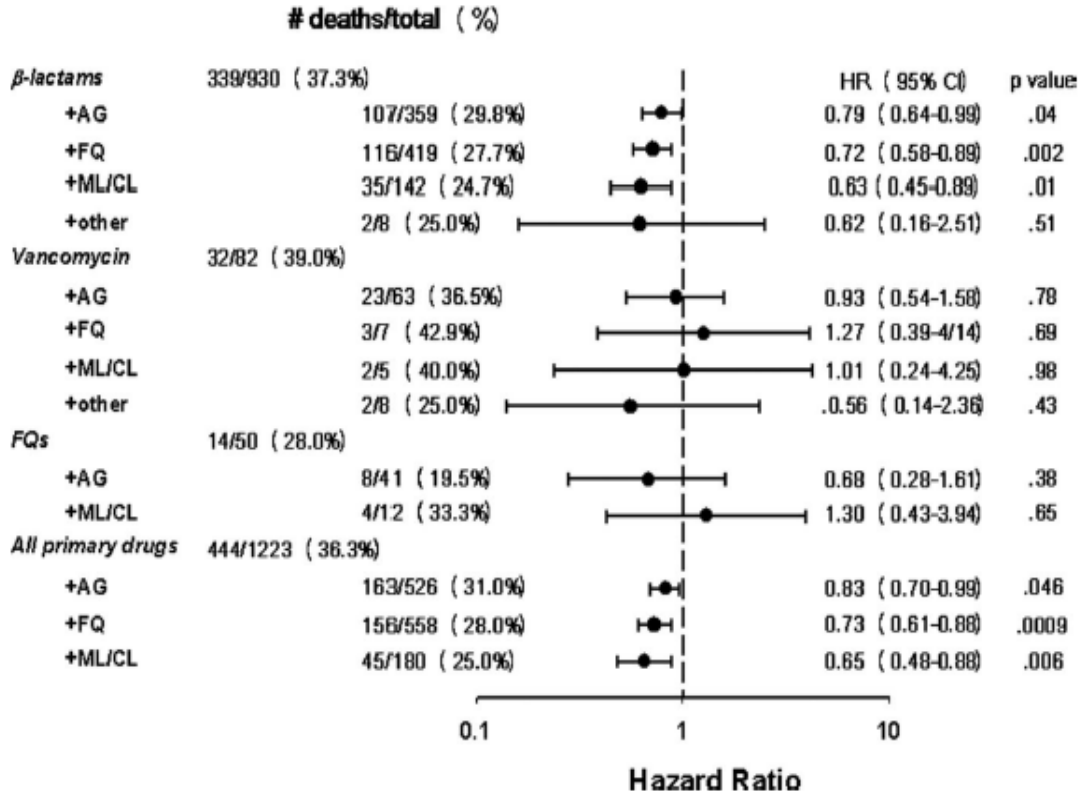


- ✓ The use of aminoglycoside (AG), fluoroquinolone (FQ), or a macrolide/clindamycin (ML/CL) in addition to a -lactam was associated with a reduced hazard ratio for death compared to -lactam alone.
- ✓ No other drug combinations demonstrated evidence of significant benefit.

Crit Care Med 2010 Vol. 38, No. 9

- ✓ La bactériologie objective la présence d'une souche de *P. aeruginosa* aux hémocultures et sur les prélèvements respiratoires
- ✓ Si Mr D n'avait pas présenté de signes en faveur d'un sepsis sévère auriez vous réalisé une association?

ETUDES CLINIQUES PAVM

Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia*

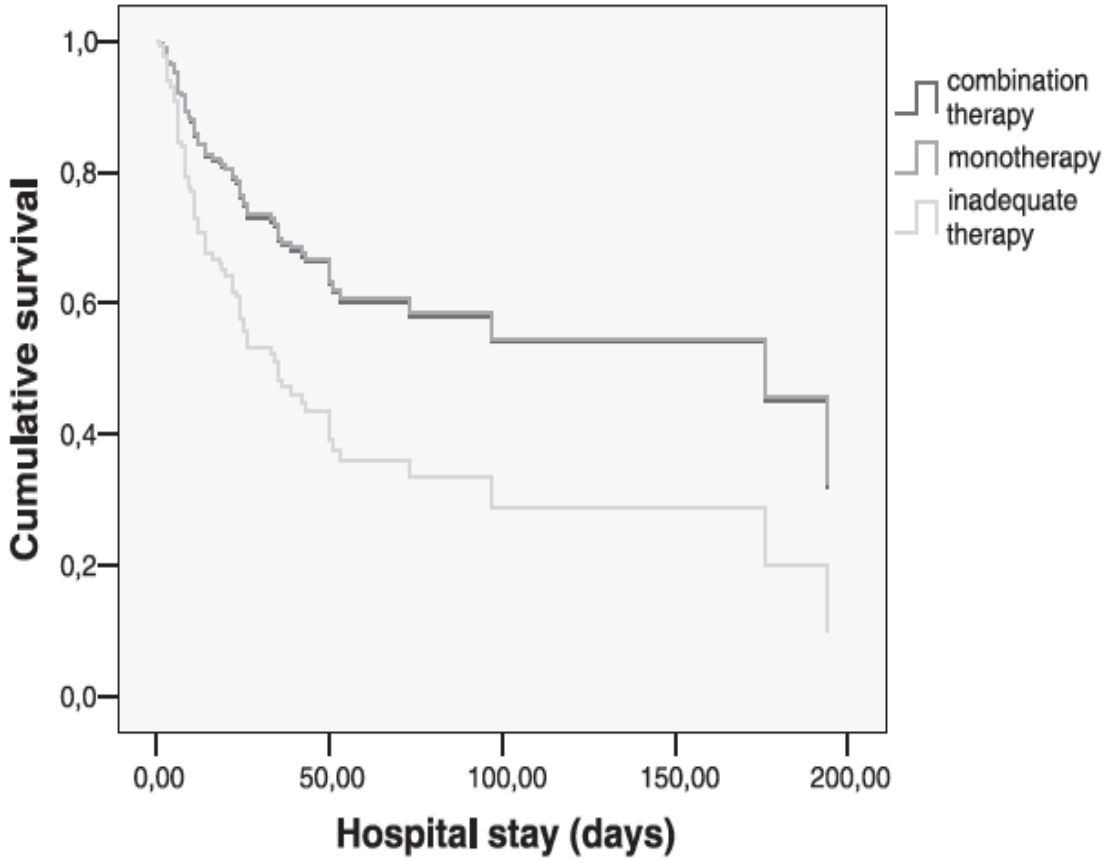
Daren K. Heyland, MD; Peter Dodek, MD; John Muscedere, MD; Andrew Day, MSc; Deborah Cook, MD; for the Canadian Critical Care Trials Group

- ✓ 740 patients
  - Meropéneme + ciprofloxacine vs Meropénème seul
- ✓ Pas de différence
  - mortalité à 28 jours
  - Durée séjour
  - Réponse clinique et microbiologique
  - Émergence de résistance
- ✓ Si *P. aeruginosa*, *Acinetobacter*, ou MDR
  - adéquation meilleure dans le groupe association mais pas de différence sur le pronostic
- ✓ Pour les patients à haut risque une association pourrait être meilleure

CCM 2008;36: 737- 745

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

Jose Garnacho-Montero, MD, PhD; Marcio Sa-Borges, MD; Jordi Sole-Violan, MD; Fernando Barcenilla, MD; Ana Escoresca-Ortega, MD; Miriam Ochoa, MD; Aurelio Cayuela, MD, PhD, MPH; Jordi Rello, MD, PhD



Crit Care Med 2007 Vol. 35, No. 8

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

Jose Garnacho-Montero, MD, PhD; Marcio Sa-Borges, MD; Jordi Sole-Violan, MD; Fernando Barcenilla, MD; Ana Escoresca-Ortega, MD; Miriam Ochoa, MD; Aurelio Cayuela, MD, PhD, MPH; Jordi Rello, MD, PhD

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

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

aHR, adjusted hazard ratio; CI, confidence interval.

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

Mary-Anne W. Aarts, MD, MSc, FRCSC; Jennifer N. Hancock, MD; Daren Heyland, MD, MSc, FRCPC; Robin S. McLeod, MD, FRCSC; John C. Marshall, MD, FRCSC

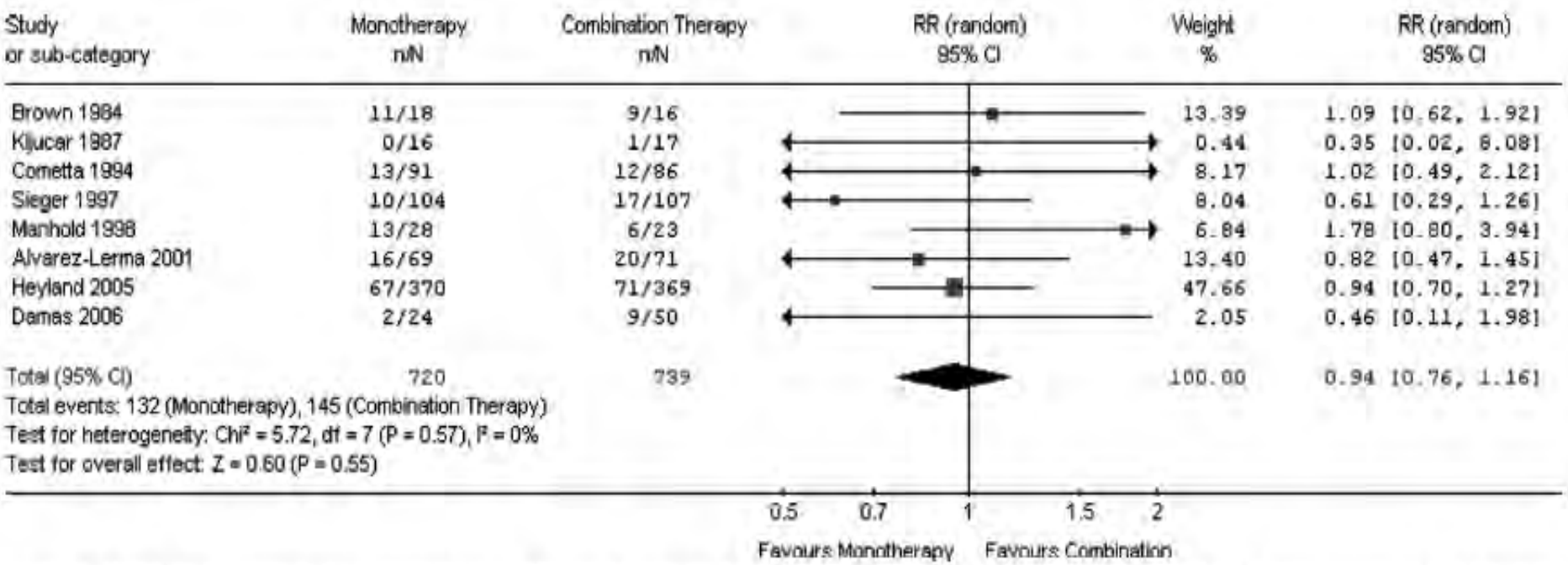


Figure 4. Mortality in pooled trials comparing monotherapy to combination therapy. There is no evidence that combination therapy improves survival when compared with monotherapy. *RR*, relative risk; *CI*, confidence interval.

(Crit Care Med 2008; 36:108–117)

Pseudomonas aeruginosa Ventilator-associated Pneumonia

Predictive Factors of Treatment Failure

Benjamin Planquette[1], Jean-Francois Timsit[2,3], Benoit Y. Misset[4], Carole Schwebel[2], Elie Azoulay[5], Christophe Adrie[3,5], Aurélien Vesin[7], Samir Jamali[8], Jean-Ralph Zahar[9], Bernard Allaouchiche[10], Bertrand Souweine[11], Michael Darmon[12], Anne-Sylvie Dumenil[13], Dany Goldgran-Toledano[14], Bruno H. Mourvillier[15], and Jean-Pierre Bédos[1]; on behalf of the OUTCOMEREA Study Group*

- ✓ A total of 314 patients presented 393 PA-VAP.
- ✓ Failure occurred for 112 of them,
- ✓ Factors associated with treatment failure were
  - ✓ age (P . 0.02);
  - ✓ presence of at least one chronic illness (P . 0.02);
  - ✓ limitation of life support (P . 0.0004);
  - ✓ a high Sepsis-Related Organ Failure Assessment score (P , 0.0001);
  - ✓ PA bacteremia (P .0.003);
  - ✓ previous use of FQ before the first PA-VAP (P . 0.0007).
- ✓ The failure risk was not influenced by the strain resistance profile or by the biantibiotic treatment, but decreased in case of VAP treatment that includes FQ (P .0.0006).
- ✓ Better evaluation of the potential benefit of an initial treatment containing FQ requires further randomized trials.

Am J Respir Crit Care Med Vol 188, Iss. 1, pp 69–76, Jul 1, 2013

ETUDES CLINIQUES
bactériémies

Monotherapy versus β-Lactam–Aminoglycoside Combination Treatment for Gram-Negative Bacteremia: a Prospective, Observational Study

- ✓ 2124 patients
- ✓ Bactériémies à Gram négatifs
  - 670 Tt inadéquat: mortalité 34%
  - 1454 Tt adéquat: mortalité 18%

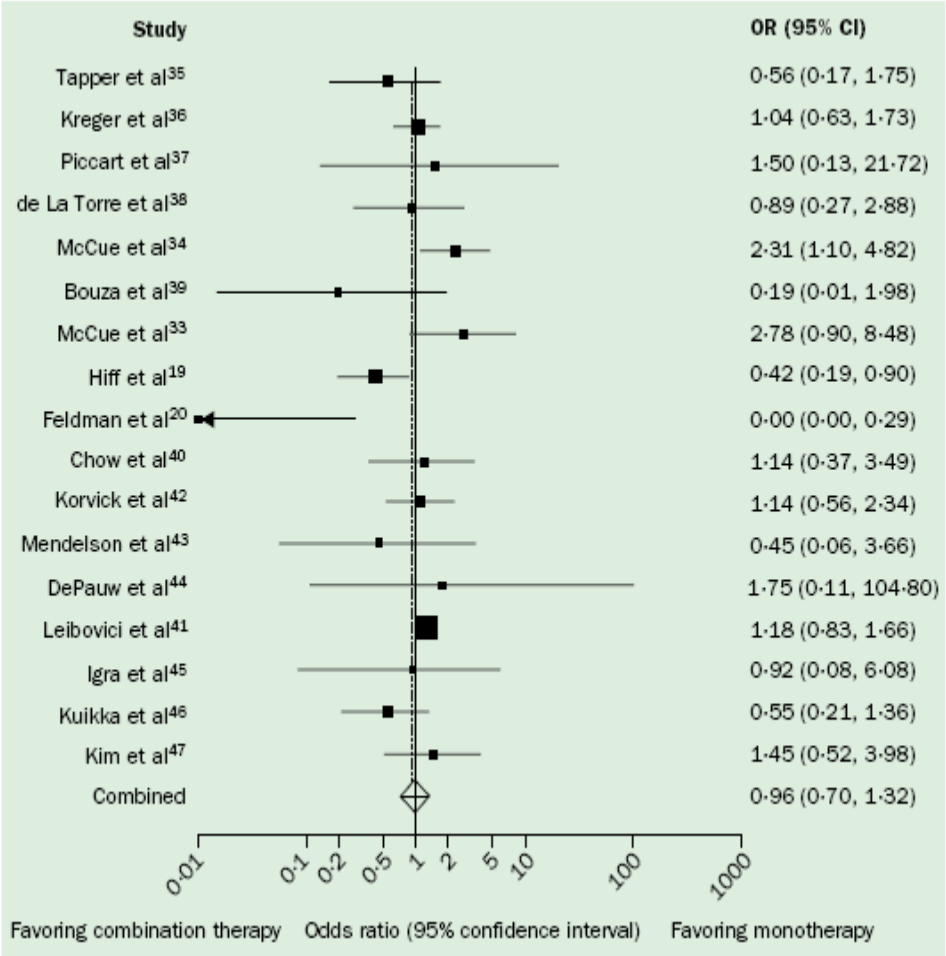
- ✓ Si approprié
  - 789 monothérapie b-lactamine: 17%
  - 327 associations: 19%
  - 249 aminoglycosides: 24%

- ✓ Pas d'avantage à l'association sauf neutropéniques (multivarié), et infections liées à *P. aeruginosa* (monovarié)

AAC 1997

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

Nasia Safdar, Jo Handelsman, and Dennis G Maki



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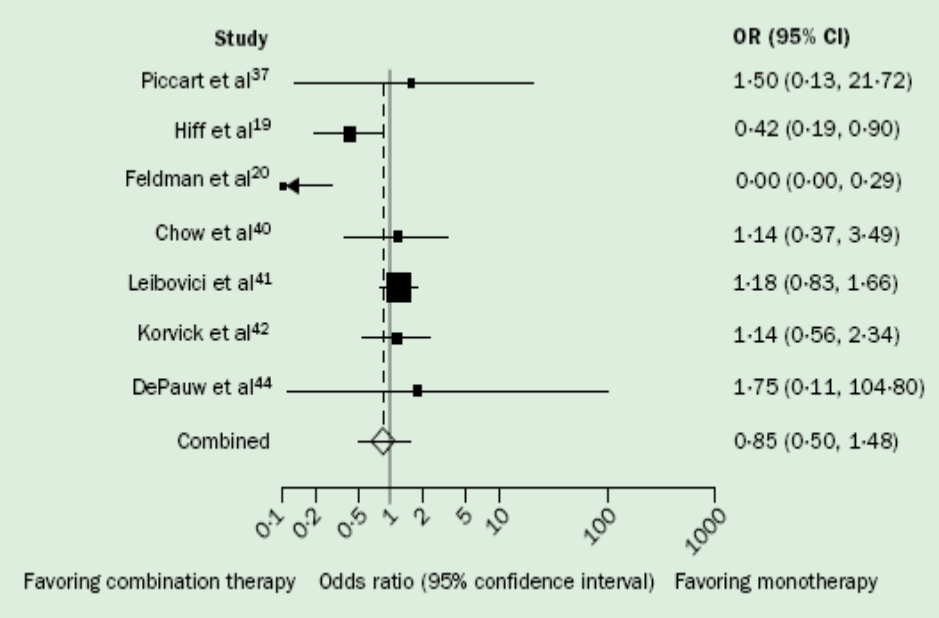
Etudes prospectives uniquement



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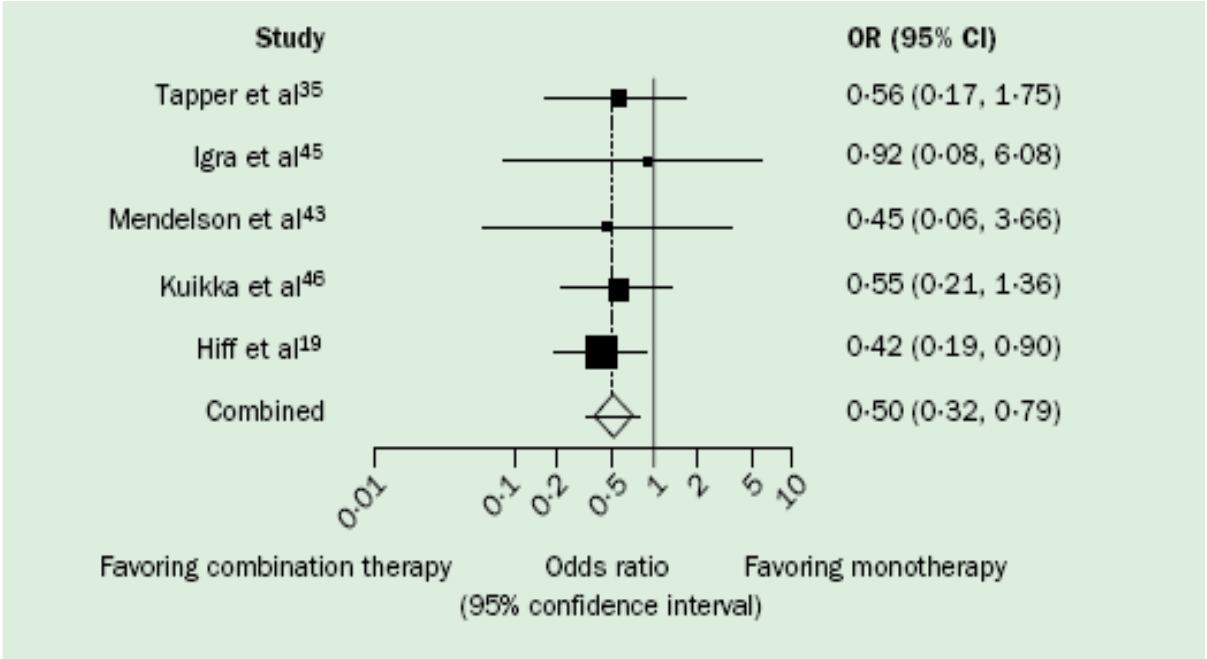
Nasia Safdar, Jo Handelsman, and Dennis G Maki

Bactériémies à *P. aeruginosa*



MAIS
Dans 4 études sur 5 aminosides en monothérapie

Adéquation?

β lactam monotherapy versus β lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials

Mical Paul, Ishay Benuri-Silbiger, Karla Soares-Weiser, Leonard Leibovici

BMJ, published 2 March 2004

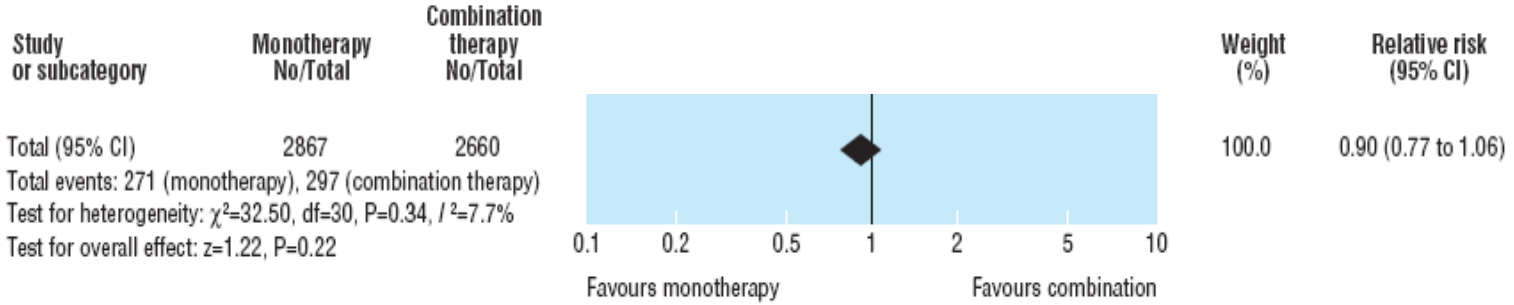


Fig 2 All cause fatality in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

Fig 3 Clinical failure in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

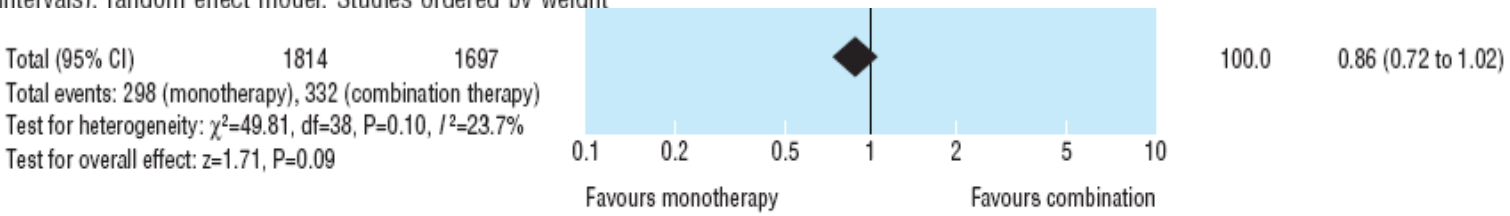


Fig 4 Bacteriological failure in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

β lactam monotherapy versus β lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials

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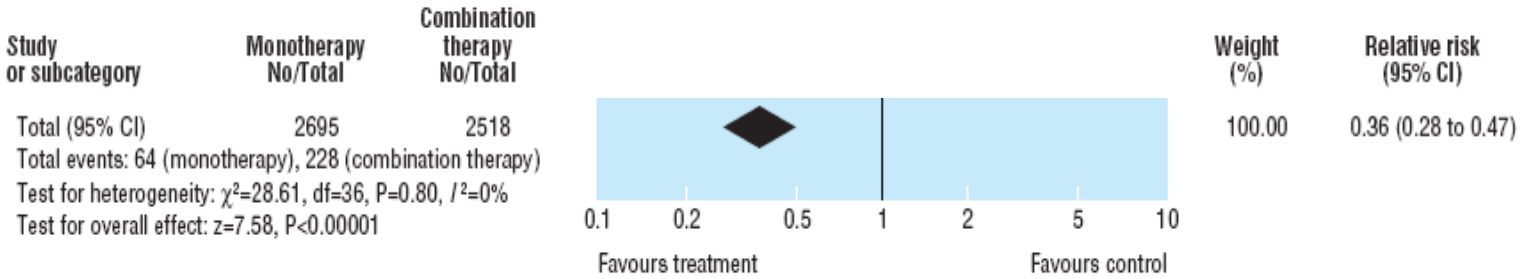
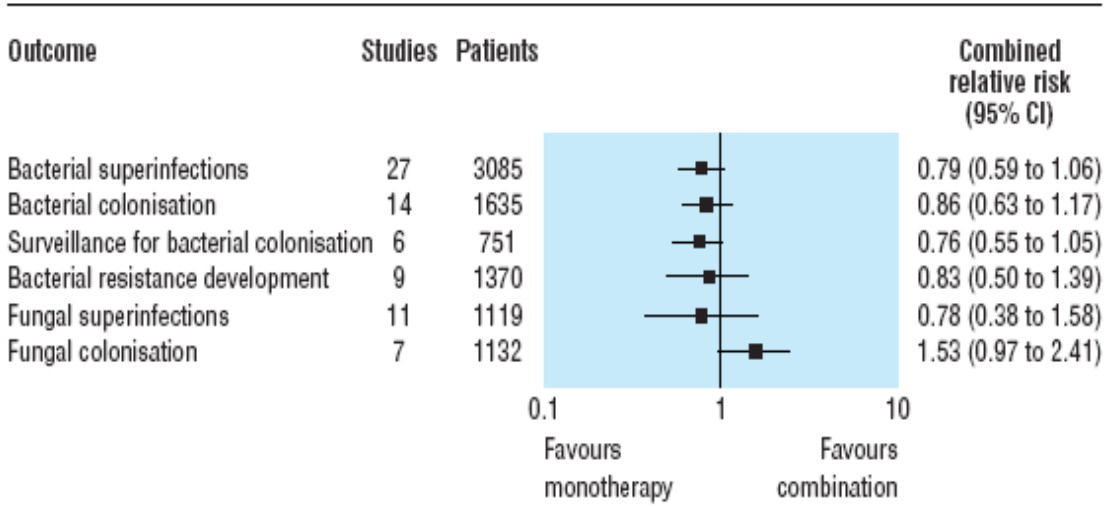


Fig 6 Adverse events: nephrotoxicity in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight



Pseudomonas: RR 1.01

BMJ, published 2 March 2004

β lactam monotherapy versus β lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials

Mical Paul, Ishay Benuri-Silbiger, Karla Soares-Weiser, Leonard Leibovici

What this study adds

There is no difference in mortality when β lactam-aminoglycoside combination therapy is compared with β lactam monotherapy

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Clinical failure and renal toxicity are more common with combination therapy

---

β lactam-aminoglycoside combination therapy does not improve clinical outcomes in patients with severe infections

BMJ, published 2 March 2004

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

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

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

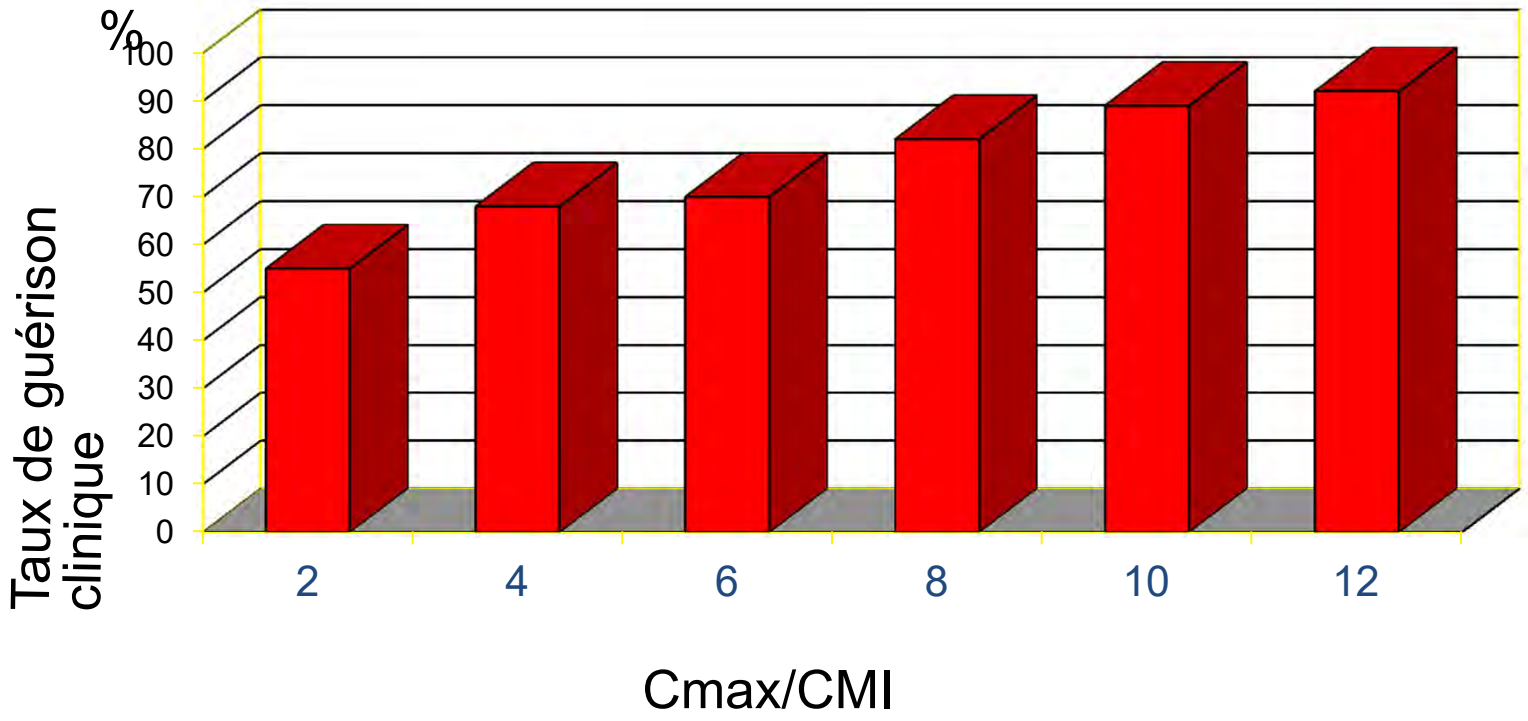
Table 4 Comparison of outcomes according to adequacy of antibiotics

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

. *BMC Infectious Diseases* 2014, **14**:161

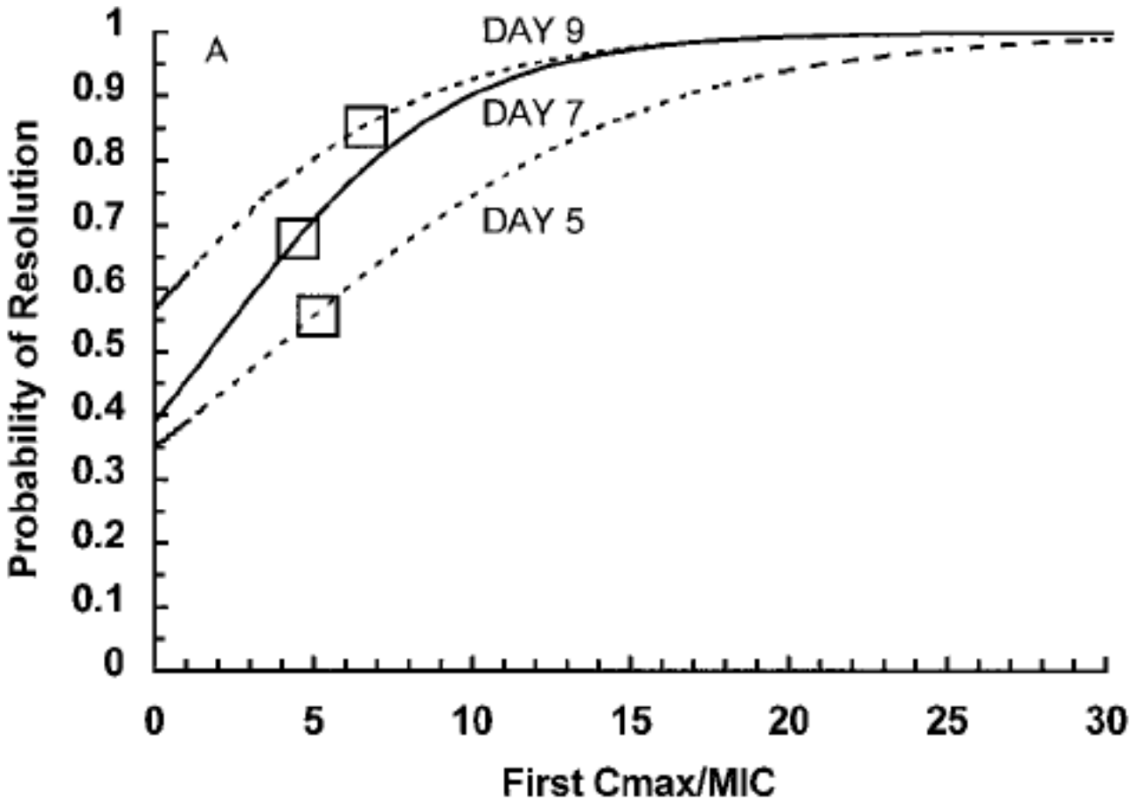
- ✓ Vous décidez de débuter une association beta-lactamine/aminoside
  - Quels sont les arguments justifiant l'utilisation des aminosides en monodose?
  - Quelle dose d'aminoside utilisez-vous?
  - Pendant combien de temps?

Aminosides
Relation Cmax/CMI - Guérison clinique



(Moore, JID 1987)

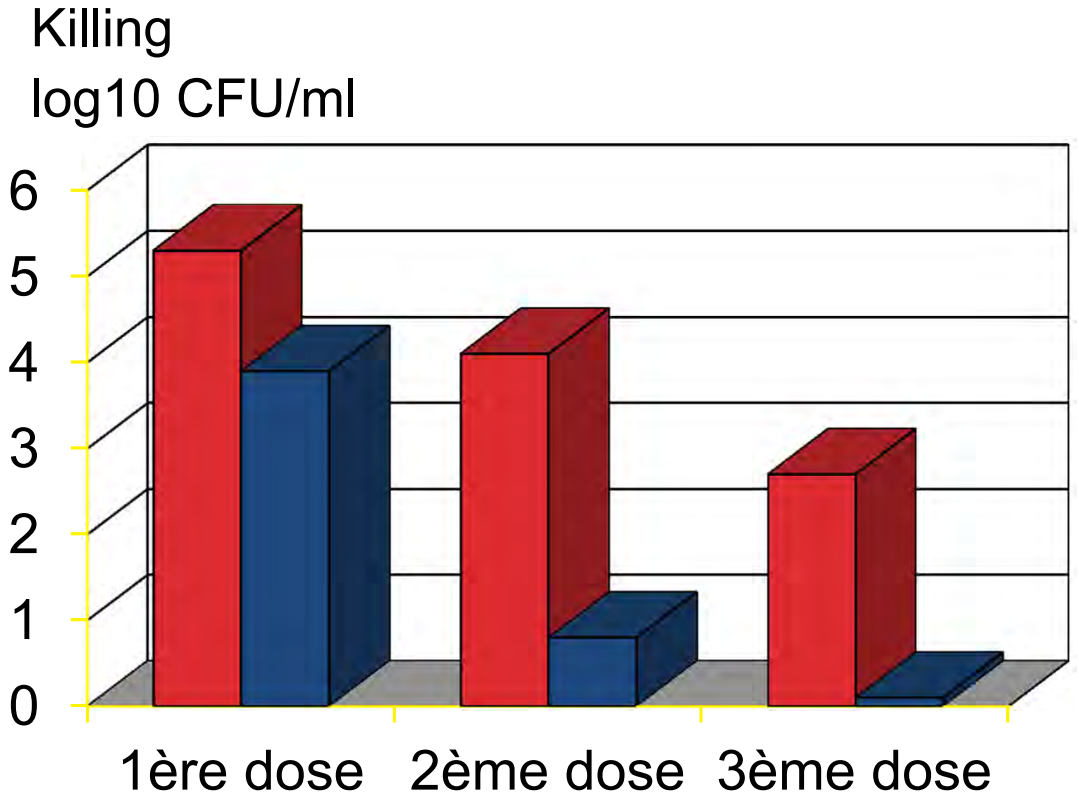
Importance de la première dose d'aminoside sur l'évolution clinique



Kashuba et al, AAC, 1999

Résistance adaptative

Bactéricidie; modèle statique *in vitro*



tobramycine

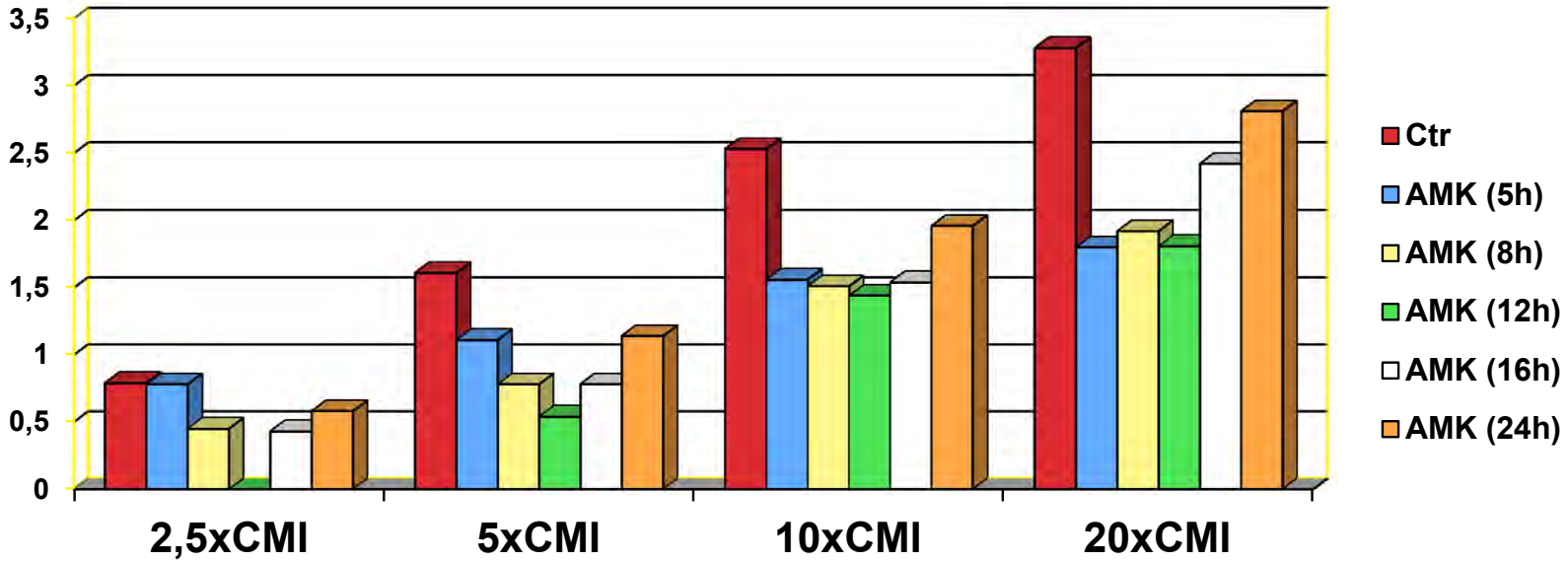
P. aeruginosa

contact = 2h

(Karlowsky et al, JAC 1994)

Résistance adaptative

Dlog CFU/ml/90min

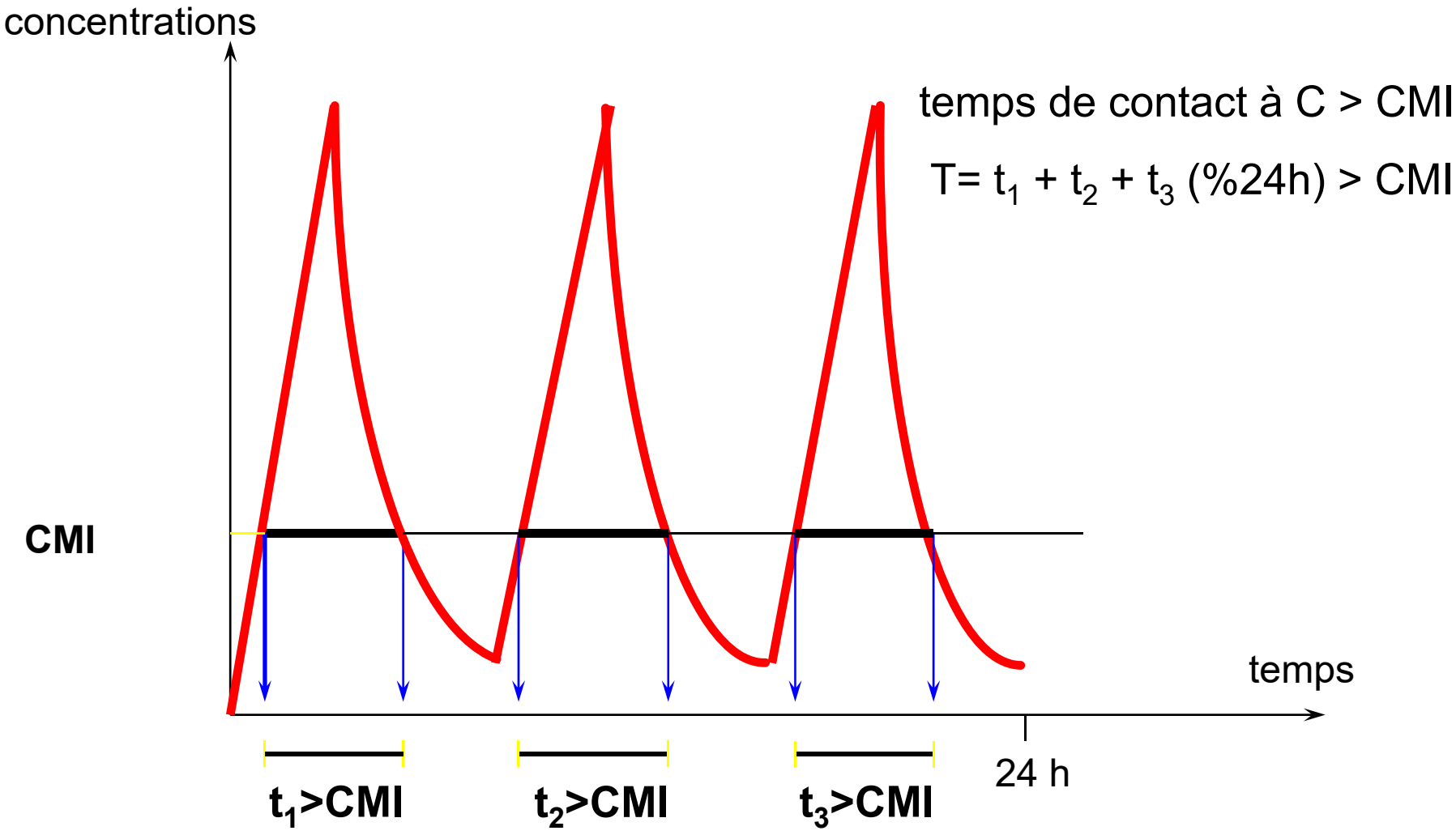


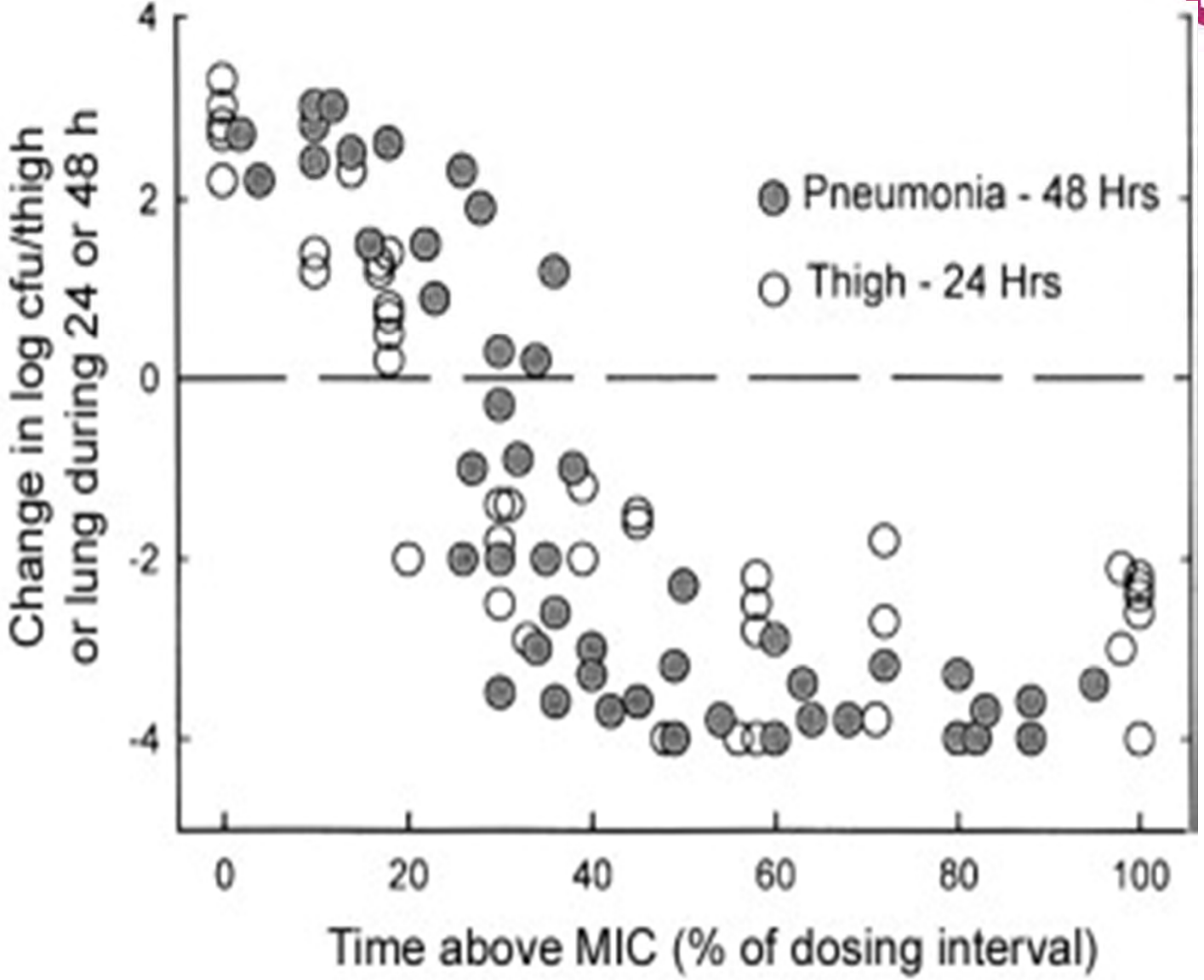
AMK in vivo : 80 mg/kg

(Xiong et al, AAC 1997)

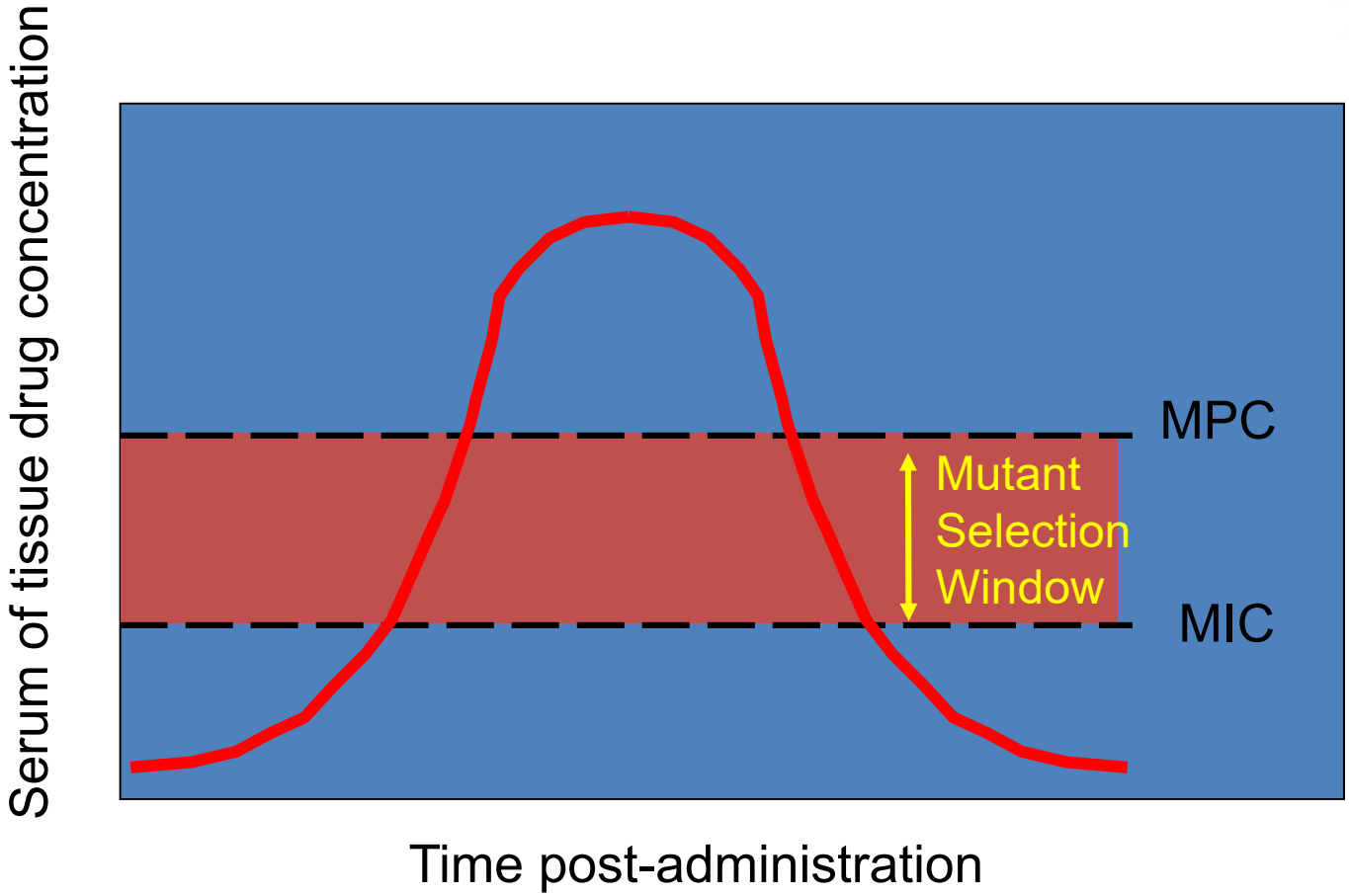
- ✓ Vous associez votre aminoside avec une beta-lactamine
  - Quelle molécules?
  - Quelles modalités d'administration?

Bêtalactamines:
paramètres pharmacodynamiques





(Craig et al, CID 2001)



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

- ✓ 18 patients de réanimation
- ✓ Dose de charge 12mg/kg, suivie de 6 g/24 h de ceftazidime
  - soit en continu (n=8)
  - soit en 3 bolus de 2g/8h (n = 10)
- ✓ Durant les 8 premières heures, concentrations sériques < 40 mg/L (5 fois la conc. crit. inf):
  - groupe perfusion continue: 1 patient / 8 (38 mg/L)
  - groupe bolus: 8 patients / 10 (2 - 33 mg/L)
- ✓ Durant les 40 heures suivantes, temps avec des concentrations sériques > 40 mg/L:
  - groupe perfusion continue: 100%
  - groupe bolus: 20 - 30%

Lipman, JAC 1999; 43: 309-11

Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (*T*>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections

Peggy S. McKinnon [a], Joseph A. Paladino [b,c], Jerome J. Schentag [b,c,*]

Patient demographics

	Cefepime ($n=38$)	Ceftazidime ($n=38$)
Age (years) (mean ± S.D.)	73 ± 12	75 ± 12
APACHE II score (mean ± S.D.)	14 ± 7	13 ± 5
Infection site (n)		
Complicated UTI	24	24
Respiratory	8	9
Skin/soft tissue	1	2
Primary bacteraemia	5	3

Table 3
Organism susceptibility as minimum inhibitory concentration (MIC) values

Isolates (n)	MIC (mg/L) (median (range))	
	Cefepime	Ceftazidime
Escherichia coli (38)	0.03 (0.015–8.0)	0.25 (0.06–16.0)
Pseudomonas aeruginosa (10)	2.0 (1.0–16.0)	2.0 (1.0–16.0)
Klebsiella sp. (7)	0.03 (0.015–2.0)	0.125 (0.06–2)

Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (*T*>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections

Peggy S. McKinnon[a], Joseph A. Paladino[b,c], Jerome J. Schentag[b,c,*]

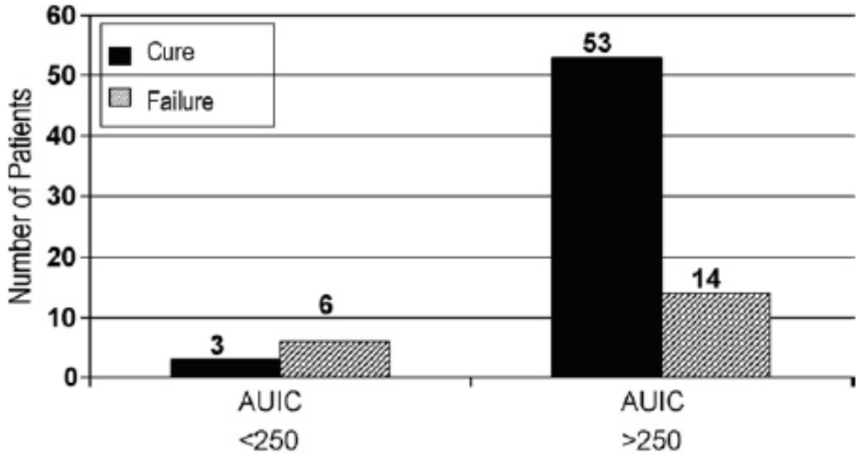


Fig. 2. Clinical cure rates for patients at 24-h area under the inhibitory curve (AUIC) values of ≥250 and <250.

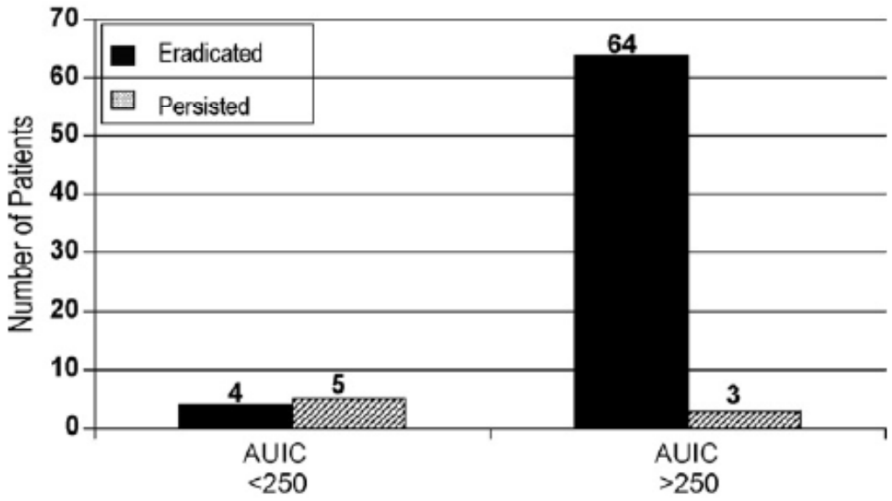


Fig. 1. Bacteriological eradication of pathogens at 24-h area under the inhibitory curve (AUIC) values of ≥250 and <250.

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

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

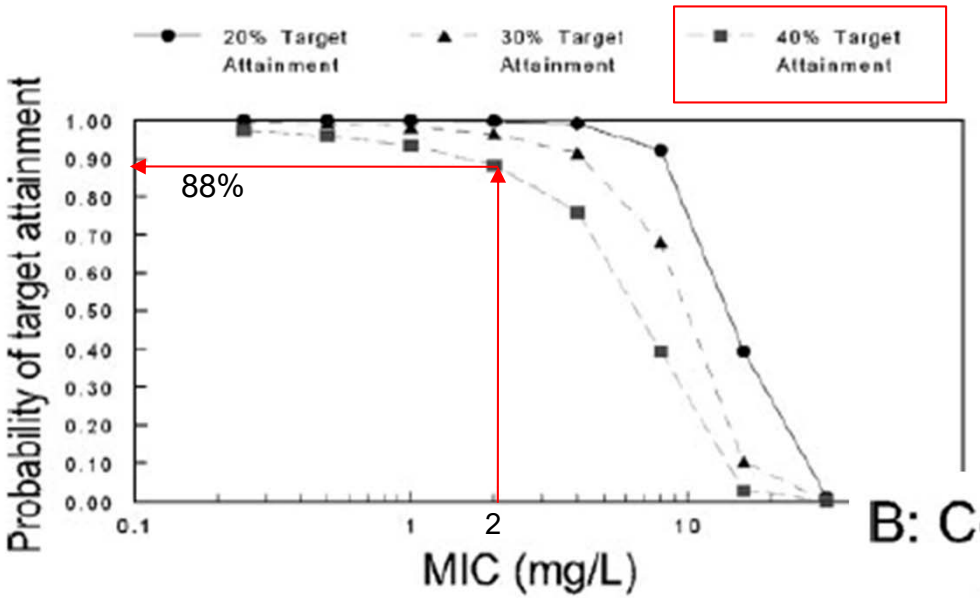
- ✓ Single-center study compared cefepime for bacteremia and/or pneumonia
  - ✓ admitted from 1 January 2008 through 30 June 2010 (a 30-min infusion of 2 g every 8 h)
  - ✓ admitted from 1 July 2010 through 31 May 2011 (a 4-h infusion of 2 g every 8 h).
- ✓ Extended infusion was associated to
  - ✓ Decreased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

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

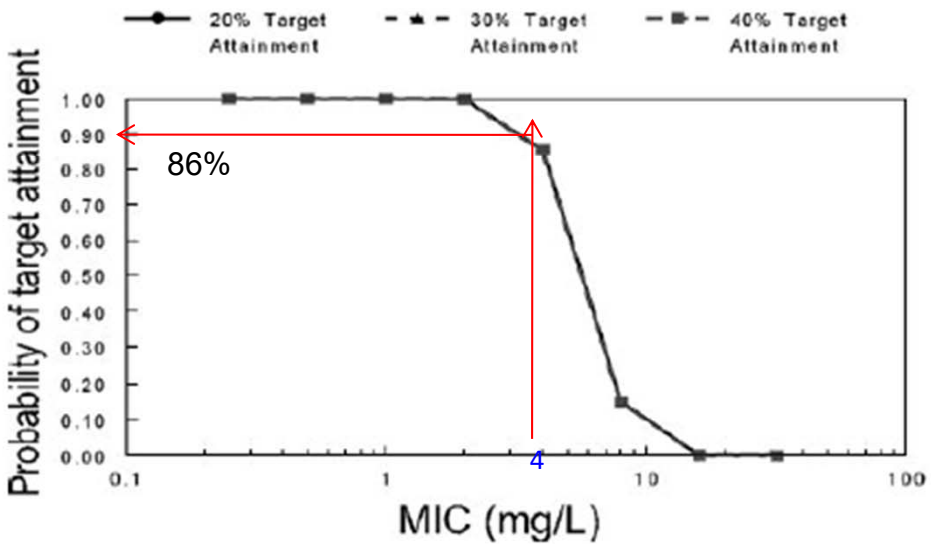
Population Pharmacokinetics and Pharmacodynamics of Continuous versus Short-Term Infusion of Imipenem-Cilastatin in Critically Ill Patients in a Randomized, Controlled Trial[▽]

Samir G. Sakka,[1]† Anna K. Glauner,[1] Jürgen B. Bulitta,[2]‡ Martina Kinzig-Schippers,[2] Wolfgang Pfister,[3] George L. Drusano,[4] and Fritz Sörgel[2,5]*

A: Intermittent infusions



B: Continuous infusion



According to the German prescribing information, the infusion solution is sufficiently stable for 4 h at 25°C.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2007, p. 3304–3310

Comparison of the pharmacodynamics of imipenem in patients with ventilator-associated pneumonia following administration by 2 or 0.5 h infusion

Sutep Jaruratanasirikul* and Teeratad Sudsai

Conclusions: The 2 h infusions of imipenem resulted in greater *t*>MICs than the 0.5 h infusion. For infections caused by pathogens with high MICs, a 2 h infusion of 1 g of imipenem every 6 h can provide plasma concentrations above the MIC of 4 mg/L for 60% of a 6 h interval.

Morbidité?
Mortalité?

Journal of Antimicrobial Chemotherapy (2009) **63**, 560–563

Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution

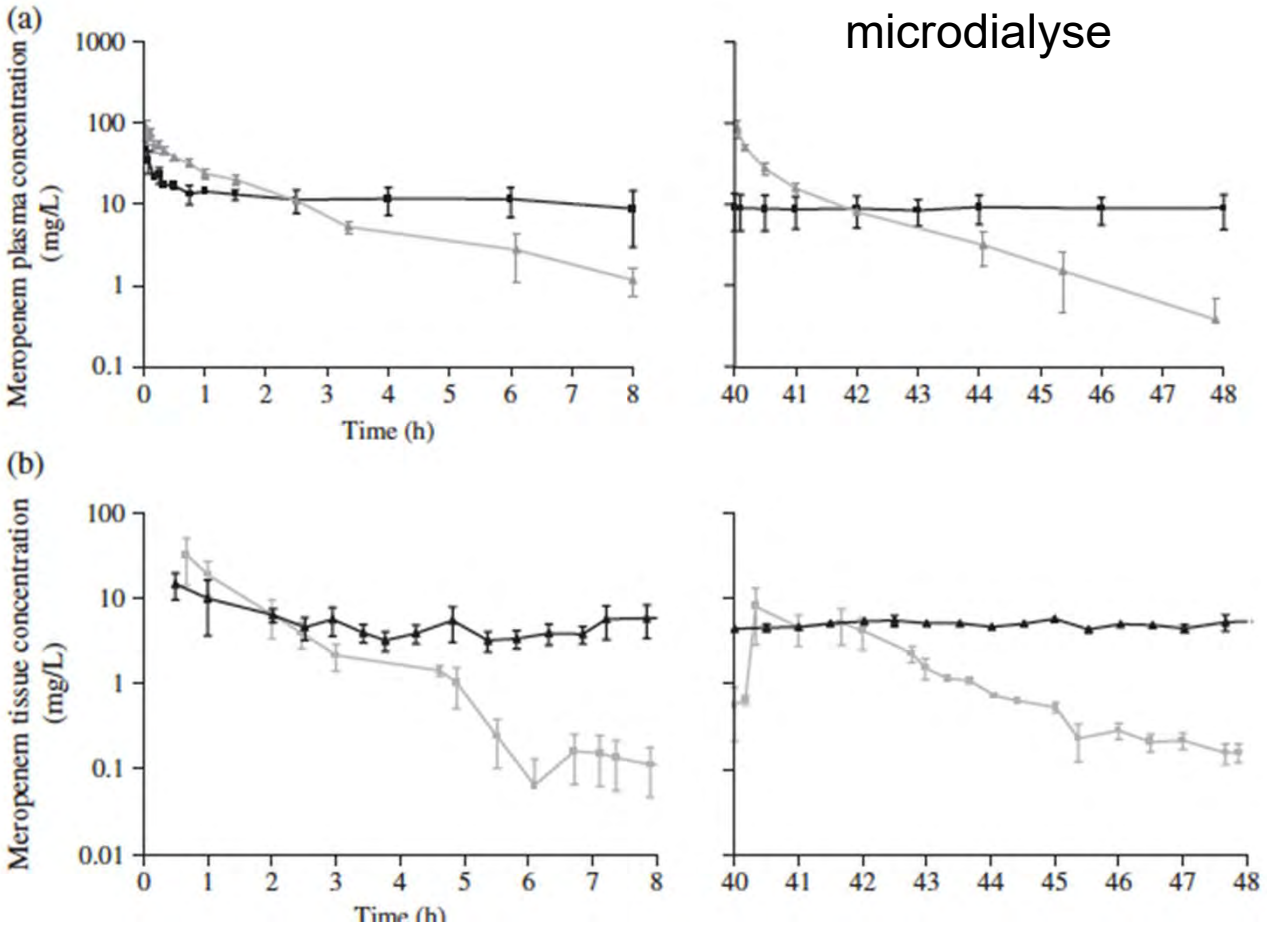
Jason A. Roberts[1–3]*, Carl M. J. Kirkpatrick[4], Michael S. Roberts[5], Thomas A. Robertson[5], Andrew J. Dalley[1] and Jeffrey Lipman[1,3]

Université de Lille 2 DROIT ET SANTÉ

10 patients septiques

Meropenem 1g/8h vs 3g continu

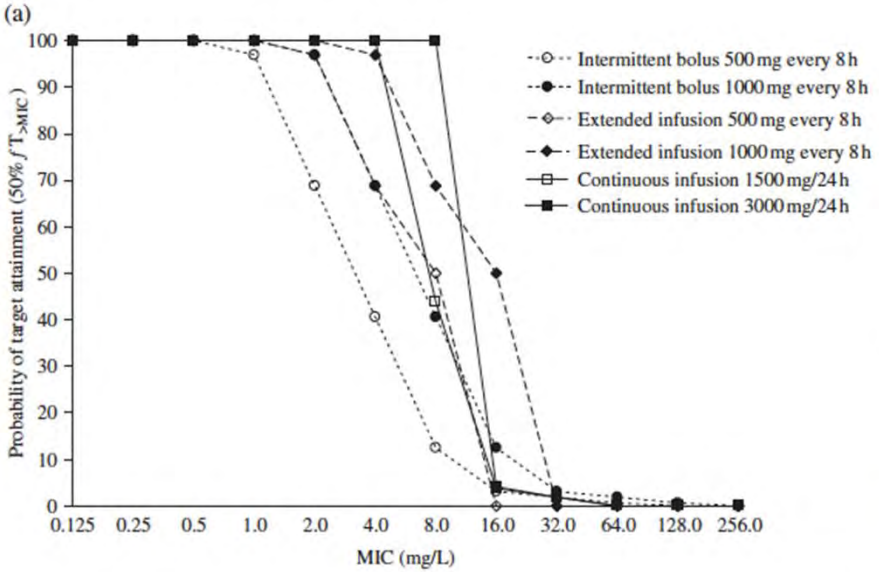
Concentration tissulaire par microdialyse

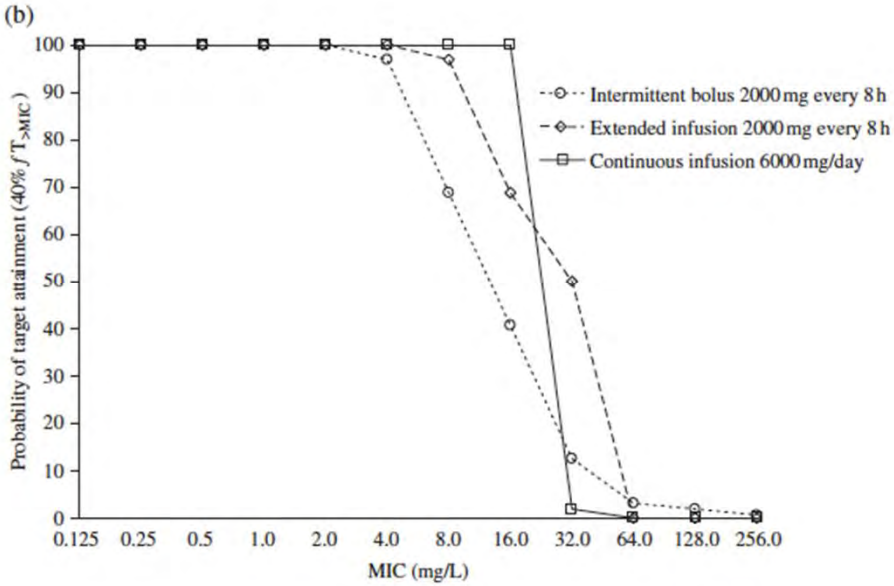


Journal of Antimicrobial Chemotherapy (2009) **64**, 142–150

Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution

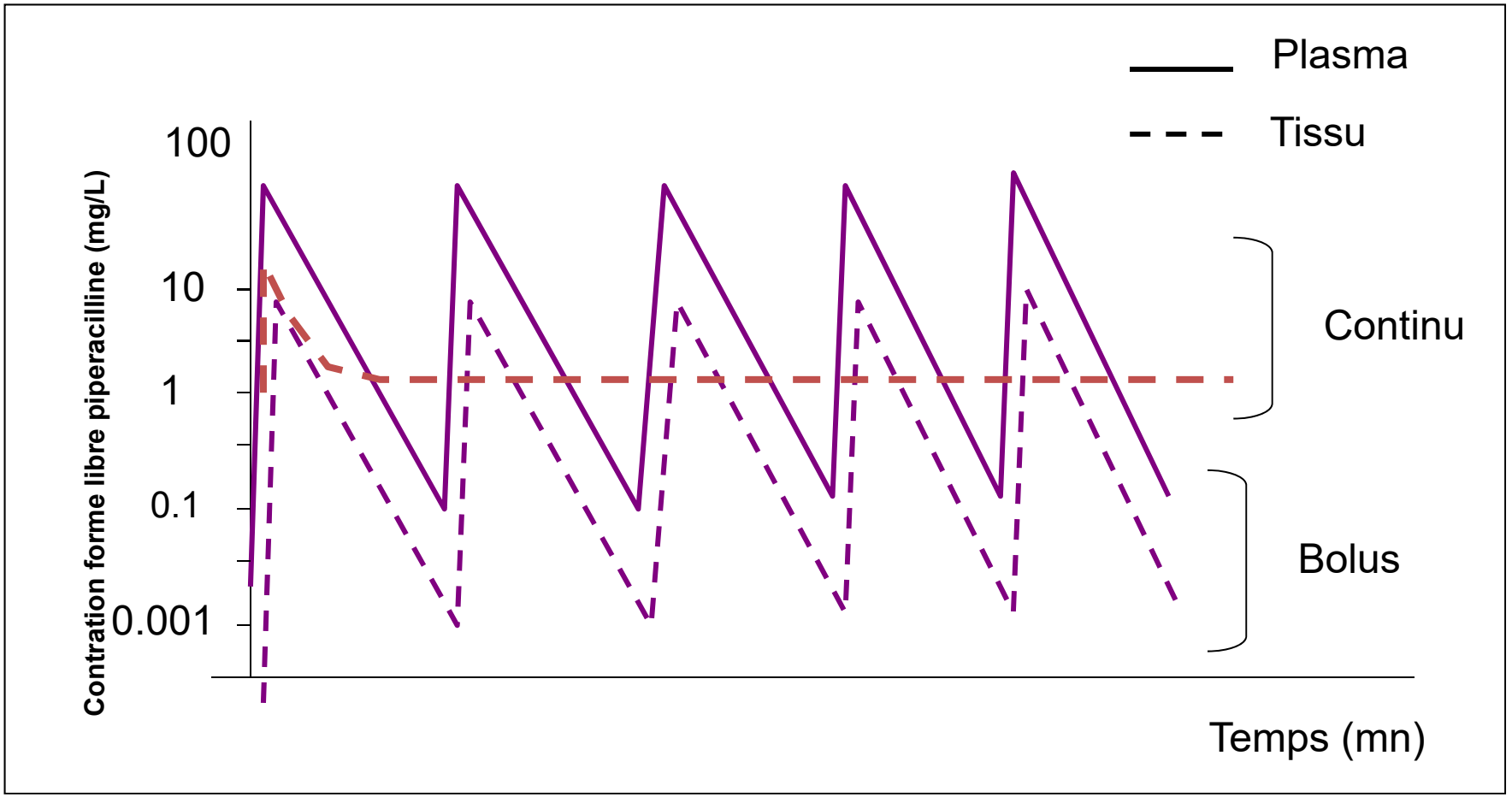
Jason A. Roberts[1–3]*, Carl M. J. Kirkpatrick[4], Michael S. Roberts[5], Thomas A. Robertson[5], Andrew J. Dalley[1] and Jeffrey Lipman[1,3]





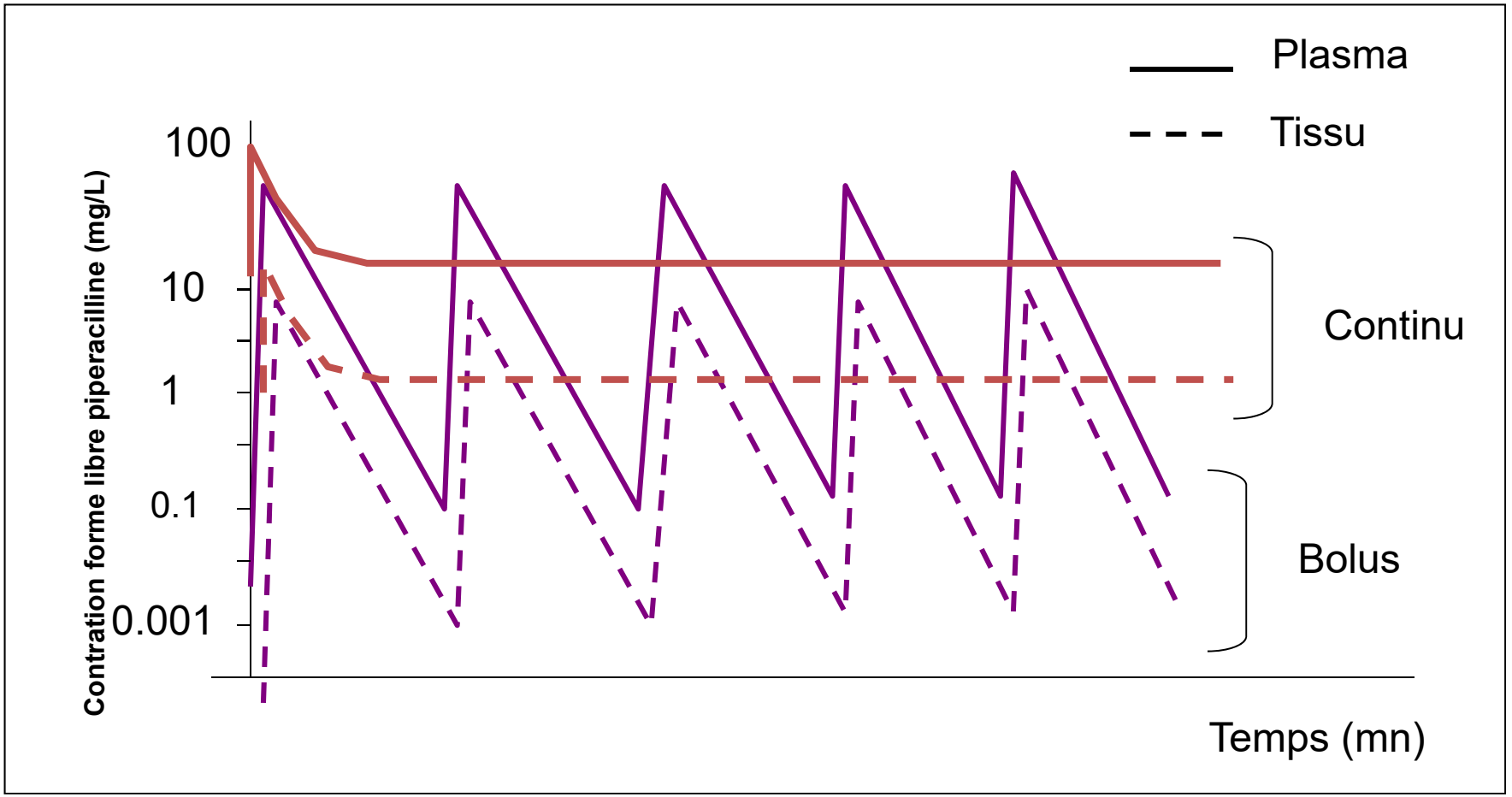
Journal of Antimicrobial Chemotherapy (2009) **64**, 142–150

Profil concentration-temps de la forme **libre** de piperacilline



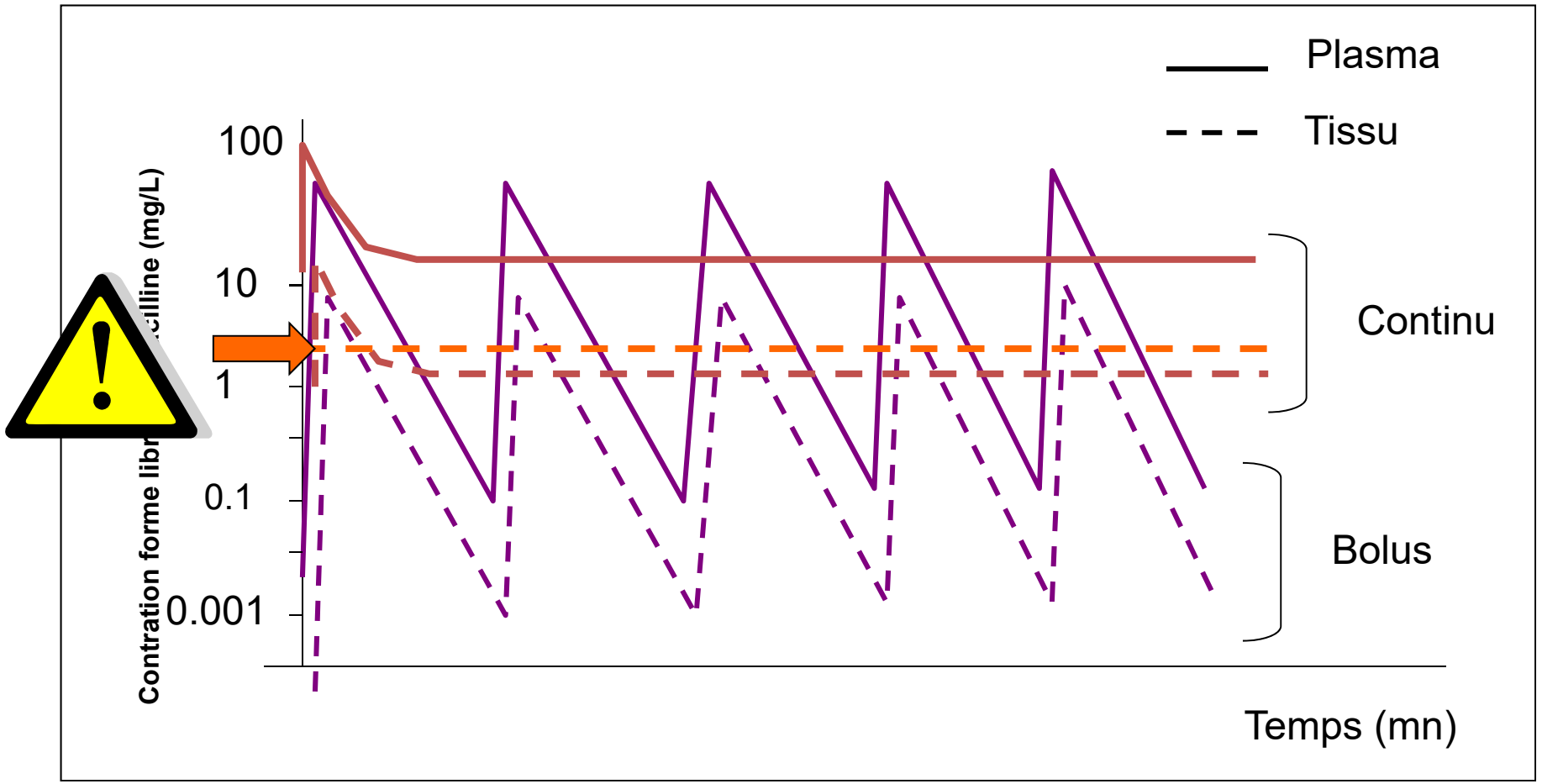
D'après JA Roberts Crit Care Med 20(

Profil concentration-temps de la forme **libre** de piperacilline



D'après JA Roberts Crit Care Med 20(

Profil concentration-temps de la forme **libre** de piperacilline



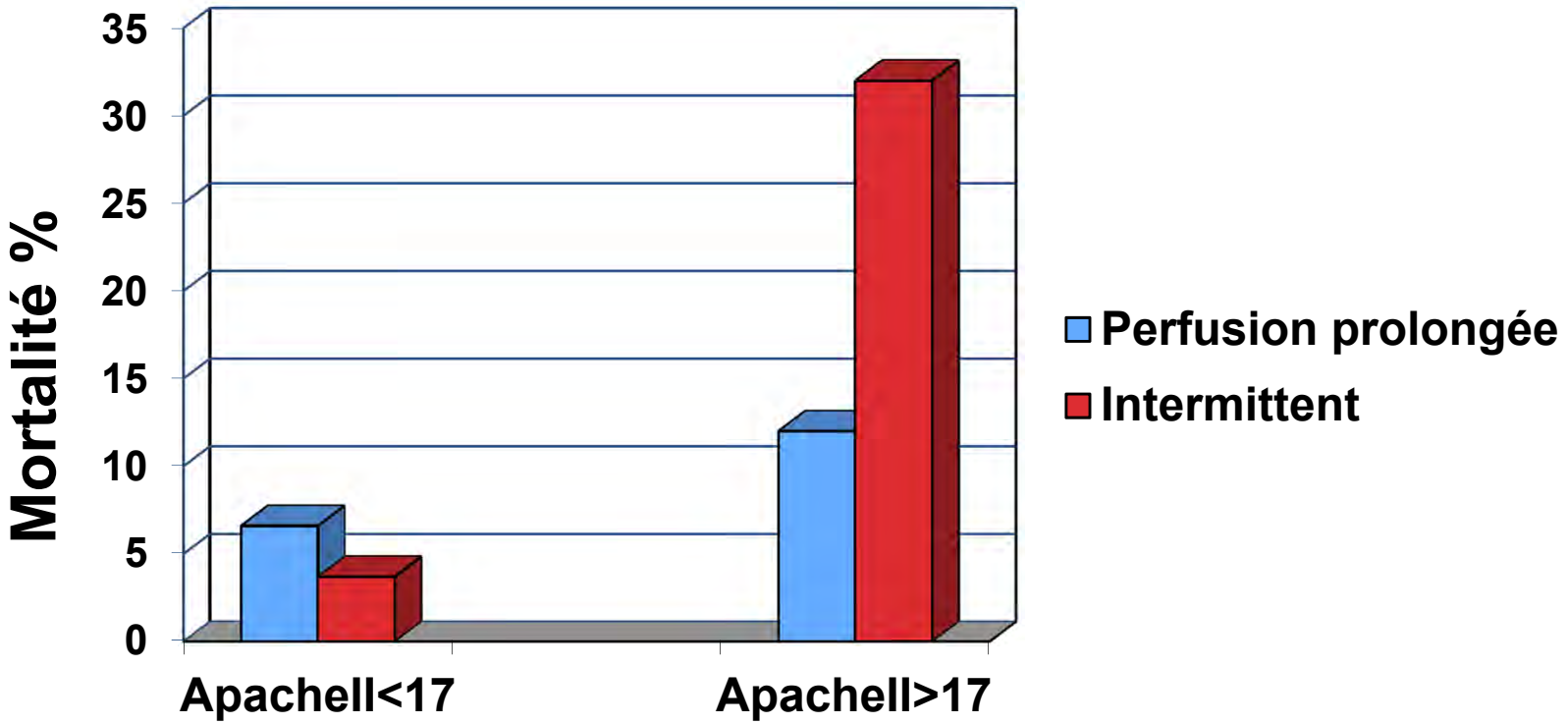
D'après JA Roberts Crit Care Med 20(

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

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

Lodise et al , CID, 2007

Mode d'administration de la pipera-tazocilline et mortalité à J14

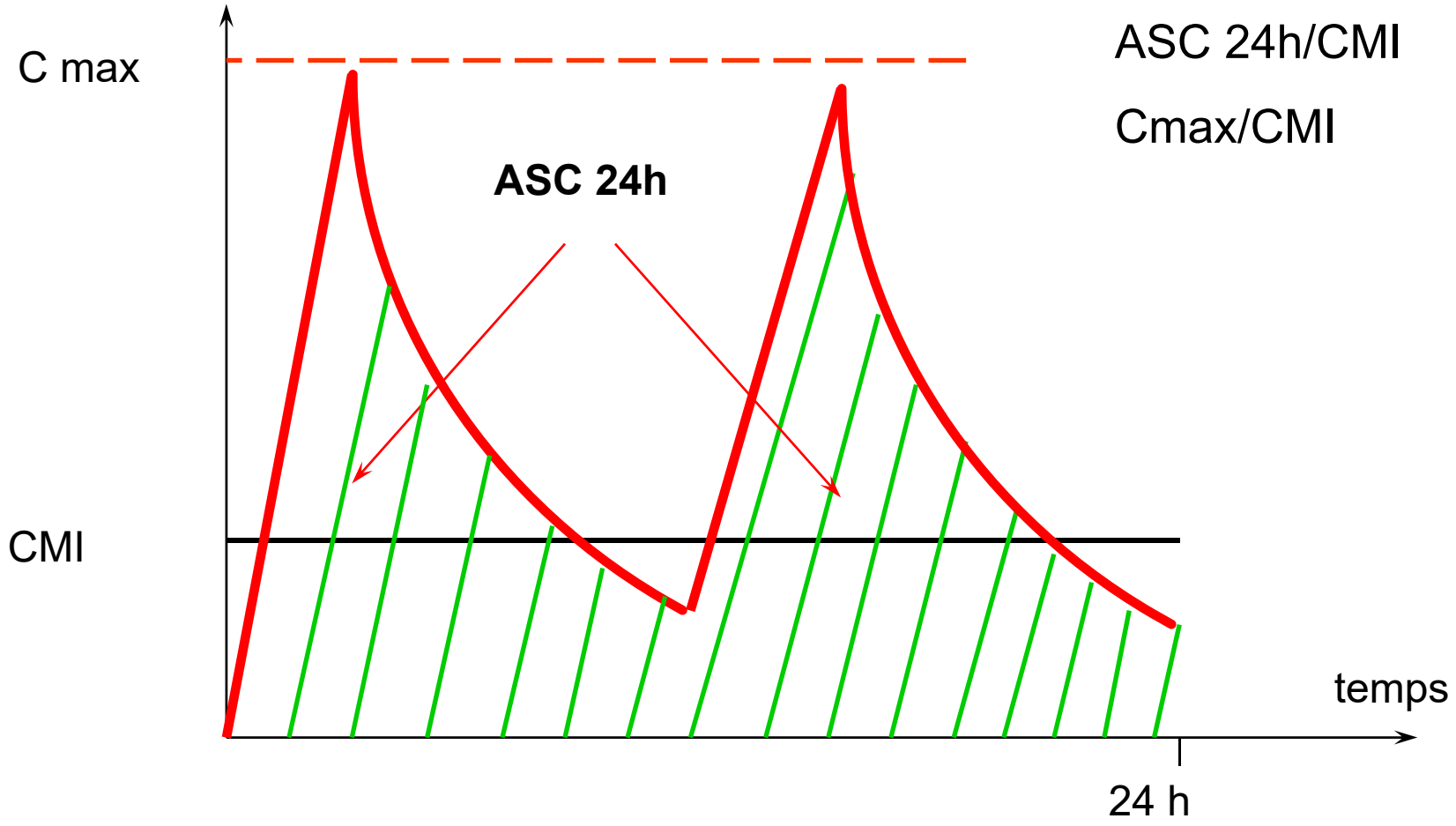


Lodise et al , CID, 2007

- ✓ Le bilan biologique initial met en évidence une insuffisance rénale avec une clairance de la créatinine évaluée à 30mL/min
  - Modifiez vous votre association initiale?

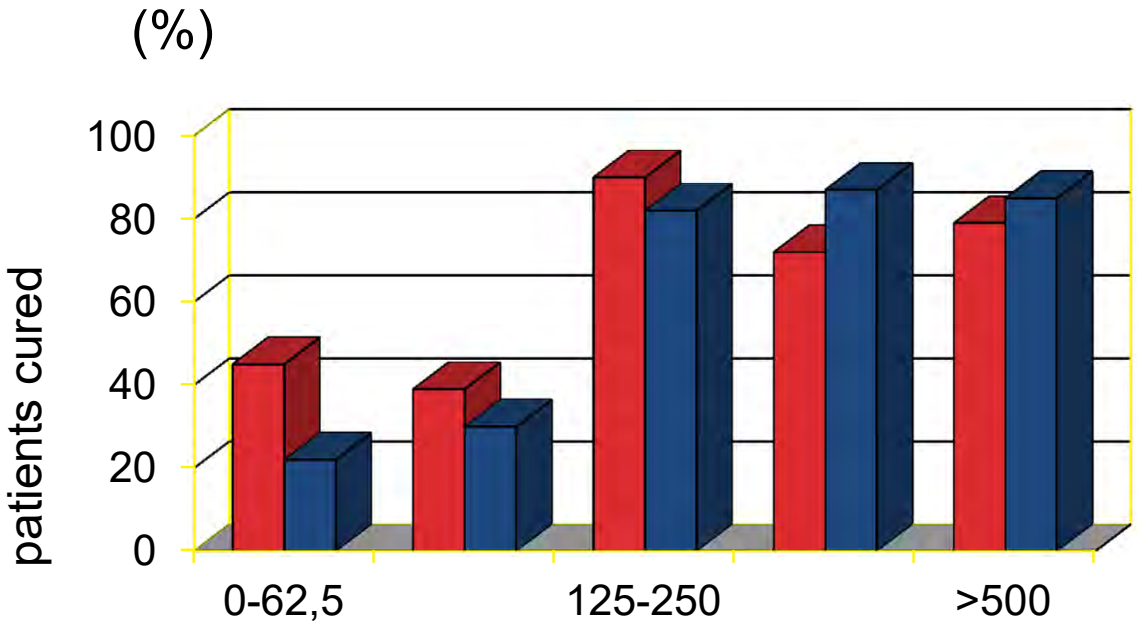
Fluoroquinolones

paramètres pharmacodynamiques



Fluoroquinolones

Relation ASC 24h/CMI et efficacité



64 patients

ciprofloxacine

Clinical

Bacteriologic

Forrest, AAC 1993

Université de Lille

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

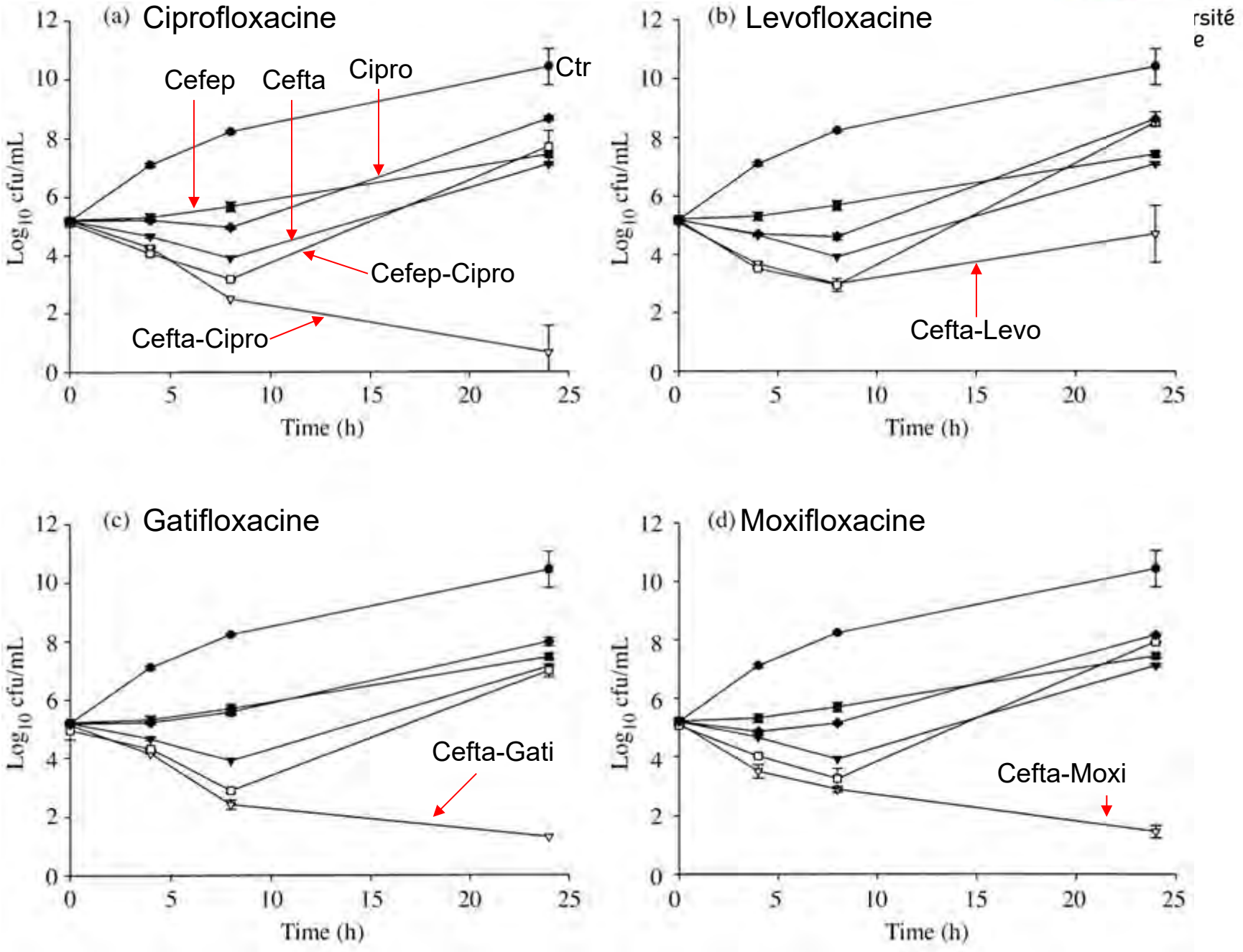
Therapy	24-h AUC/MIC ratio	Patients with resistance/ total patients (%)		
		All patients	Ciprofloxacin treatment	β-Lactam treatment
Monotherapy	<100	14/17 (82)	12/14 (86)	2/3(67)
Monotherapy	⩾100	17/84 (20)	4/44 (9)	13/40 (31)
Combination	⩾100	1/27 (4)	0/16 (0)	1/27 (4)

Craig et al CID 2001

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

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

Craig et al CID 2001

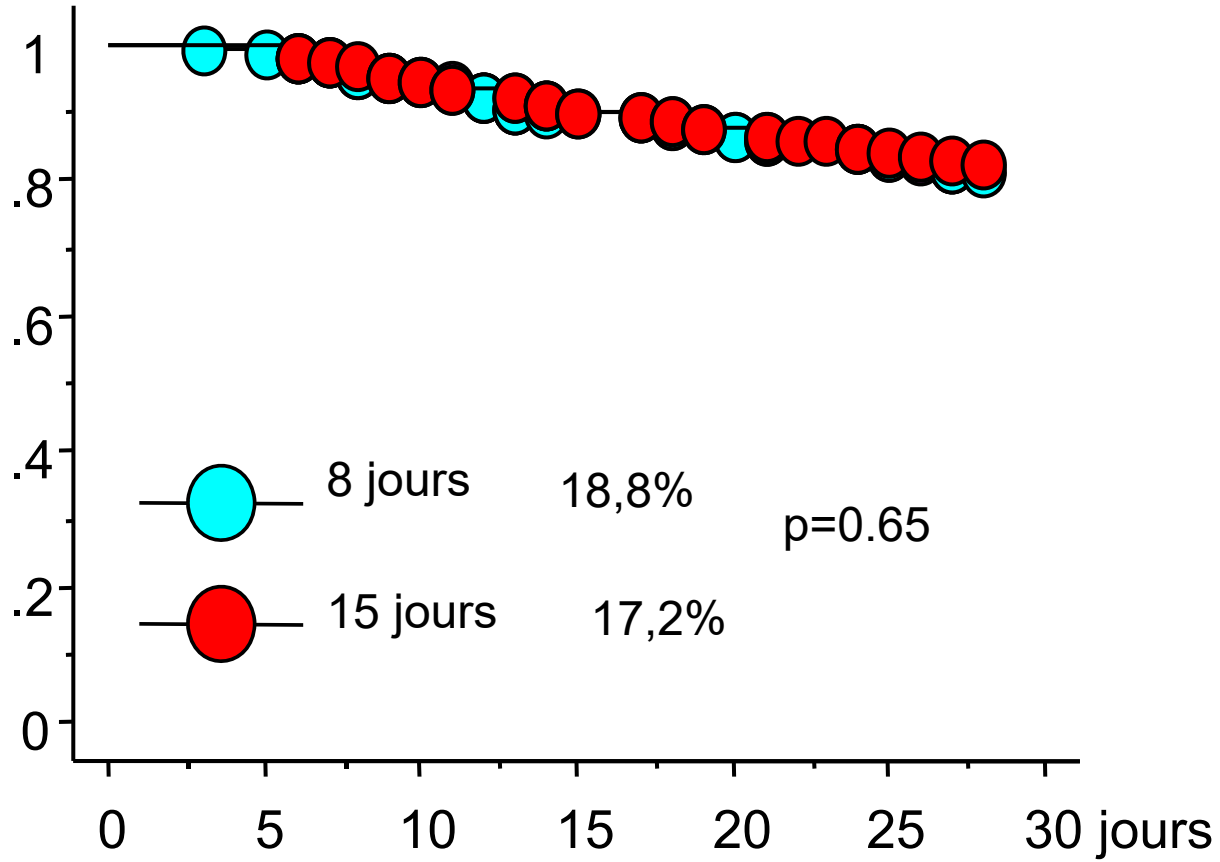


Fish et al, JAC 2002

- ✓ Mr D s'améliore à 48h
  - Pas besoin de remplissage supplémentaire
  - Pas de recours aux inotropes
  - Baisse de la température à 38°C

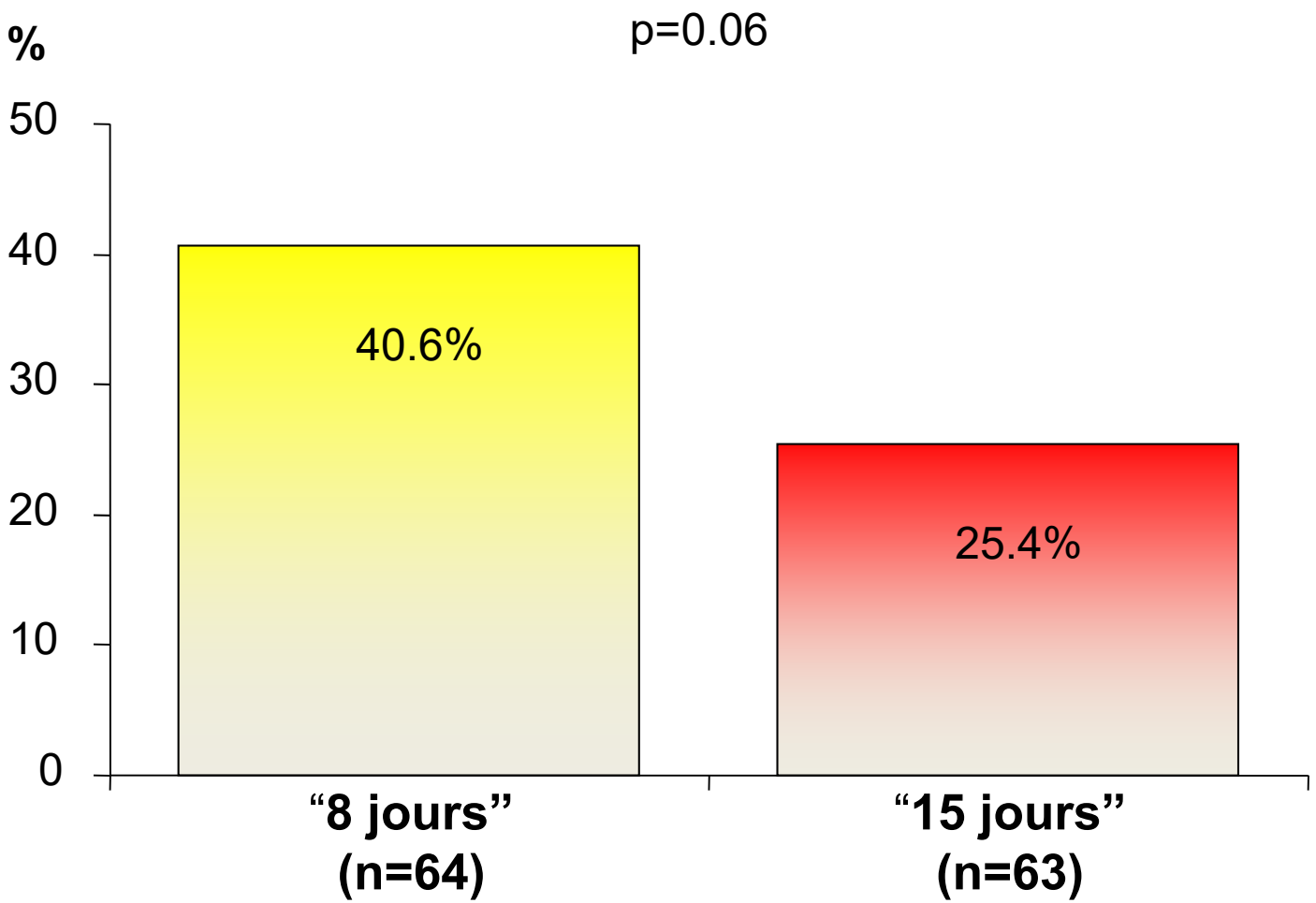
  Comment adaptez vous votre traitement?
  - Durée de chaque molécule

Mortalité à J 28 en fonction de la durée de traitement



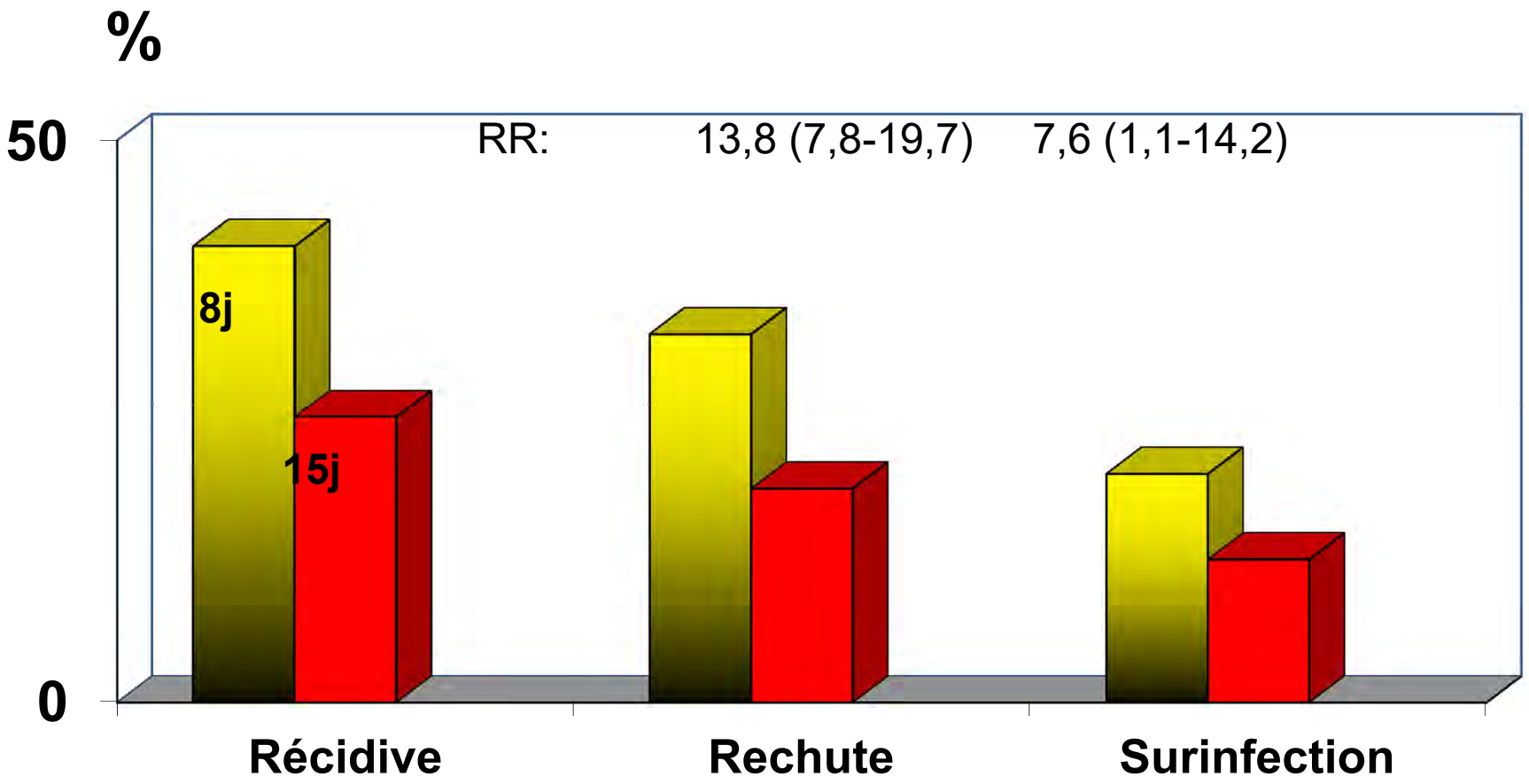
Chastre et al, JAMA 2003

Taux de récidive de l'infection pulmonaire



Chastre et al, JAMA 2003

BGN

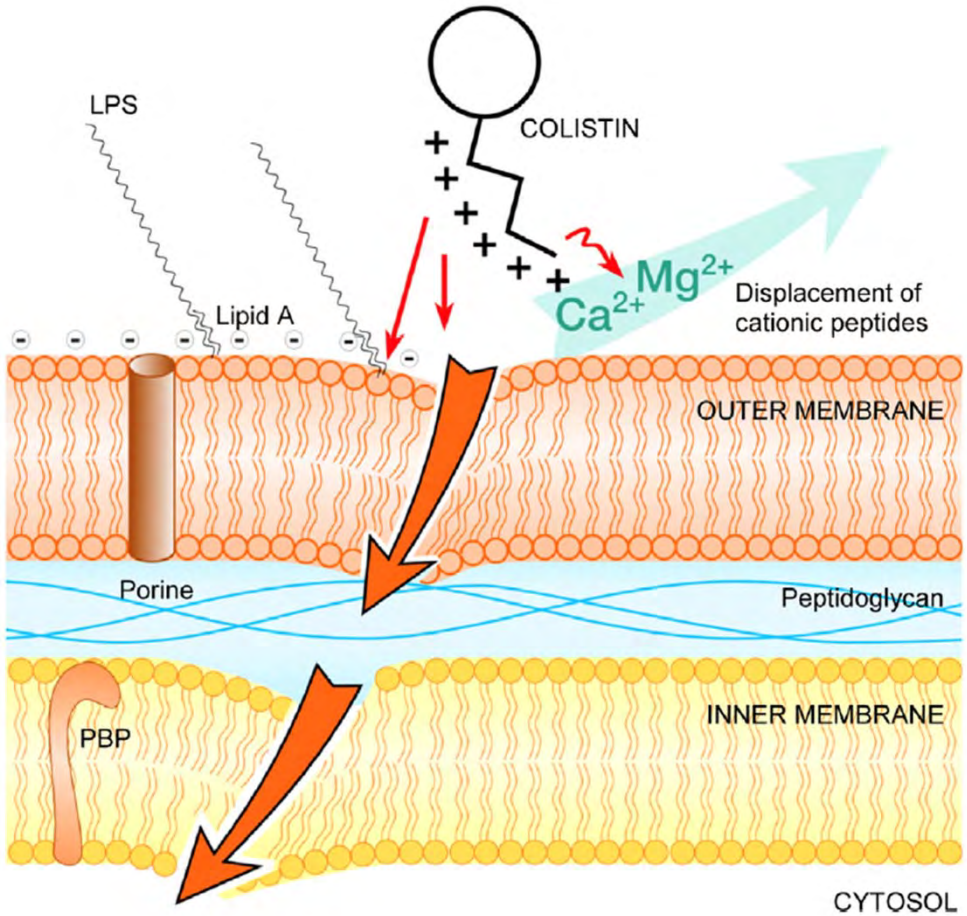


Chastre et al, JAMA 2003

- ✓ Après une amélioration initiale, l'état clinique de Mr D se redégrade sur le plan respiratoire
- ✓ Vous arrêtez votre antibiothérapie et réalisez de nouveaux prélèvements.

Vous débutez une nouvelle antibiothérapie empirique, quelles molécules?

- ✓ Le laboratoire de bactériologie vous rend une antibiogramme isolant un Acinetobacter MDR



Intensive Care Med (2005) 31:1058–1065
DOI 10.1007/s00134-005-2691-4

ORIGINAL

Rosa Reina
Elisa Estenssoro
Gabriela Sáenz
Héctor S. Canales
Romina Gonzalvo
Gabriela Vidal
Gustavo Martins
Andrea Das Neves
Oscar Santander
Carlos Ramos

Safety and efficacy of colistin in *Acinetobacter* and *Pseudomonas* infections: a prospective cohort study

- ✓ Prospective study
- ✓ 185 patients infected with *Acinetobacter baumannii* and *Pseudomonas aeruginosa*
- ✓ Hospitalisation> 48 h
  - 55 colistin group
  - 130 non colistin group
- ✓ No difference for age, APACHE II score, comorbidities, and SOFA score

Table 2 Outcomes and sites of infection in colistin and noncolistin groups (*LOS* length of stay)

	Colistin group (n=55)	Noncolistin group (n=130)	p
Treatment duration (days)	13±5	13±6	0.8
Basal creatinine (mg/dl)[a]	0.9±0.2	0.9±0.2	0.6
End creatinine (mg/dl)[b]	1.0±0.3	1.0±0.3	0.9
Day of diagnosis of infection[c]	12 (7–21)	7 (6–13)	0.0001[d]
Inappropriate empirical treatment	55 (100%)	10 (8%)	0.00001
Treatment delay (hours)[e]	96±24	12±4	0.00001
Alive at hospital discharge	39 (71%)	96 (74%)	0.2
Length of MV (days)[f]	28 (15–48)	20 (12–27)	0.02[d]
LOS ICU (days)[c]	40 (21–58)	26 (16–43)	0.03[d]
LOS hospital (days)[c]	61 (29–88)	36 (26–70)	0.54[d]
Acinetobacter infections	36 (65%)	69 (53%)	0.2
Mortality	10 (27%)	21 (30%)	0.8
Pseudomonas infections	19 (35%)	61 (47%)	0.3
Mortality	7 (37%)	17 (28%)	0.5
Ventilator-associated pneumonia	29 (53%)	86 (66%)	0.2
Mortality	10 (32%)	21 (24%)	0.2
Primary bacteremia	9 (16%)	25 (19%)	0.2
Mortality	2 (22%)	9 (36%)	0.1
Urinary tract infection	10 (18%)	11 (8%)	0.1
Mortality	2 (20%)	2 (20%)	0.2
Other infections[g]	7 (13%)	8 (6%)	0.3
Mortality	3 (43%)	3 (38%)	0.3

Int Care Med 2005

ORIGINAL ARTICLE 10.1046/j.1469-0691.2004.01043.x

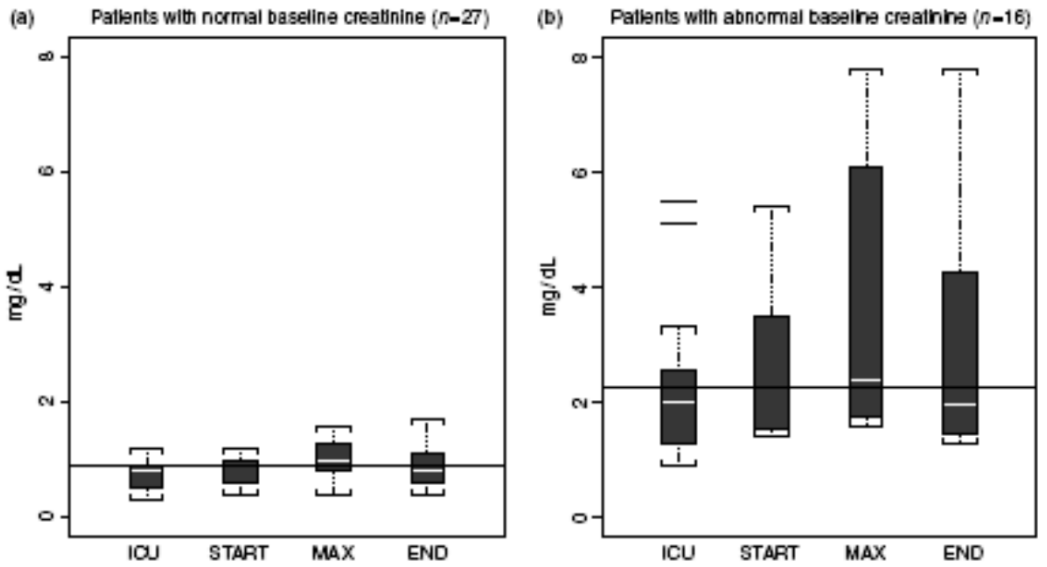
Université de Lille 2 DROIT ET SANTÉ

Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old antibiotic

A. S. Michalopoulos[1], S. Tsiodras[2], K. Rellos[1], S. Mentzelopoulos[1] and M. E. Falagas[2,3,4]

[1]Intensive Care Unit and [2]Department of Medicine, Henry Dunant Hospital; [3]Alfa HealthCare, Athens, Greece; and [4]Tufts University School of Medicine, Boston, MA, USA

- ✓ Retrospective study
- ✓ 43 ICU patients
- ✓ Multi-drug-resistant pathogens (*P aeruginosa-A baumannii*)



- ✓ **Clinical response: 74,4%**
- ✓ **Renal function alteration 18,6%**
- ✓ **Mortality 27,9%**

Colistin is an option

Clin Microb Infect 2005

Quelle posologie ?

Recommandations actuelles (en 2 à 4 injections)

		colistiméthate
Vidal	**50 000 UI/kg/j**	**280 mg/j**
UK	**1-2 MUI x 3/j** ➔ **pour 70 kg**	**240-480 mg/j**
USA	**2.5-5 mg/kg/j coli base**	**400-800 mg/j**

Révision libellé AMM

75 000 à 150 000 U/kg/j
sans dépasser 12 M UI par j
en 2 ou 3 injections

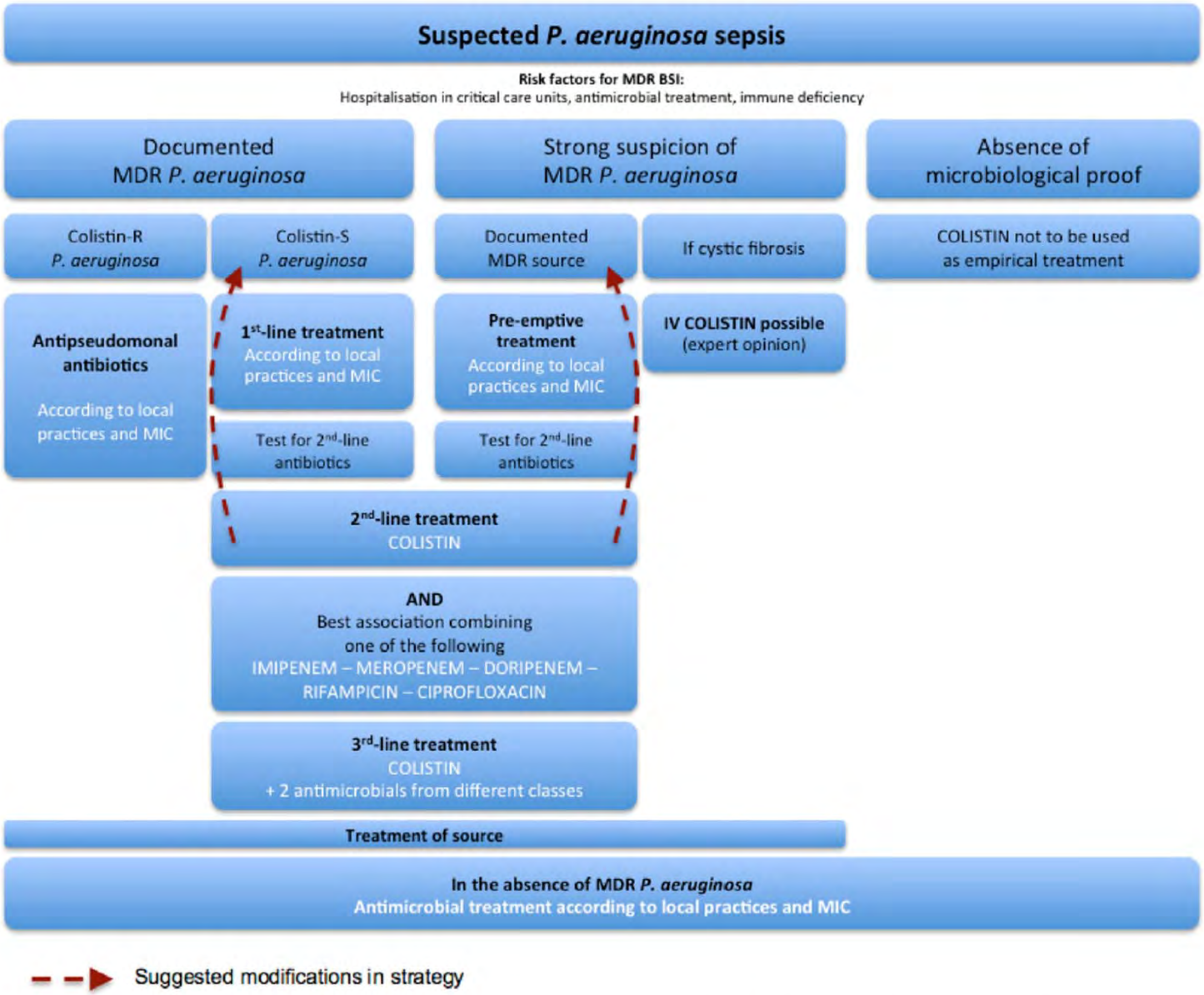


Figure 2 A strategy for treatment management of suspected *P. aeruginosa* BSI.

ELSEVIER

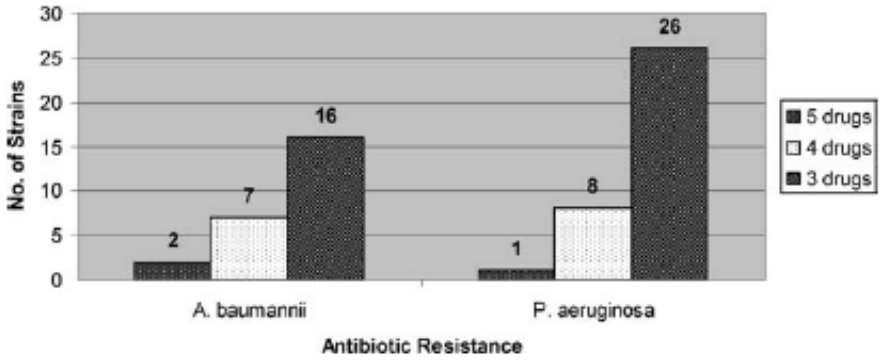
International Journal of Antimicrobial Agents 27 (2006) 224–228

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.ischemo.org

In vitro activities of non-traditional antimicrobials alone or in combination against multidrug-resistant strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolated from intensive care units

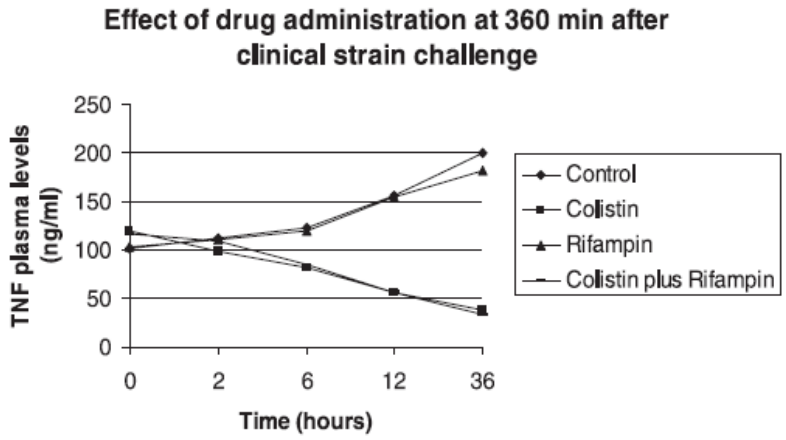
Funda Timurkaynak[a,*], Fusun Can[b], Özlem Kurt Azap[a], Müge Demirbilek[b], Hande Arslan[a], Sedef Özbalıkçı Karaman[a]

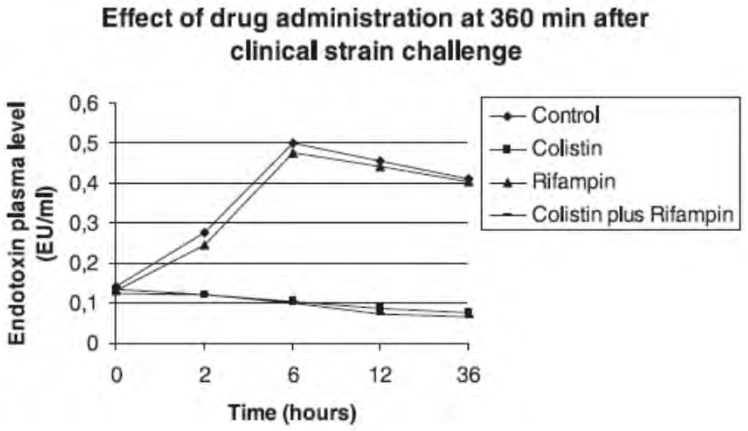


Strain	Antibiotic combination of colistin +	FICI	Interpretation
114	Rifampicin	0.5	Synergistic
	Meropenem	1.5	Indifferent
	Doxycycline	0.62	Partially synergistic
	Azithromycin	0.62	Partially synergistic
144	Rifampicin	1	Additive
	Meropenem	1.25	Indifferent
	Doxycycline	0.75	Partially synergistic
	Azithromycin	0.75	Partially synergistic
108	Rifampicin	0.31	Synergistic
	Meropenem	1	Additive
	Doxycycline	1	Additive
	Azithromycin	2	Indifferent
205	Rifampicin	0.51	Partially synergistic
	Meropenem	1	Additive
	Doxycycline	0.75	Partially synergistic
	Azithromycin	N.D.	N.D.
166	Rifampicin	0.62	Partially synergistic
	Meropenem	1.5	Indifferent
	Doxycycline	0.51	Partially synergistic
	Azithromycin	1	Additive

Table 3. Efficacy of administration of intravenous colistin and rifampin in a rat model after intraperitoneal injection of 2×10^{10} colony-forming units (CFU) of multiresistant *Pseudomonas aeruginosa* at 0 and 360 mins

Treatment	Lethality[a] No. Dead/Total 0[b]	Lethality[a] No. Dead/Total 360[b]	Lethality[a] % 0	Lethality[a] % 360	Qualitative Blood Culture No. Positive/Total 0	Qualitative Blood Culture No. Positive/Total 360	Bacterial Count in Peritoneal Fluid CFU/mL, mean ± SD 0	Bacterial Count in Peritoneal Fluid CFU/mL, mean ± SD 360
No treatment (control group C_2 and C_4)	15/15	15/15	100	100	15/15	15/15	$7.0 \times 10^8 \pm 2.4 \times 10^8$	$9.0 \times 10^9 \pm 4.1 \times 10^9$
COL 1 mg/kg	8/15[c]	9/15[c]	53.3	60	9/15[c]	9/15[c]	$5.6 \times 10^5 \pm 1.8 \times 10^{5c}$	$3.1 \times 10^5 \pm 6.9 \times 10^{5c}$
RA 10 mg/kg	15/15	15/15	100	100	15/15	15/15	$4.9 \times 10^8 \pm 1.7 \times 10^{8c}$	$7.9 \times 10^9 \pm 2.1 \times 10^9$
COL 1 mg/kg plus RA 10 mg/kg	4/15[c]	4/15[c]	26.6	26.6	5/15[c]	5/15[c]	$2.0 \times 10^2 \pm 0.6 \times 10^{2c,d}$	$3.0 \times 10^2 \pm 0.6 \times 10^{2c,d}$





Cirioni et al, Crit Care Med 2007

Taux de mutation élevé
+ mécanisme d'action ➔ **colimycine et quoi …?**

Pour certaines souches
(dont quelques souches coli -R)
la coli restaure la sensibilité aux pénèmes

Ullman ICAAC 2009 - Souli AAC 2009

En pratique ➔ tester les associations

International Journal of Infectious Diseases xxx (2011) xxx.e1–xxx.8

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Review

The revival of fosfomycin

Argyris S. Michalopoulos *, Ioannis G. Livaditis, Vassilios Gougoutas

Studies dealing with the curative use of fosfomycin in adult patients (intravenous administration)

Study	Patients (*n*)	Age, mean years	Pathogens	Infection	Combination therapy	Mortality (%)
Alvarez et al.[71]	1	-	*Serratia marcescens*	Endophthalmitis	Ceftriaxone + amikacin	0
Boulard et al.[72]	4	-	*Staphylococcus epidermidis*	CSF shunt infection	Aminoglycoside	0
Bureau-Chalot et al.[73]	1	-	*Stomatococcus mucilaginosus*	Spondylodiscitis	Cefotaxime	0
Florent et al.[70]	72	55	Multiple	Multiple	Multiple	13
Gillard et al.[74]	8	-	-	Pyogenic discitis	Quinolone[a]	0
Guerin et al.[75]	1	46	*Pseudomonas aeruginosa*	Prostatitis	Aztreonam	0
May et al.[76]	7	-	Multiple	Meningitis	Ceftriaxone	-
Meissner et al.[69]	60	37.4	Multiple	Chronic osteomyelitis	No combination therapy	26.4
Michalopoulos et al.[65]	11	67.5	MDR *Klebsiella pneumoniae*	ICU-acquired infection	Multiple	18.2
Mirakhur et al.[33]	15	23	*Pseudomonas aeruginosa*	Cystic fibrosis	Multiple	0
Nakayama et al.[77]	1	64	MRSA	Toxic shock syndrome	Vancomycin	0
Nissen et al.[78]	17	-	Multiple	Pneumonia	Ampicillin	6
Ortler et al.[79]	1	35	*Staphylococcus aureus*	Wound infection	Cefmenoxime	0
Portier et al.[80]	16	-	MRSA	Bacteremia; bone/ joint infection/meningitis	Cefotaxime	0
Roualdes et al.[81]	2	-	*Staphylococcus epidermidis*, *Staphylococcus capitis*, *Micrococcus varians*	CSF shunt infection	Vancomycin, rifampin	0
Silbermann et al.[82]	1	17	*Staphylococcus epidermidis*	Meningitis	Vancomycin	0
Ueda et al.[83]	65	-	Multiple	Multiple	0	46.1
Yamaguchi et al.[66]	1	64	MRSA	Pneumonia and sepsis	Arbekacin	0
Zink et al.[84]	1	81	*Staphylococcus albus*	Ventriculoatrial shunt meningitis	Gentamicin	0

[a] Eighteen patients received usually a fluoroquinolone with a beta-lactam or fosfomycin.

Synergy of fosfomycin with carbapenems, colistin, netilmicin, and tigecycline against multidrug-resistant *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* clinical isolates

G. Samonis · S. Maraki · D. E. Karageorgopoulos · E. K. Vouloumanou · M. E. Falagas

Table 3 Synergy of fosfomycin combinations against the isolates studied

Antibiotic in combination with fosfomycin	*Klebsiella pneumoniae*, all isolates (*N*=65)	ESBL-producing *Klebsiella pneumoniae* (*N*=14)	Serine carbapenemase-producing *Klebsiella pneumoniae* (*N*=50)	ESBL-producing *Escherichia coli* (*N*=20)	MDR *Pseudomonas aeruginosa* (*N*=15)
Isolates exhibiting synergy, *n* (%)					
Imipenem	49 (75.4)	11 (78.6)	37 (74.0)	11 (55.0)	7 (46.7)
Meropenem	41 (63.1)	6 (42.9)	35 (70.0)	5 (25.0)	8 (53.3)
Doripenem	43 (66.2)	6 (42.9)	37 (74.0)	6 (30.0)	11 (73.3)
Colistin	19 (29.2)	1 (7.1)	18 (36.0)	3 (15.0)	2 (13.3)
Netilmicin	27 (41.5)	6 (42.9)	21 (42.0)	5 (25.0)	2 (13.3)
Tigecycline	18 (27.7)	3 (21.4)	15 (30.0)	5 (25.0)	2 (13.3)

Abbreviations: ESBL: extended-spectrum β-lactamase; MDR: multidrug-resistant

Eur J Clin Microbiol Infect Dis

Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria

Pinyo Rattanaumpawan, Jintana Lorsutthitham, Puangpaka Ungprasert, Nasikarn Angkasekwinai and Visanu Thamlikitkul*

- 100 adults who developed Gram-negative VAP.
- systemic antibiotics according to the decisions of their responsible physicians
- randomized to receive an additional 4 mL of nebulized sterile normal saline (NSS) (**n.**49) or nebulized CMS equivalent to 75 mg of colistin base in 4 mL of NSS (**n.**51) every 12 h until systemic antibiotic therapy of VAP was ended

Table 2. Clinical and microbiological outcomes of the study patients

	CMS group (n=51)	NSS group (n=49)	% Risk difference (95% CI)	Risk ratio (95% CI)	P value
28 day clinical outcome					
favourable outcome	51.0%	53.1%	−2.1% (−22%-18%)	0.96 (0.66-1.40)	0.84
death due to VAP	39.2%	36.7%	2.5% (−17%-22%)	1.07 (0.65-1.76)	0.80
overall mortality	43.1%	40.8%	2.3% (−17%-22%)	1.06 (0.67-1.68)	0.81
Favourable microbiological outcome	60.9%	38.2%	22% (3%-41%)	1.57 (1.03-2.37)	0.03
Incidence of complication	31.4%	24.5%	7% (−11%-24%)	1.28 (0.68-2.42)	0.44
bronchospasm	7.8%	2.0%	6% (−3%-14%)	3.84 (0.45-33.19)	0.36
renal impairment	25.5%	22.4%	3% (−14%-20%)	1.13 (0.56-2.29)	0.82

J Antimicrob Chemother 2010; **65**: 2645–2649

Ceftazidime–avibactam: an evidence-based review of its pharmacology and potential use in the treatment of Gram-negative bacterial infections

Philippe Lagacé-Wiens[1,2]
Andrew Walkty[1,2]
James A Karlowsky[1,2]

Organism	Ceftazidime–avibactam			Ceftazidime			Ceftriaxone			Cefepime		
	$MIC_{50/90}$	MIC range	%S	$MIC_{50/90}$	MIC range	%S	$MIC_{50/90}$	MIC range	%S	$MIC_{50/90}$	MIC range	%S
Pseudomonas aeruginosa	2/8	≤0.06–>16	94.7	4/32	≤0.25–>32	82.8	16/>64	≤0.25–>64	N/A	4/16	≤0.25–>64	84.9
Multidrug-resistant	8/>16	4–>16	60.0	>16/>16	4–>16	4.	N/A	N/A	N/A	N/A	N/A	NA
AmpC-derepressed	4/8	≤1–64	96.2	64/>126	8–>128	3.8	N/A	N/A	N/A	N/A	N/A	NA

Core Evidence 2014:9 13–25

- ✓76 souches Acinetobacter XDR, 95 souches de Pseudomonas
- ✓9 associations in vitro

Synergy test results via checkerboard against *AB* (n=76)

Interaction	Minocycline -colistin	Tigecycline -amikacin	Minocycline -Amikacin	Minocycline -Doripenem	Doripenem-Tigecycline	Tigecycline -colistin	Doripenem -Colistin	Doripenem-Colistin-Minocycline	Doripenem-Colistin Tigecycline
Synergistic	6.6%	2.6%	1.3%	2.6%	3.9%	0.0%	5.3%	6.6%	2.6%
Additive	78.9%	17.1%	13.2%	9.2%	23.7%	0.0%	25.0%	55.2%	51.3%
Indifferent	14.5%	80.3%	84.2%	88.2%	72.4%	86.8%	69.7%	38.2%	46.1%
Antagonistic	0.0%	0.0%	1.3%	0.0%	0.0%	13.2%	0.0%	0.0%	0.0%

Synergy test results via checkerboard against *PsA* (n=95)

Interaction	Doripenem-colistin	Cefepime-tobramycin	Cefepime -colistin	Doripenem-Amikacin	Doripenem-Tobramycin	Piperacillin/tazobactam-Amikacin	Piperacillin/tazobactan -Colistin
Synergistic	0.0%	3.2%	1.1%	8.5%	1.1%	3.2%	0.0%
Additive	26.6%	36.2%	29.8%	39.3%	34.0%	21.3%	14.9%
Indifferent	73.4%	60.6%	69.1%	51.1%	64.9%	75.5%	85.1%
Antagonistic	0.0%	0.0%	0.0%	1.1%	0.0%	0.0%	0.0%

Bremmer et al, ID Week 2015 poster 1830

Correlation of checkerboard results with clinical outcomes among *AB* and *PsA*

	Syn/Add	Ind/Ant	p value		SAC Well	> SAC	p value
AB (n=18)							
Clinical Cure	1/3 (33)	6/15 (40)	1.00		4/8 (50)	3/10 (30)	0.63
Microbiological Clearance	3/3 (100)	7/15 (47)	0.22		7/8 (88)	3/10 (30)	0.02
30 day all-cause mortality	2/3 (67)	7/15 (47)	1.00		3/8 (38)	6/10 (60)	0.63
Apache II	18	21	0.24		20	20.5	0.29
Charlson Score	4	5	0.58		4	5	0.32
PsA (n=12)							
Clinical Cure	2/5 (40)	1/7 (14)	0.52		3/10 (30)	0/2 (0)	1.00
Microbiological Clearance	2/5 (40)	1/7 (14)	0.52		3/10 (30)	0/2 (0)	1.00
30 day all-cause mortality	3/5 (60)	4/7 (57)	1.00		6/10 (60)	1/2 (50)	1.00
Apache II	19	21	0.10		18.5	24.5	0.08
Charlson Score	2	1	0.89		1	1	0.77

Syn= synergistic; Add= additive; Ind;= indifferent; Ant= antagonistic; SAC= serum achievable concentration; > SAC= greater than serum achievable concentration

Bremmer et al, ID Week 2015 poster 1830