Association d'antibiotiques en dehors des situations d'urgence

T Doco-Lecompte

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Les arguments pour une association

- **Synergie d'action** ⟶ **2 > 1**
- Augmenter la vitesse de bactéricidie ⟶ 2 + rapides que 1
- Eviter la sélection de mutants résistants ⟶ 2 moins sélectionnants que 1
- Elargir le spectre d 'activité ⟶ 2 pour 2 germes différents
- Réduire la dose de chacun des composants ⟶ $\frac{1}{2} + \frac{1}{2} = 1$

Mécanisme de synergie

- Action de 2 AB > somme des actions des 2 AB pris séparément
- 2 cibles différentes : ex : Blactamines + aminosides
- Synergie (ou antagonisme) *in vitro* ≠ synergie *in vivo* (paramètres pharmacocinétiques et pharmacodynamiques)
- Données expérimentales ++
- Données cliniques parfois contradictoires avec données *in vitro*

Exemples de synergie

Endocardites infectieuses à streptocoque

Antibiotiques	% rechutes
Pénicilline (14 jours)	15 %
Pénicilline (4 semaines)	0.6 %
Pénicilline + Strepto (2 semaines)	2 %
Pénicilline 4 sem. + Strepo 2 sem.	1 %

Exemples de synergie

Endocardites infectieuses à entérocoques

Synergie *in vitro* : Bétalactamine ou glycopeptide +aminoside

Expérimentation animale :

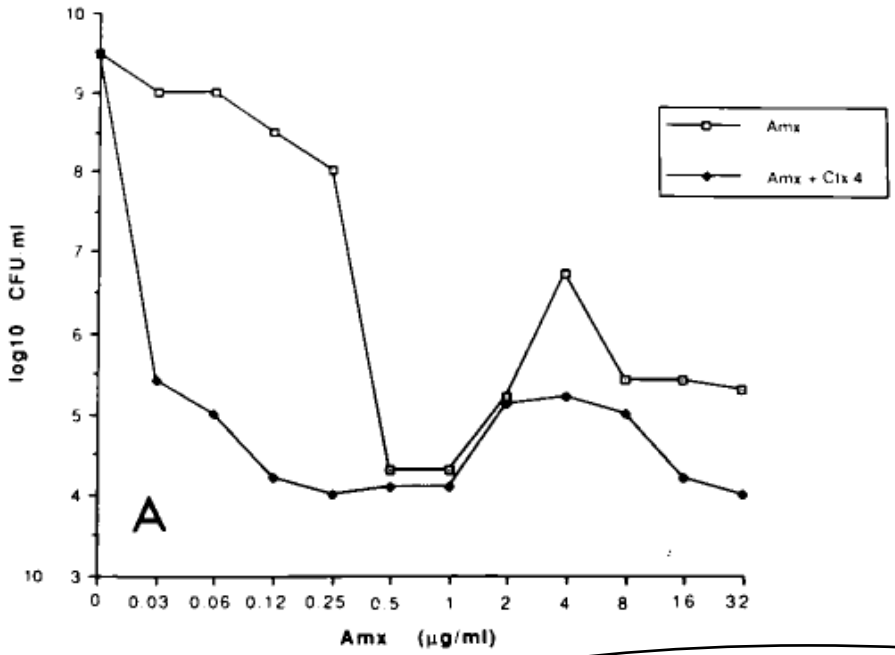
β lactamine < glycopeptide + aminoside

< β lactamine + aminoside

Clinique : Association impérative pendant tout le traitement (4-6 semaines) mais…

Olaison et al . CID. 2002 Enterococcal endocarditis in Sweden, 1995-1999: can shorter therapy with aminoglycosides be used?

Synergie in vitro de l'association amoxicilline + cefotaxime sur E faecalis : Mainardi et al AAC 1995



The synergy between amoxicillin and cefotaxime could be explained, at least for strain JH2-2, by the partial saturation of PBPs 4 and 5 by amoxicillin at 0.06 µg/ml combined with the total saturation of PBPs 2 and 3 by cefotaxime at 4 µg/ml. This would suggest that if PBPs 2 and 3 are not essential targets, they might participate in building the cell wall, particularly when the low-molecular-weight PBPs begin to be inactivated, which could be the case when the latter are partially saturated with amoxicillin.

Exemples de synergie

- Endocardites infectieuses à staphylocoque méticilline sensible

Synergie in vitro :

Méticilline + gentamicine > Méti

Clinique : Péni M + aminoside

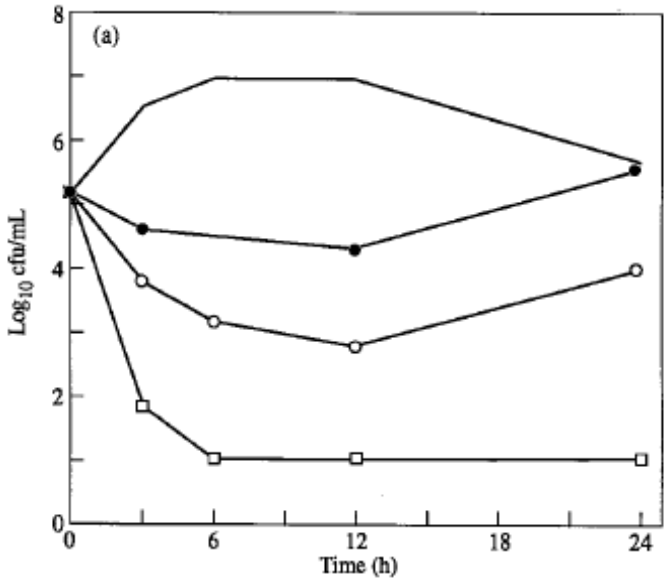


Figure 2. In-vitro kill-kinetic studies of strain 11724 for ceftriaxone (○), amoxycillin (●) and their combination (□) at (a) 0.5 × MIC and (b) 1 × MIC. ——, control with no drug.

Synergie in vitro de l'association amoxicilline + ceftriaxone sur PRP

P Chavanet, JAC. 1998

Synergie in vitro de l'association vancomycine + ceftriaxone sur PRP

N Desbiolles, AAC 2001

These difficulties in the interpretation of in-vitro observations justify the use of an in-vivo experimental study. Our in-vivo results were concordant with our in-vitro data. *In vivo*, the combination of amoxycillin with ceftriaxone was much more effective than either single drug alone. These effects have been observed with a range of local antibiotic concentrations achievable in humans.[30–43,45]

Exemples de synergie

- **Brucellose**

Antibiotiques	% rechutes
Cyclines	10 à 100 %
Tétracycline + streptomycine	1 à 10 %
Doxycycline + rifampicine	1 à 5 %

AB bactériostatique, émergence de résistance

Monothérapie

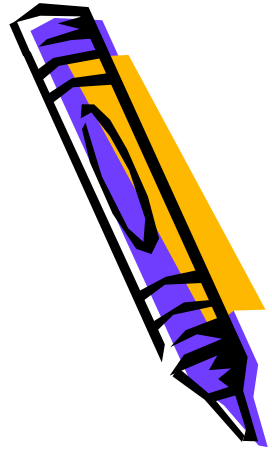
Ceftriaxone : échecs

Ciprofloxacine : résultats contradictoires

Nouveaux macrolides : plutôt non

Tigécyclines ?

Associations non conventionnelles



- Blactamines + Fluoroquinolones : pas de synergie in vivo, effet additif
- Glycopeptides + fluoroquinolones ?
- Fluoroquinolones + aminosides ?
- Glycopeptide +
  Dalfopristine/quinupristine ?
  Daptomycine ?

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In Vitro Bactericidal Activities of Linezolid in Combination with Vancomycin, Gentamicin, Ciprofloxacin, Fusidic Acid, and Rifampin against *Staphylococcus aureus*

Patrick Grohs,[1] Marie-Dominique Kitzis,[2] and Laurent Gutmann[1,3]*

Hôpital Européen Georges Pompidou,[1] Hôpital Saint Joseph,[2] and Laboratoire de Recherche Moléculaire sur les Antibiotiques, Université Paris VI,[3] Paris, France

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The in vitro activities of linezolid were determined alone and in combination with vancomycin, ciprofloxacin, gentamicin, fusidic acid, or rifampin against five methicillin-susceptible *Staphylococcus aureus* (MSSA) and five methicillin-resistant *S. aureus* (MRSA) strains. Similar responses were obtained against MSSA and MRSA. When combined with fusidic acid, gentamicin, or rifampin, linezolid prevented selection of resistant mutants but showed no synergy. When linezolid was combined with vancomycin and ciprofloxacin, a slight antagonism was observed. While the combination with linezolid may reduce the emergence of mutants resistant to the associated drugs, the absence of synergy, especially in the case of vancomycin and ciprofloxacin, does not argue in favor of such combinations.

Les arguments pour une association

Synergie d 'action

Augmenter la vitesse de bactéricidie

Eviter la sélection de mutants résistants

Elargir le spectre d 'activité

Réduire la dose de chacun des composants

Antibiotiques « rapides » : aminosides, rifampicine, fluoroquinolones

Antibiotiques « lents » : glycopeptides

Antibiotiques « moyens » : β lactamines

Deux « rapides » associés ne s 'accélèrent pas

La vitesse est donnée par le plus rapide des deux.

Augmenter la vitesse de bactéricidie

- **Staphylocoque Méticilline S**
  - In vitro : βlactamine + aminoside plus rapide que monothérapie
  - Clinique : pas de démonstration

Endocardites infectieuses à staphylocoque méticilline sensible

Synergie in vitro :

Méticilline + gentamicine > Méti

Clinique : Péni M + aminoside 5j puis Péni M seule (valve native)

Staphylocoque méti R

- Vancomycine = lent
- + aminoside ou + rifadine

mais

- émergence de résistants à la rifadine
- arguments supplémentaire pour faire triple antibiothérapie dans états infectieux graves (glycopeptides +aminosides +rifampicine)

O. Ju . et al Eur J Clin Microbiol Infect Dis 2006

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Exemples de sélection de mutants

Mycobacterium tuberculosis

Résistance primaire

Résistance secondaire :

Rifampicine : $1/10^8$

INH et streptomycine : $1/10^5$

Ethambutol : $1/10^3$

	MutiR	INH	Strepto	Rifamp	ETB
Iaire	1,1%	5,5 %	4,6 %	1,2 %	0,7 %
IIaire	7,1%	14,3 %	14,3 %	8 %	2,7 %

Exemples de sélection de mutants

Staphylococcus aureus

Rifampicine : $1/10^8$
Fluoroquinolones : $1/10^6$
Acide fucidique : $1/10^7$ - $1/10^8$
Fosfomycine
Dicloxacilline
Vancomycine

Influence of previous exposure to antibiotic therapy on the susceptibility pattern of Pseudomonas aeruginosa bacteremic isolates.

Al Amari EB et al CID 2001, 33

- Etude cas contôle : 267 bactériémies à P aeruginosa
  - Cas = bactériémie à germes R à au moins un anti pyo
  - Contrôles = bactériémie à germes S aux antipyo

Analyse univariée : patients exposés à un antipyo + à risque d'avoir une bactériémie à pyo R que patients non exposés

Characteristic	Total no. (%)	Resistance to antipseudomonal agents: ⩾1 resistance (cases; *n* = 81)	Resistance to antipseudomonal agents: No resistance (controls; *n* = 186)	OR (95% CI)	*P*
Previous antipseudomonal therapy[a]					
No	201 (75.3)	55	146	—	—
Yes	64 (24.0)	26	38	1.8 (0.96–3.4)	.09
Monotherapy	54 (20.2)	22	32	1.8 (0.92–3.6)	.07
Combination therapy[b]	10 (3.7)	4	6	1.8 (0.35–7.8)	.47

Influence of previous exposure to antibiotic therapy on the susceptibility pattern of Pseudomonas aeruginosa bacteremic isolates.

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Risque selon l'antibiotique

Antipseudomonal agent, included in previous therapy	Resistance of the bacteremic strain to this agent		OR (95% CI)	*P*
	Yes (cases)	No (controls)		
Ceftazidime				
Yes	3	5	—	
No	13	246	11.4 (1.6–64.7)	.008
Piperacillin[a]				
Yes	3	6	—	
No	26	231	4.4 (0.67–22.1)	.06
Imipenem[a]				
Yes	11	25	—	
No	30	186	2.7 (1.1–6.5)	.02
Ciprofloxacin				
Yes	0	9	—	
No	15	243	0.0 (0.0–9.1)	1.0
Aminoglycoside				
Yes	6	26	—	
No	37	198	1.2 (0.39–3.4)	.61

[a] One isolate was not tested against piperacillin, and 15 were not tested against imipenem.

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

Analyse multivariée : monothérapie antérieure par antipyo associée à risque de R à ce même AB alors que ce risque n'est pas augmenté avec une association

AAC 2003, 47 : 2756

Effectiveness of Combination Antimicrobial Therapy for *Pseudomonas aeruginosa* Bacteremia

Eric Chamot,[1]† Emmanuelle Boffi El Amari,[2] Peter Rohner,[3] and Christian Van Delden[4]*

TABLE 4. Baseline characteristics of study subjects in relation to categories of definitive antipseudomonal therapy and summary of univariate survival analysis from receipt of the antibiogram to end of follow-up for 98 patients[a]

Characteristic	% of episodes with:			No. who died/total no. (Kaplan-Meier %)[b]	Univariate HR (95% CI)	*P* value
	Adequate combination therapy (n = 46)	Adequate monotherapy (n = 33)	Inadequate therapy (n = 19)			
All patients	100.0	100.0	100.0	29/98 (32.4)		
Empirical antimicrobial therapy						
Adequate combination therapy	58.7	12.1	26.3	5/36 (16.0)	1.0 (referent)	
Adequate monotherapy	30.4	81.8	42.1	15/49 (33.9)	2.5 (0.88–6.9)	0.09
Inadequate therapy	10.9	6.1	31.6	9/13 (71.2)	6.8 (2.3–20.3)	0.001
Adequate monotherapy or inadequate therapy	41.3	87.9	73.7	24/62 (42.1)	3.2 (1.2–8.4)	0.02
Definitive antimicrobial therapy						
Adequate combination therapy	100.0	0.0	0.0	10/46 (21.7)	1.0 (referent)	
Adequate monotherapy	0.0	100.0	0.0	9/33 (32.5)	1.2 (0.50–2.9)	0.68
Inadequate therapy	0.0	0.0	100.0	10/19 (57.9)	3.6 (1.4–8.9)	0.006
Adequate monotherapy or inadequate therapy	0.0	100.0	100.0	19/52 (42.2)	1.8 (0.86–4.0)	0.12

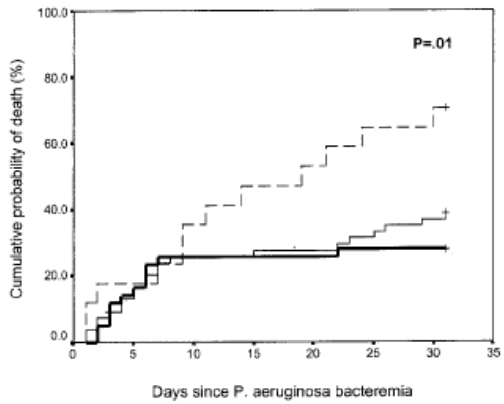

FIG. 1. Cumulative risk of death for patients who received adequate empirical combination therapy (bold solid line), adequate empirical monotherapy (narrow solid line), and inadequate empirical therapy (broken line).

We suggest that clinicians who suspect *P. aeruginosa* bacteremia initiate empirical therapy with two antipseudomonal agents. In the case of proven *P. aeruginosa* bacteremia, this combination therapy could be changed to monotherapy on the basis of the specific susceptibility pattern of the initial isolate.

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Elargir le spectre : exemples

Infections génito-pelviennes

Bactériologie « large » : Intracellulaires, entérocoques, BGN, anaérobies

› Recommandations :

βlactamine + cycline ou fluoroquinolone

Elargir le spectre : exemples

Fièvre chez le neutropénique

- Staphylocoque, BGN, streptocoque
- Recommandations :

  blactamine + aminoside ou fluoroquinolone
- En cas d 'échec :

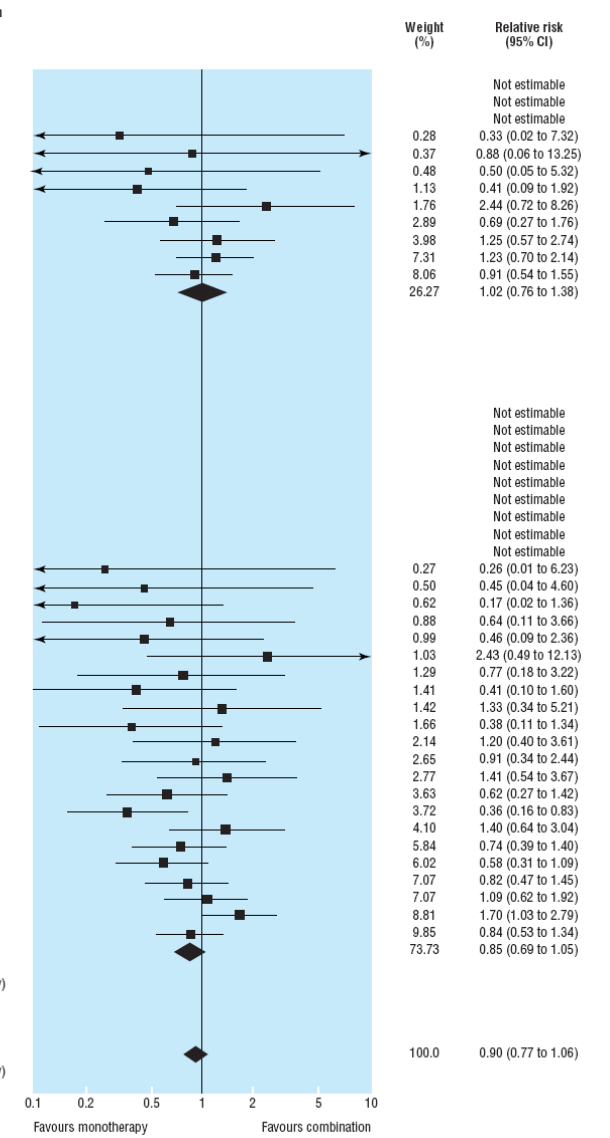
  + glycopeptides
  + antifongiques

Les associations AB sont elles indispensables?

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 2004



Study or subcategory	Monotherapy No/Total	Combination therapy No/Total	Weight (%)	Relative risk (95% CI)
01 Same β lactam				
Abrams 1979	0/12	0/12		Not estimable
Cardozo 2001	0/56	0/48		Not estimable
Sandberg 1997	0/37	0/36		Not estimable
Sculler 1982	0/10	1/10	0.28	0.33 (0.02 to 7.32)
Carbon 1987	1/25	1/22	0.37	0.88 (0.06 to 13.25)
Ribera 1996	1/45	2/45	0.48	0.50 (0.05 to 5.32)
Korzeniowski 1982	2/33	6/41	1.13	0.41 (0.09 to 1.92)
Klastersky 1973	7/22	3/23	1.76	2.44 (0.72 to 8.26)
D'Antonio 1992	7/144	10/142	2.89	0.69 (0.27 to 1.76)
Kljucar 1990	11/49	9/50	3.98	1.25 (0.57 to 2.74)
Cometta 1994	24/148	19/144	7.31	1.23 (0.70 to 2.14)
Dupont 2000	21/111	24/116	8.06	0.91 (0.54 to 1.55)
Subtotal (95% CI)	692	689	26.27	1.02 (0.76 to 1.38)
Total events: 74 (monotherapy), 75 (combination therapy)				
Test for heterogeneity: χ^2=5.68, df=8, P=0.68, I^2=0%				
Test for overall effect: z=0.14, P=0.89				
02 Different β lactam				
Duff 1982	0/31	0/43		Not estimable
Havig 1973	0/24	0/26		Not estimable
Naime Libien 1992	0/15	0/15		Not estimable
Rasmussen 1986	0/29	0/30		Not estimable
Thompson 1993	0/80	0/40		Not estimable
Trujillo 1992	0/16	0/14		Not estimable
Wiecek 1986	0/10	0/10		Not estimable
Wing 1998	0/117	0/62		Not estimable
Yellin 1993	0/56	0/34		Not estimable
Bergeron 1988	0/37	1/29	0.27	0.26 (0.01 to 6.23)
Cone 1985	1/21	2/19	0.50	0.45 (0.04 to 4.60)
Speich 1998	1/44	6/45	0.62	0.17 (0.02 to 1.36)
Thompson 1990	2/49	3/47	0.88	0.64 (0.11 to 3.66)
Hoepelman 1988	2/45	4/41	0.99	0.46 (0.09 to 2.36)
Koehler 1990	5/73	2/71	1.03	2.43 (0.49 to 12.13)
Jaspers 1998	3/39	4/40	1.29	0.77 (0.18 to 3.22)
Stille 1992	3/186	6/151	1.41	0.41 (0.10 to 1.60)
Landau 1990	4/20	3/20	1.42	1.33 (0.34 to 5.21)
Warren 1983	3/56	9/64	1.66	0.38 (0.11 to 1.34)
Gomez 1990	6/39	5/39	2.14	1.20 (0.40 to 3.61)
Mouton 1995	7/116	8/121	2.65	0.91 (0.34 to 2.44)
Arich 1987	8/25	5/22	2.77	1.41 (0.54 to 3.67)
Felisart 1985	7/37	11/36	3.63	0.62 (0.27 to 1.42)
Smith 1984	7/94	19/93	3.72	0.36 (0.16 to 0.83)
McCormick 1997	13/65	9/63	4.10	1.40 (0.64 to 3.04)
Mouton 1990	14/105	19/106	5.84	0.74 (0.39 to 1.40)
Sieger 1997	13/104	23/107	6.02	0.58 (0.31 to 1.09)
Alvarez Lerma 2001	16/69	20/71	7.07	0.82 (0.47 to 1.45)
Brown 1984	11/18	9/16	7.07	1.09 (0.62 to 1.92)
Finer 1992	40/249	21/222	8.81	1.70 (1.03 to 2.79)
Rubinstein 1995	31/306	33/274	9.85	0.84 (0.53 to 1.34)
Subtotal (95% CI)	2175	1971	73.73	0.85 (0.69 to 1.05)
Total events: 197 (monotherapy), 222 (combination therapy)				
Test for heterogeneity: χ^2=26.06, df=21, P=0.20, I^2=19.4%				
Test for overall effect: z=1.48, P=0.14				
Total (95% CI)	2867	2660	100.0	0.90 (0.77 to 1.06)
Total events: 271 (monotherapy), 297 (combination therapy)				
Test for heterogeneity: χ^2=32.50, df=30, P=0.34, I^2=7.7%				
Test for overall effect: z=1.22, P=0.22				

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 risl (95% confidence intervals), random effect model. Studies ordered by weight

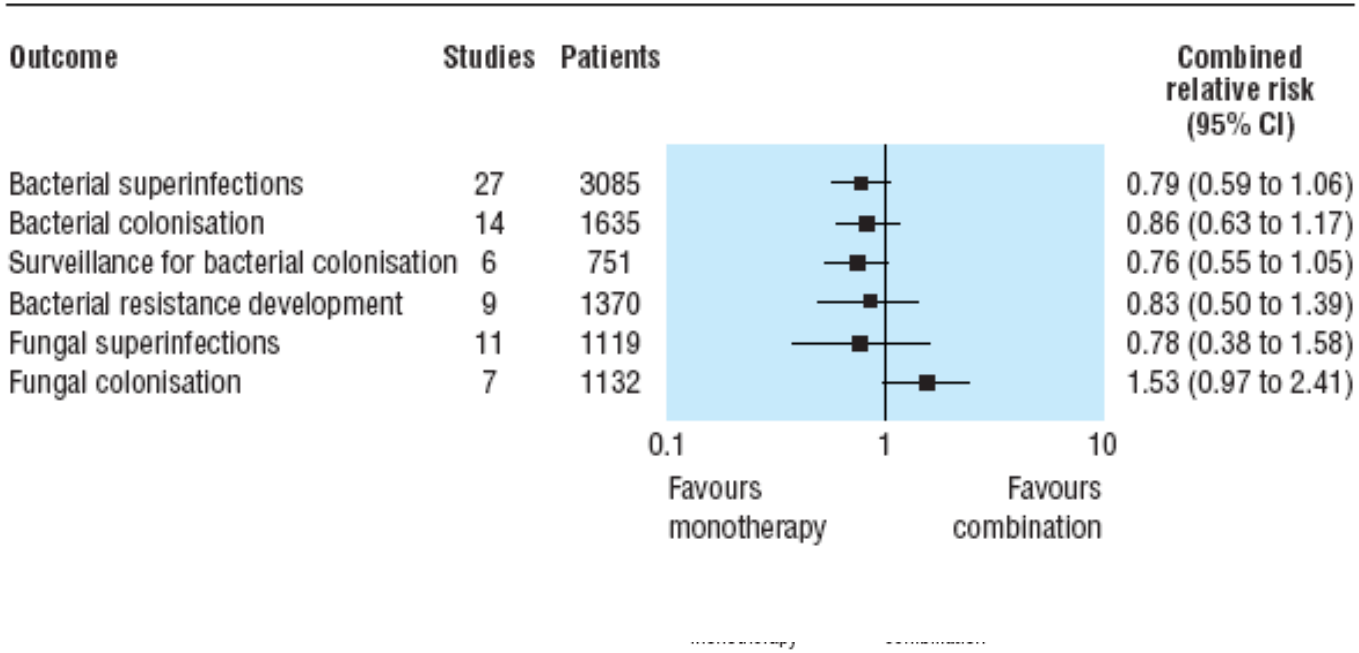


Fig 5 Summary relative risks for outcome relating to resistance development in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

β lactam monotherapy versus β lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis

BMJ VOLUME 326 24 MAY 2003

Mical Paul, Karla Soares-Weiser, Leonard Leibovici

What is already known on this topic

Cancer patients with neutropenia and fever can be treated with a single broad spectrum β lactam antibiotic or with a combination of a β lactam and an aminoglycoside

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Many randomised trials have compared monotherapy with combination therapy for these patients, but no consensus has been reached regarding the superiority of one regimen over the other

What this study adds

There is no survival advantage with combination therapy

Broad spectrum β lactam monotherapy is more successful than a narrower spectrum β lactam agent combined with an aminoglycoside

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Combination therapy is associated with a significantly higher rate of adverse events, mainly nephrotoxicity