Session SRLF / SPILF : « Infections graves »

Quels traitements pour les infections graves à BGN ?

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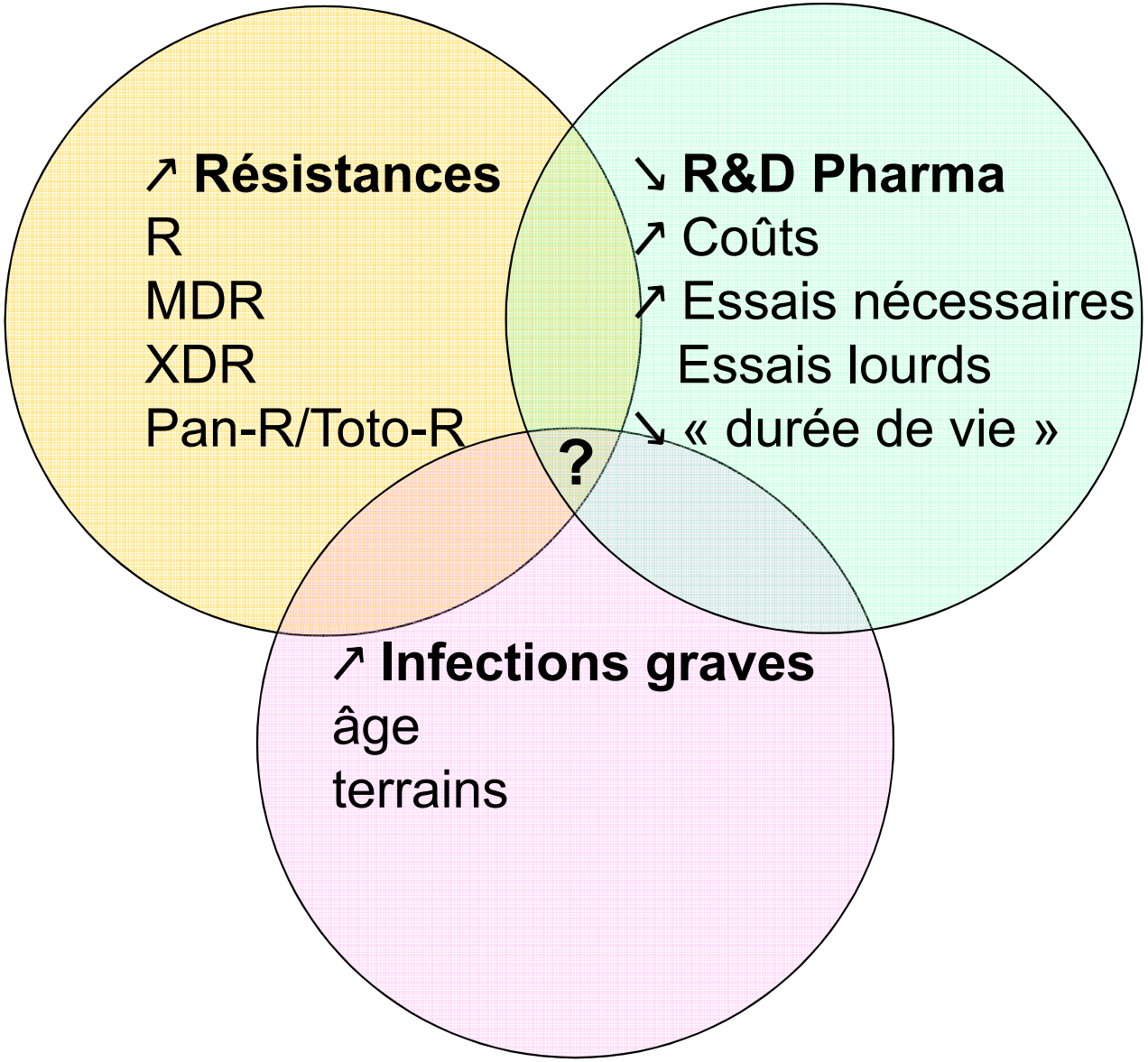
« Perfect storm »

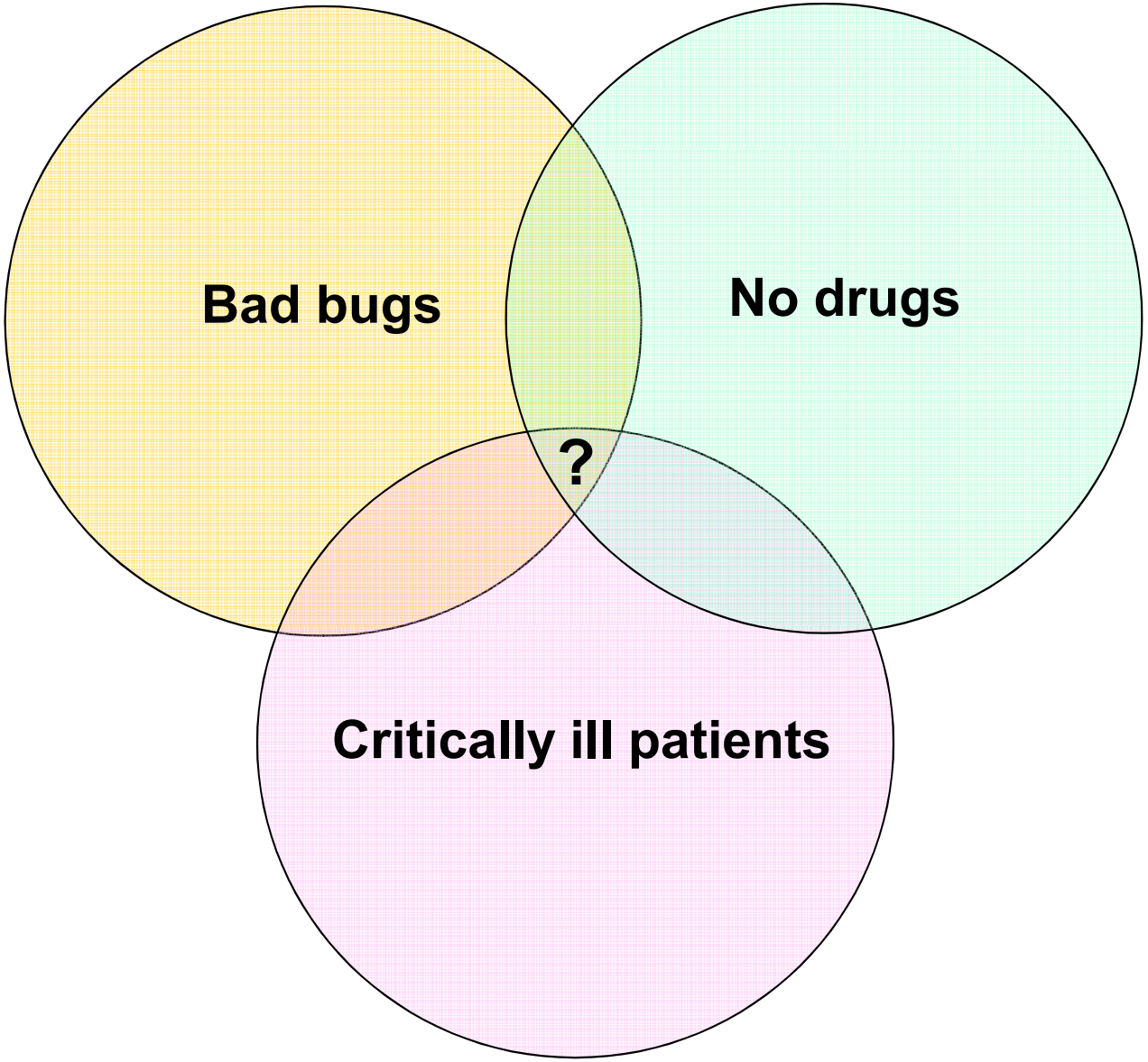


« Bad bugs, no drugs, no ESKAPE »

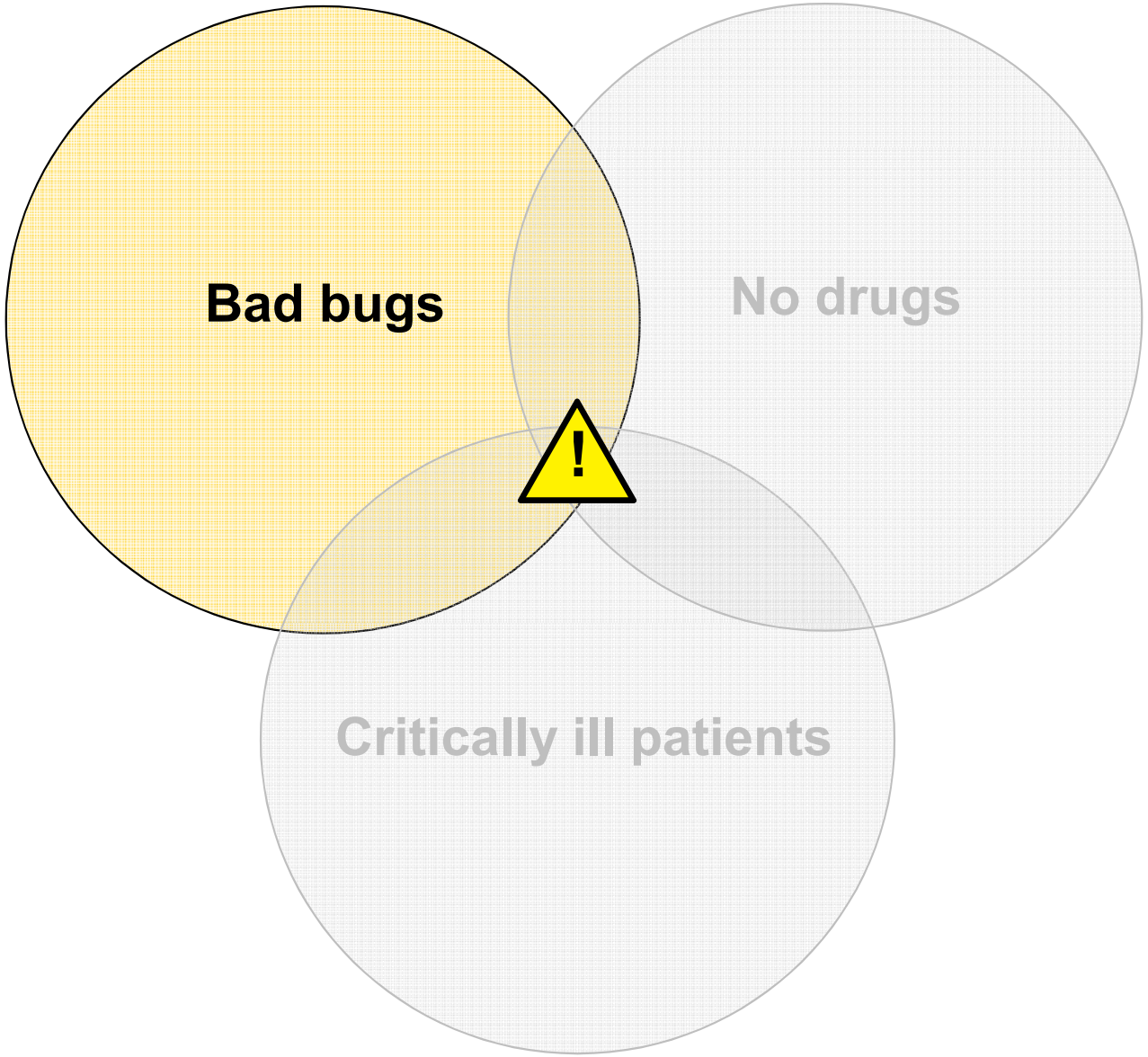
- ***E****nterococcus faecium*
- ***S****taphylococcus aureus*
- ***K****lebsiella pneumoniae*
- ***A****cinetobacter baumannii*
- ***P****seudomonas aeruginosa*
- ***E****nterobacter spp.*

Boucher CID 2009

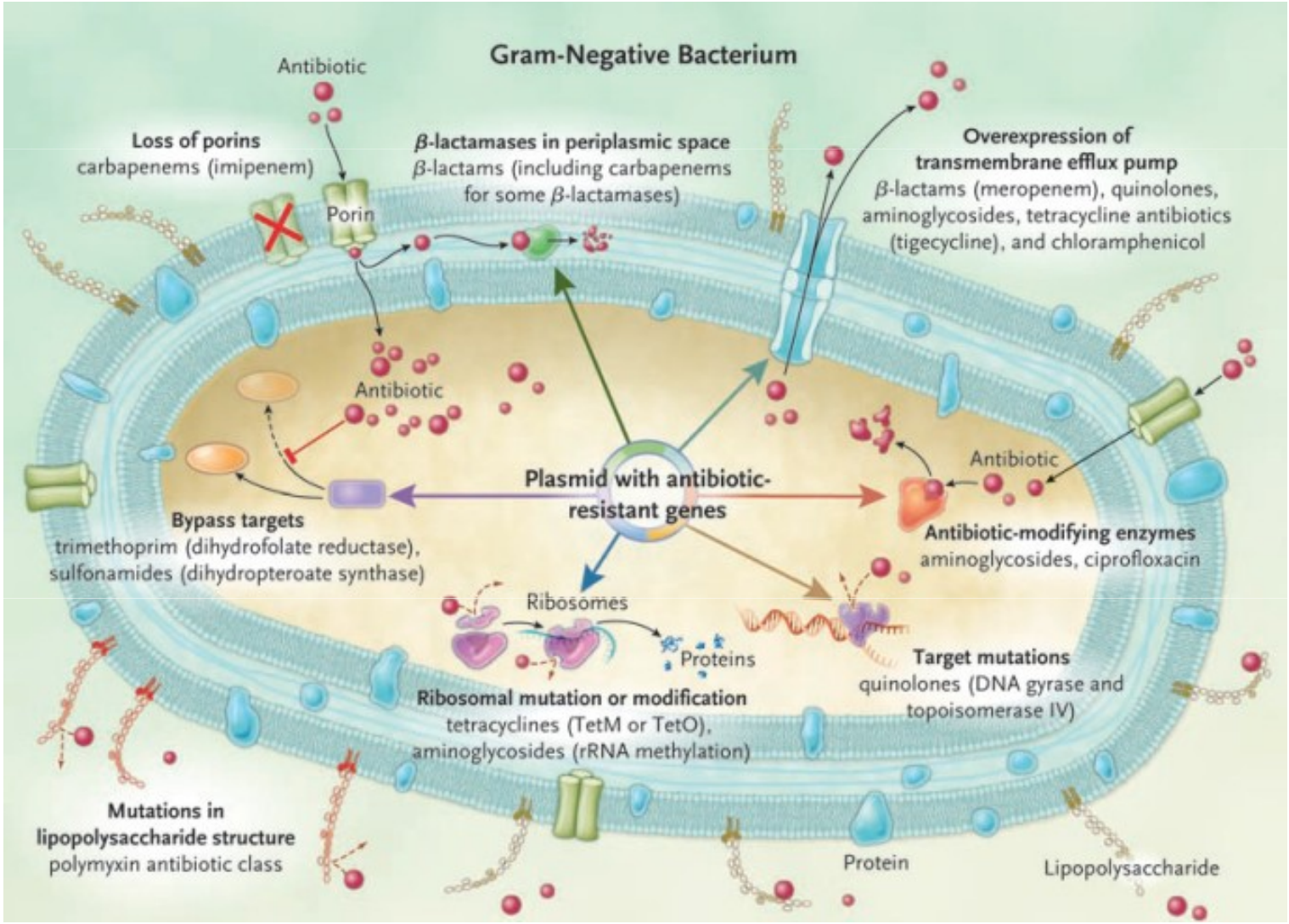
« Perfect storm »



« Perfect storm »



Mécanismes de résistance



Peleg NEJM 2010

Résistances (Europe)

E. coli

Country	Aminopenicillins		Fluoroquinolones		Third-gen. cephalosporins		Aminoglycosides		Multiresistance*	
	N	%R (95%CI)	N	%R (95%CI)	N	%R (95%CI)	N	%R (95%CI)	N	%R (95%CI)
France	9017	54.6 (54-56)	9007	17.5 (17-18)	9022	7.2 (7-8)	9025	7.2 (7-8)	9000	2.9 (3-3)

K. pneumoniae

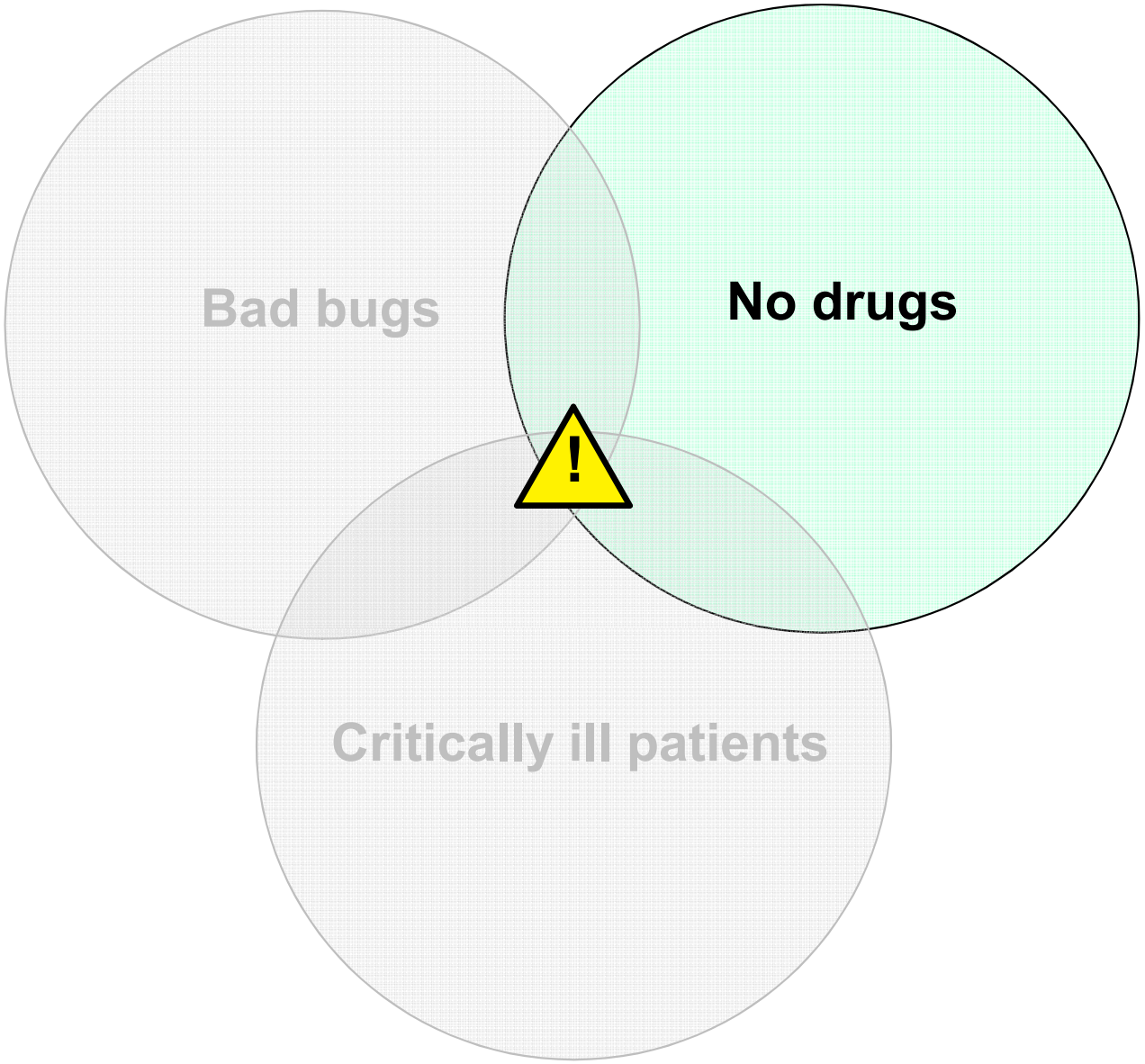
Country	Fluoroquinolones		Third-gen. cephalosporins		Aminoglycosides		Multiresistance*	
	N	%R (95%CI)	N	%R (95%CI)	N	%R (95%CI)	N	%R (95%CI)
France	1527	21.8 (20-24)	1542	17.8 (16-20)	1542	17.7 (16-20)	1527	14.8 (13-17)

P. aeruginosa

Country	Piperacillin± tazobactam		Fluoroquinolones		Ceftazidime		Aminoglycosides		Carbapenems		Multiresistance*	
	N	%R (95%CI)	N	%R (95%CI)	N	%R (95%CI)	N	%R (95%CI)	N	%R (95%CI)	N	%R (95%CI)
France	1125	20.3 (18-23)	1181	22.8 (20-25)	1009	12.7 (11-15)	1121	18.6 (16-21)	1186	17.8 (16-20)	1191	14.7 (13-17)

EARSS/EARS-Net

« Perfect storm »



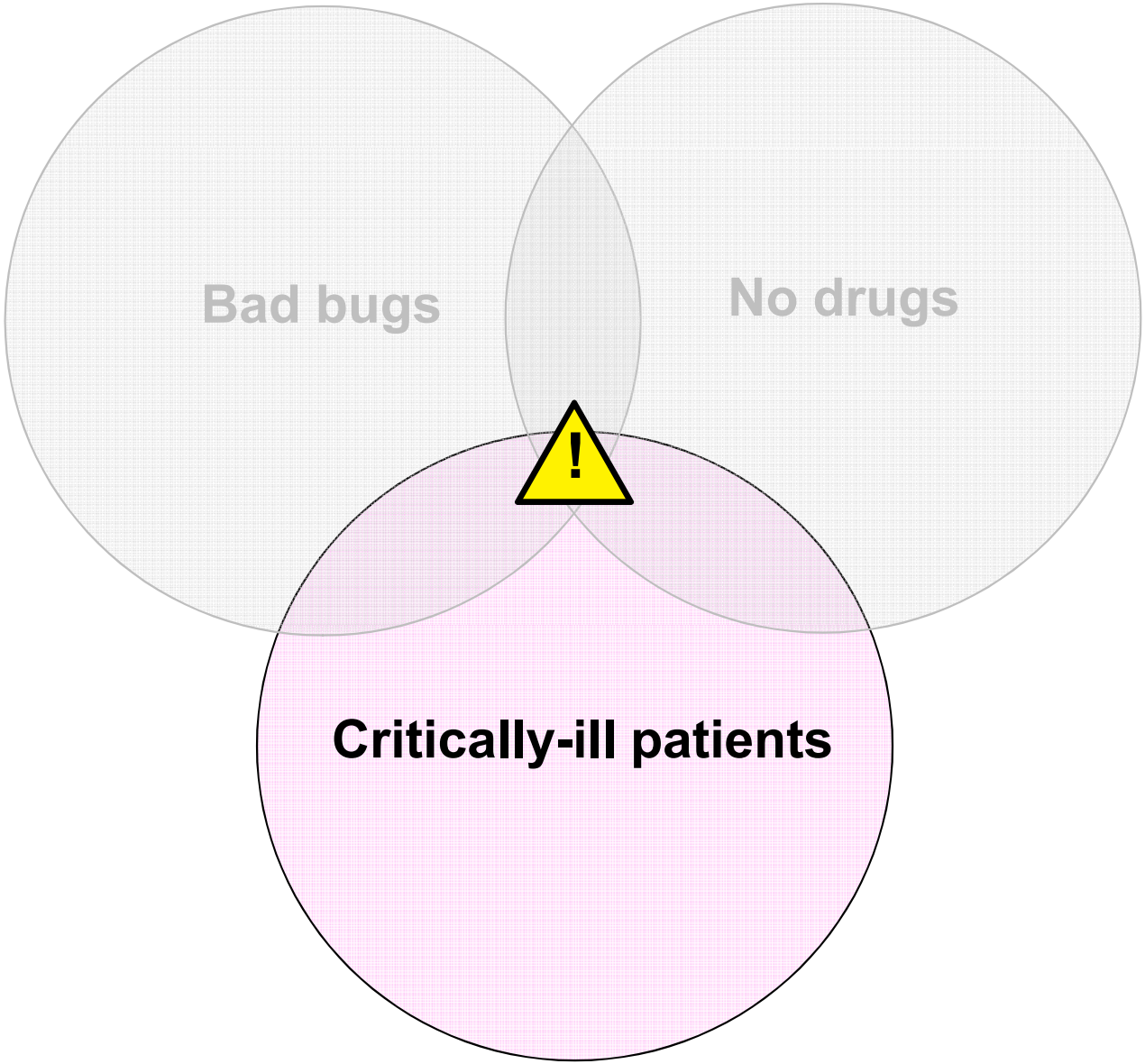
No drugs

R&D « pipeline » en Anti-BGN ?

Name of agent	Gram-positive bacteria				Gram-negative bacteria			Phase of development
	MRSA	VISA/VRSA	PRSP	VRE	3rd Gen Cep. R ENB	Carb. R ENB	Carb. R NF GNB	
WAP 8294A2[P]	●							I
PZ-601[*]	●	●	●	●	●			I
ME 1036[*]	●	●	●		●			I
NXL 101	●	●	●	●				I
Friulimicin B[P]	●	●	●	●				I
Oritavancin	●	●	●	●				Filed
Telavancin	●	●	●	●				Filed
Ceftobiprole medocaril[‡]	●	●	●					Filed
Ceftaroline fosamil [†]	●	●	●					III
Tomopenem[‡]	●	●	●		●	●	●	II
hLF1-11[P]	●	●			●	●	●	II
Lactoferrin[P]	●	●			●	●	●	I
Talactoferrin-alfa[P]	●	●			●	●	●	II
Opebacan[P]					●	●	●	III
NXL 104/ceftazidime[§]					●	●	●	I
●	12	10	9	5	4	2	2	
●	1	2	0	0	4	4	4	
Total	**13**	**12**	**9**	**5**	**8**	**6**	**6**	

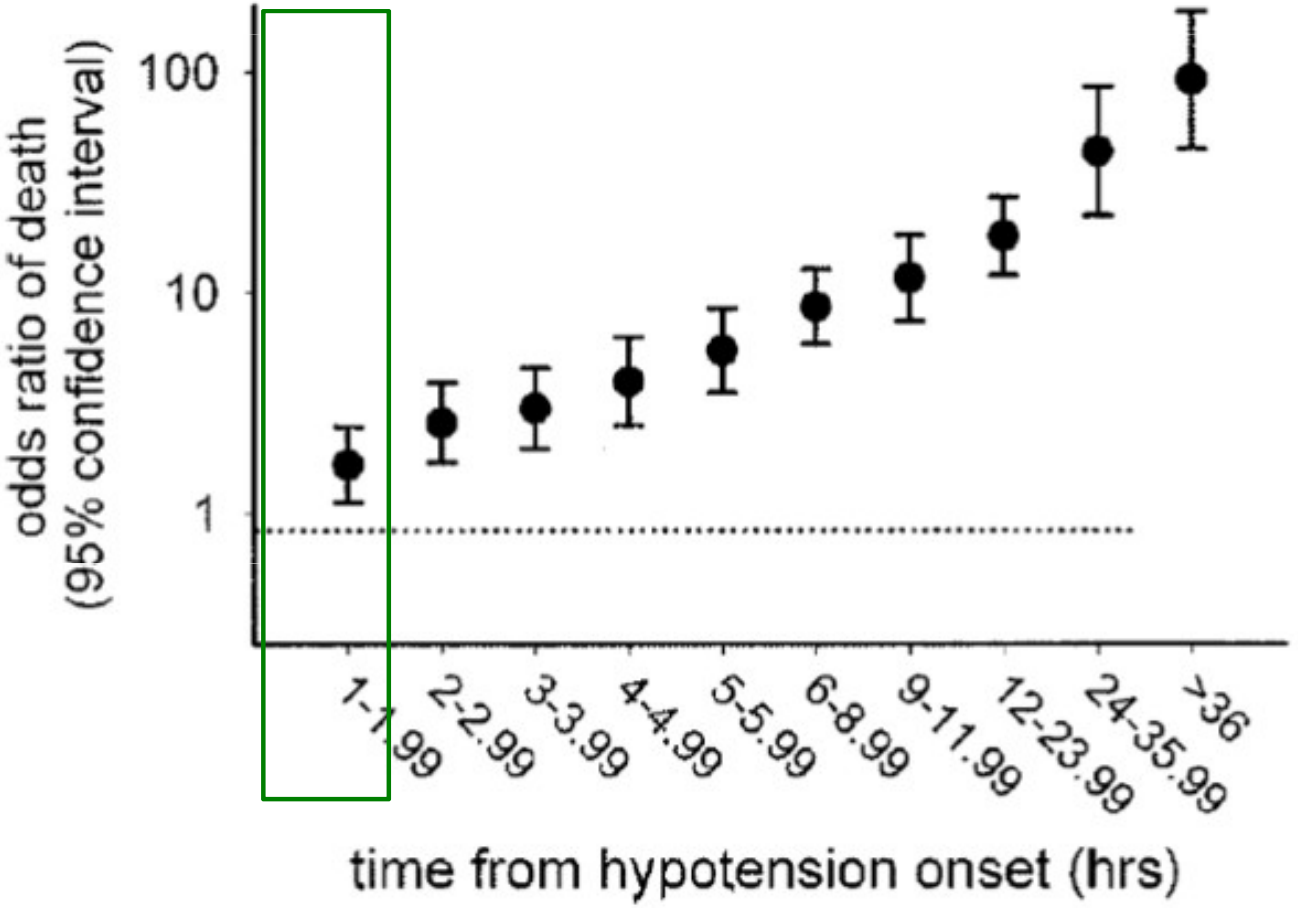
Freire-Moran Drug Resist Updates 2011

« Perfect storm »



Infections graves : le délai

Rapidité de mise en oeuvre du ttt ATB



Kumar Crit Care Med 2006

Pronostic = adéquation

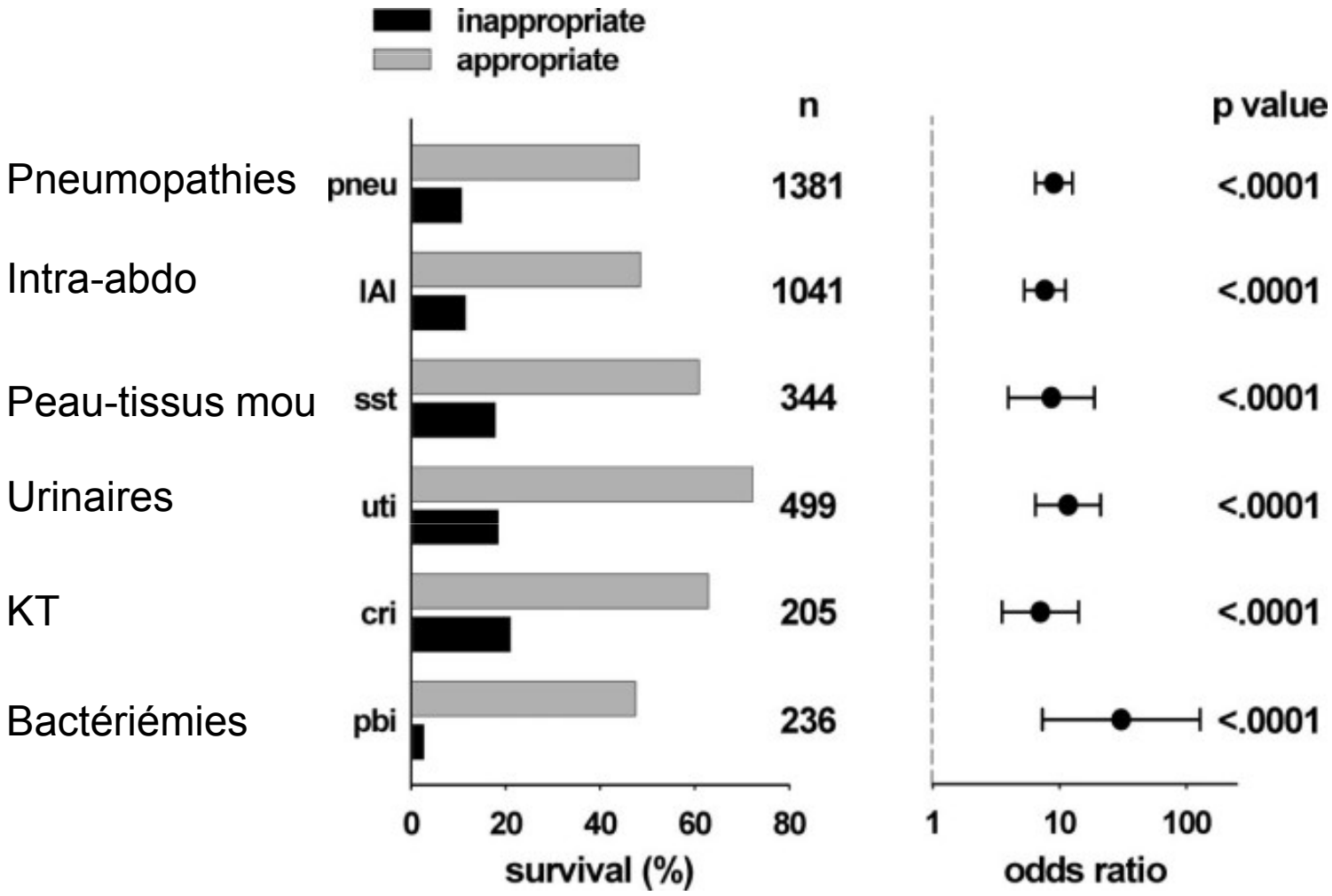
Prospectif 2000 Patients dont 665 antibiothérapies

42%

Risk Factor	AOR†	95% CI	p Value
Inadequate antimicrobial therapy	4.26	3.35–5.44	< 0.001
Acquired organ system derangements (one-organ increments)	3.25	2.98–3.54	< 0.001
Use of vasopressors	2.20	1.81–2.66	< 0.001
Underlying malignancy	1.81	1.44–2.27	0.009
APACHE II score (one-point increments)	1.05	1.04–1.07	< 0.001
Increasing age (1-yr increments)	1.02	1.01–1.03	< 0.001
Surgical patient	0.40	0.33–0.49	< 0.001
Intercept	0.0013	0.0008–0.0021	

Kollef Chest 1999

Pronostic = adéquation



Kumar Crit Care Med 2006

La stratégie classique

Antibiothérapie large spectre selon :
foyer/gravité
écologies
service/institution/pays
FdR

= pari microbiologique

Prélèvements
diagnostics

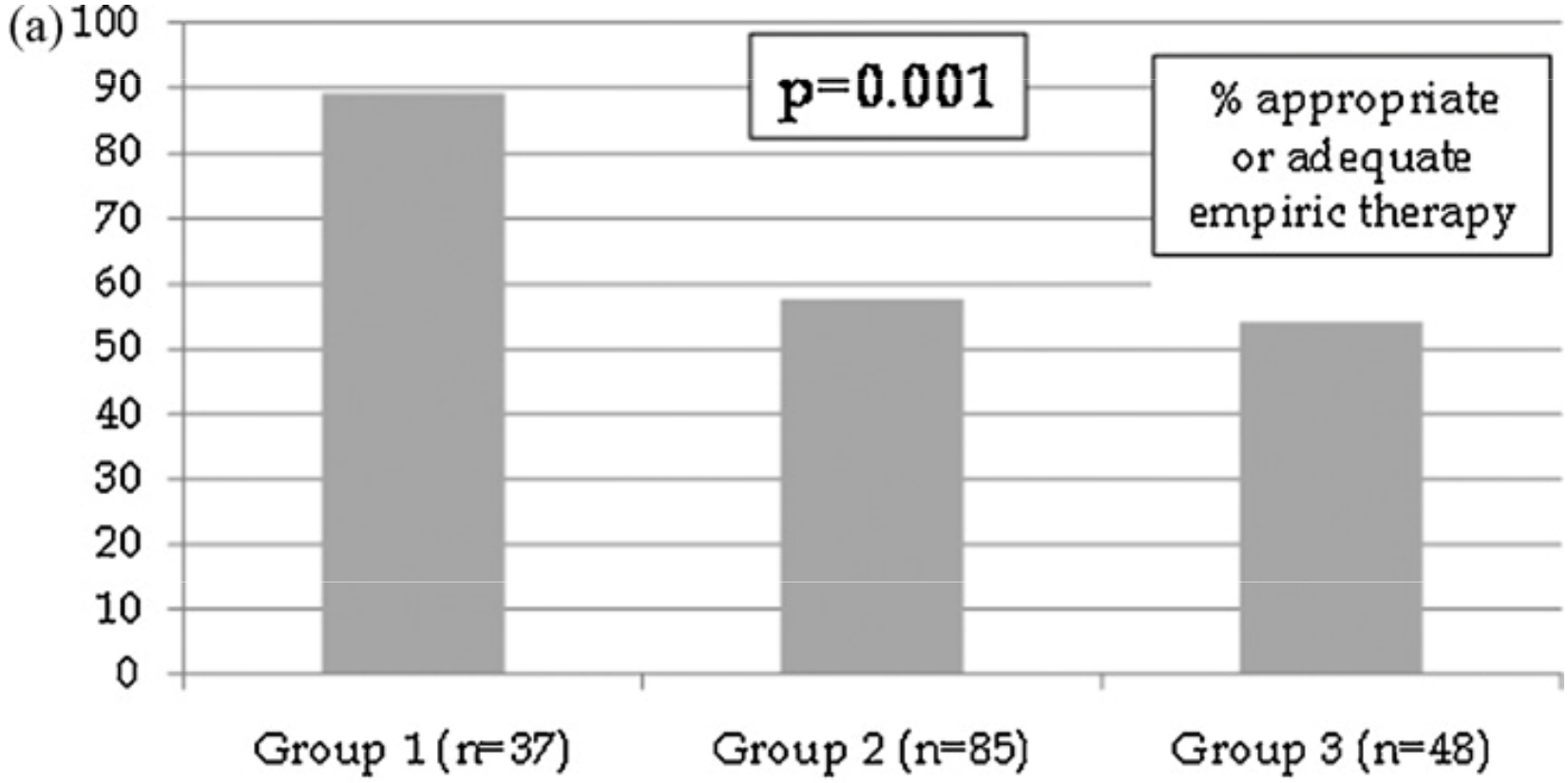
Adéquation?

Un pari...*tricher?*

Adéquation

(très) large spectre

Infections nosocomiales graves, BGN = 74%



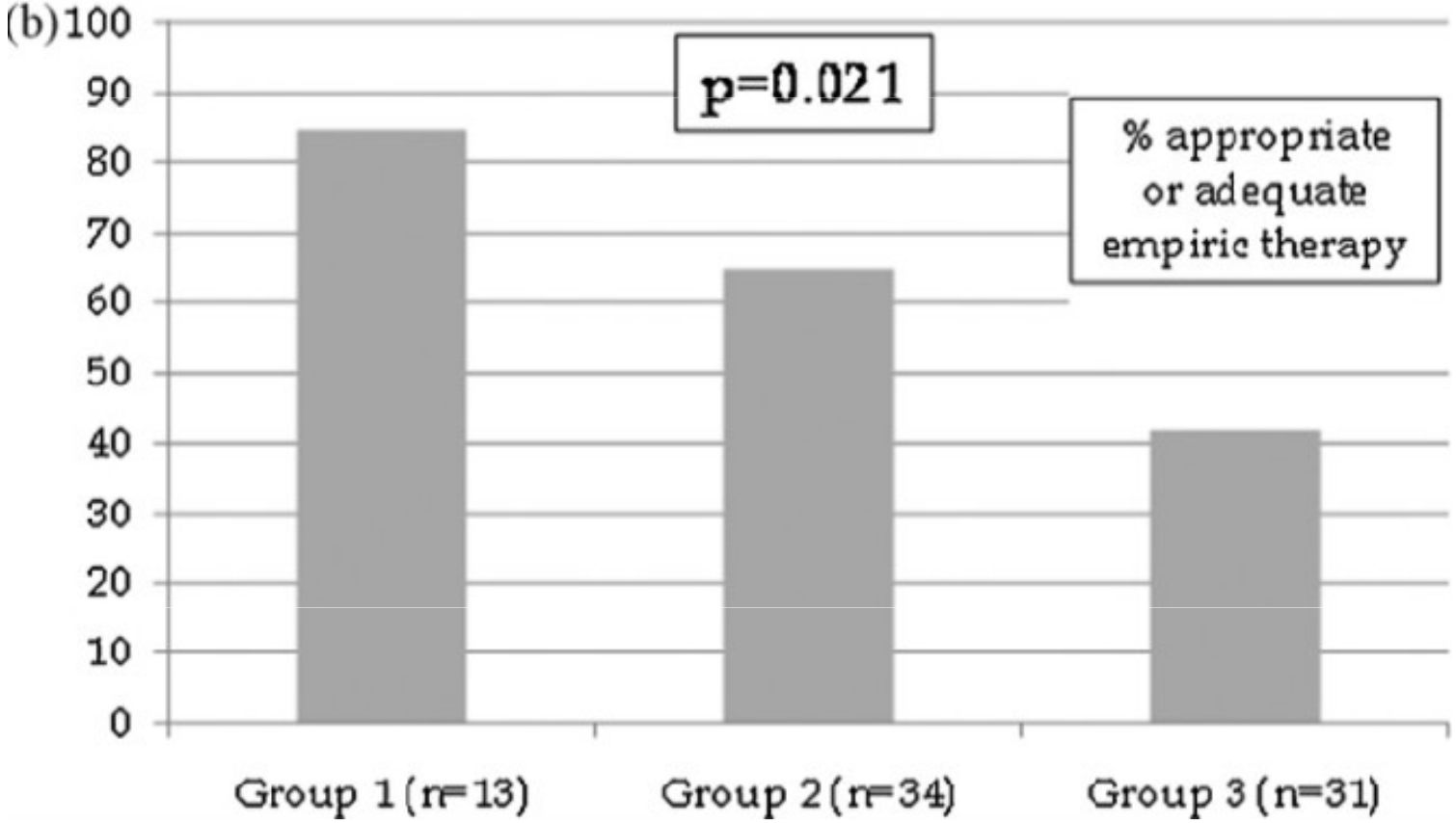
	Group 1 (n=37)	Group 2 (n=85)	Group 3 (n=48)
Profil d'ATB	« Anti-ßLSE » + « Anti-Pyo » (MER±…)	« Anti-Pyo » (PIP/TAZ±…) (CAZ±…) (CIP±…)	« communautaire »

Vogelaers Int J Antimicrob Agents 2010

Adéquation

(très) large spectre

Même en tenant compte des facteurs de risque de multirésistance



« Anti-ßLSE »
+
« Anti-Pyo »
(MER±…)

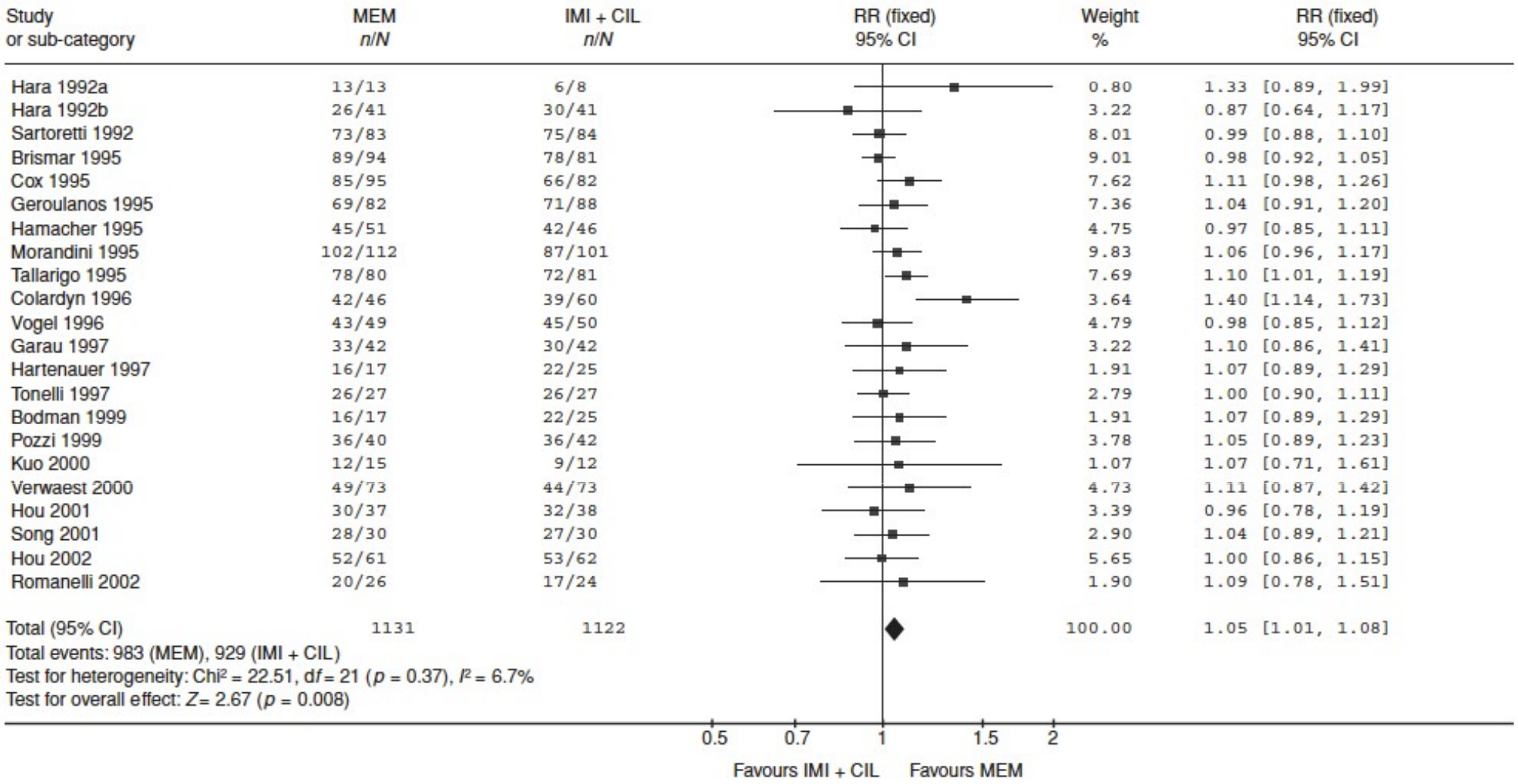
« Anti-Pyo »
(PIP/TAZ±…)
(CAZ±…)
(CIP±…)

« communautaire »

Vogelaers Int J Antimicrob Agents 2010

Méropénème pour tous?

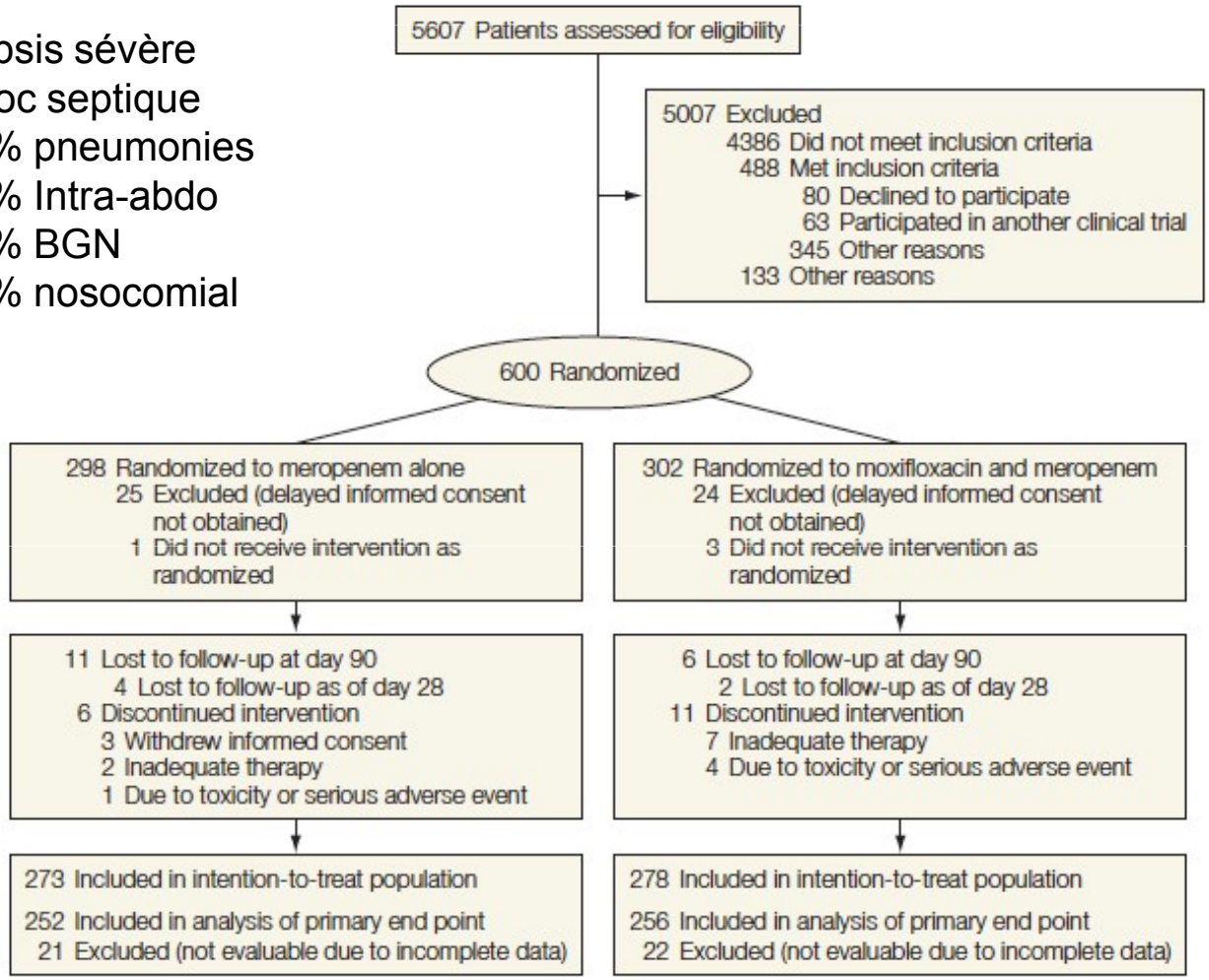
Réponse clinique



Edwards Curr Med Res Op 2005

Méropénème pour tous?

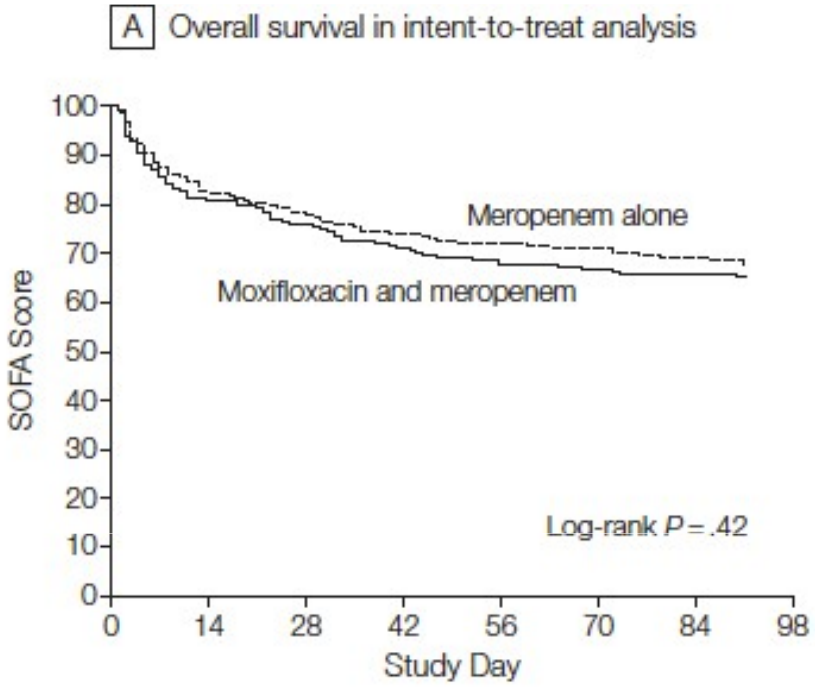
Sepsis sévère
Choc septique
40% pneumonies
40% Intra-abdo
50% BGN
50% nosocomial



Brunkhorst JAMA 2012

Méropénème pour tous?

Sur défaillances d'organe (SOFA score)



No. of patients at risk							
Meropenem alone	273	222	211	193	188	184	179
Moxifloxacin and meropenem	276	224	210	193	186	180	177

Brunkhorst JAMA 2012

Méropénème pour tous?

Antibiotic exposure	Adjusted effect on resistance to antibiotic (95% CI)	*P*
Fluoroquinolone	4.0 (2.5–6.5)[a]	.001
Third-generation cephalosporin	3.5 (2.4–5.1)[b]	<.001
Ampicillin-sulbactam	2.3 (1.2–4.1)[c]	.008
Imipenem	5.7 (3.7–8.7)[d]	<.001

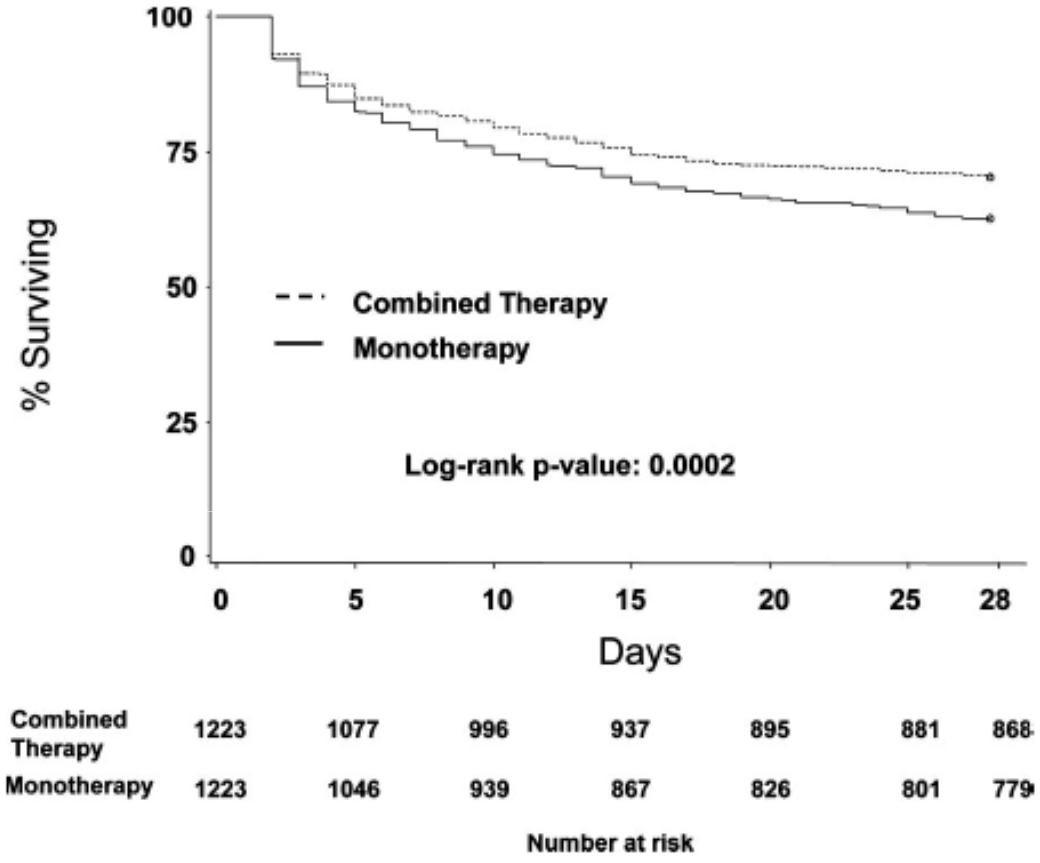
Harbarth CID 2001

Quelles pistes ?

- Associations
- Optimisation PK/PD
- Identification rapide
- Désescalade précoce
- Prélèvements de surveillance
- Adaptation aux souches multirésistantes
- Traitments non-antibiotiques

Associations vs. monothérapies

2446 chocs septiques
Mono vs. associations



Kumar Crit Care Med 2010

Associations vs. monothérapies

2446 chocs septiques
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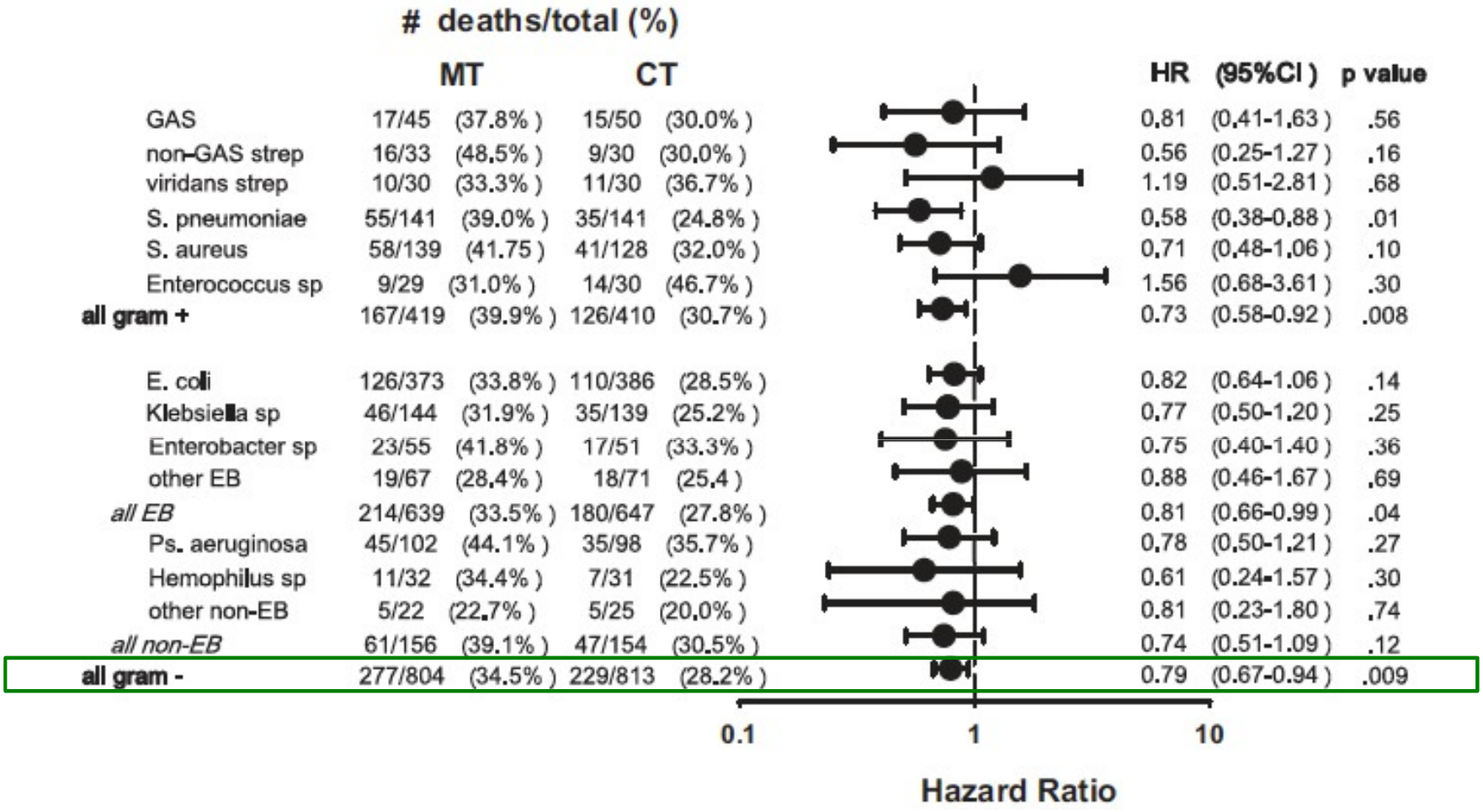
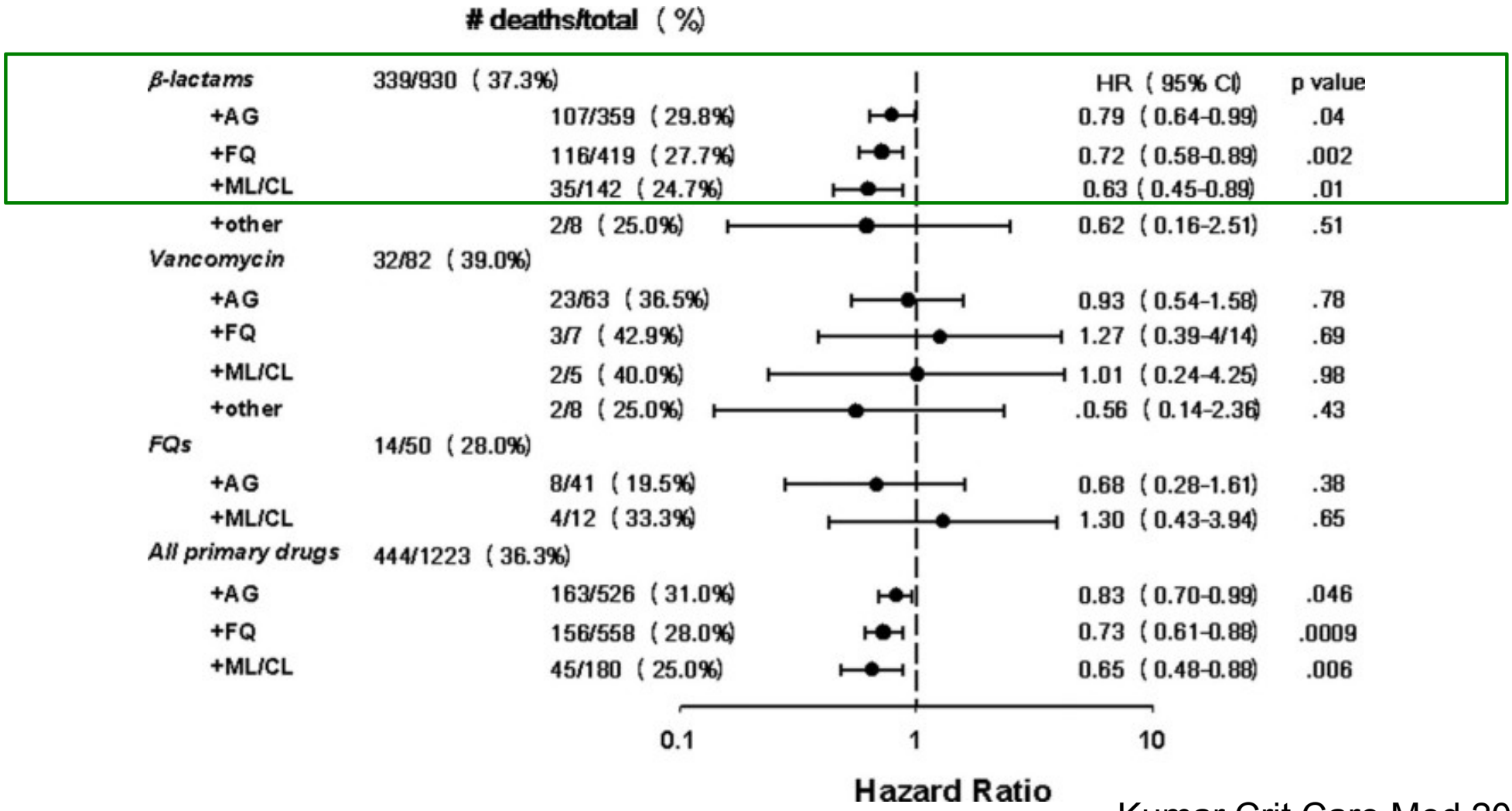


Kumar Crit Care Med 2010

Associations vs. monothérapies

2446 chocs septiques
Mono vs. associations



Kumar Crit Care Med 2010

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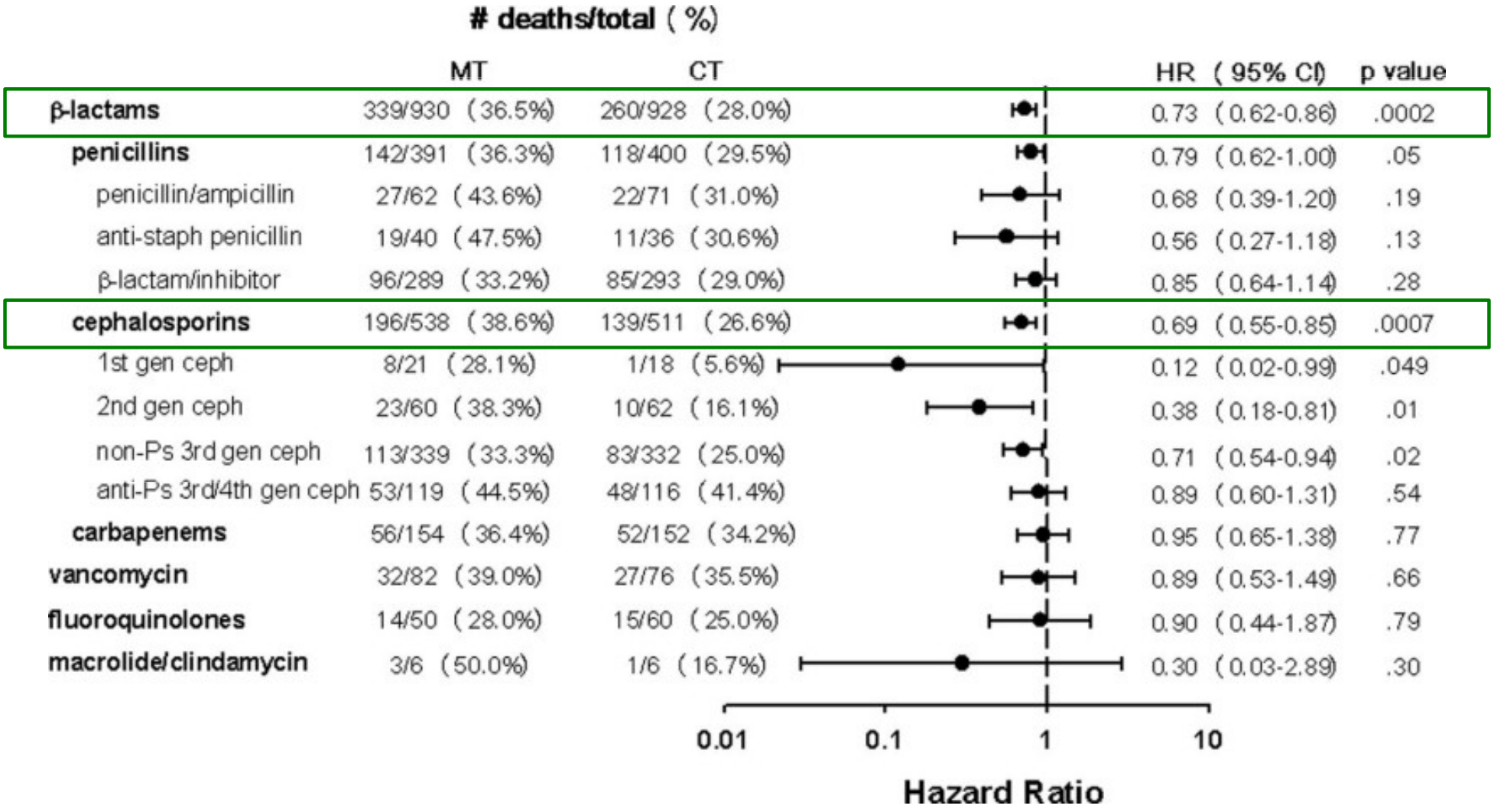
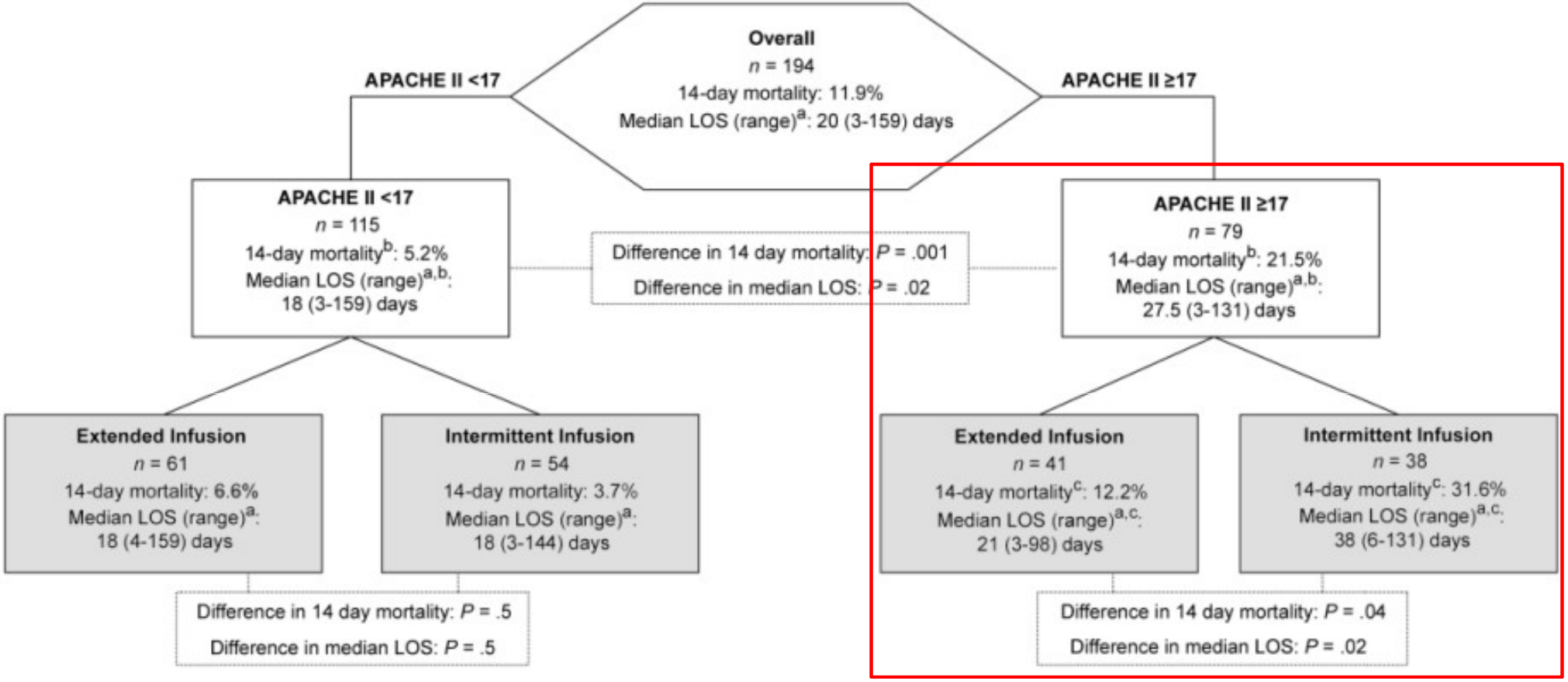


Kumar Crit Care Med 2010

Optimisation modes d'administration anti-BGN

Perfusion "étendue" PIP/TAZ (sur 4h/8h)

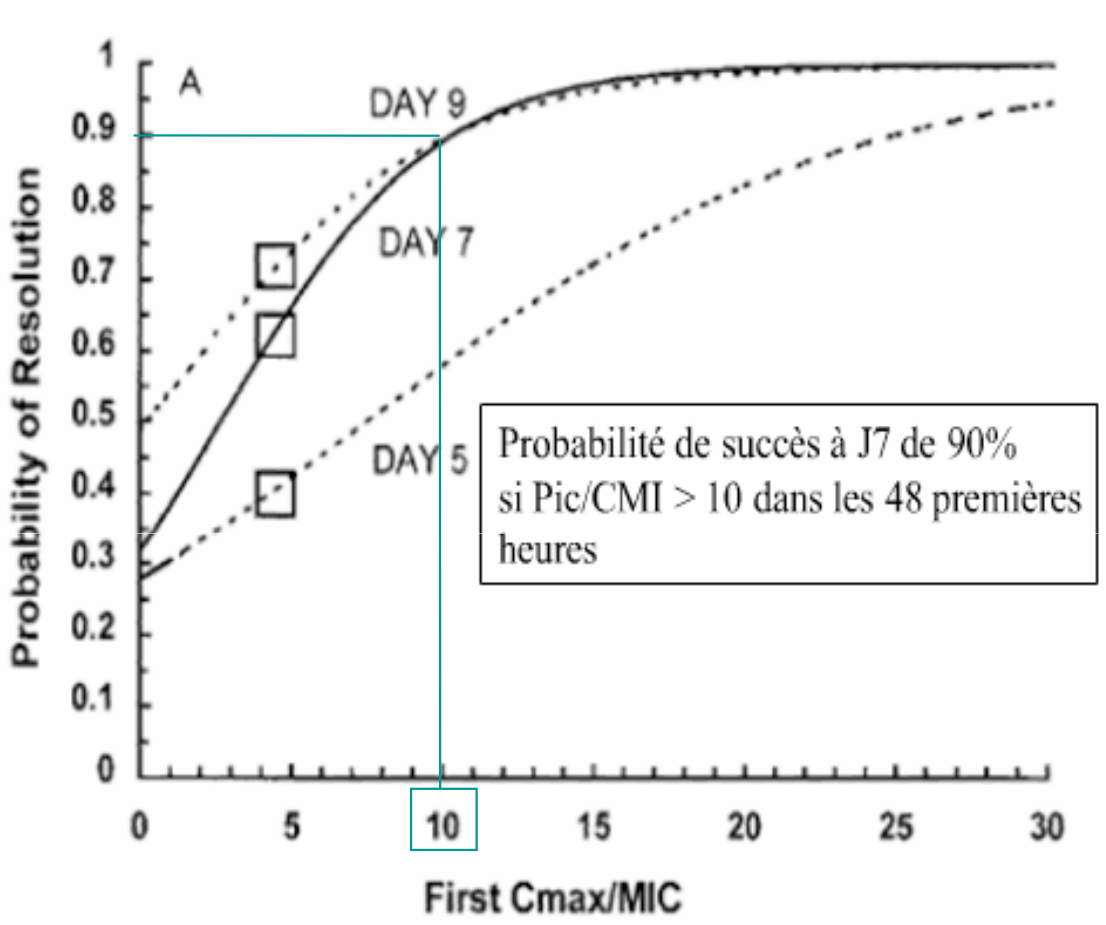
infections à *P. aeruginosa* (50% pneumopathies)



Lodise CID 2007

Optimisation aminosides : premier pic

Pneumopathie BGN sous aminosides



Kashuba *AAC* 1999

Optimisation aminosides : pic/dose

74 patients de réanimation
Cible 8 x CMI *Enterobacteriaceae / P. aeruginosa* (S<8, R>16 microg/ml)
Pic> 64µg/mml

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)

25-30 mg/kg POIDS REEL!

Taccone Crit Care 2010

Identification rapide

E-tests directs = 24h?

Sensibilités sans identification
6 E-tests directs sur boîtes d'échantillons

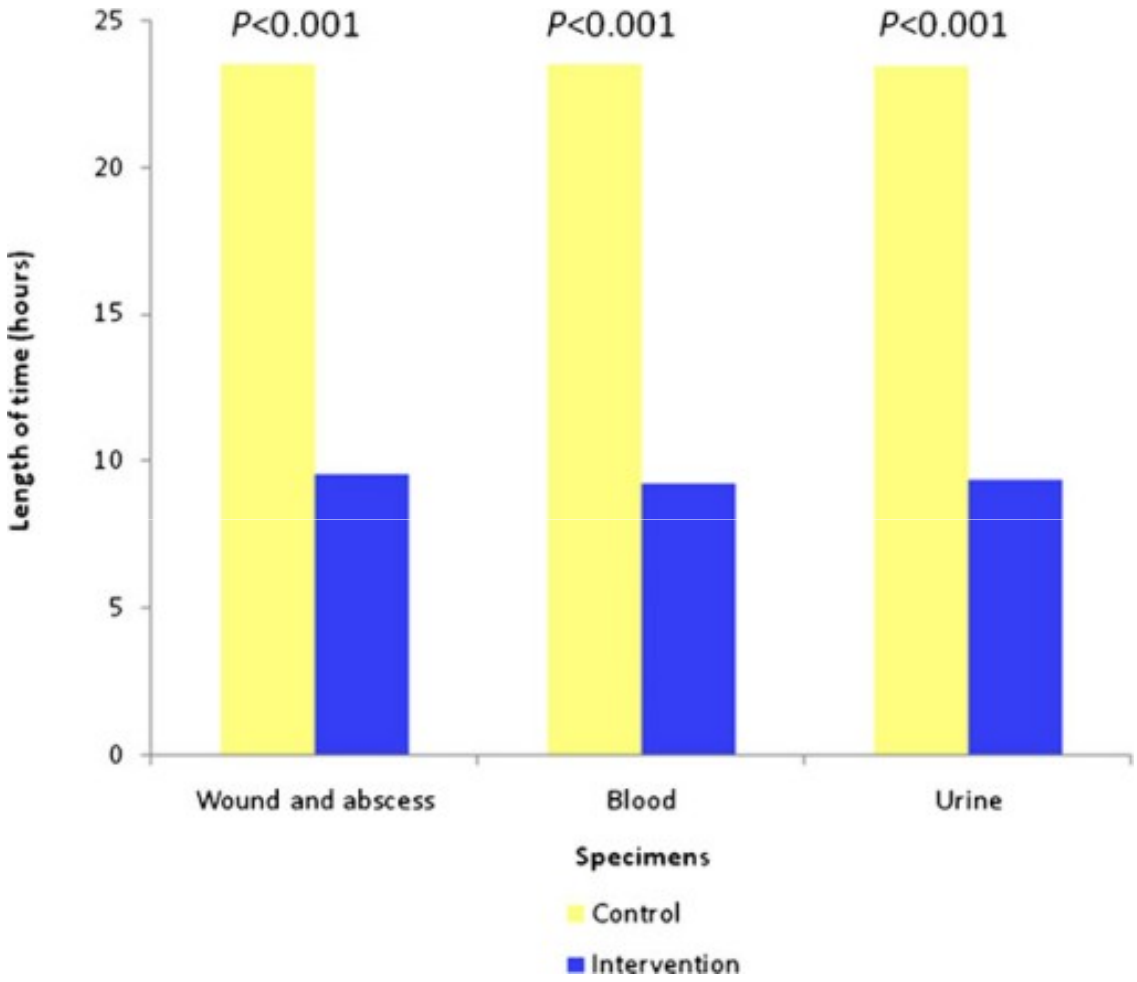
Outcome	E-test group (n = 167)	Control group (n = 83)	P
Fever, mean days ± SD	4.61 ± 5.06	7.84 ± 6.24	<.01
Antibiotic therapy, mean days ± SD	15.72 ± 9.47	18.92 ± 10.92	.02
Defined daily doses of antibiotic therapy, mean ± SD	31.43 ± 24.47	42.72 ± 34.13	.01
Median cost, in €, of antibiotic per episode (IQR)	666 (236–1360)	984 (437–1601)	.03
Percentage of adequate days of antibiotic therapy	95.22	76.26	<.01
Percentage of adequate defined daily doses of antibiotic therapy	91.28	68.26	<.01
Clostridium difficile–associated diarrhea, no. of patients (%)	3 (1.8)	8 (9.6)	<.01
Median no. of days on mechanical ventilation from VAP diagnosis (IQR)	8 (3–19)	12 (6–21)	.04

Délai moyen 1,4j 4,2j
Rendu sensibilité

Bouza CID 2007

Identification rapide

Vitek®-2 = 9h?



Galar Eur J Clin Microbiol Infect Dis. 2012

Identification rapide

Vitek®-2 = 9h?

Patients de Maladies Infectieuses

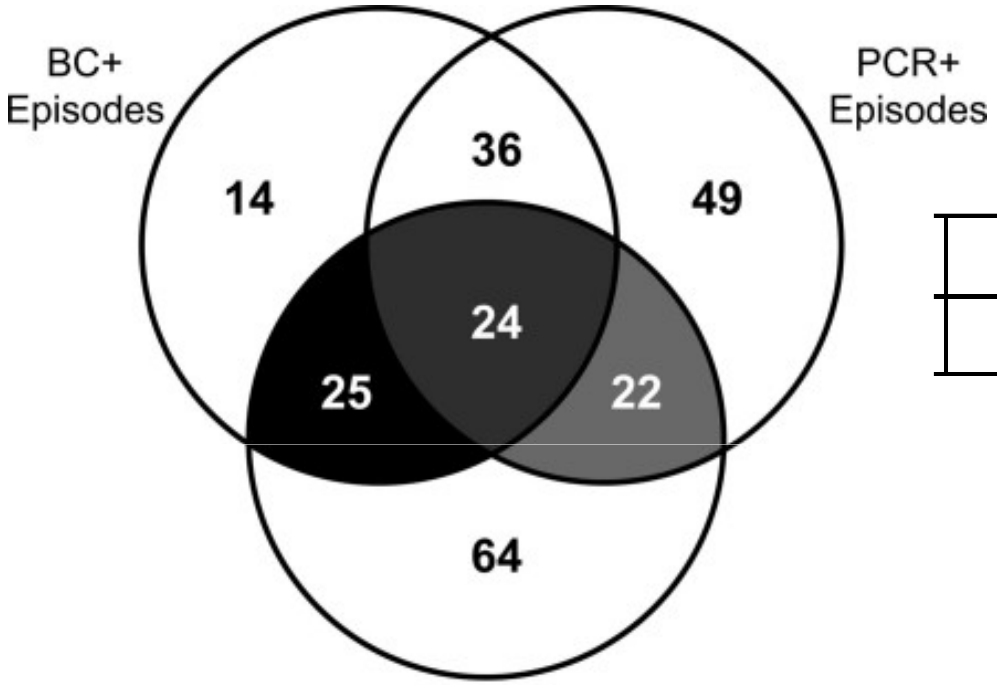
Index-positive culture	Group	Descriptive parameters	Conventional Hospitalization Unit (days)
Wound and abscess specimens	Control (n=107)	Median (IQR)	11.3 (7.1–17.0)
	Intervention (n=136)	Median (IQR)	8.3 (4.6–15.9)
	p-value[b]		<0.05
Blood specimens	Control (n=56)	Median (IQR)	17.0 (6.4–28.0)
	Intervention (n=55)	Median (IQR)	16.0 (7.6–22.7)
	p-value[b]		0.682
Urine specimens	Control (n=40)	Median (IQR)	13.3 (6.5–16.4)
	Intervention (n=30)	Median (IQR)	9.5 (6.7–11.6)
	p-value[b]		<0.05

Galar Eur J Clin Microbiol Infect Dis. 2012

Identification rapide

PCR = 6h?

436 patients traités pour sepsis
117 pathogènes identifiés



Episodes with modifications of initial empiric antimicrobial treatment

PCR	Culture
5.9 (5.4 - 6.5)	25.3 (11.4-31.9)

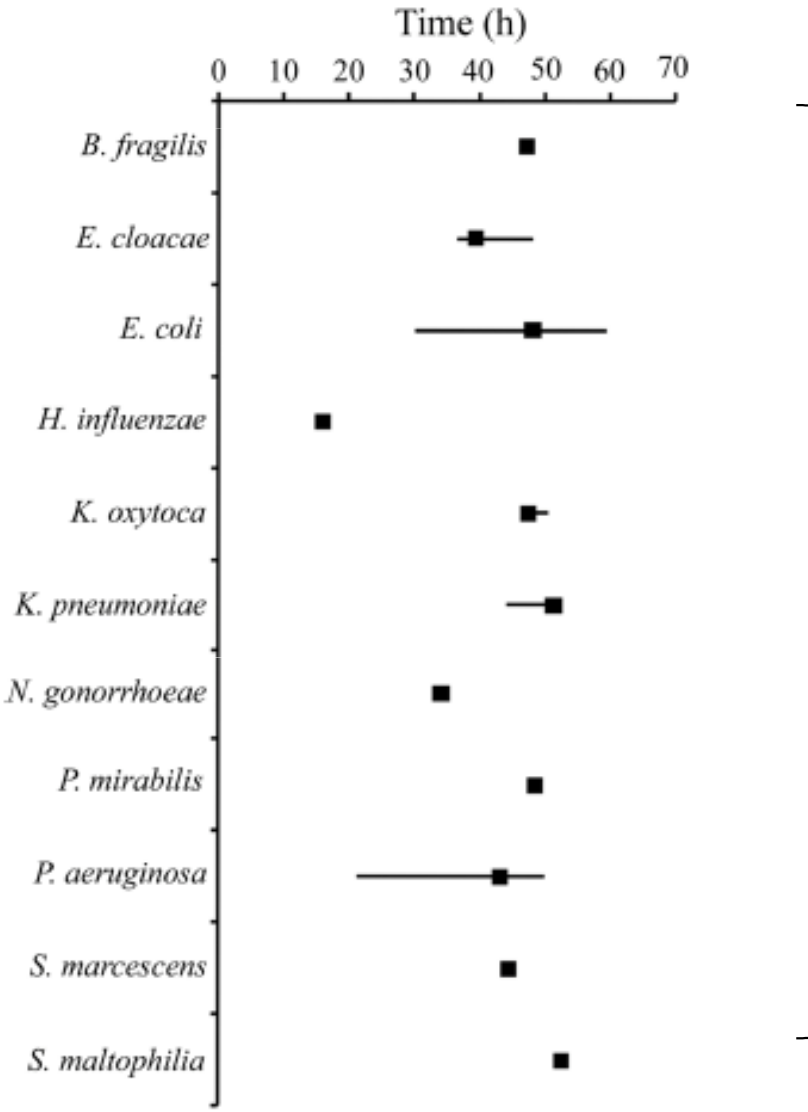
Lehmann Crit Care Med 2009

Tran Surgery 2012

Identification rapide

Spectrométrie de masse (MALDI-TOF) = 20 min?

Identification conventionelle



MALDI-TOF

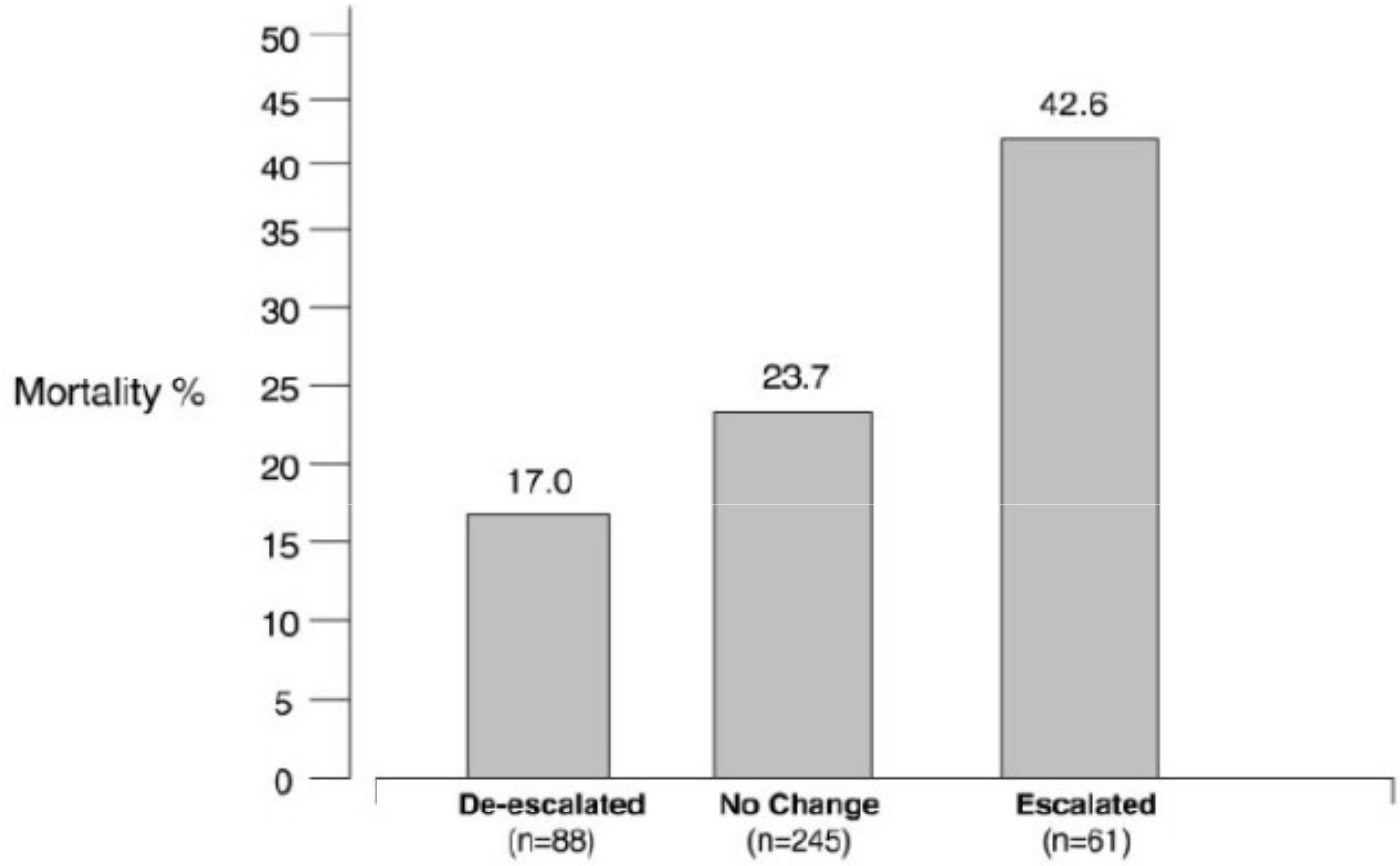
20 minutes

Buchan J Clin Microbiol

Désescalade

Faisable

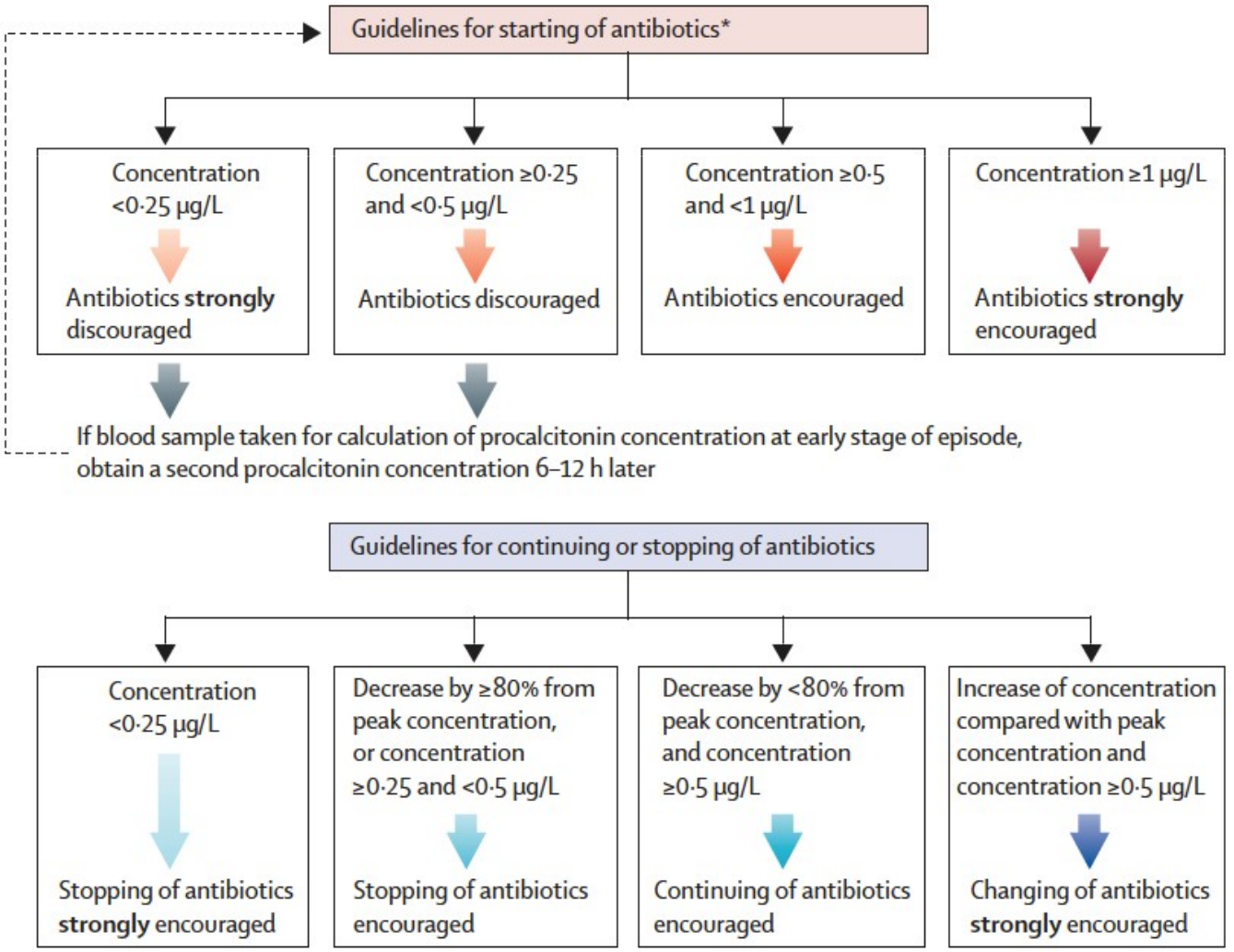
22% de 398 PAVM



Kollef Chest 2006

Désescalade

Procalcitonine ?



Bouadma *Lancet* 2010

Stratégie alternative :

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surveillance microbiologique

Prélèvements
de **« surveillance microbiologique »**

pari ciblé = ATBttt **adaptée**
au dernier prélèvement +

Prélèvements
diagnostics

Adéquation?

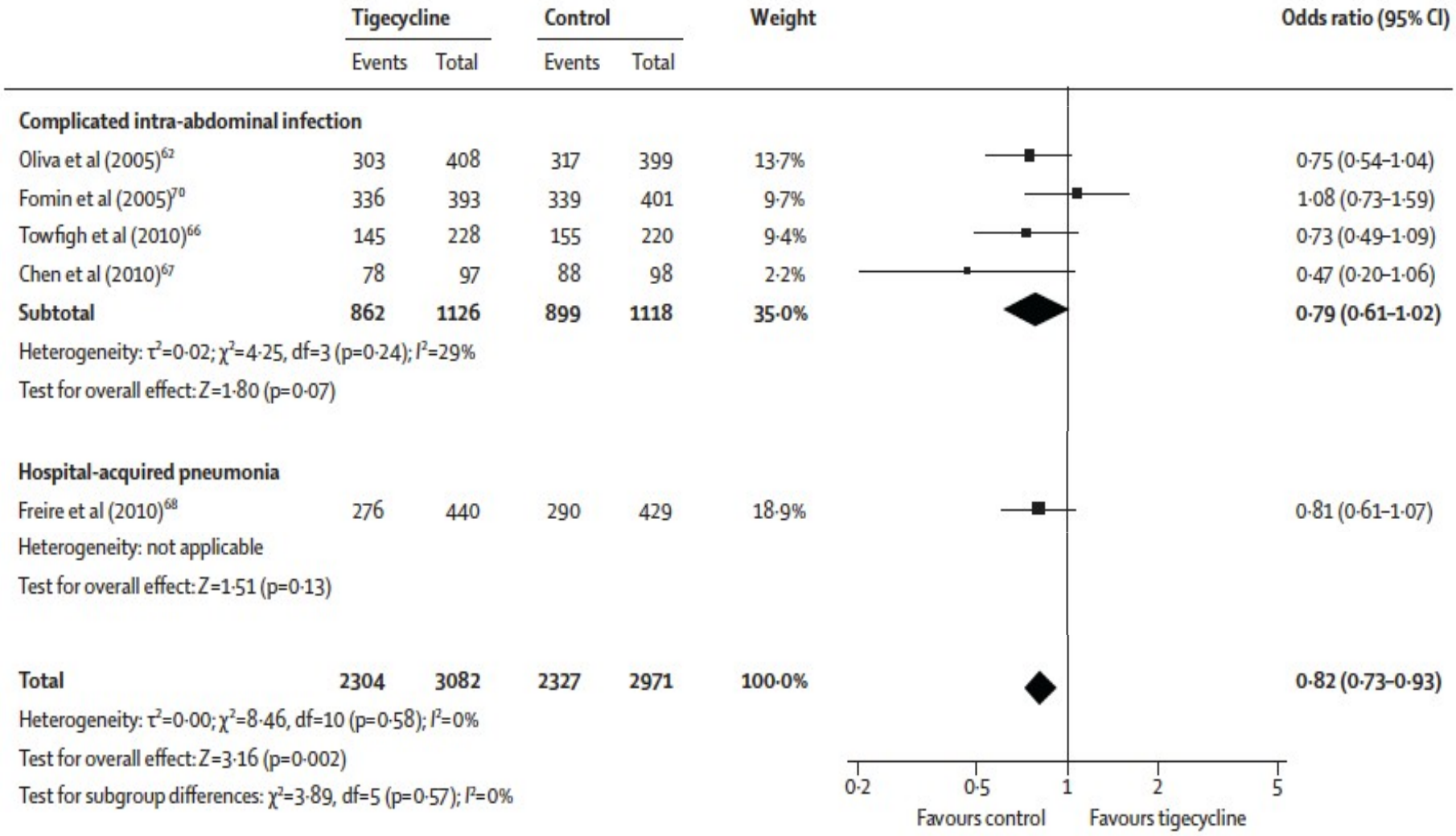
Prélèvements de surveillance microbiologique

Surveillance colonisation tracheale X 2/sem ou anale x 1/sem

VAP cases ($n = 27$)	
Pathogen predicted by previous colonization ($n = 22$)	
Adequate therapy	20 (91%)
Inadequate therapy	2 (9%)
Pathogen not predicted by previous colonization ($n = 5$)	
Adequate therapy	2 (40%)
Inadequate therapy	3 (60%)
BSI cases ($n = 54$)	
Pathogen predicted by previous colonization ($n = 42$)	
Adequate therapy	36 (86%)
Inadequate therapy	6 (14%)
Pathogen not predicted by previous colonization ($n = 12$)	
Adequate therapy	6 (50%)
Inadequate therapy	6 (50%)

Papadomichelakis Intens Care Med 2008

Tigecycline



	Tigecycline Events	Tigecycline Total	Control Events	Control Total	Weight	Odds ratio (95% CI)
Complicated intra-abdominal infection						
Oliva et al (2005)[62]	303	408	317	399	13·7%	0·75 (0·54–1·04)
Fomin et al (2005)[70]	336	393	339	401	9·7%	1·08 (0·73–1·59)
Towfigh et al (2010)[66]	145	228	155	220	9·4%	0·73 (0·49–1·09)
Chen et al (2010)[67]	78	97	88	98	2·2%	0·47 (0·20–1·06)
Subtotal	**862**	**1126**	**899**	**1118**	**35·0%**	**0·79 (0·61–1·02)**
Heterogeneity: τ^2=0·02; χ^2=4·25, df=3 (p=0·24); I^2=29%						
Test for overall effect: Z=1·80 (p=0·07)						
Hospital-acquired pneumonia						
Freire et al (2010)[68]	276	440	290	429	18·9%	0·81 (0·61–1·07)
Heterogeneity: not applicable						
Test for overall effect: Z=1·51 (p=0·13)						
Total	**2304**	**3082**	**2327**	**2971**	**100·0%**	**0·82 (0·73–0·93)**
Heterogeneity: τ^2=0·00; χ^2=8·46, df=10 (p=0·58); I^2=0%						
Test for overall effect: Z=3·16 (p=0·002)						
Test for subgroup differences: χ^2=3·89, df=5 (p=0·57); I^2=0%						

Tasina Lancet ID 2011

Tigecycline

	TYGACIL		Comparator		Risk Difference*
Infection Type	n/N	%	n/N	%	% (95% CI)
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.3, 1.7)
cIAI	42/1382	3.0	31/1393	2.2	0.8 (-0.4, 2.0)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.0, 2.4)
HAP	66/467	14.1	57/467	12.2	1.9 (-2.4, 6.3)
Non-VAP[a]	41/336	12.2	42/345	12.2	0.0 (-4.9, 4.9)
VAP[a]	25/131	19.1	15/122	12.3	6.8 (-2.1, 15.7)
VAP+bacteremia	9/18	**50%**	1/13	**7.7%**	
DFI	7/553	1.3	3/508	0.6	0.7 (-0.5, 1.8)
Overall Adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1, 1.2)**

Tasina Lancet ID 2011

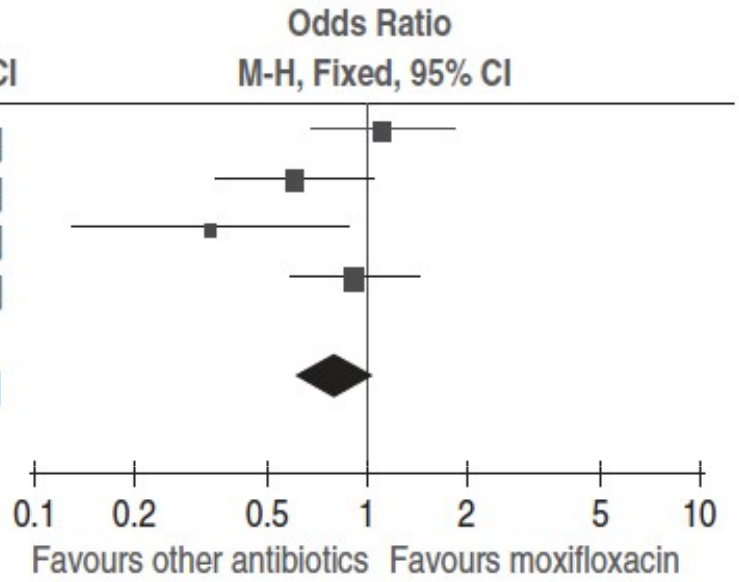
Moxifloxacine

Infections Intra-abdo compliquées

Study or Subgroup	Comparator			Odds Ratio M-H, Fixed, 95% CI
Malangoni2006	PIT/TAZ AMOX/CLAV			1.11 [0.68, 1.82]
NCT004927262011	ETP			0.60 [0.35, 1.04]
Solomkin2009	CTRX/MTZ			0.34 [0.13, 0.87]
Weiss2009	CTRX/MTZ			0.91 [0.58, 1.43]
Total (95% CI)	955	979	100.0%	0.80 [0.61, 1.04]
Total events	817	860		

Heterogeneity: $Chi^2 = 6.21$, $df = 3$ ($p = 0.10$); $I^2 = 52\%$

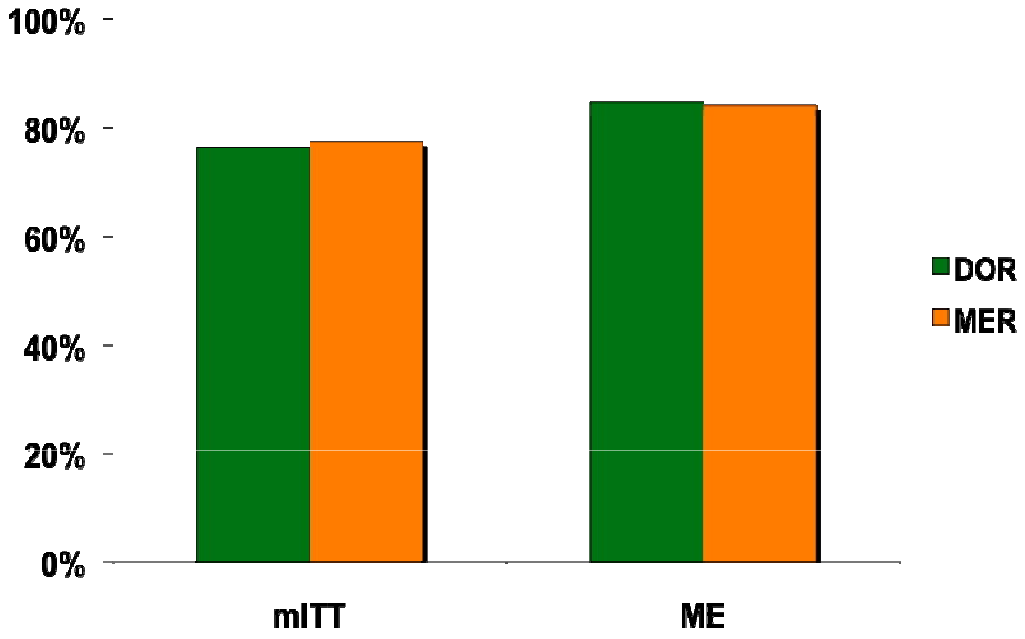
Test for overall effect: $Z = 1.67$ ($p = 0.09$)



Mu Int J Clin Pract 2012

Doripénème

- Infections intra-abdo n=476
- Peu graves (appendicites cholecystites)



Mais 25% des *P. aeruginosa/A. baumannii* carbapénèmes-R *Restent S au Doripénème*

Lucasti, Clin Ther 2008

Doripénème

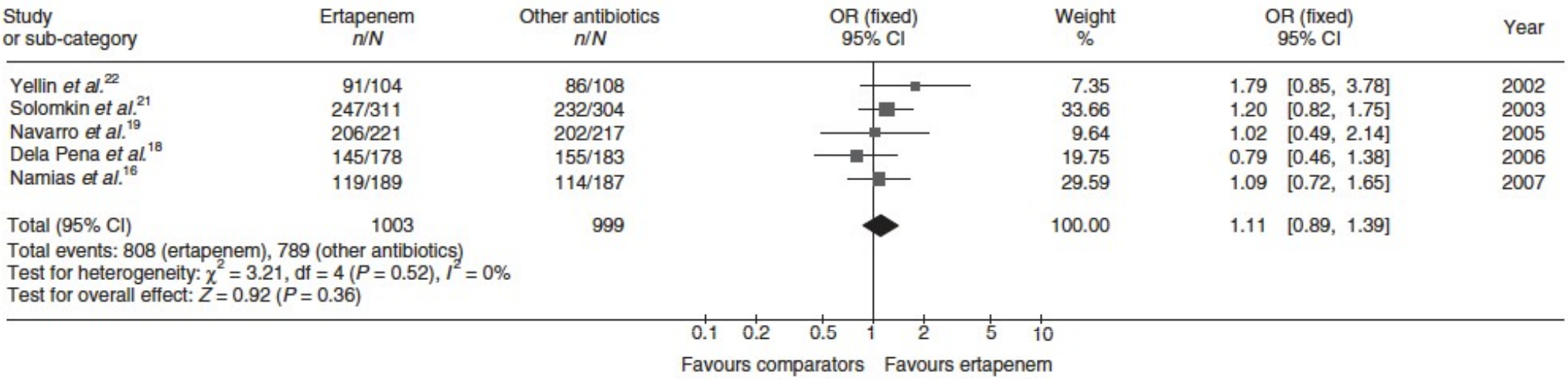
Phases III Infections Intra-Abdo compliquées ou PAVM à ***P. aeruginosa***

	Doripenem		Comparator		Difference (%)	95% CI (%)
	n/N	(%)	*n/N*	(%)		
Clinical Success at TOC for Subjects with *P. aeruginosa* at Baseline Who Received Adjunctive Antipseudomonal Therapy						
cIAI*						
mITT†	7/9	77.8	2/4	50.0	27.8	−28.2, 83.8
ME	7/7	100.0	2/3	66.7	33.3	−20.0, 86.7
CE	7/7	100.0	2/3	66.7	33.3	−20.0, 86.7
NP/VAP‡						
mITT†	18/32	56.3	13/40	32.5	23.8	1.3, 46.2
ME	18/24	75.0	13/30	43.3	31.7	−8.2, 45.1
CE	18/24	75.0	13/23	56.5	18.5	−8.2, 45.1
Clinical Success at TOC for Subjects with *P. aeruginosa* at Baseline Who Did Not Receive Adjunctive Antipseudomonal Therapy						
cIAI*						
mITT†	30/38	78.9	24/31	77.4	1.5	−18.1, 21.1
ME	27/34	79.4	23/29	79.3	0.1	−20.0, 20.2
CE	28/35	80.0	23/29	79.3	0.7	−19.1, 20.5
NP/VAP						
mITT†	13/20	65.0	6/18	33.3	31.7	1.5, 61.9
ME	13/14	92.9	6/10	60.0	32.9	−0.4, 66.1
CE	13/14	92.9	6/10	60.0	32.9	−0.4, 66.1

Jenkins Curr Med Res Op 2009

Ertapénème

Infections Intra-Abdo compliquées



Falagas Aliment Pharmacol Ther 2008

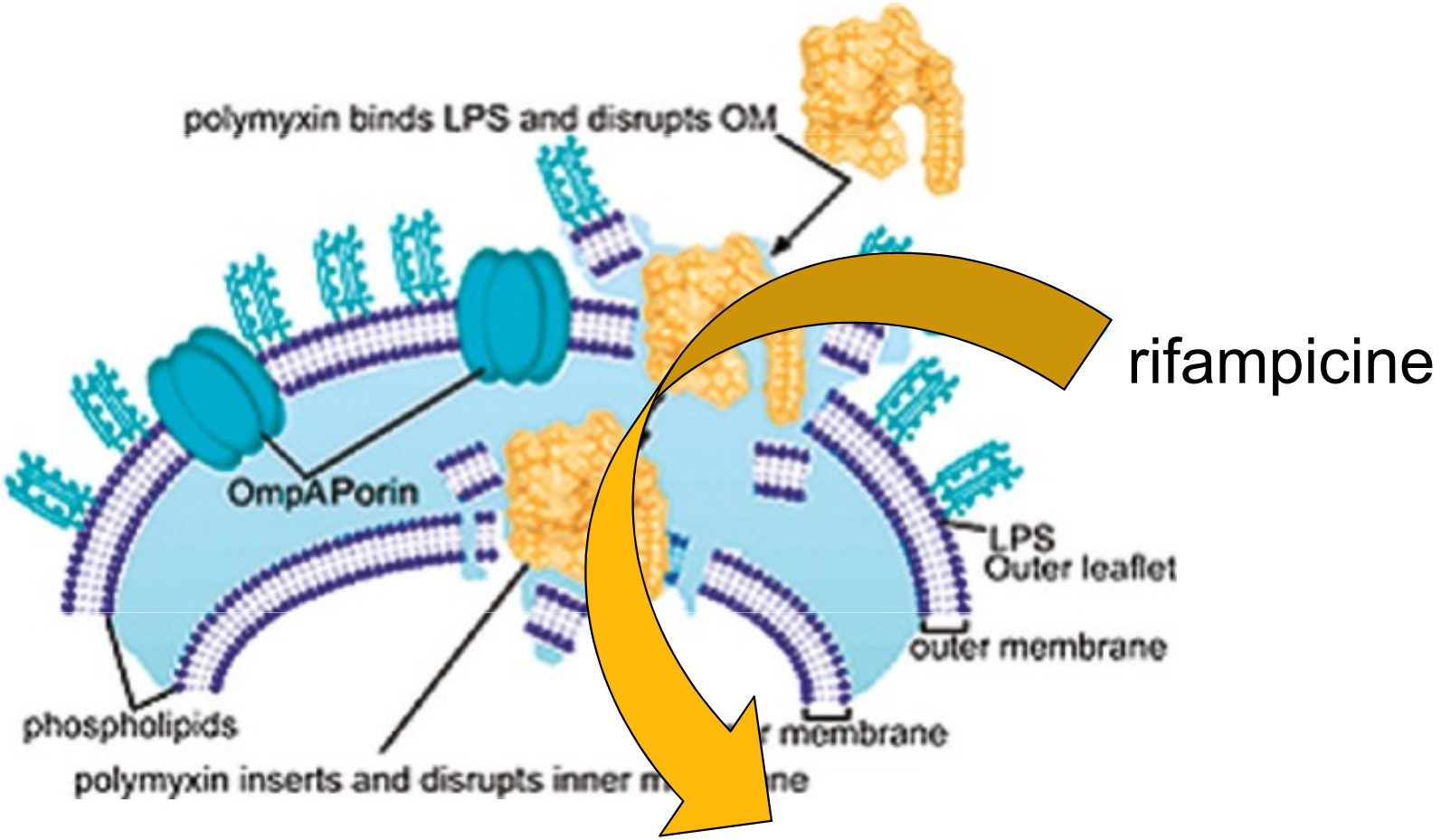
Colistine : synergies in vitro

Tableau 2 Synergies in vitro.
In-vitro synergy.

Formulation de colistine	Synergie testée	Pathogène	Souches (*n*)	Souches S (%)	Étude	Méthode
Colistine	Rifampicine	*A. baumannii*	13	85	Hogg et al., 1998 [75]	Échiquier
Colistine	Rifampicine	*A. baumannii*	5	80	Timurkaynak et al., 2006 [76]	Échiquier
Colistine	Rifampicine	*A. baumannii*	8	100	Li et al., 2007 [77]	Échiquier
Colistimethate	Rifampicine	*A. baumannii*	6	100	Giamarellos-Bourboulis et al., 2002 [78]	Courbes de bactéricidie
Colistimethate	Rifampicine	*A. baumannii*	8	100	Song et al., 2007 [79]	Courbes de bactéricidie
Colistine	Rifampicine	*P. aeruginosa*	5	40	Timurkaynak et al., 2006 [76]	Échiquier
Colistine	Rifampicine	*P. aeruginosa*	7	14	Timurkaynak et al., 2006 [76]	Échiquier
Colistine	Rifampicine	*P. aeruginosa*	7	14	Tascini et al., 2004 [80]	Échiquier
Colistimethate	Rifampicine	*P. aeruginosa*	17	12	Giamarellos-Bourboulis et al., 2002 [81]	Courbes de bactéricidie
Colistine	Rifampicine	*P. aeruginosa*	2	100	Tascini et al., 2004 [80]	Courbes de bactéricidie
Colistimethate	Rifampicine	*S. maltophilia*	24	63	Giamarellos-Bourboulis et al., 2002 [82]	Courbes de bactéricidie
Colistimethate	Cotrimoxazole	*S. maltophilia*	24	42	Giamarellos-Bourboulis et al., 2002 [82]	Courbes de bactéricidie
Colistine	Méropénème	*A. baumannii*	5	60	Timurkaynak et al., 2006 [76]	Échiquier
Colistine	Azithromycine	*A. baumannii*	5	60	Timurkaynak et al., 2006 [76]	Échiquier
Colistine	Minocycline	*A. baumannii*	13	92	Tan et al., 2007 [83]	Courbes de bactéricidie
Colistine	Imipénème	*K. pneumoniae (VIM-1)*	42	50	Souli et al., 2009 [84]	Courbes de bactéricidie

Kipnis Antibiotiques 2010

Rifampicine



Velkov J Med Chem 2010

Colistine : études comparatives

Tableau 4 Études comparatives.
Comparative studies.

Auteur, année, référence	Patients (*n*)	Pathologies mono/assoc (%)	Pathogènes mono/assoc (%)	Dose de colisméthate et comparateurs	Durée (j)	Issue du traitement mono versus assoc
Conway et al., 1997 [121]	53	Poussées de bronchopneumopathie chez des patients atteints de mucoviscidose et colonisés par *P. aeruginosa*	*P. aeruginosa*	Colisitne 2 M UI/8 h en monothérapie ($n = 36$) vs Colistine 2 M UI/8 h avec un autre antibiotique sur antibiogramme (aztreonam, azlocillin, piperacillin, ceftazidime, imipinem, ou ciprofloxacin) ($n = 35$)	12	Amélioration et résolution clinique chez tous les patients. Normalisation CRP : 58,3 % vs 84,5 % ($p < 0,05$) Amélioration VEMS : 0,12 (−0,06 à 0,29) vs 0,6 (0,4 to 0,8) ($p < 0,01$) Amélioration signifiactive du poids en association : +1,52 kg ($p < 0,01$) NS en monotherapie +0,36 kg ($p = 0,16$)
Garnacho-Montero et al., 2003 [109]	35	PAVM	*A. baumanii*	Colistine 2,5—5,0 mg/kg/j en 3 injections ($n = 21$) vs Imipénème 2—3 g/j ($n = 14$)	14,7 ± 4,1 (10—21) vs 13,2 ± 4,2 (10—21)	Guérison clinique 57 % dans les deux groupes Mortalité : 61,9 % vs 64,2 % (NS) Mortalité attribuable PAVM : 38 % vs 35,7 % (NS)
Reina et al., 2005 [131]	185	PAVM (53 %/66 %)	*A. baumannii* (65 %/60 %) *P. aeruginosa* (35 %/53 %)	Colistine 5 mg/kg/j en 3 injections ($n = 55$) vs non-colistine ($n = 130$) carbapénèmes (81 %)	13 ± 5	Guerison clinique à j6 15 % vs 17 % (NS) mortalité 29 % vs 24 % (NS)
Falagas et al., 2006 [124]	71	Pneumonie (42,9 %/ 40,4 %), urinaire (28,6/ 5,3 %), intra-abdomniale (14,3 %/8,8 %), spondylodiscite (7,1 %/ 1,8 %), parties molles (0 %/ 5,3 %), bactériémie (7,1 %/ 28,1 %), cathéter (0 %/ 8,8 %), probabiliste (0 %/ 1,8 %)	*A. baumannii* (29 %/55 %), *P. aeruginosa* (53 %/27 %), *K. pneumoniae* (12 %/12 %), *S. maltophilia* (6 %/0 %), *E. cloacae* (0 %/1,7 %), *E. coli* (0 %/1,7 %)	Colistine 4,6 ± 2,3 M UI/j ($n = 14$) vs colistine 5,5 ± 2,2 M UI/ j + méropénème 4,8 ± 1,6 g/j ($n = 57$)	14,2 ± 7,3 vs 18	Guérison clinique 85,7,% vs 68,4 % ($p = 0,32$) Mortalité hospitalière 0 % vs 36,8 % ($p = 0,007$)
Kallel et al., 2007 [132]	120	PAVM appariées	*A. baumannii* (51,7 %/61,7 %) *P. aeruginosa* (41,4 %/38,3 %)	6 colistine 6 M UI en 3 injections ($n = 60$) vs imipénème 2 g/j en 4 injections ($n = 60$)	9,5 ± 3,8 (5—22) vs 8,9 ± 2,8 (5—20)	Guérison clinique 75 % vs 71,7 % ($p = 0,68$) Mortalité en réanimation 41,7 % vs 35 % ($p = 0,45$) et hospitalière 41,7 % vs 38,3 % ($p = 0,7$)

Kipnis Antibiotiques 2010

Colistine : études comparatives

Rios et al., 2007 [133]	61	PAVM	*A. baumannii* (56 %/44 %) *P. aeruginosa* (50 %/50 %)	Colistine 5 mg/kg/j ($n = 30$) vs imipénème 2 g/j ($n = 11$) ou méropénème 3 g/j ($n = 19$)	12,2 ± 5,8 vs 12,0 ± 6,2	Mortalité 36,6 % si antibiothérapie appropriée vs inappropriée 70,0 % ($p = 0,014$) et appropriée plus fréquente si carbapénèmes ($n = 20$) vs colistine ($n = 14$) (NS)
Trottier et al., 2007 [126]	271	LBA (72,3 %), bactériémie (16,2 %), culture de cathéter (6,3 %), urines (1,8 %), site opératoire (2,2 %) et abcès (1,1 %)	*A. baumanii*	Colistine 2 M UI/8 h (75,6 %) vs antibiotiques adaptés à l'antibiogramme	13 ± 8,9	Guérison clinique : 75,1 % vs 69,7 % (NS)
Koomanachai et al., 2007 [127]	93	Pneumonie (54 %/?), bactériemie (9 %/?), intra-abdomniale (5 %/?), urinaire (4 %/?), parties molles (5 %/?) et sinusite (1 %/?)	*A. baumanii* (91 %/81 %), *P. aeruginosa* (9 %/20 %)	Colistine 5 mg/kg/j en 2 injections ($n = 78$, 71 *A. baumannii* + 7 *P. aeruginosa*) vs antibiotiques adaptés à l'antibiogramme carbapénèmes (6), céfopérazone/sulbactam (3), céfopérazone/ sulbactam + netilmicine (4) et céfoperazone/ sulbactam + carbapénème (2) ($n = 15$ patients 12 *A. baumannii* + 3 *P. aeruginosa*)	11,9	Amélioration clinique : 80,8 % vs 26,7 % ($p < 0,001$) mortalité à 30 j : 46,2 % vs 80 % ($p = 0,03$) et eradication bactérienne 94,9 %) vs 0 % ($p < 0001$)
Hachem et al., 2007 [128]	95	Bactériémie (45 %/34 %), Pneumonie (55 %/47 %), urinaire (0 %/11 %), site opératoire (0 %/8 %)	*P. aeruginosa*	Colistine 5 mg/kg/j en 2 à 4 injections ($n = 31$) vs non-colistine ($n = 64$)	20 (5–58) vs 20 (3–120)	Amélioration clinique 52 % vs 31 ($p = 0,055$) Régression logistique multiple : amelioration clinique colistine vs autres = 2,9 (IC 95 % : 1,1 à 7,6) ($p = 0,026$)
Gounden et al., 2009 [111]	64	Bactériémie (31 %/31 %), ECBC/AET (78 %/88 %), écouvillon de plaie (18,8 %/34,4 %), LCR (3,1 %/0 %), cathéter (31 %/28 %), urines (15,6 %/12,5 %)	*A. baumannii*	Colistine 2 M UI/8 h ($n = 32$) vs tobramycine 5–6 mg/kg/j ($n = 32$)	8 (5–13) vs 7 (6–10)	Mortalité en reanimation 34,4 % vs 21,9 % ($p = 0,54$) Éradication bactérienne : 50 % vs 55 % ($p = 0,79$) Temps d'éradication j3 vs j4 ($p = 0,46$)

Colistine : études comparatives

Non-randomisée

Risk factor	HR (95% CI)[a] all patients, $n=495$	HR (95% CI)[a] bacteraemia, $n=220$
Colistin arm of the study	1.27 (1.01–1.60), $P=0.049$	1.65 (1.18–2.31), $P=0.004$
Age[b]	1.03 (1.02–1.04), $P<0.001$	1.02 (1.01–1.04), $P<0.001$
McCabe score		not significant
no fatal disease	0.53 (0.38–0.73), $P<0.001$	
ultimately fatal disease	0.65 (0.47–0.90), $P=0.001$	
rapidly fatal disease	reference	
Independent functional capacity on admission	0.80 (0.62–1.05), $P=0.104$	not significant
Hospitalization in medical ward at onset of infection	1.56 (1.19–2.05), $P=0.001$	2.37 (1.61–3.50), $P<0.001$
Mechanical ventilation at onset of infection	not significant	1.44 (0.95–2.18), $P=0.085$
Bacteraemia	1.37 (1.08–1.73), $P=0.008$	not relevant
SOFA score at onset of infection[b]	1.13 (1.09–1.18), $P<0.001$	1.12 (1.05–1.18), $P<0.001$
Albumin at onset of infection[b]	0.79 (0.62–0.99), $P=0.049$	not significant

Paul JAC 2010

Recommandations?

Organism	First-line therapy	Second-line therapy
Empirical therapy[b]		
Monomicrobial infection	Carbapenem	Piperacillin-tazobactam (low inoculum)
	Tigecycline (not in urinary tract infections) with or without an antipseudomonal agent	Colistin
Mixed gram-positive and gram-negative infection	Anti-MRSA agent plus a carbapenem	Anti-MRSA agent plus piperacillin-tazobactam (low inoculum)
	Tigecycline (not in urinary tract infections) with or without an antipseudomonal agent	Anti-MRSA agent plus colistin
Directed therapy[c]		
ESBL-producing Enterobacteriaceae	Carbapenems	Tigecycline (not in urinary tract infections)
	Piperacillin-tazobactam (low inoculum)	Fluoroquinolone
	Fosfomycin (oral formulation for simple urinary tract infections)	Colistin
Carbapenemase-producing Enterobacteriaceae	Tigecycline	Fosfomycin (parenteral formulation)
	Colistin	
Multidrug resistant *Pseudomonas aeruginosa*	Antipseudomonal agent (among carbapenems, use doripenem or meropenem)	Colistin
		Combination therapy

Kanj Mayo Clin Proc 2011

Recommandations?

Organism	Recommended therapy
Pseudomonas aeruginosa	Antipseudomonal β-lactam
ESBL-producing Enterobacteriaceae	Carbapenem
Ceftazidime resistant	
Enterobacter cloacae	Fluoroquinolone, carbapenem, or cefepime
Carbapenem resistant	
Acinetobacter baumannii	Colistin/polymyxin B, tigecycline, or ampicillin/sulbactam, depending on susceptibility and location of infection
Stenotrophomonas maltophilia	Trimethoprim/sulfamethoxazole plus ticarcillin/clavulanate

Paterson CID 2008

Conclusions

- En attendant
  - de vraies nouvelles molécules
  - Des vrais adjuvants non-antibiotiques

→ « vieilles » molécules/ nouveaux modes d'administration

→ Nouvelles techniques d'identification rapide

→ Nouveaux biomarqueurs et désescalade?

→ « préserver » les carbapénèmes

→ « explorer » de « nouvelles vieilles » molécules

- Fosfomycine?
- Cefoxitine?