Comment je traite les infections graves à BGN:

MONOTHERAPIE

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Associations d'antibiotiques: intuitivement tentantes….

Intérêts théoriques :

1. **Elargissement spectre** (probabiliste)

2. **Obtention d'une synergie améliorant le pronostic**

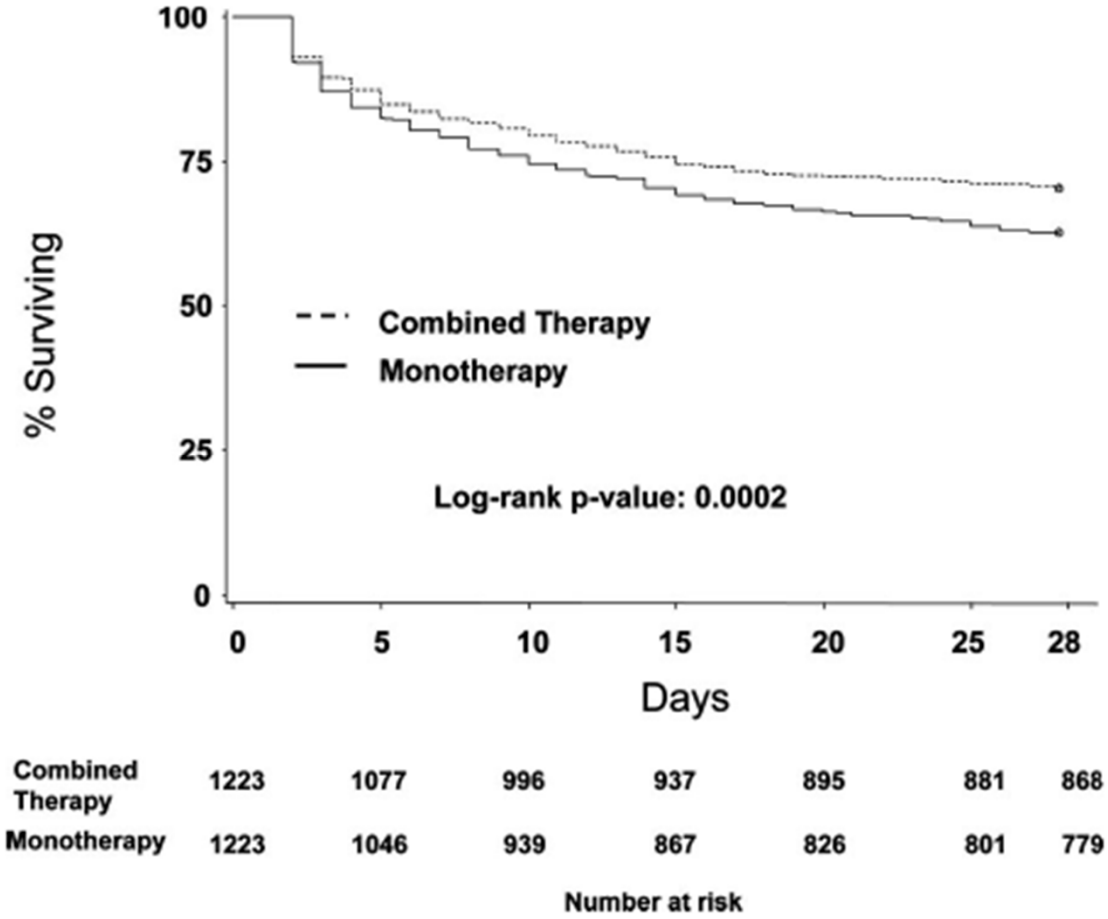
3. **Prévention émergence de mutants R**

Mais se méfier des dogmes….

1. Elargissement du spectre

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

Etude rétrospective, 1996-2007, Canada, USA, Arabie Saoudite



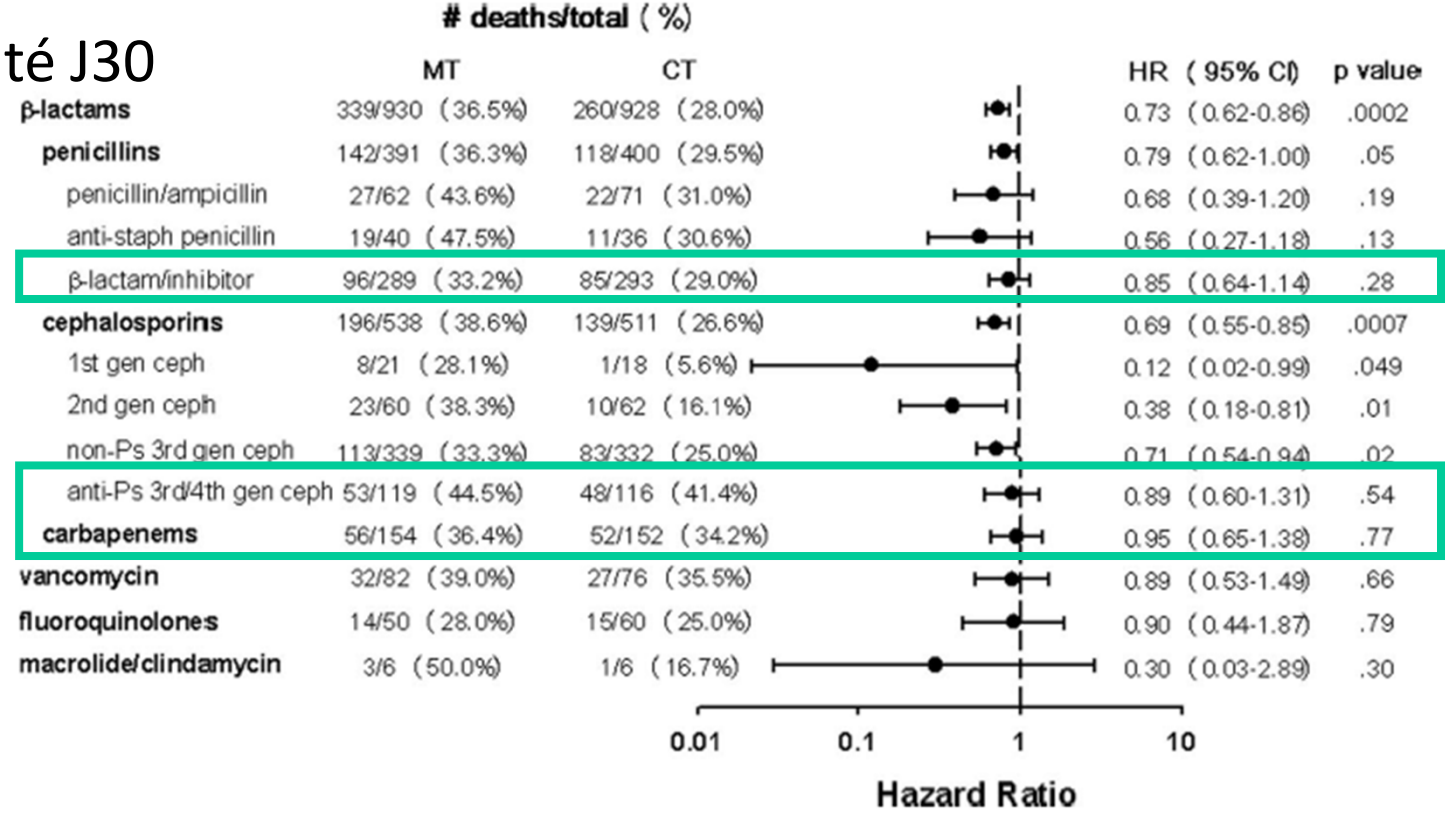
Kumar, Crit Care Med 2010

1. Elargissement du spectre

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

Etude rétrospective, 1996-2007, Canada, USA, Arabie Saoudite, 4662 patients

Mortalité J30



Kumar, Crit Care Med 2010

2. Obtention d'une synergie

Unpredictable Response of *Pseudomonas aeruginosa* to Synergistic Antibiotic Combinations In Vitro

HERBERT S. HEINEMAN* AND WENDELL M. LOFTON

AAC 1978,
méthode de l'échiquier

TABLE 1. *Patterns of ticarcillin-aminoglycoside synergism against 45 strains of P. aeruginosa*

No. of strains	Synergistic pairs[a]		
	TC-GM[b]	TC-TM	TC-AK
7	+	+	+
1	+	+	−
2	+	−	+
4	−	+	+
5	+	−	−
4	−	+	−
11	−	−	+
11	−	−	−

[a] + and −, Presence and absence, respectively, of synergism, defined as inhibition by a pair in which the concentration of each member is one-fourth or less of its MIC when tested alone.

[b] TC, Ticarcillin; GM, gentamicin; TM, tobramycin; AK, amikacin.

→ Souche-dépendante,
Antibiotique-dépendante

2. Obtention d'une synergie

In Vitro Activity of Ciprofloxacin in Combination with Ceftazidime, Aztreonam, and Azlocillin against Multiresistant Isolates of *Pseudomonas aeruginosa*

CARLOS I. BUSTAMANTE,[1,2]* RAYNER C. WHARTON,[2] AND JAMES C. WADE[1,2]

AAC 1990, échiquier

TABLE 2. Inhibitory activities of the ciprofloxacin–beta-lactam combinations

Beta-lactam in combination	No. of isolates for which combination was synergistic/no. evaluable (%)[a]			
	Susceptible to both	Ciprofloxacin resistant	Beta-lactam resistant	Resistant to both
Ceftazidime	15/90	2/4	9/12	1/2
Aztreonam	14/78	2/3	1/25	0/2
Azlocillin	14/83	2/3	1/19	1/3
Total	43/251 (17)	6/10 (60)	11/56 (20)	2/7 (29)

→ Imprévisible!

2. Obtention d'une synergie

Antibiotic Therapy for *Pseudomonas aeruginosa* Bacteremia: Outcome Correlations in a Prospective Study of 200 Patients

MEGAN HILF, M.S., VICTOR L. YU, M.D., JOANN SHARP, B.S., JEFFREY J. ZURAVLEFF, M.D., JOYCE A. KORVICK, M.D., ROBERT R. MUDER, M.D. *Pittsburgh, Pennsylvania*

TABLE I

Clinical Parameters and Outcome in 143 patients with Bacteremia Receiving Combination Therapy (Patients Receiving Monotherapy or No Antipseudomonal Agent Therapy Are Excluded from This Analysis)

Clinical Parameter	Number of Patients	Percent Mortality	p Value
Neutrophils <100/mL	26	31 (8/26)	NS (0.08)*
Neutrophils 100–3,000/mL	17	47 (8/17)	
Neutrophils >3,000/mL	100	22 (22/100)	
McCabe criteria [57]			
Non-fatal	63	21 (13/63)	NS*
Ultimately fatal	57	28 (16/57)	
Rapidly fatal	23	39 (9/23)	
Severity of illness			
Critical‡	37	47 (18/37)	0.001†
Noncritical	106	19 (20/106)	
Portal§			
Pneumonia	20	35 (7/20)	NS (0.09)*
Urinary tract	16	13 (2/16)	
Intravascular	7	43 (3/7)	
Other	100	26 (26/100)	

Echiquier et courbes de bactéricidie

TABLE II

Correlation of Results of *in Vitro* Synergy Testing with Outcome

	Percent Died	Percent Survived	p Value*
Checkerboard			
Synergistic†	3 (4/123)	11 (13/123)	NS
Nonsynergistic	24 (29/123)	63 (77/123)	
Kill curve			
Synergistic	12 (15/123)	46 (56/123)	NS (0.10)
Nonsynergistic	15 (18/123)	28 (34/123)	

Hilf, Am J Med 1989

3. Prévention de la résistance

Prospective Randomized Comparison of Imipenem Monotherapy with Imipenem plus Netilmicin for Treatment of Severe Infections in Nonneutropenic Patients† AAC 1994

A. COMETTA,[1]* J. D. BAUMGARTNER,[1] D. LEW,[2] W. ZIMMERLI,[3] D. PITTET,[2] P. CHOPART,[2] U. SCHAAD,[2] C. HERTER,[2] P. EGGIMANN,[1] O. HUBER,[2] B. RICOU,[2] P. SUTER,[2] R. AUCKENTHALER,[2] R. CHIOLERO,[1] J. BILLE,[1] C. SCHEIDEGGER,[3] R. FREI,[3] AND M. P. GLAUSER[1]

TABLE 1. Patient characteristics at randomization

Characteristic	Value for treatment group	
	Imipenem alone (n = 142)	Imipenem + netilmicin (n = 138)
Mean age ± SD (yr)	57.7 ± 17.7	54.0 ± 18.3
Mean wt ± SD (kg)	70.4 ± 13.5	68.4 ± 5.2
Mean APACHE II score ± SD (points)	9.8 ± 4.5	9.6 ± 5.2
No. of patients		
Male/female	103/39	99/39
In intensive care unit	99	105
In intensive care unit with mechanical ventilation	66	70
On antibiotics at randomization	79	87
With pneumonia (plus mechanical ventilation)	91 (48)	86 (49)
With peritonitis	39	39
With sepsis of other origin	12	13

Imipénème 500 mgx4/j

3. Prévention de la résistance

TABLE 2. Microbiological documentation of infections

Type of infection	No. of cases in treatment group	
	Imipenem alone	Imipenem + netilmicin
Pneumonia		
Microbiologically documented/total	46/91	50/86
Gram negative bacteria[a]	37	44
P. aeruginosa	17	17
Escherichia coli	8	10
Klebsiella sp.	10	7
Other	12	18
Gram positive bacteria	6	2
Mixed flora	3	4
Peritonitis[b]		
Escherichia coli	24	27
Enterococcus faecalis	15	8
P. aeruginosa	7	6
Other aerobes	23	19
Anaerobes	15	12
Bacteremia		
Total	13	12
Gram negative	8	10
Gram positive	5	2
From the following origin:		
Pulmonary	6	5
Abdominal	4	4
Urinary	1	1
Catheter	1	0
Unknown	1	2

TABLE 3. Response to the treatment

Characteristic	Value for group	
	Imipenem alone (n = 142)	Imipenem + netilmicin (n = 138)
No. of successes (% of total)	113 (80)	119 (86)
No. of failures	29	19
No. of deaths due to infection (%)	18 (13)	13 (9)
No. of failures due to:		
Lack of clinical improvement (development of resistant *P. aeruginosa*)	19 (5)	11 (7)
Development of sepsis syndrome or septic shock	7	3
Superinfection	3	5
No. of failures/total no. of cases		
Pneumonia (total)	16/91	14/86
Microbiologically documented pneumonia	10/45	8/50
Peritonitis	8/39	3/39[a]
Sepsis of other origin	5/12	2/13

[a] P = 0.09; all other P values were >0.10.

Cometta, AAC 1994

Développement de la résistance bactérienne

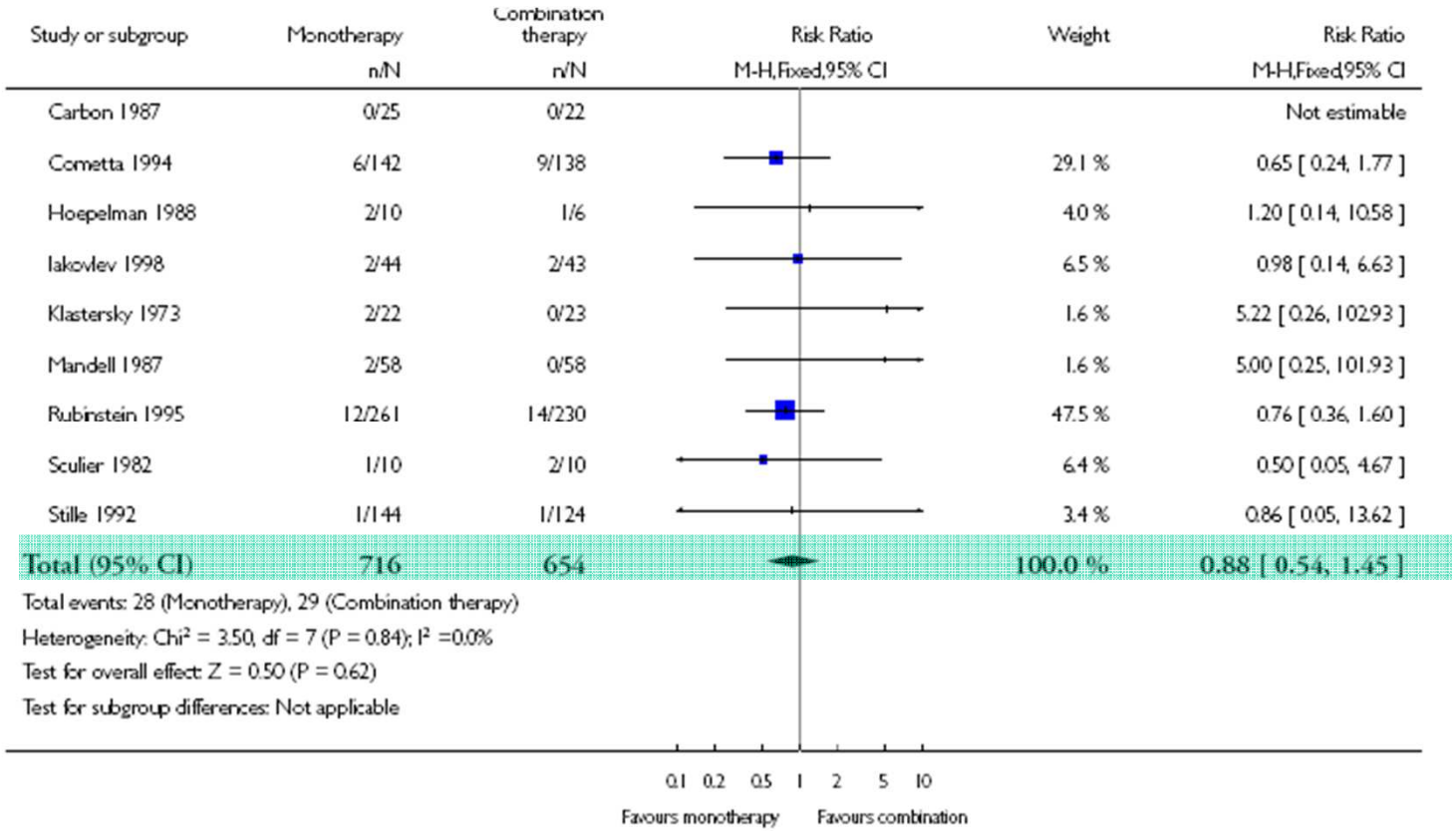
THE COCHRANE COLLABORATION®

Janvier 2014

Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis (Review)

Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L

Métaanalyse, 69 études randomisées, 7863 patients



Association d’antibiotiques versus monothérapie

Inconvénients théoriques :

- Plus d’effets secondaires ?
- Plus de pression de sélection: surinfections bactériennes et fongiques ?
- Coût ?
- Durées d’hospitalisation ?

Effets secondaires

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Métaanalyse, 69 études randomisées, 7863 patients

	RR [IC 90%] **BL vs BL + AG**
Néphrotoxicité	0,30 [0,23-0,39]
Néphrotoxicité Aminosides 1 inj/j	0,17 [0.06-0,53]

Surinfections/colonisation

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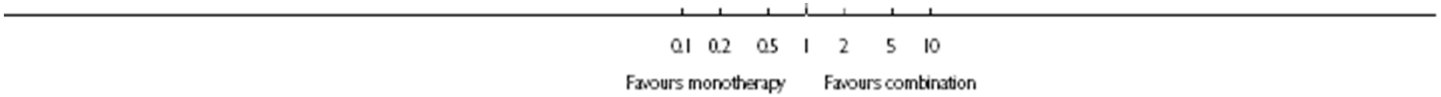
Study or subgroup	Monotherapy n/N	Combination therapy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Surinfections bactériennes					
Total (95% CI)	1595	1540		100.0 %	0.75 [0.57, 0.99]
Surinfections fongiques					
Total (95% CI)	561	558		100.0 %	0.79 [0.42, 1.48]
Colonisation bactérienne					
Total (95% CI)	824	811		100.0 %	0.85 [0.65, 1.10]



Efficacité: que disent les études???

- β-lactamines ± aminosides

- β-lactamines ± fluoroquinolones

- *Pseudomonas aeruginosa*

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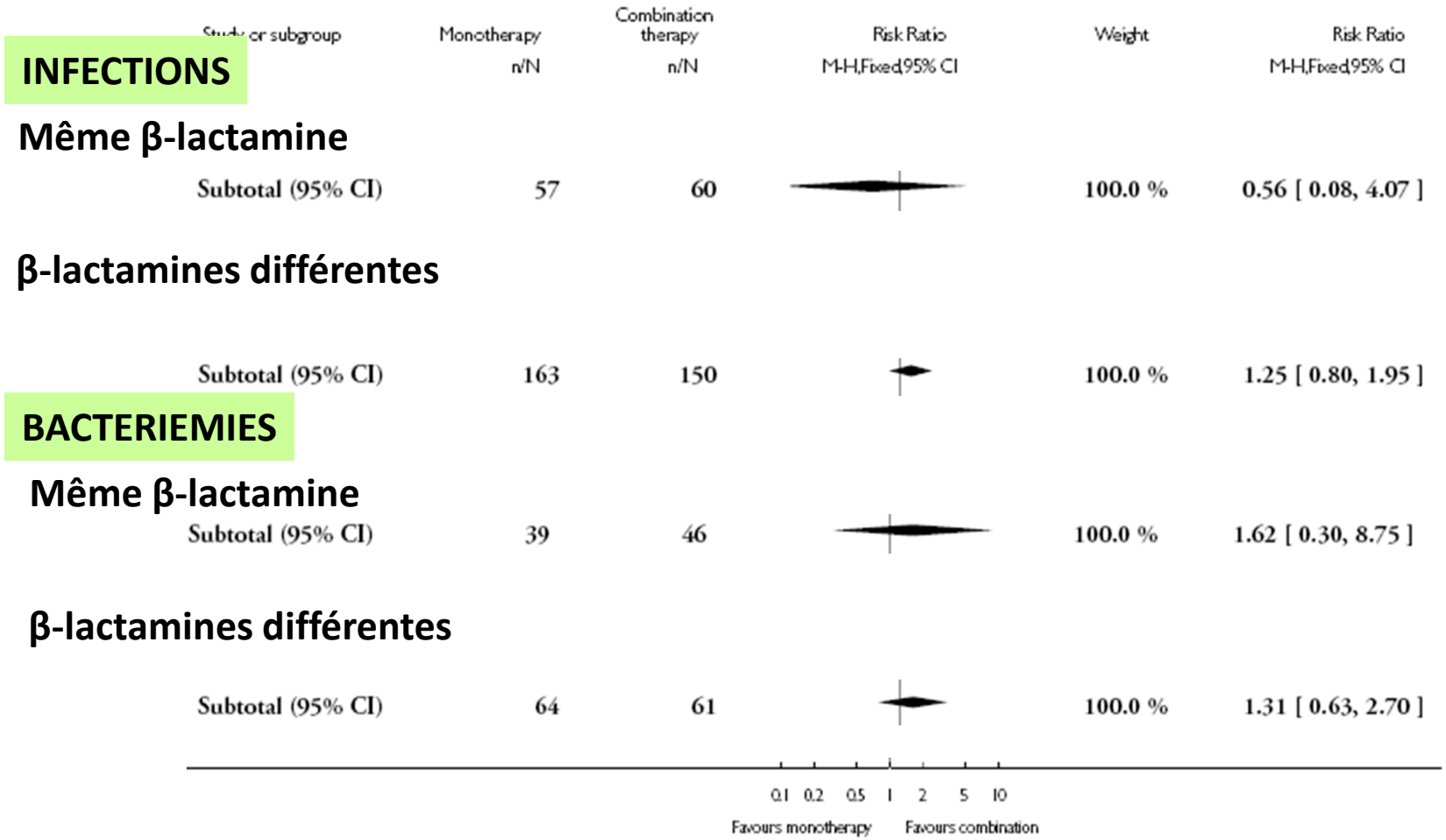
BL ± AG: MORTALITE sepsis à Gram neg



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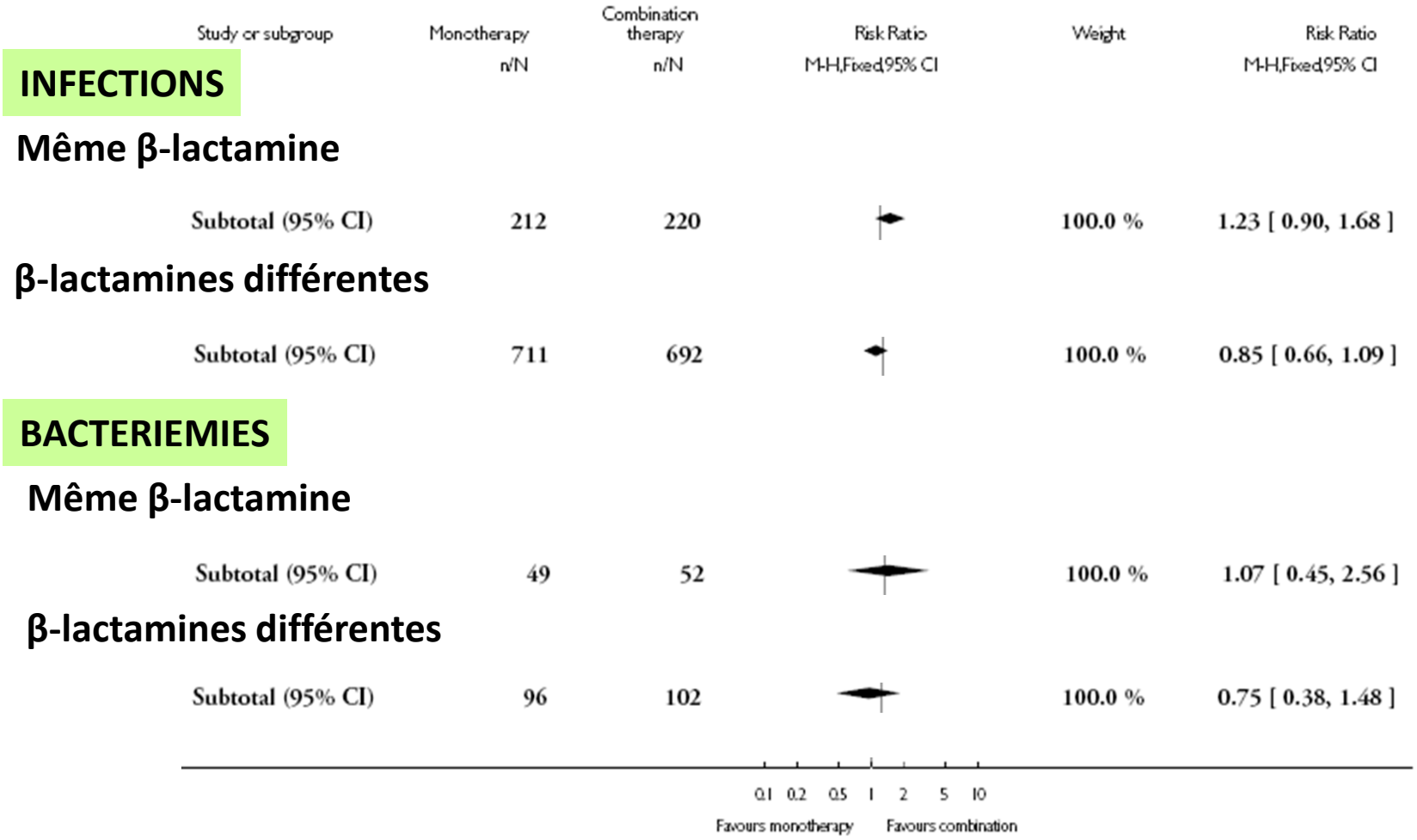
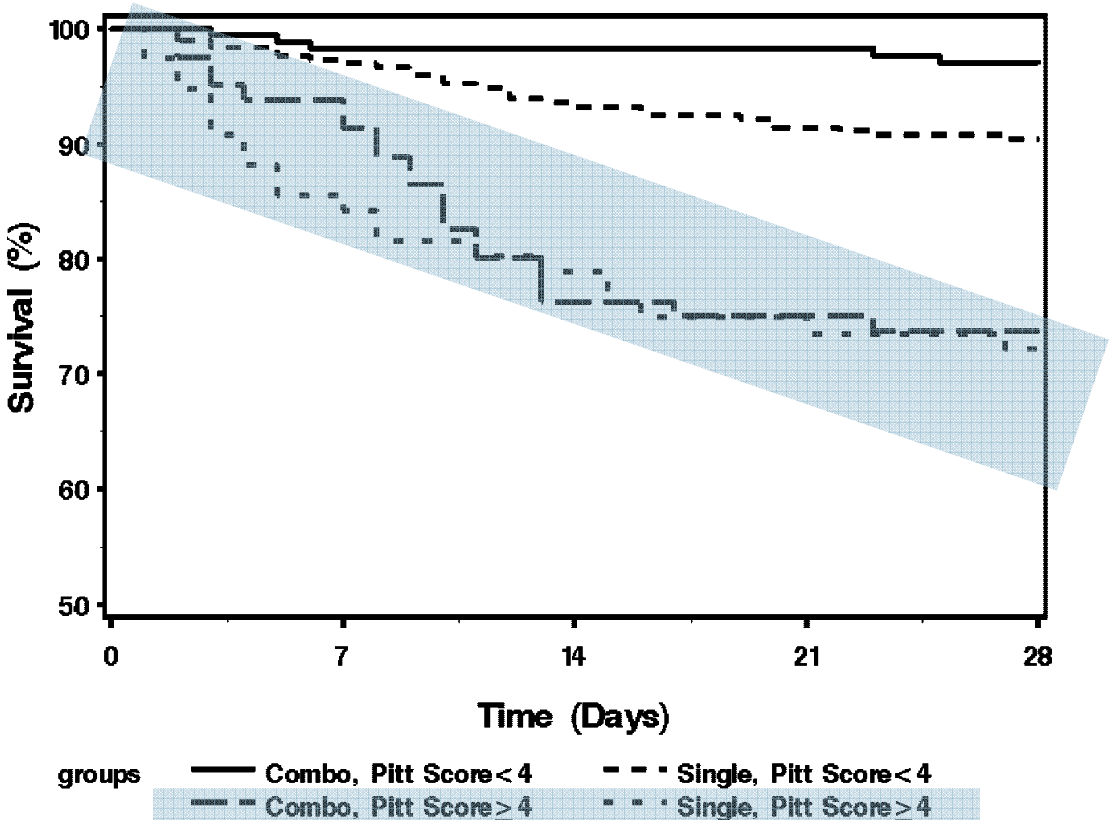
BL ± AG: ECHEC CLINIQUE sepsis à Gram neg



BL ± FQ: MORTALITE bactériémies à Gram neg

β-Lactam and Fluoroquinolone Combination Antibiotic Therapy for Bacteremia Caused by Gram-Negative Bacilli[▽]

Etude rétrospective, 702 bactériémies à BGN, traitement empirique
AB commencés <24h après résultats HC, poursuivis au moins 48h



Critère principal
Mortalité 28j:
Pas de bénéfice pour les patients les plus graves

Al-Hasan, AAC 2009

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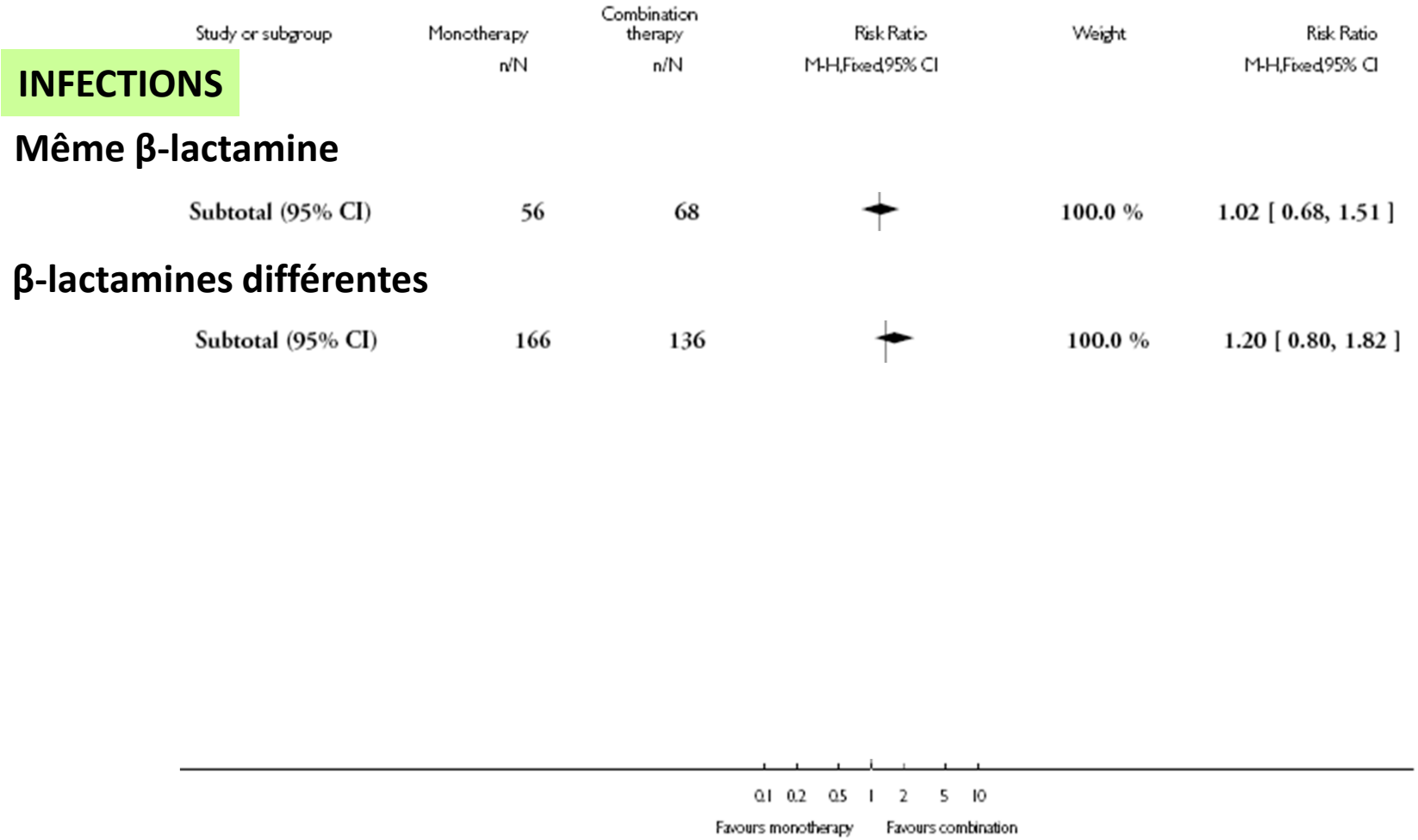
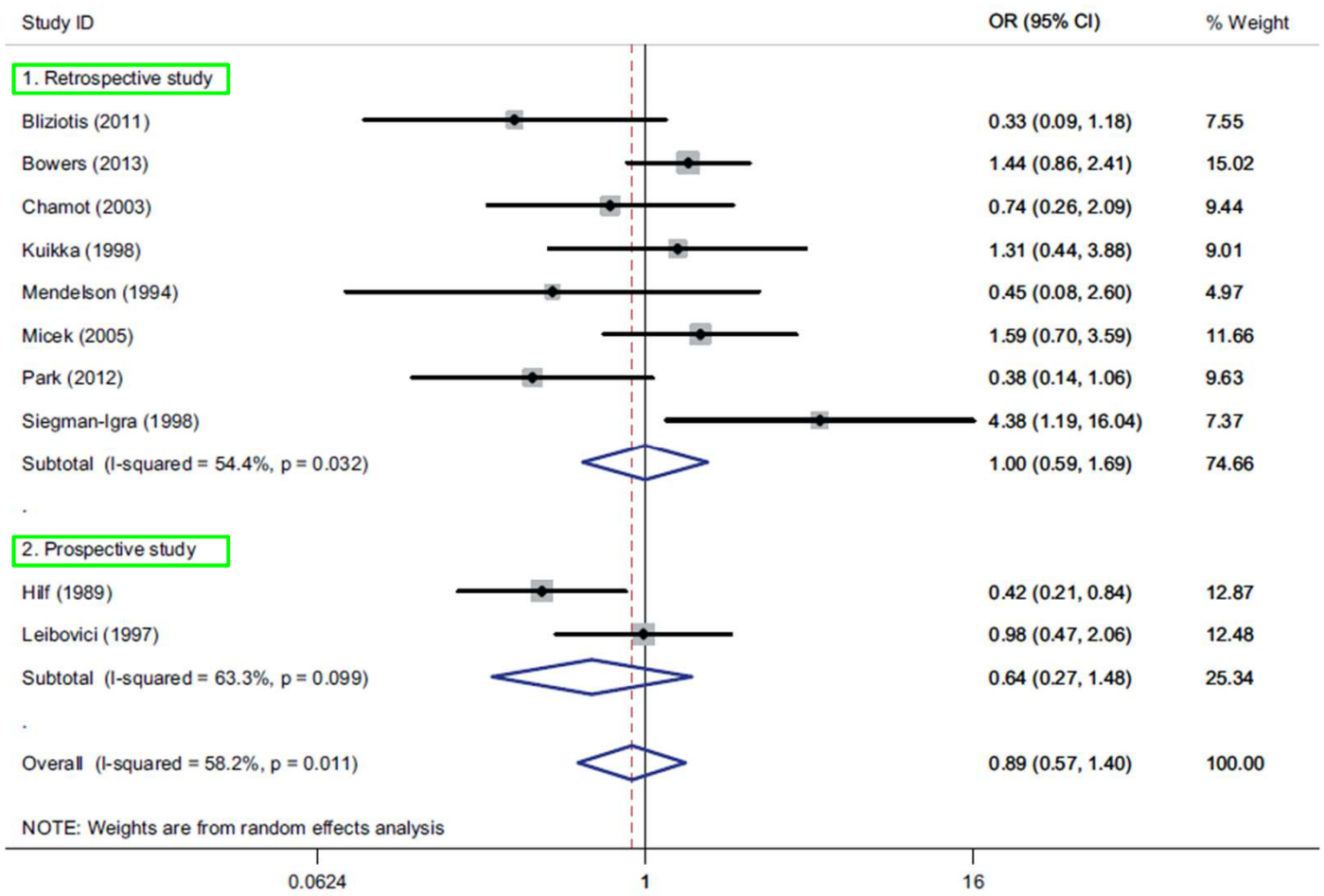
P. aeruginosa et BL ± AG: ECHEC CLINIQUE



P. aeruginosa et BL ± AG/FQ: ECHEC CLINIQUE

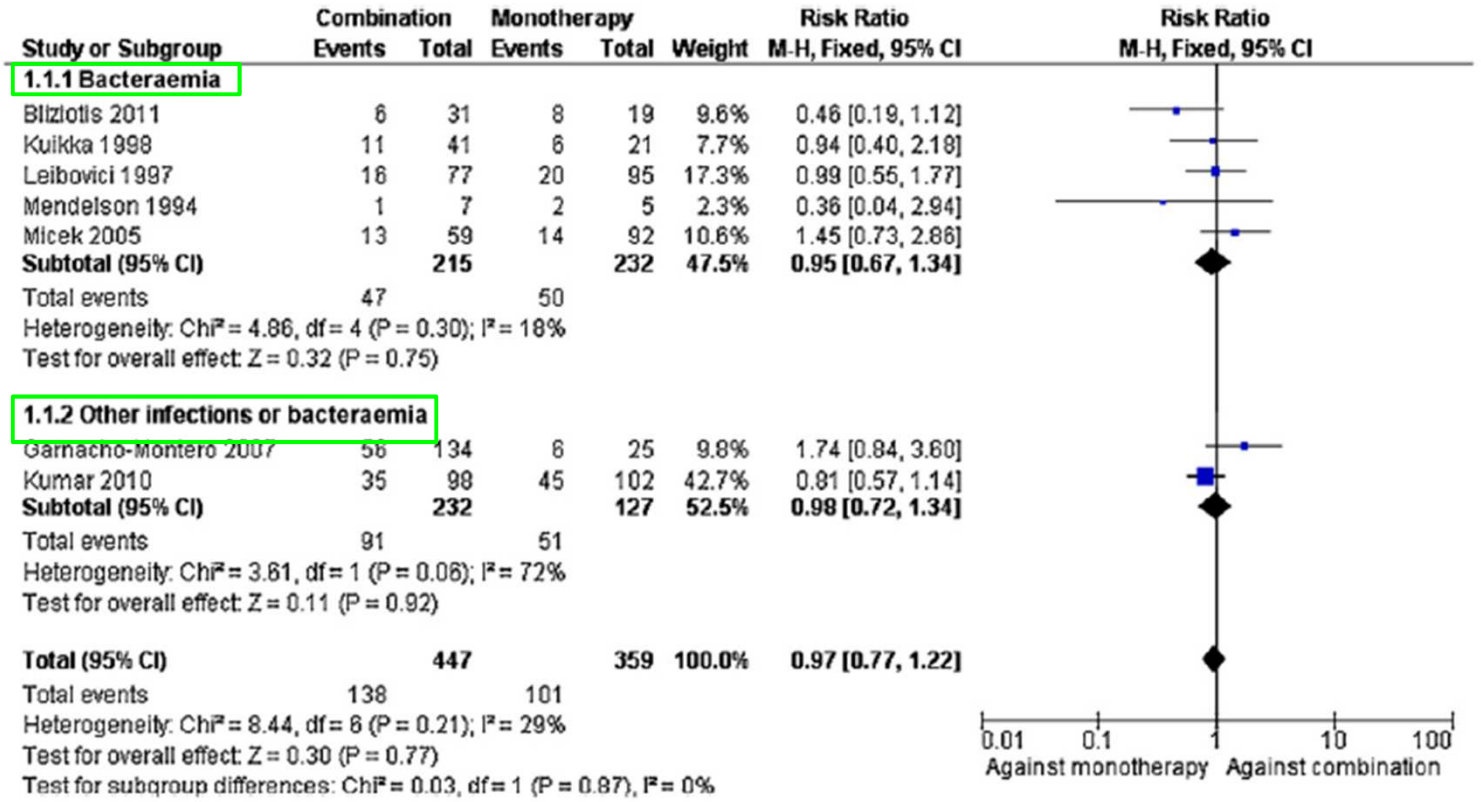
Métaanalyse, bactériémies:



Hu, IJAA 2013

P. aeruginosa et BL ± AG/FQ: ECHEC CLINIQUE

Métaanalyse, infections:



Vardakas, IJAA 2013

P. aeruginosa: PAVM, Outcomerea

Rétrospectif, 1997-2011, 12 réanimations françaises, 393 épisodes

Facteurs de risque d'échec:

Characteristics	Alive without Recurrence within 14 Days (*n* = *202*)	Treatment Failure within 14 Days (*n* = *112*)	Univariate *P* Value	Multivariate* SHR (95% CI)	Multivariate* *P* Value
Initial adequate treatment					
None	33 (16.3)	20 (17.9)	0.6	—	—
Monotherapy	55 (27.2)	35 (31.3)		—	
Bitherapy/tritherapy	114 (56.4)	57 (50.9)			

Facteurs associés à la sortie sans rechute à J14:

Characteristics	Dead or PA-VAP Recurrence or in ICU at Day 14 (*n* = *239*)	Discharged Alive without PA-VAP Recurrence within 14 Days (*n* = *75*)	Univariate *P* Value	Multivariate* SHR (95% CI)	Multivariate* *P* Value
Initial adequate treatment					
None	46 (19.2)	7 (9.3)	0.08	—	—
Monotherapy	62 (25.9)	28 (37.3)		—	
Bitherapy/tritherapy	131 (54.8)	40 (53.3)		—	

Planquette, Am J Respir Crit Care Med 2013

En faveur de la bithérapie: une étude beaucoup citée…

Etude prospective non randomisée, 200 patients, bactériémies à *Pseudomonas aeruginosa*

TABLE III

Mortality Rates for Patient Subgroups Receiving Combination Antibiotic Therapy and Monotherapy (For All Subgroups, Combination Therapy Was Superior to Monotherapy)

Patient Subgroup	Number of Patients	Percent Mortality Combination	Percent Mortality Single Agent	p Value*
All patients	186†	27 (38/143)	47 (20/43)	0.023
Nosocomial origin	143	32 (34/108)	51 (18/35)	0.04
Pneumonia	28	35 (7/20)	88(7/8)	0.033
Critically ill‡	49	47 (18/37)	92 (11/12)	0.016
Immunosuppressed	107	33 (28/86)	48 (10/21)	NS
Malignancy§	85	32 (21/66)	47 (9/19)	NS
Non-critically ill	137	19 (20/106)	29 (9/31)	NS
Neutropenia (<3,000/mL)	49	37 (16/43)	57 (4/7)	NS

NS = not significant.
* Fisher exact test (two-tailed).
† Fourteen patients received no antipseudomonal antibiotics (since therapy was often empiric prior to knowledge of *Pseudomonas* in the blood culture); all died.
‡ "Critically ill" was defined as mechanical ventilatory support, acute hypotensive episode, or coma.
§ Includes hematologic malignancies and solid tumors.

<u>Facteurs indépendants de survie à J10:</u>

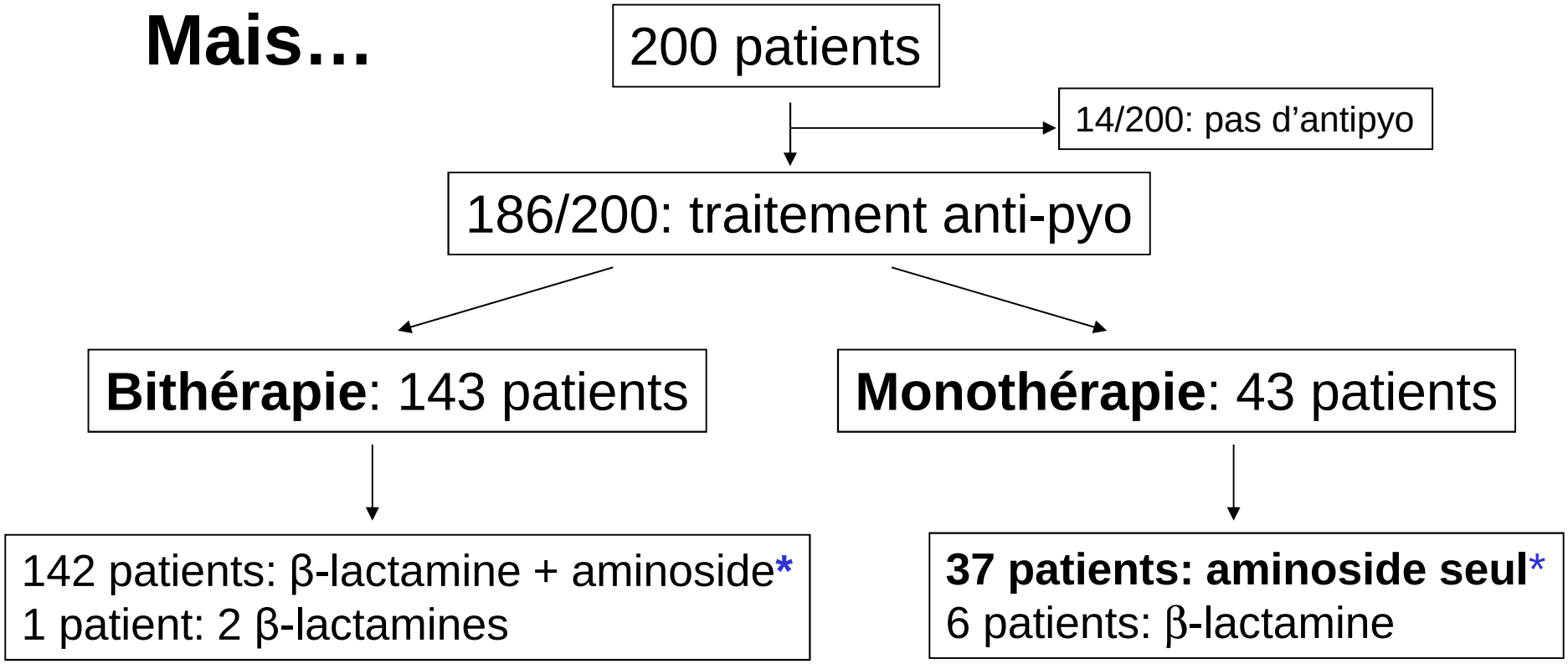
- Association d'antibiotiques
- Porte d'entrée urinaire
- Absence de neutropénie

Hilf, Am J Med 1989

En faveur de la bithérapie: une étude beaucoup citée…

Etude prospective non randomisée, 200 patients, bactériémies à *Pseudomonas aeruginosa*

Mais…



***pas de dosages**

Hilf, Am J Med 1989

Conclusion

BITHERAPIE:

- **Pas de bénéfice prouvé en terme d'efficacité**

- **Inconvénients démontrés:**

  toxicité majorée

  surinfections bactériennes

- **Réévaluation ++++ de l'antibiothérapie empirique**

➔ **dès que documentation disponible: MONOTHERAPIE**