

Papers

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

Abstract

Objective To compare β lactam monotherapy with β lactam-aminoglycoside combination therapy for severe infections.

Data sources Medline, Embase, Lilacs, Cochrane Library, and conference proceedings, to 2003; references of included studies; contact with all authors. No restrictions, such as language, year of publication, or publication status.

Study selection All randomised trials of β lactam monotherapy compared with β lactam-aminoglycoside combination therapy for patients without neutropenia who fulfilled criteria for sepsis.

Data selection Two reviewers independently applied selection criteria, performed quality assessment, and extracted the data. The primary outcome assessed was all cause fatality by intention to treat. Relative risks were pooled with the random effect model (relative risk < 1 favours monotherapy).

Results 64 trials with 7586 patients were included. There was no difference in all cause fatality (relative risk 0.90, 95% confidence interval 0.77 to 1.06). 12 studies compared the same β lactam (1.02, 0.76 to 1.38), and 31 studies compared different β lactams (0.85, 0.69 to 1.05). Clinical failure was more common with combination treatment overall (0.87, 0.78 to 0.97) and among studies comparing different β lactams (0.76, 0.68 to 0.86). There was no advantage to combination therapy among patients with Gram negative infections (1835 patients) or *Pseudomonas aeruginosa* infections (426 patients). There was no difference in the rate of development of resistance. Nephrotoxicity was significantly more common with combination therapy (0.36, 0.28 to 0.47). Heterogeneity was not significant for these comparisons.

Conclusions In the treatment of sepsis the addition of an aminoglycoside to β lactams should be discouraged. Fatality remains unchanged, while the risk for adverse events is increased.

Introduction

Treatment with a combination of β lactam and an aminoglycoside is purported to be superior to β lactam monotherapy for sepsis on the basis of potential advantages such as in vitro synergism and prevention of development of resistance.¹⁻⁷ Textbooks and guidelines advise the combination for specific pathogens, such as *Pseudomonas aeruginosa* and other Gram negative bacteria, and for infections commonly caused by these pathogens.^{8,9} In aiming for optimal antibiotic treatment of severe infections, hospital clinicians tend to use combination therapy despite the lack

of direct evidence for its effectiveness. Observational studies show that 25-30% of patients with bacteraemia,^{10,11} surgical infections,¹² or pneumonia,^{13,14} 50% of those with klebsiella bacteraemia,¹⁵ and 56% of patients with septic shock in the intensive care unit¹⁶ are given β lactam-aminoglycoside combination therapy.

We performed a systematic review and meta-analysis of randomised trials comparing β lactam-aminoglycoside combination therapy with β lactam monotherapy for severe infections in patients without neutropenia.

Methods

We searched Medline, Embase, Lilacs, the Cochrane Library (all up to March 2003), conference proceedings of the Interscience Conference on Antimicrobial Agents and Chemotherapy (1995-2002), and citations of included trials with the terms: (aminoglycoside* OR specific aminoglycosides) AND ((infect* OR sepsis OR bacter* OR septicemia OR specific infections/pathogens) OR combi*). We included studies regardless of date, language, or publication status, and we contacted authors for complementary information.

We included all randomised and quasi-randomised trials that compared any β lactam monotherapy with any combination of a β lactam and an aminoglycoside for severe infections. Severe infection was defined as clinical evidence of infection, plus evidence of a systemic response to infection.¹⁷ We excluded studies with a dropout rate above 30%, unless intention to treat analysis was given for mortality or failure outcomes, and studies with more than 15% of patients with neutropenia, neonates, and preterm babies.

The primary outcome assessed was all cause fatality by the end of study follow up and up to 30 days. Secondary outcomes included treatment failure, defined as death, non-resolving primary infection, any modification to allocated antibiotics, or any therapeutic invasive intervention not defined by protocol; bacteriological failure, defined as persistence of primary pathogen; bacterial and fungal superinfections and colonisation; adverse events; and length of hospital stay. We separated studies that compared the same β lactam from studies that compared different β lactams. We performed subgroup analyses for *P aeruginosa* infections, any Gram negative infection, bacteraemia, and specific sources of infection.



A full list of references to excluded studies can be found on bmj.com

Two reviewers independently applied inclusion and exclusion criteria and extracted the data. We extracted outcomes by intention to treat, unless the reasons for exclusions were not presented. In this case, we used the presented results (per protocol analysis) in the main analysis and compared them with results using all randomised patients and assuming failure for drop outs. Heterogeneity was assessed with a χ^2 test and the I^2 measure.¹⁸ We expected heterogeneity with respect to outcomes and used the random effects model, comparing it to a fixed effect model.¹⁹ We calculated relative risks with 95% confidence intervals and numbers needed to treat. Study quality measures extracted were allocation generation and concealment, blinding, intention to treat or per protocol analysis, designation of drop outs to treatment arms, number of drop outs, follow up and outcome predefinitions, and publication status.²⁰ The effect of these measures was examined through sensitivity analysis.

We examined a funnel plot of the log of the relative risk against the weight to estimate potential selection bias (such as publication bias) and to assess whether effect estimates were associated with study size.

Results

We evaluated 144 eligible randomised trials and included 64 in the review (fig 1). The trials included 7586 patients, nearly all adults, and were performed between the years 1968-2001. The median number of patients per trial was 87 (range 20-580). Trials differed by the population targeted, type of infection, and antibiotics compared (table 1). The major conditions were severe sepsis, pneumonia, or Gram negative infections (41 trials), abdominal infections (11 trials), urinary tract infections (7 trials), and Gram positive infections (5 trials). Allocation to antibiotics was empirical in 56 trials. The same β lactam was compared in 20 trials, while all other trials compared one β lactam to a different, narrower spectrum β lactam combined with an aminoglycoside.

All cause fatality—Forty three trials including 5527 patients reported all cause fatality. There was no significant difference between monotherapy and combination therapy when we combined these studies (relative risk 0.90, 95% confidence interval 0.77 to 1.06, fig 2). There was no difference among the 12 studies with 1381 patients that compared the same β lactam (1.02, 0.76 to 1.38) or among studies that compared different β lactams (0.85, 0.69 to 1.05). The heterogeneity for this comparison was low ($I^2 = 7.7\%$).

Treatment failure—We compared clinical and bacteriological failures in 63 and 43 trials, respectively (figs 3 and 4). For both comparisons, monotherapy was not significantly different from combination therapy among studies that compared the same β lactam. Monotherapy was significantly superior to combination therapy among studies that compared different β lactams. The overall comparison favoured monotherapy for clinical failure (0.87, 0.78 to 0.97; 6616 patients; number needed to treat 34, 20 to 147) and for bacteriological failure (0.86, 0.72 to 1.02; 3511 patients).

Subgroup analysis—Major effectiveness outcomes were compared within the defined patient subgroups expected to benefit most from combination therapy (tables 2 and 3). We did not detect an advantage to combination therapy with any subgroup tested. Mortality was higher among patients with *P aeruginosa* (21%), Gram negative infections (13%), and bacteraemia (15%), and outcomes were similar with combination versus monotherapy. Patients with infections outside the urinary tract (mainly pneumonia) had significantly fewer failures with monotherapy. Five trials specifically assessed Gram positive infections,

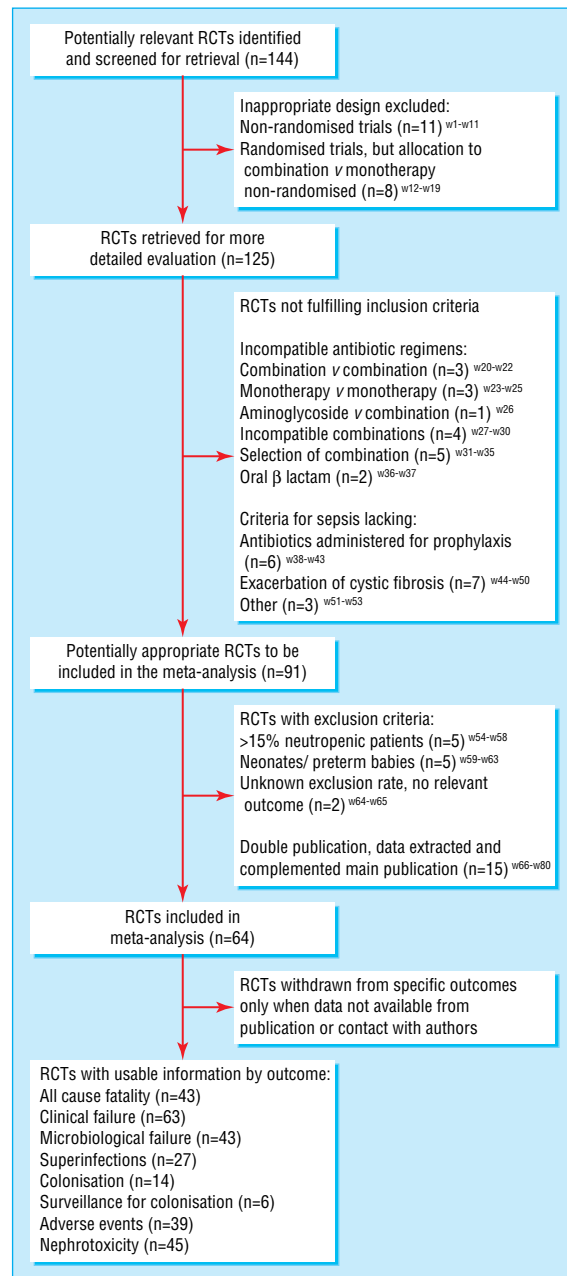


Fig 1 Detail of trial selection. The list of excluded references (w1-w80) can be found on bmj.com

endocarditis in four (table 1).^{21 32 48 63 69} Combined relative risks for fatality and failure favoured monotherapy, although differences were non-significant.

Development of resistance—Combination therapy did not lower bacterial superinfection or colonisation rates, which we would have expected if combination therapy prevented the development of resistance (fig 5). Relative risks tended in favour of monotherapy for bacterial superinfections (0.79, 0.59 to 1.06). Rates of fungal superinfection were similar. Six studies performed routine surveillance cultures, and nine assessed the development of resistance among pretreatment isolates. In these also we found no advantage with combination therapy. Twenty six studies reported coverage rates of the allocated treatment, although outcomes were not related to coverage. Among studies with different β lactams, the monotherapy β lactam provided broader coverage than the combination β lactam in 13 studies, the opposite occurring in two studies. Combined coverage of the

Table 1 Characteristics of included studies: patients and intervention

Study	No of patients	Age (years)*	Participants/infection	Intervention
Abrams ²¹ 1979	24	Median 27.5	IV drug users with <i>Staphylococcus aureus</i> endocarditis	Oxacillin (4 weeks) v oxacillin (4 weeks) + gentamicin (2 weeks)
Aguilar ²² 1992	36	40 (range 16-70)	Severe infections	Ceftizoxime v penicillin + gentamicin
Alvarez Lerma ²³ 2001	140	62 (14.5)	Mechanically ventilated adults in intensive care unit with hospital acquired pneumonia. Inotropic support in 66%	Meropenem v ceftazidime + amikacin
Arich ²⁴ 1987	47	68 (17)	Enterobacteriaceae bacteraemia	Cefotaxime v cefazolin + tobramycin
Bergeron ²⁵ 1988	77	63.5	Severe biliary infections	Cefoperazone v ampicillin + tobramycin
Biglino ²⁶ 1991	22	47 (8.5)	Severe sepsis in immune deficient patients (73%) without neutropenia	Imipenem v imipenem + netilmicin
Brown ²⁷ 1984	34	60 (17)	Hospital acquired Gram negative pneumonia, 85% of patients in intensive care unit	Moxalactam v carbenicillin + tobramycin
Carbon ²⁸ 1987	74	70 (15)	Enterobacteriaceae bacteraemia; 15% patients with septic shock	Cefotaxime v cefotaxime + amikacin
Cardozo ²⁹ 2001	110	7.7 (0.7)	Acute appendicitis	Amoxicillin-sulbactam v amoxicillin-sulbactam + gentamicin once daily
Cometta ³⁰ 1994	313	56 (18)	Hospital acquired pneumonia, sepsis, or severe diffuse peritonitis; 73% of patients in intensive care unit, mechanically ventilated in 48%	Imipenem v imipenem + netilmicin
Cone ³¹ 1985	57	65	Pneumonia or bacteraemia	Ceftazidime v ticarcillin + tobramycin
Coppens ³² 1983	66	No data	Staphylococcal infections	Cefamandole v cefamandole + tobramycin
D'Antonio ³³ 1992	300	Median 37	Fever in immune deficient patients without neutropenia	Ceftriaxone v ceftriaxone + amikacin
Duff ³⁴ 1982	74	Adults	Endomyometritis after delivery or pelvic cellulitis after hysterectomy	Cefoxitin v penicillin + gentamicin
Dupont ³⁵ 2000	227	61.5 (18)	Severe generalised peritonitis with surgically proved intra-abdominal infections	Piperacillin-tazobactam v piperacillin-tazobactam + amikacin
Felisart ³⁶ 1985	73	55 (10)	Patients with advanced cirrhosis and severe infections, mostly spontaneous bacterial peritonitis	Cefotaxime v ampicillin + tobramycin
Finer ³⁷ 1992	471	61 (18)	Serious bacterial infections; 5% of patients in critical sepsis	Ceftazidime v ureidopenillin + aminoglycoside used routinely
Gerecht ³⁸ 1989	46	66 (29-92)	Cholangitis with positive blood or bile cultures	Mezlocillin v ampicillin + gentamicin
Gomez ³⁹ 1990	78	No data	Gram negative bacteraemia; 11.5% of patients in critical sepsis	Ceftazidime v cefradine + amikacin
Havig ⁴⁰ 1973	68	65	Acute cholecystitis	Ampicillin v penicillin + streptomycin (intramuscular)
Hoepelman ⁴¹ 1988	86	60 (range 16-90)	Serious bacterial infections	Ceftriaxone v cefuroxime + gentamicin
Holloway ⁴² 1985	43	Adults	Gram negative bacteraemia or pneumonia	Ticarcillin-clavulanate v piperacillin + tobramycin
Iakovlev ⁴³ 1998	95	41.5 (2.5)	Severe hospital acquired infections	Meropenem v ceftazidime + amikacin
Jaspers ⁴⁴ 1998	79	76 (range 65-91)	Sepsis syndrome	Meropenem v cefuroxime + gentamicin once daily
Klastersky ⁴⁵ 1973	75	Adults	Patients with disseminated cancer and life threatening infections, presumed Gram negative	Carbenicillin v carbenicillin + gentamicin
Kljucar ⁴⁶ 1990	100	>14	Patients in intensive care unit with hospital acquired pneumonia, mechanically ventilated	Ceftazidime v ceftazidime + tobramycin
Koehler ⁴⁷ 1990	144	66 (range 18-91)	Hospital acquired pneumonia; 5% of patients with critical sepsis	Ceftazidime v piperacillin + tobramycin
Korzeniowski ⁴⁸ 1982	78	38.6	Drug addicts and non-addicts with <i>S aureus</i> endocarditis	Nafcillin (4 weeks) v nafcillin (4 weeks) + gentamicin (2 weeks)
Landau ⁴⁹ 1990	40	75 (9)	Complicated urinary tract infection	Ceftriaxone v cefazolin + gentamicin
Limson ⁵⁰ 1988	40	22-78	Severe Gram negative infections	Ceftazidime v ticarcillin + amikacin
Mandell ⁵¹ 1987	110	65 (range 17-95)	Pneumonia (mostly hospital acquired)	Ceftazidime v cefazolin or ticarcillin + tobramycin
Martin ⁵² 1991	116	40	Pyelonephritis	Ceftriaxone v ampicillin + gentamicin
McCormick ⁵³ 1997	128	51 (1.7)	Patients with cirrhosis and sepsis	Ceftazidime v mezlocillin + netilmicin
Mergoni ⁵⁴ 1987	42	52 (18)	Patients in intensive care unit with severe infections	Azlocillin v azlocillin + amikacin
Moreno ⁵⁵ 1997	70	39.6	Renal or kidney-pancreas transplant patients with suspected bacterial infection	Imipenem v piperacillin + tobramycin
Mouton ⁵⁶ 1990	211	58 (range 18-82)	Patients in intensive care unit with pneumonia or bacteraemia	Imipenem v cefotaxime + amikacin
Mouton ⁵⁷ 1995	237	61 (range 18-4)	Community or hospital acquired serious infections, excluding intra-abdominal sepsis; 10% of patients in critical sepsis	Meropenem v ceftazidime + amikacin
Muller ⁵⁸ 1987	106	51.5	Biliary infections	Piperacillin v cefoperazone v ampicillin + tobramycin
Naime Libien ⁵⁹ 1992	30	2.8 (3.3)	Severe lower respiratory tract infections	Ceftizoxime v penicillin + gentamicin
Piccart ⁶⁰ 1984	105	Median 63 (range 19-90)	Cancer patients (only non-neutropenic included in review) with suspected Gram negative infections. Gram positive bacteraemia excluded	Cefoperazone v cefoperazone + amikacin
Rapp ⁶¹ 1984	35	Adults	Patients in neurosurgical intensive care unit with hospital acquired pneumonia	Ceftazidime v ticarcillin + tobramycin
Rasmussen ⁶² 1986	59	61 (4)	Patients in urosurgical department with urinary tract infections, mostly postoperative	Cefotaxime v ampicillin + netilmicin

Study	No of patients	Age (years)*	Participants/infection	Intervention
Ribera ⁶³ 1996	90	26.7 (4)	Intravenous drug addicts, 90.5% HIV positive, with <i>S aureus</i> right sided endocarditis	Cloxacillin v cloxacillin + gentamicin
Rubinstein ⁶⁴ 1995	580	56	Hospital acquired bacterial infections: pneumonia, primary sepsis, or upper urinary tract infections; 9.3% with life threatening infections	Ceftazidime v ceftriaxone + tobramycin once daily
Sage ⁶⁵ 1987	61	54 (range 14-85)	Suspected life threatening sepsis, caused by enterobacteriaceae or staphylococci	Cefotaxime v cefotaxime + netilmicin
Sandberg ⁶⁶ 1997	73	Median 54 (range 18-89)	Women with pyelonephritis	Cefotaxime v cefotaxime + tobramycin once daily
Sanfilippo ⁶⁷ 1989	26	16-19	Acute pelvic inflammatory disease	Mezlocillin v penicillin + tobramycin
Sculier ⁶⁸ 1982	20	21-78	Patients in neurosurgical intensive care unit with Gram negative pneumonia, mechanically ventilated	Mezlocillin v mezlocillin + sisomicin
Sexton ⁶⁹ 1998	67	56 (18)	Native valve endocarditis caused by penicillin-susceptible streptococci	Ceftriaxone (4 weeks) v ceftriaxone (2 weeks) + gentamicin (2 weeks)
Sieger ⁷⁰ 1997	211	54.5 (range 17-87)	Hospital acquired pneumonia; 70% mechanically ventilated, 27% with severe pneumonia	Meropenem v ceftazidime + tobramycin
Smith ⁷¹ 1984	195	58.5 (19)	Serious infections, 21% of patients in septic shock	Cefotaxime v nafcillin + tobramycin
Speich ⁷² 1998	89	64.6 (18)	Severe pneumonia, community acquired in 89%	Piperacillin-tazobactam v amoxicillin-clavulanic acid + gentamicin or netilmicin once daily
Stille ⁷³ 1992	337	55 (range 19-93)	Non-life threatening infections of abdominal, gynaecological, or respiratory tract origin	Imipenem v cefotaxime + gentamicin
Sukoh ⁷⁴ 1994	63	66 (range 29-91)	Patients with underlying pulmonary disease and respiratory tract infections	Cefoperazone/sulbactam v cefoperazone/sulbactam + aminoglycoside
Takamoto ⁷⁵ 1994	171	66 (range 17-93)	Respiratory tract infections	Imipenem v imipenem + amikacin
Thompson ⁷⁶ 1990	96	57	Acute cholangitis	Piperacillin v ampicillin + tobramycin
Thompson ⁷⁷ 1993	120	44	Biliary infections	Cefepime v mezlocillin + gentamicin
Trujillo ⁷⁸ 1992	30	40 (10)	Severe skin and soft tissue or respiratory tract infections	Ceftizoxime v ampicillin + gentamicin
Vergnon ⁷⁹ 1985	30	61 (13)	Severe bronchopulmonary infections	Cefoperazone v ampicillin + tobramycin
Verzasconi ⁸⁰ 1995	93	58 (22)	Acute pyelonephritis or complicated urinary tract infections	Amoxicillin-clavulanic acid v amoxicillin + gentamicin
Warren ⁸¹ 1983	123	Median 45 (range 18-95)	Life threatening infections caused by Gram negative bacilli; 12% of patients in septic shock	Cefoperazone v cefamandole + tobramycin
Wiecek ⁸² 1986	20	Adults	Pyelonephritis	Ceftazidime v cefotaxime + tobramycin
Wing ⁸³ 1998	179	23 (5)	Pregnant women <24 weeks' gestation with pyelonephritis	Cefazolin v ceftriaxone v ampicillin + gentamicin
Yellin ⁸⁴ 1993	112	35 (range 20-66)	Cholecystitis proved by surgery	Cefepime v mezlocillin + gentamicin

*Mean (SD) unless stated differently.

β lactam and the aminoglycoside equalled monotherapy in these studies.

Drop outs and adverse events—The dropout rate was 12.6% and similar in both study groups (1.01, 0.85 to 1.20, 24 studies, 3631 patients). Few patients (2%) discontinued treatment because of adverse events with no difference between study groups (0.89, 0.52 to 1.52, 15 studies, 3042 patient). Nephrotoxicity was more common with combination therapy in nearly all studies, and the combined relative risk was 0.36 (0.28 to 0.47, fig 6), corresponding to a number needed to harm of 15 (14 to 17) for combination therapy.

Sensitivity analysis—Figure 7 shows sensitivity analyses for measures of study quality. Two studies were quasi-randomised as they used patient identifications numbers for allocation (table 4).³⁴⁻⁴⁹ Concealment of allocation was adequate in 33% (21/64) of studies, and generation of allocation was adequate in 53% (34/64). Seven studies used some type of blinding, most commonly of outcome assessors only. Extraction of data by intention to treat was possible in 46% (20/43) of studies for fatality and in 21% (13/63) for failure (table 4).⁴ All sensitivity comparisons were non-significant. Adequate concealment and generation of allocation were associated with relative risks closer to 1 for fatality. The advantage of monotherapy was more significant in trials that used some type of blinding. Smaller trials showed larger effect estimates regarding failure. Analysis per protocol and by the fixed effect model did not affect results. The funnel plot for treatment failure generated a nearly symmetrical “funnel distribution.”

Discussion

Main findings

In this systematic review of all randomised trials we have shown that β lactam-aminoglycoside combination therapy and β lactam monotherapy for the treatment of sepsis have similar effects in patients without neutropenia.

Twenty trials compared the same β lactam. All cause fatality, the most significant and objective outcome, was not reduced by the addition of aminoglycosides. Clinical and bacteriological failure, which may be prone to bias with non-blinded trials and are of much lesser relevance to patients, were not significantly different. However, rates of adverse event increased with the aminoglycoside. Nephrotoxicity was much more common with combination therapy, while vestibular damage and ototoxicity, other important morbidities associated with aminoglycosides, were not routinely examined.

Forty four trials compared a broad spectrum, usually novel, β lactam with a “routine” combination regimen. Rates of appropriate antibiotic treatment with combination therapy and monotherapy were similar when reported. Fatality was not significantly different. Failures were significantly more common with combination therapy. Among all trials, we found no evidence for any potential prevention of infection by resistant isolates with combination therapy.

How should these findings be interpreted?

It can be debated which design appropriately examines the clinical interpretation of synergism, studies comparing same or different β lactams. Synergism has been defined as a 2 log₁₀ or

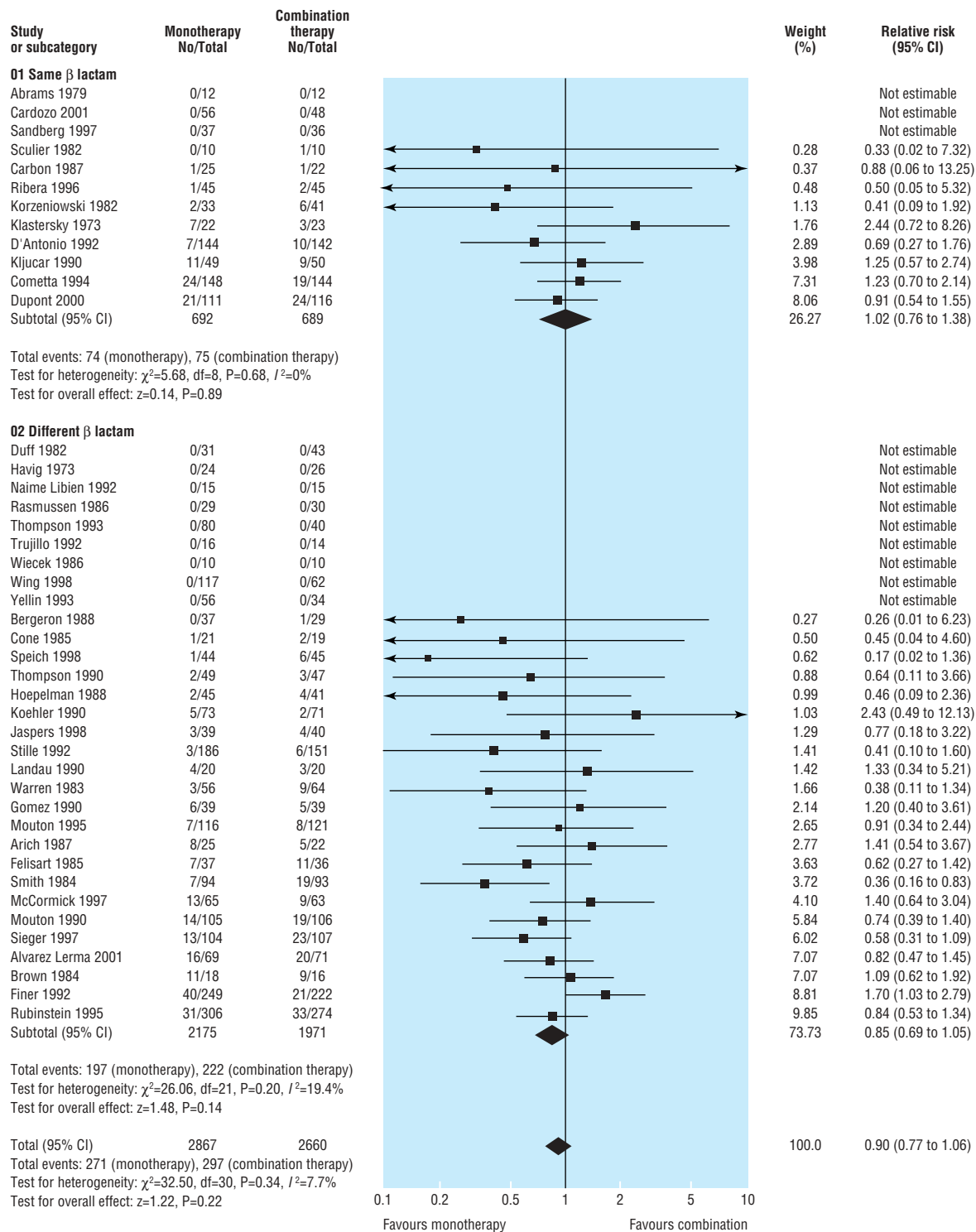


Fig 2 All cause fatality in comparison of β lactam monotherapy v β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

greater reduction in bacterial count with the combination versus that with each of the agents alone.⁸⁶ In studies comparing the same β lactam this is directly tested, but the effect of increasing the antibiotic spectrum cannot be separated from a synergistic effect. In studies comparing different β lactams the spectrum of coverage was similar in both arms. However, synergism can be examined only indirectly. If we assume that the aminoglycoside offers more than its additional coverage, the combination arm should perform as well, or better, than the broader spectrum β

lactam monotherapy. With the former design we did not detect an advantage to the combination, while with the latter we found an advantage to monotherapy.

Weaknesses of the study

The quality of included studies was poor overall. We did not detect bias induced by any of the measures assessed. We could not obtain data on all cause fatality for 33% of studies. It is unlikely that missing results would shift the results for studies

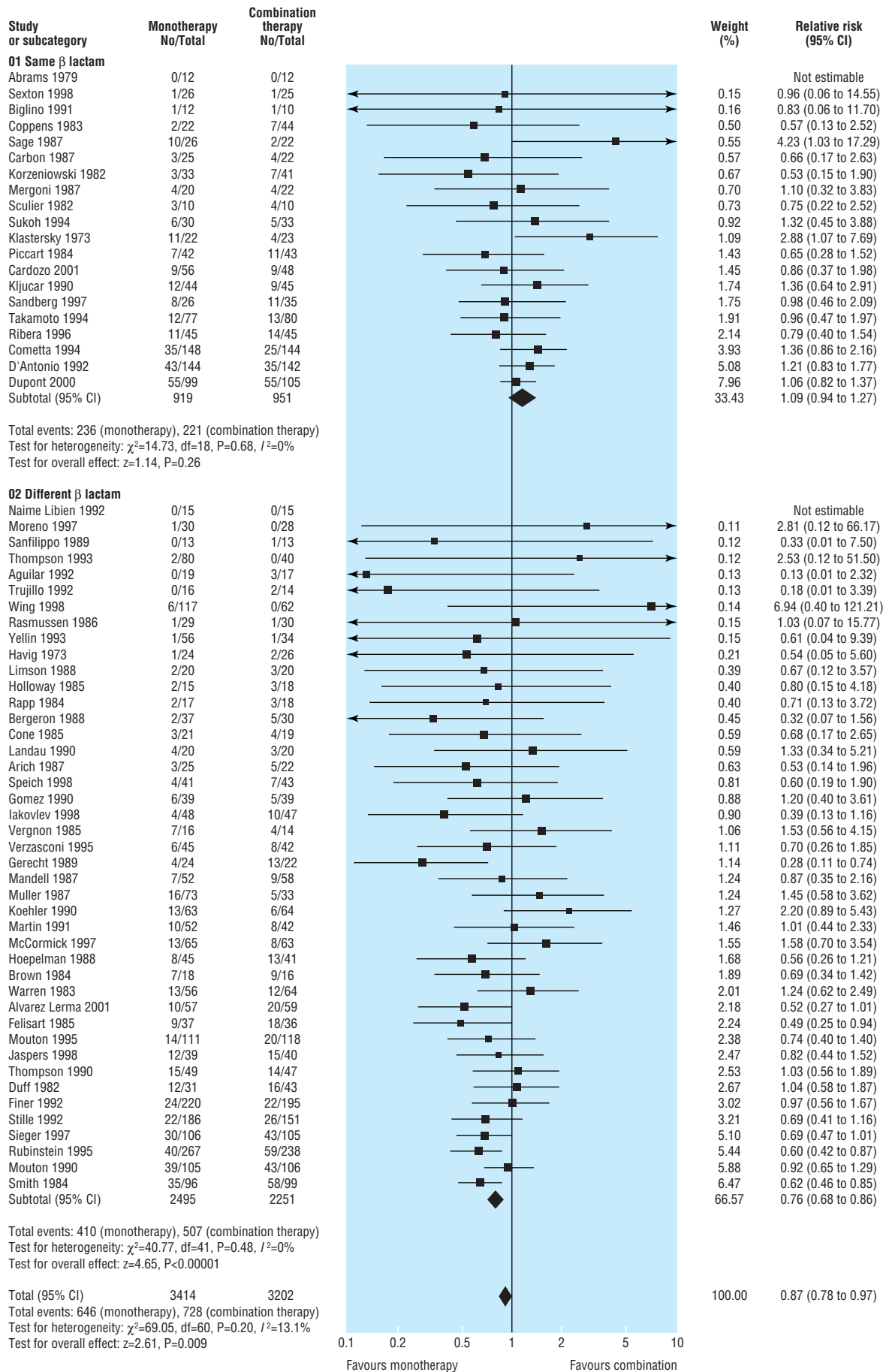


Fig 3 Clinical failure in comparison of β lactam monotherapy v β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

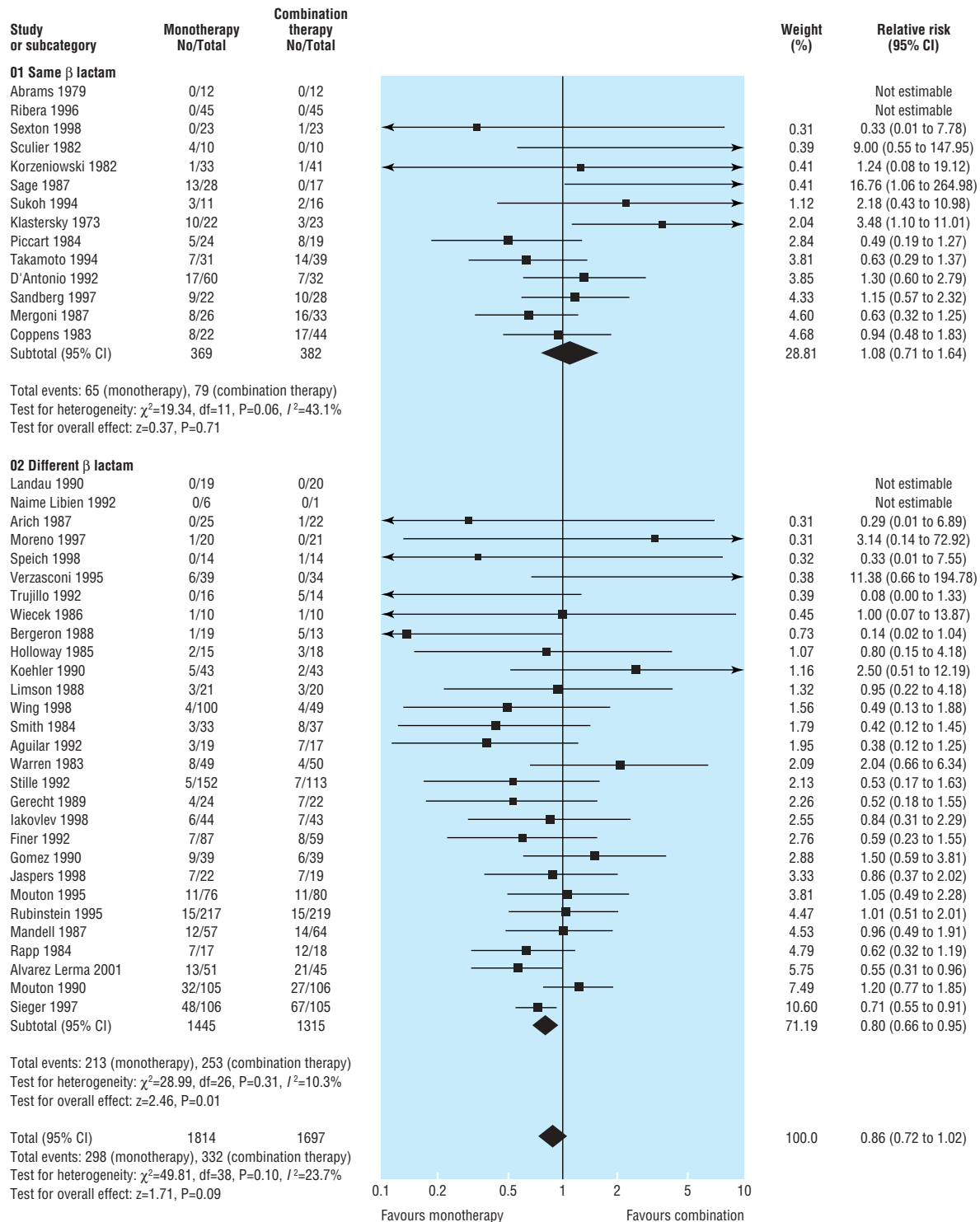


Fig 4 Bacteriological failure in comparison of β lactam monotherapy v β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

comparing the same β lactam (relative risk 1.02, 0.76 to 1.38), but it is of concern that studies comparing different β lactams (0.85, 0.69 to 1.05) may not detect important harm to patients.

Our assessment of treatment effects for patients with *P aeruginosa*, Gram negative, and blood infections relies on subgroup analysis. We did not detect an advantage for combination therapy among these patients. Only few patients with documented *P aeruginosa* infections could be evaluated. The types of infections addressed by included studies—severe

infections acquired in the hospital or pneumonia acquired in intensive care units—suggest that further infections were caused by this pathogen.

Does further evidence support our findings?

Suggestions for combination treatment for *P aeruginosa* rely mostly on a prospective observational study of 200 patients with *P aeruginosa* bacteraemia, in which combination therapy was associated with improved survival and in which synergistic com-

Table 2 All cause fatality in comparison of β lactam monotherapy v β lactam-aminoglycoside combination therapy for treatment of sepsis: subgroup analyses

	Same β lactam			Different β lactam		
	Studies	Patients	RR (95% CI)	Studies	Patients	RR (95% CI)
<i>Pseudomonas aeruginosa</i> infections	1	9	NA	2	29	1.50 (0.07 to 32.84)
Gram negative infections	3	117	0.58 (0.08 to 4.43)	5	313	1.20 (0.79 to 1.83)
Bacteraemia*	1	11	NA	5	193	1.40 (0.72 to 2.71)
Non-urinary tract infections	3	351	0.89 (0.53 to 1.49)	13	1458	0.76 (0.57 to 1.03)
<i>Staphylococcus aureus</i> endocarditis	3	188	0.44 (0.12 to 1.59)	0	0	—

NA=not assessed.

*Excluding studies restricted to Gram positive infections.

binations were associated with a trend for improved survival compared with non-synergistic combinations.⁸⁷ A similar study focusing on *Klebsiella* bacteraemia found an advantage for combination therapy only among patients with hypotension,¹⁵ while other studies have not found such an advantage.^{10–12 88}

Immunocompromised patients are the most likely to gain from enhanced bactericidal activity possibly offered by β lactam-aminoglycoside combination therapy.⁹ In a comparison of β lactam monotherapy with β lactam-aminoglycoside combination therapy restricted to patients with neutropenia we found no advantage to combination treatment.⁸⁹ Although the approach to the management of patients with and without neutropenia is separated in clinical practice, this similarity supports a biological basis underlying our results.

Implications for practice

Antibiotic treatment is nearly always instituted empirically and is often continued with no isolate to direct specific treatment. Most trials assessed this scenario and do not support a benefit for combination therapy. Clinicians may still opt for combination empirical treatment to increase the probability of appropriate empirical treatment, which has indeed been shown to improve survival.^{90 91} Current evidence suggests that aminoglycoside monotherapy may be inadequate for infections outside the urinary tract.^{10 92 93} Thus, for the purpose of enhancing antimicrobial spectrum, aminoglycosides may constitute a poor choice. Combination treatment is considered for patients with

severe infections. However, these are the patients most prone to harm by the addition of an aminoglycoside. With no proved survival benefit, combination therapy may be unjustifiable. Several studies, included in the overall and subgroup analyses, directly assessed semiempirical combination versus monotherapy. These, similarly, do not support combination therapy for specific pathogens, when detected.

Implications for further research

Should further research be conducted to assess combination versus monotherapy? Novel β lactams should not be compared with older generation β lactams or penicillins combined with aminoglycosides. The reason for further trials assessing the addition of an aminoglycoside to a β lactam seems dubious as well. The relative risks and confidence intervals available with all current evidence do not point to a potential benefit overall or in specific subgroups of patients. Furthermore, assessment of efficacy among subgroups such as patients with *P aeruginosa* infections probably requires an unachievable number of patients treated empirically at the time benefit of antibiotic treatment is most evident.

We included in our review a small subset of trials that assessed the value of addition of an aminoglycoside in Gram positive infections. Three studies assessed staphylococcal endocarditis,^{21 48 63} one study assessed any staphylococcal infection,³² and one assessed streptococcal endocarditis.⁶⁹ β lactam-aminoglycoside treatment is well ingrained in existing

Table 3 Clinical failure in comparison of β lactam monotherapy v β lactam-aminoglycoside combination therapy for treatment of sepsis: subgroup analyses

	Same β lactam			Different β lactam		
	Studies	Patients	RR (95% CI)	Studies	Patients	RR (95% CI)
<i>Pseudomonas aeruginosa</i> infections	6	124	1.01 (0.68 to 1.49)	12	302	1.09 (0.65 to 1.83)
Gram negative infections	10	432	1.15 (0.82 to 1.59)	18	1403	0.88 (0.67 to 1.17)
Bacteraemia*	5	141	1.22 (0.59 to 2.52)	17	624	0.67 (0.48 to 0.93)†
Non-urinary tract infections§	10	1148	1.03 (0.66 to 1.60)	31	2945	0.71 (0.61 to 0.82)†
Gram positives/endocarditis	5	305	0.71 (0.41 to 1.22)	0	0	—

*Excluding studies restricted to Gram positive infections.

†P<0.05.

§Significant advantage for monotherapy when all studies are combined, P=0.01.

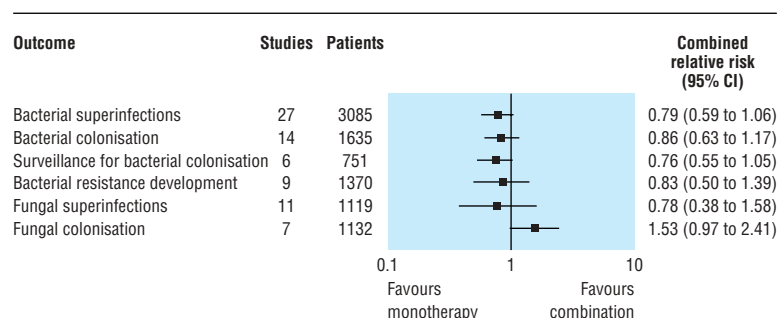


Fig 5 Summary relative risks for outcome relating to resistance development in comparison of β lactam monotherapy v β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

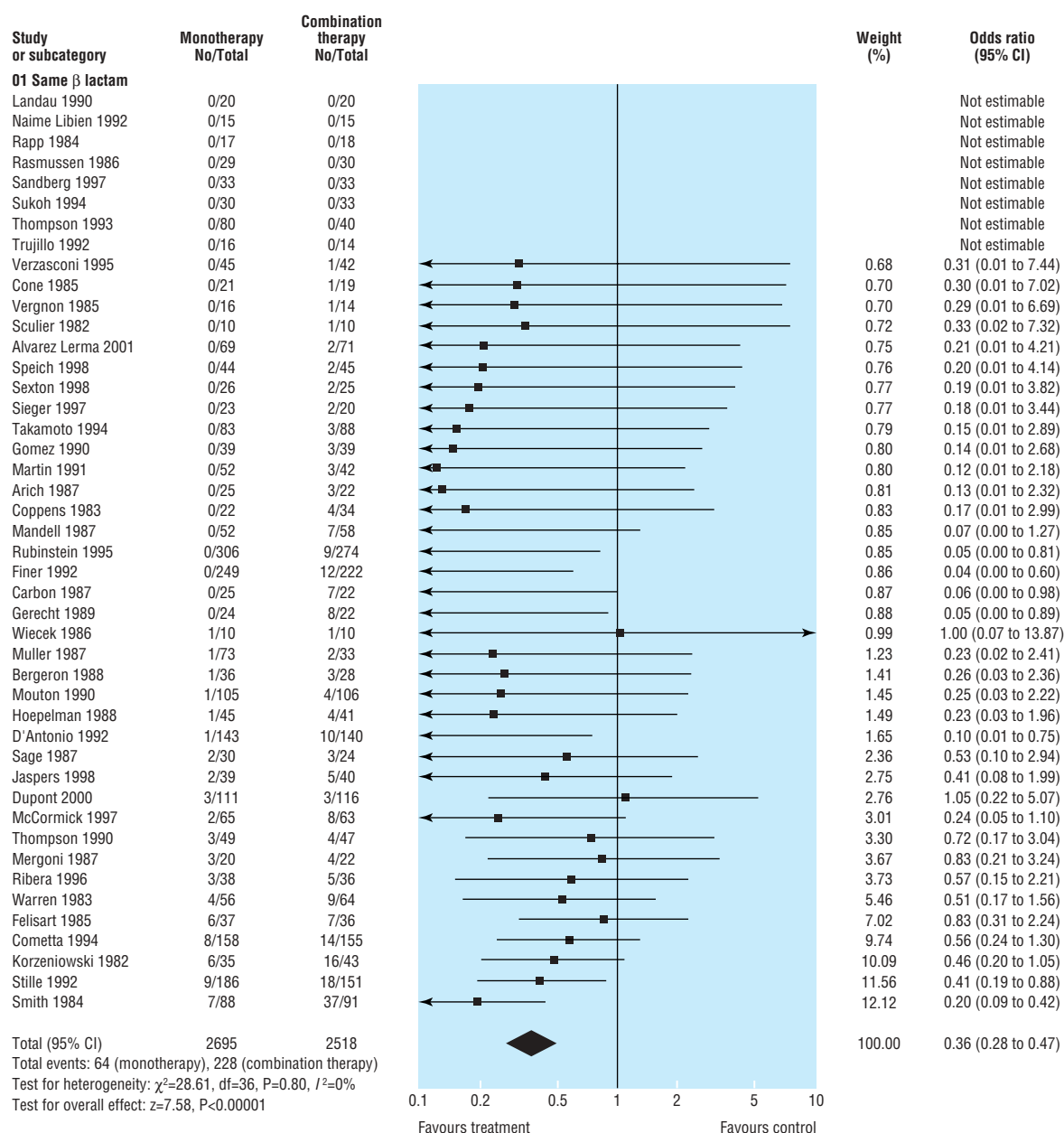


Fig 6 Adverse events: nephrotoxicity in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

guidelines and clinical practice with these infections,⁹⁴ yet our results do not point to a clinical benefit with combination therapy. With these infections, further studies should assess whether the addition of an aminoglycoside is justified.

We thank the Cochrane Infectious Diseases Group for their support, review process, and help in obtaining papers; all the authors who responded for our requests for additional data; and Rika Fujiya, who translated the Japanese studies. The protocol for this review with the detailed search strategy and methods is published in the Cochrane Library.⁹⁵ The complete review will be published in the forthcoming issue of the Cochrane Library. Contributors: MP and LL performed the search. All authors selected trials for inclusion, performed data extraction and quality assessment of the trials, and analysed the data. MP and LL contacted authors and requested missing data. All authors participated drafting the manuscript for the Cochrane review and for the journal article. MP is guarantor for the article.

Funding: This work was supported by an EU 5th framework grant (TREAT project, grant No 1999-11459).

Competing interests: None declared.

Ethical approval: Not required.

- Giamarellou H, Zissis NP, Tagari G, Bouzou J. In vitro synergistic activities of aminoglycosides and new beta-lactams against multidrug-resistant *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 1984;25:534-6.
- Giamarellou H. Aminoglycosides plus beta-lactams against gram-negative organisms. Evaluation of in vitro synergy and chemical interactions. *Am J Med* 1986;80:126-37.
- Klasterky J, Meunier-Carpentier F, Prevost JM. Significance of antimicrobial synergism for the outcome of gram negative sepsis. *Am J Med Sci* 1977;273:157-67.
- Klasterky J, Zinner SH. Synergistic combinations of antibiotics in gram-negative bacillary infections. *Rev Infect Dis* 1982;4:294-301.
- Den Hollander JG, Horrevorts AM, van Goor ML, Verbrugh HA, Mouton JW. Synergism between tobramycin and ceftazidime against a resistant *Pseudomonas aeruginosa* strain, tested in an in vitro pharmacokinetic model. *Antimicrob Agents Chemother* 1997;41:95-100.
- Mouton JW. Combination therapy as a tool to prevent emergence of bacterial resistance. *Infection* 1999;27:S24-8.
- Wu YL, Scott EM, Po AL, Tariq VN. Ability of azlocillin and tobramycin in combination to delay or prevent resistance development in *Pseudomonas aeruginosa*. *J Antimicrob Chemother* 1999;44:389-92.
- Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001;163:1730-54.
- Moellering RS. Principles of anti-infective therapy. In: Mandell GL, Bennet JE, Dolin R, eds. *Mandell, Douglas, and Bennet's principles and practice of infectious diseases*. 5th ed. Philadelphia: Churchill Livingstone, 2000.

Table 4 Characteristics of included studies: methods

Study	Location	Extra data*	Randomisation procedure	Blinding	Lost to follow up		Length of follow up
					Fatality†	Clinical failure	
Abrams ²¹ 1979	USA		No data	Open	0 PP‡	0 PP	4 weeks
Aguilar ²² 1992	Mexico	Lilacs	No data	Open	—	No data, presumed ITT§	10 days
Alvarez Lerma ²³ 2001	Multicentre, Spain	Methods	Computer generated, central randomisation concealed by sealed opaque envelopes	Open	ITT	17%	14 days after treatment
Arich ²⁴ 1987	France	Methods	Random number table, concealed by sealed opaque envelopes	Open	28%	28%	No data
Bergeron ²⁵ 1988	Multicentre, Canada	No	No data	Open	14%	13%	4-6 weeks after treatment
Biglino ²⁶ 1991	Italy	No	No data	Open	—	No data, presumed ITT	
Brown ²⁷ 1984	USA	No	Random number table without further detail	Outcome assessors blinded	29%	29%	In hospital stay
Carbon ²⁸ 1987	Multicentre, France	No	No data	Open	No data, presumed ITT	No data, presumed ITT	No data
Cardozo ²⁹ 2001	Paraguay	Methods, outcomes Lilacs	Numerical assignation without further detail	Open	No data, presumed ITT	No data, presumed ITT	No data
Cometta ³⁰ 1994	Multicentre, Switzerland	Methods, outcomes	Random number table, concealed by sealed opaque envelopes	Open	7%	7%	No data
Cone ³¹ 1985	USA	No	No data	Open	—	30%	End of treatment
Coppens ³² 1983	Belgium	No	Consecutively numbered envelopes	Open	—	17%	No data
D'Antonio ³³ 1992	Italy	Methods, outcomes	Random number table concealed by sealed opaque envelopes	Open	ITT	5%	End of treatment
Duff ³⁴ 1982	USA	Methods, outcomes	Hospitalisation number without further detail	Open	ITT	ITT	24 hours after treatment
Dupont ³⁵ 2000	Multicentre, France	No	Computer generated, central randomisation	Outcome assessors blinded	6%	15%	4 weeks after treatment
Felisart ³⁶ 1985	Spain	No	Random number table without further detail	Open	ITT	ITT	48 hours after treatment
Finer ³⁷ 1992	Multicentre, UK	Methods, outcomes	Computer generated concealed by sealed, opaque envelopes	Open	ITT	12	2-4 weeks after treatment
Gerecht ³⁸ 1989	USA	No	Computer generated random number table	Open	—	5%	8 weeks after treatment
Gomez ³⁹ 1990	Spain	Methods, other studies CL/Embase	Computer generated concealed by sealed, closed envelopes	Open;	0 PP	0 PP	4 weeks after treatment
Havig ⁴⁰ 1973	Norway	No	Randomisation list applied consecutively	Open	24%	24%	In hospital stay
Hoepelman ³¹ 1988	Netherlands	Methods, outcomes, other studies	Randomisation list concealed by sealed opaque envelopes	Open	ITT	ITT	In hospital stay
Holloway ⁴² 1985	USA	No	No data	Open	—	23%	No data
Iakovlev ⁴³ 1998	Multicenter, Russia	No	Envelopes without further detail	Open	—	ITT	4 weeks after treatment
Jaspers ⁴⁴ 1998	Multicentre, Netherlands	Methods	Random number table; sealed opaque envelopes	Open	ITT	ITT	4-6 weeks after treatment
Klastersky ⁴⁵ 1973	Belgium	No	No data	Open	9%	9%	No data
Kljucar ⁴⁶ 1990	Germany	Reprint, outcomes, methods	Computer generated code in consecutive closed numbered envelopes	Open	0.7%	0.7%	4-6 after treatment
Koehler ⁴⁷ 1990	Multicentre, Germany	CL/Embase	No data	Open	ITT	12%	End of treatment
Korzeniowski ⁴⁸ 1982	Multicentre, USA	No	Random number table, central randomisation	Open	3%	3%	4 weeks after treatment
Landau ⁴⁹ 1990	Israel	No	Patient identification number without further detail	Open	No data, presumed ITT	No data, presumed ITT	No data
Limson ⁵⁰ 1988	The Philippines	No	No data	Open	—	26%	No data
Mandell ⁵¹ 1987	Multicentre, Canada	Other studies	Consecutive sealed envelopes	Open	—	15%	4 weeks after treatment
Martin ⁵² 1991	Belgium	No	Random number table	Open	—	19%	4-6 weeks after treatment
McCormick ⁵³ 1997	Ireland	Methods	Random numbers table concealed by sealed opaque envelopes	Open	13%	13%	2 weeks after treatment
Mergoni ⁵⁴ 1987	Italy	Methods	Sealed opaque envelopes without further detail	Open	—	No data, presumed ITT	No data

Study	Location	Extra data*	Randomisation procedure	Blinding	Lost to follow up		Length of follow up
					Fatality†	Clinical failure	
Moreno ⁵⁵ 1997	Spain	Lilacs	No data	Open	—	17%	No data
Mouton ⁵⁶ 1990	Multicentre, France	No	No data	Open	ITT	ITT	No data
Mouton ⁵⁷ 1995	Multicentre, Europe	No	No data	Open	ITT	18%	2-4 weeks after treatment
Muller ⁵⁸ 1987	Bicentre, USA	No	Computer generated lists without further detail	Open	—	19%	No data
Naime Libien ⁵⁹ 1992	Mexico	Lilacs	No data	Open	No data, presumed ITT	No data, presumed ITT	No data
Piccart ⁶⁰ 1984	Belgium	No	No data	Open	—	19%	No data
Rapp ⁶¹ 1984	USA	No	No data	Open	—	ITT	End of treatment
Rasmussen ⁶² 1986	Denmark	Methods, outcomes	Random number table, concealed by sealed envelopes	Open	5%	5%	2 weeks
Ribera ⁶³ 1996	Spain	Methods, outcomes	Random number table, concealed by sealed opaque envelopes	Open	ITT	ITT	6 months
Rubinstein ⁶⁴ 1995	Multicentre	Methods, outcomes	Computer generated code concealed with sealed opaque numbered envelopes	Outcome assessors blinded	ITT	13%	2 weeks after treatment
Sage ⁶⁵ 1987	UK	No	Pre-prepared envelopes, without further detail	Open	—	21%	No data
Sandberg ⁶⁶ 1997	Multicentre, Sweden	Methods, outcomes	Computer generated lists concealed by sealed opaque envelopes	Open	ITT	16%	4-6 weeks after treatment
Sanfilippo ⁶⁷ 1989	USA	Embase	Computer generated code, central randomisation	Double blind, placebo controlled	No data, presumed ITT	No data, presumed ITT	4 weeks after discharge
Sculier ⁶⁸ 1982	Belgium	No	No data	Open	ITT	ITT	1 weeks after treatment
Sexton ⁶⁹ 1998	Multicentre, USA	No	No data	Open	24	24	3 months
Sieger ⁷⁰ 1997	Multicentre, USA	No	No data	Open	ITT	ITT	1 month
Smith ⁷¹ 1984	USA	No	Random number table, central randomisation. Drugs administered in identically labelled and coloured antibiotic bottles	Double blind, placebo controlled	6.5%	2.5%	2-4 days after treatment
Speich ⁷² 1998	Multicentre, Switzerland	Methods, outcomes	Computer generated code concealed by sealed opaque envelopes	Open	ITT	6%	10-14 days after treatment
Stille ⁷³ 1992	Multicentre, Germany/ Austria	No	Computer generated list, without further detail	Open	ITT	ITT	1-3 days after treatment
Sukoh ⁷⁴ 1994	Japan	Methods	Envelopes, without further detail	Open	—	ITT	No data
Takamoto ⁷⁵ 1994	Multicentre, Japan	No	Computer generated code concealed in envelopes	Open	—	8%	No data
Thompson ⁷⁶ 1990	Multicentre, USA	No	Computer generated, without further detail	Open	9%	9%	3 weeks after treatment
Thompson ⁷⁷ 1993	Multicentre, USA	No	Computer generated, without further detail	Open	18%	18%	1 month
Trujillo ⁷⁸ 1992	Mexico	Lilacs	No data	Open	No data, presumed ITT	No data, presumed ITT	No data
Vergnon ⁷⁹ 1985	France	No	No data	Open	No data, presumed ITT	No data, presumed ITT	End of treatment
Verzasconi ⁸⁰ 1995	Bicentre, Switzerland	No	No data	Single blind	—	6	No data
Warren ⁸¹ 1983	USA	No	Random numbers contained within consecutively numbered sealed envelopes	Open	2%	2%	2 weeks after treatment
Wiecek ⁸² 1986	Poland	No	No data	Open	No data, presumed ITT	No data, presumed ITT	3 weeks
Wing ⁸³ 1998	Bicentre, USA	Outcomes	Computer generated random number table concealed by sealed opaque envelopes	Open	ITT	ITT	2 weeks after treatment
Yellin ⁸⁴ 1993	USA	Methods	Random number table, central randomisation	Provider blinded	15%	15%	6 weeks

PP=per protocol; ITT=intention to treat.

*Complementary data from authors. Source database listed when article was not available from Medline (CL=Cochrane Library; Ref=reference search). Several additional articles, available in Medline, identified through reference search and retrieved from Medline.

†For studies reporting comparative fatality.

‡Trials randomised patients at onset of infectious episode and assessed only patients with specific isolate or diagnosis. No drop outs among patients defined assessable by protocol.

§Study referred only to "included" patients, without specifying explicitly number of randomised and assessed patients. No referral to drop outs. Study was assessed as intention to treat.

10 Leibovici L, Paul M, Poznanski O, Drucker M, Samra Z, Konigsberger H, et al. Monotherapy versus beta-lactam-aminoglycoside combination treatment for gram-negative bacteraemia: a prospective, observational study. *Antimicrob Agents Chemother* 1997;41:1127-33.

11 Siegman-Igra Y, Ravona R, Primerman H, Giladi M. Pseudomonas aeruginosa bacteraemia: an analysis of 123 episodes, with particular emphasis on the effect of antibiotic therapy. *Int J Infect Dis* 1998;2:211-5.

12 Crabtree TD, Pelletier SJ, Gleason TG, Pruett TL, Sawyer RG. Analysis of aminoglycosides in the treatment of gram-negative infections in surgical patients. *Arch Surg* 1999;134:1293-9.

13 Montravers P, Veber B, Auboyer C, Dupont H, Gauzit R, Korinek AM, et al. Diagnostic and therapeutic management of nosocomial pneumonia in surgical patients: results of the Eole study. *Crit Care Med* 2002;30:368-75.

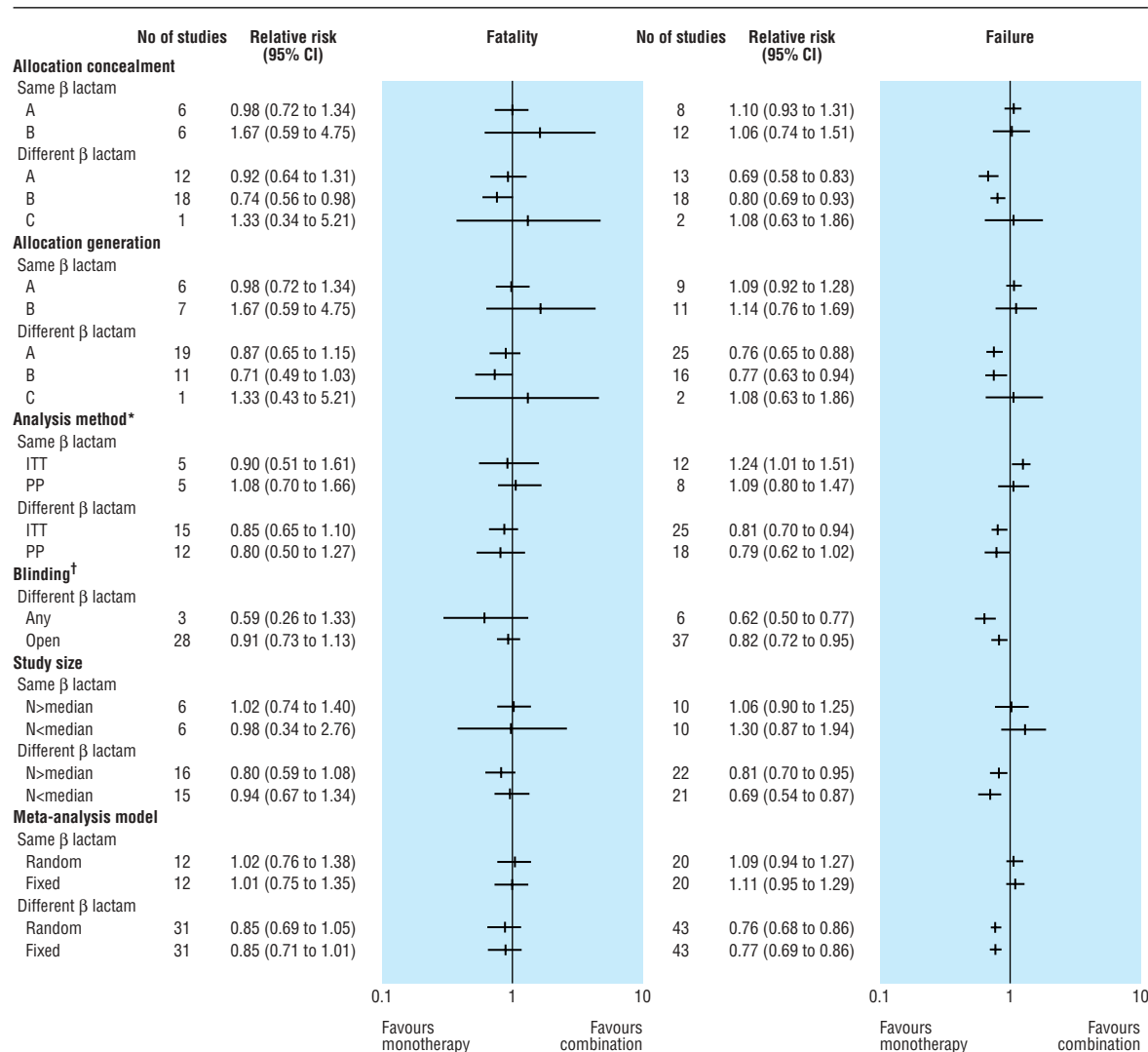


Fig 7 Sensitivity analyses Randomisation methods were classified as A=adequate; B=unknown; C=inadequate.⁸⁵ Central randomisation, inaccessible computer randomisation, and sealed opaque envelopes were considered adequate for allocation concealment. Table of random numbers, computer generated lists, and consecutive selection were considered adequate for allocation generation. *Fatality comparison includes studies that reported results for all randomised patients (ITT=intention to treat) v studies reporting results for evaluable patients only (PP=per protocol). Studies that did not state method of analysis and did not refer to drop outs are not included. Failure comparison includes studies that reported results or drop outs for all randomised patients (drop outs counted as failures, ITT) v studies performed per protocol that did not state number of drop outs per study arm (PP). Results with all studies combined in this graph differ from those attained in main comparison because drop outs are counted as failures (relative risk 0.92, 0.82 to 1.03). †Comparison for studies comparing same β lactam was not performed as only one study used blinding

14 Grasela TH Jr, Welage LS, Walawander CA, Timm EG, Pelter MA, Poirier TI, et al. A nationwide survey of antibiotic prescribing patterns and clinical outcomes in patients with bacterial pneumonia. *DICP* 1990;24:1220-5.

15 Korvick JA, Bryan CS, Farber B, Beam TR Jr, Schenfeld L, Muder RR, et al. Prospective observational study of Klebsiella bacteraemia in 230 patients: outcome for antibiotic combinations versus monotherapy. *Antimicrob Agents Chemother* 1992;36:2639-44.

16 Leone M, Bourgoin A, Cambon S, Dubuc M, Albanese J, Martin C. Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. *Crit Care Med* 2003;31:462-7.

17 Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. *Chest* 1992;101:1481-3.

18 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

19 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.

20 Clarke M, Oxman AD, eds. *Cochrane reviewers' handbook 4.1.6*. Oxford: Update Software, 2003.

21 Abrams B, Sklaver A, Hoffman T, Greenman R. Single or combination therapy of staphylococcal endocarditis in intravenous drug abusers. *Ann Intern Med* 1979;90:789-91.

22 Ramirez de Aguilar R. [Clinical trial on efficacy and safety of ceftazoxime compared with penicillin-gentamicin of manafing of adult severe infections.] (In Spanish.) *Compend Invest Clin Latinoam* 1992;12:75-8.

23 Alvarez Lerma F. Efficacy of meropenem as monotherapy in the treatment of ventilator-associated pneumonia. *J Chemother* 2001;13:70-81.

24 Arich C, Gouby A, Bengler C, Ardilouze JL, Dubois A, Joubert P, et al. [Comparison of the efficacy of cefotaxime alone and the combination cefazolin-tobramycin in the treatment of enterobacterial septicemia.] (In French.) *Pathol Biol (Paris)* 1987;35:613-5.

25 Bergeron MG, Mendelson J, Harding GK, Mandell L, Fong IW, Rachlis A, et al. Cefoperazone compared with ampicillin plus tobramycin for severe biliary tract infections. *Antimicrob Agents Chemother* 1988;32:1231-6.

26 Biglino A, Bonasso M, Giannini P. Imipenem/cilastatin as empirical treatment of severe infections in compromised patients. *J Chemother* 1991;3 suppl 1:208-12.

27 Brown RB, Lemeshow S, Teres D. Moxalactam vs carbenicillin plus tobramycin: treatment of nosocomial gram-negative bacillary pneumonias in non-neutropenic patients. *Curr Ther Res Clin Exp* 1984;36:557-64.

28 Carbon C, Auboyer C, Becq Giraudon B, Bertrand P, Gallais H, Mouton Y, et al. Cefotaxime (C) vs cefotaxime + amikacin (C + A) in the treatment of septicemia due to enterobacteria: a multicenter study. *Chemioterapia* 1987;6(2 suppl):367-8.

29 Cardozo M, Basualdo W, Martínez R, Matsumura K, González-Cabello M, Navarro D, et al. [Evaluation of the association amoxicillin/sulbactam to a amoxicillin/sulbactam more gentamicins in childs with peritonitis of apendicular origin.] (In Spanish.) *Pediatr (Asunción)* 2001;28:15-9.

30 Cometta A, Baumgartner JD, Lew D, Zimmerli W, Pittet D, Chopart P, et al. Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. *Antimicrob Agents Chemother* 1994;38:1309-13.

31 Cone LA, Woodard DR, Stoltzman DS, Byrd RG. Ceftazidime versus tobramycin-carbapenem in the treatment of pneumonia and bacteremia. *Antimicrob Agents Chemother* 1985;28:33-6.

32 Coppens L, Hanson B, Klasterky J. Therapy of staphylococcal infections with cefamandole or vancomycin alone or with a combination of cefamandole and tobramycin. *Antimicrob Agents Chemother* 1983;23:36-41.

33 D'Antonio D, Fioritoni G, Iacone A, Dell'Isola M, Natale D, D'Arcangelo L, et al. Randomized comparison of ceftriaxone versus ceftriaxone plus amikacin for the empirical

What is already known on this topic

Early appropriate antibiotic treatment for severe infections decreases mortality

In vitro studies have shown that the bactericidal activity of a β lactam may be enhanced by the addition of an aminoglycoside

Prospective studies have suggested that the combination also has a clinical advantage

What this study adds

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

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

- treatment of infections in patients with altered host defense: microbiological and clinical evaluation. *Chemotherapy* 1992;38:420-7.
- 34 Duff P, Keiser JF. A comparative study of two antibiotic regimens for the treatment of operative site infections. *Am J Obstet Gynecol* 1982;142:996-1003.
 - 35 Dupont H, Carbon C, Carlet J. Monotherapy with a broad-spectrum beta-lactam is as effective as its combination with an aminoglycoside in treatment of severe generalized peritonitis: a multicenter randomized controlled trial. The Severe Generalized Peritonitis Study Group. *Antimicrob Agents Chemother* 2000;44:2028-33.
 - 36 Fierant J, Rimola A, Arroyo V, Perez-Ayuso RM, Quintero E, Gines P, et al. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. *Hepatology* 1985;5:457-62.
 - 37 Finer N, Gousta P. Cefazidime versus aminoglycoside and (ureido)penicillin combination in the empirical treatment of serious infection. *J Royal Soc Med* 1992;85:530-3.
 - 38 Gerecht WB, Henry NK, Hoffman WW, Muller SM, LaRusso NF, Rosenblatt JE, et al. Prospective randomized comparison of mezlocillin therapy alone with combined ampicillin and gentamicin therapy for patients with cholangitis. *Arch Intern Med* 1989;149:1279-84.
 - 39 Gomez J, Moldenauer F, Ruiz G, Canteras M, Redondo C, Molina B, et al. [Monotherapy (cefazidime) versus combination therapy (cefradine + amikacin) in gram-negative bacteremia. A prospective, randomized study, 1987.] (In Spanish.) *Rev Esp Quimioter* 1990;3:35-40.
 - 40 Havig O, Hertzberg J. Effect of ampicillin, chloramphenicol, and penicillin-streptomycin in acute cholecystitis. *Scand J Gastroenterol* 1973;8:55-8.
 - 41 Hoepelman IM, Rozenberg-Arska M, Verhoef J. Comparison of once daily ceftriaxone with gentamicin plus cefuroxime for treatment of serious bacterial infections. *Lancet* 1988;i:1305-9.
 - 42 Holloway WJ. Treatment of infections in hospitalized patients with ticarcillin plus clavulanic acid. A comparative study. *Am J Med* 1985;79:168-71.
 - 43 Iakovlev SV, Iakovlev VP, Derevianko II, Kira EF, Meropenem SG. [Multicenter open randomized trial of meropenem in comparison to ceftazidime and amikacin used in combination in severe hospital infections.] (In Russian.) *Antibiot Khimioter* 1998;43:15-23.
 - 44 Jaspers CA, Kieft H, Speelberg B, Buiting A, van MKM, Ruys CJ, et al. Meropenem versus cefuroxime plus gentamicin for treatment of serious infections in elderly patients. *Antimicrob Agents Chemother* 1998;42:1233-8.
 - 45 Klastersky J, Cappel R, Daneau D. Therapy with carbenicillin and gentamicin for patients with cancer and severe infections caused by gram-negative rods. *Cancer* 1973;31:331-6.
 - 46 Kljucar S, Heimesaat M, von Pritzbuere E, Bauernfeind A. Comparative clinical trial with ceftazidime (CAZ) versus ceftazidime plus tobramycin (TOB) versus azlocillin (AZL) plus tobramycin in ventilated patients with nosocomial lower respiratory tract infections (LRTI). Abstract 953. 30th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1990; Atlanta, GA. American Society for Microbiology; 1990.
 - 47 Koehler CO, Arnold H. Controlled clinical study of ceftazidime (3 x 1 g daily) versus piperacillin + tobramycin in patients with nosocomial pneumonia. *Int J Exp Clin Chemother* 1990;3:211-8.
 - 48 Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. *Ann Intern Med* 1982;97:496-503.
 - 49 Landau Z, Feld S, Krupsky M. [Ceftriaxone or combined ceftazolin-gentamicin for complicated urinary tract infections.] (In Hebrew.) *Harefuah* 1990;118:152-3.
 - 50 Limson BM, Navarro Almaro E, Litam P, Que E, Kua LT. Cefazidime versus a combination of amikacin and ticarcillin in the treatment of severe infections. *Clin Ther* 1988;10:589-93.
 - 51 Mandell LA, Nicolle LE, Ronald AR, Landis SJ, Duperval R, Harding GK, et al. A prospective randomized trial of ceftazidime versus ceftazolin/tobramycin in the treatment of hospitalized patients with pneumonia. *J Antimicrob Chemother* 1987;20:95-107.
 - 52 Martin PY, Unger PF, Auckenthaler R, Waldvogel FA. [Efficacy and costs of treatment with ceftriaxone compared to ampicillin-gentamycin in acute pyelonephritis.] (In French.) *Rev Med Suisse Romande* 1991;111:609-17.
 - 53 McCormick PA, Greenslade L, Kibbler CC, Chin JK, Burroughs AK, McIntyre N. A prospective randomized trial of ceftazidime versus netilmicin plus mezlocillin in the empirical therapy of presumed sepsis in cirrhotic patients. *Hepatology* 1997;25:833-6.
 - 54 Mergoni M, Stocchetti N, De Cristofaro A, Antonioni M, Zucconi P. Azlocillin versus azlocillin plus amikacin in the treatment of severe infections in intensive care unit patients. *Chemioterapia* 1987;6:286-9.
 - 55 Moreno A, Vilarde J, Ricart MJ, Claramonte X, Campistol JM, Oppenheimer F. [Efficacy of several empirical antibacterial treatment regimens in renal transplant patients with fever.] (In Spanish.) *Rev Espanol Quimioter* 1997;10:138-45.
 - 56 Mouton Y, Deboscker Y, Bazin C, Fourrier F, Moulrout S, Philippon A, et al. [Prospective, randomized, controlled study of imipenem-cilastatin versus cefotaxime-amikacin in the treatment of lower respiratory tract infection and septicemia at intensive care units.] (In French.) *Presse Med* 1990;19:607-12.
 - 57 Mouton YJ, Beuscart C. Empirical monotherapy with meropenem in serious bacterial infections. Meropenem Study Group. *J Antimicrob Chemother* 1995;36 suppl A:145-56.
 - 58 Muller EL, Pitt HA, Thompson JE, Jr., Doty JE, Mann LL, Manchester B. Antibiotics in infections of the biliary tract. *Surg Gynecol Obstet* 1987;165:285-92.
 - 59 Naime Libién J, Viguera Rendón A, Sánchez Díaz G, Abraham Jalil A. [Clinical study to evaluate efficacy and safety of ceftizoxime compared vs penicillin-gentamicin combination in the treatment of severe respiratory infections.] (In Spanish.) *Compend Invest Clin Latinoam* 1992;12:42-8.
 - 60 Piccart M, Klastersky J, Meunier F, Lagast H, Van Laethem Y, Weerts D. Single-drug versus combination empirical therapy for gram-negative bacillary infections in febrile cancer patients with and without granulocytopenia. *Antimicrob Agents Chemother* 1984;26:870-5.
 - 61 Rapp RP, Young B, Foster TS, Tibbs PA, O'Neal W. Cefazidime versus tobramycin/ticarcillin in treating hospital acquired pneumonia and bacteremia. *Pharmacotherapy* 1984;4:211-5.
 - 62 Rasmussen D, Bremmelgaard A, Rasmussen F, Thorup J. Treatment of serious urological infections with cefotaxime compared to ampicillin plus netilmicin. *Dan Med Bull* 1986;33:49-51.
 - 63 Ribera E, Gomez-Jimenez J, Cortes E, del Valle O, Planes A, Gonzalez-Alujas T, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis. A randomized, controlled trial. *Ann Intern Med* 1996;125:969-74.
 - 64 Rubinstein E, Lode H, Grassi C, Castelo A, Ward K, Alanko K, et al. Cefazidime monotherapy vs. ceftazidime/tobramycin for serious hospital-acquired gram-negative infections. *Clin Infect Dis* 1995;20:1217-28.
 - 65 Sage R, Nazareth B, Noone P. A prospective randomised comparison of cefotaxime vs. netilmicin vs. cefotaxime plus netilmicin in the treatment of hospitalised patients with serious sepsis. *Scand J Infect Dis* 1987;19:331-7.
 - 66 Sandberg T, Alestig K, Eilard T, Ek E, Hebelka M, Johansson E, et al. Aminoglycosides do not improve the efficacy of cephalosporins for treatment of acute pyelonephritis in women. *Scand J Infect Dis* 1997;29:175-9.
 - 67 Sanfilippo JS, Schikler KN. Mezlocillin versus penicillin and tobramycin in adolescent pelvic inflammatory disease: a prospective study. *International Pediatrics* 1989;4:53-6.
 - 68 Sculier JP, Coppens L, Klastersky J. Effectiveness of mezlocillin and endotracheally administered sisomicin with or without parenteral sisomicin in the treatment of Gram-negative bronchopneumonia. *J Antimicrob Chemother* 1982;9:63-8.
 - 69 Sexton DJ, Tenenbaum MJ, Wilson WR, Steckelberg JM, Tice AD, Gilbert D, et al. Ceftriaxone once daily for four weeks compared with ceftazidime plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. Endocarditis Treatment Consortium Group. *Clin Infect Dis* 1998;27:1470-4.
 - 70 Sieger B, Berman SJ, Geckler RW, Farkas SA. Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. Meropenem Lower Respiratory Infection Group. *Crit Care Med* 1997;25:1663-70.
 - 71 Smith CR, Ambinder R, Lipsky JJ, Petty BG, Israel E, Levitt R, et al. Cefotaxime compared with nafcillin plus tobramycin for serious bacterial infections. A randomized, double-blind trial. *Ann Intern Med* 1984;101:469-77.
 - 72 Speich R, Imhof E, Vogt M, Grossebacher M, Zimmerli W. Efficacy, safety, and tolerance of piperacillin/tazobactam compared to co-amoxiclav plus an aminoglycoside in the treatment of severe pneumonia. *Eur J Clin Microbiol Infect Dis* 1998;17:313-7.
 - 73 Stille W, Shah PM, Ullmann U, Hoffstedt B, Kreis C, Bommersbach B, et al. Randomized multicenter clinical trial with imipenem/cilastatin versus cefotaxime/gentamicin in the treatment of patients with non-life-threatening infections. *Eur J Clin Microbiol Infect Dis* 1992;11:683-92.
 - 74 Sukoh M, Inoue T, Morita Y, Ito K, Togano Y, Yamanaka K, et al. [Clinical evaluation of combination therapy of sulbactam/cefoperazone and aminoglycoside in respiratory tract infections.] (In Japanese.) *Jpn J Antibiot* 1994;47:170-80.
 - 75 Takamoto M, Ishibashi T, Toyoshima H, Tanaka H, Tamaru N, Watanabe K, et al. Imipenem/cilastatin sodium alone or combined with amikacin sulfate in respiratory infections. [Japanese.] *Jpn J Antibiot* 1994;47:1131-44.
 - 76 Thompson JE, Jr, Pitt HA, Doty JE, Coleman J, Irving C. Broad spectrum penicillin as an adequate therapy for acute cholangitis. *Surg Gynecol Obstet* 1990;171:275-82.
 - 77 Thompson JE, Jr, Bennion RS, Roettger R, Lally KP, Hopkins JA, Wilson SE. Cefepime for infections of the biliary tract. *Surg Gynecol Obstet* 1993;177(suppl):30-40.
 - 78 Zavala Trujillo I. [Research on efficacy and safety of ceftizoxime in treating lower respiratory tract and skin and soft tissues infections.] (In Spanish.) *Compend Invest Clin Latinoam* 1992;12:31-41.
 - 79 Vergnon JM, Vincent M, Ros A, Brun Y, Brune J. [Comparative clinical trial of cefoperazone versus ampicillin + tobramycin in severe bronchopulmonary and pleural infectious pathology.] (In French.) *Rev Pneumol Clin* 1985;41:205-11.
 - 80 Verzasconi R, Rodoni P, Monotti R, Marone C, Mombelli G. [Amoxicillin and clavulanic acid versus amoxicillin plus gentamicin in the empirical initial treatment of urinary tract infections in hospitalized patients.] (In German.) *Schweiz Med Wochenschr* 1995;125:1533-9.
 - 81 Warren JW, Miller EH, Jr., Fitzpatrick B, DiFranco DE, Caplan ES, Tenney JH, et al. A randomized, controlled trial of cefoperazone vs. cefamandole-tobramycin in the treat-

- ment of putative, severe infections with gram-negative bacilli. *Rev Infect Dis* 1983;5(suppl 1):173-80S.
- 82 Wiecek A, Kokot F, Andrzejowska H, Grzeszczak W. [Clinical evaluation of ceftazidime and the combined administration of cefotaxime and tobramycin in the treatment of urinary tract infections. Prospective and randomized studies.] (In Polish.) *Pol Tyg Lek* 1986;41:1242-6.
- 83 Wing DA, Hendershott CM, Debuque L, Millar LK. A randomized trial of three antibiotic regimens for the treatment of pyelonephritis in pregnancy. *Obstet Gynecol* 1998;92:249-53.
- 84 Yellin AE, Berne TV, Appleman MD, Heseltine PN, Gill MA, Okamoto MP, et al. A randomized study of cefepime versus the combination of gentamicin and mezlocillin as an adjunct to surgical treatment in patients with acute cholecystitis. *Surg Gynecol Obstet* 1993;177(suppl):23-40.
- 85 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12.
- 86 Levison ME. Pharmacodynamics of antibacterial drugs. *Infect Dis Clin North Am* 2000;14:281-91, vii.
- 87 Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteraemia: outcome correlations in a prospective study of 200 patients. *Am J Med* 1989;87:540-6.
- 88 Chow JW, Fine MJ, Shlaes DM, Quinn JP, Hooper DC, Johnson MP, et al. Enterobacter bacteraemia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991;115:585-90.
- 89 Paul M, Soares-Weiser K, Leibovici L. β lactam monotherapy versus β lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ* 2003;326:1111.
- 90 Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999;115:462-74.
- 91 Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998;244:379-86.
- 92 Bailey JA, Virgo KS, DiPiro JT, Nathens AB, Sawyer RG, Mazuski JE. Aminoglycosides for intra-abdominal infection: equal to the challenge? *Surgical Infections* 2002;3:315-35.
- 93 Bodey GP, Middleman E, Umsawadi T, Rodriguez V. Infections in cancer patients. Results with gentamicin sulfate therapy. *Cancer* 1972;29:1697-701.
- 94 Bayer AS, Bolger AF, Taubert KA, Wilson W, Steckelberg J, Karchmer AW, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation* 1998;98:2936-48.
- 95 Paul M, Leibovici L, Grozinsky SG, Silbiger I, Soares-Weiser K. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for treating sepsis (protocol for Cochrane Review). *Cochrane Library*. Issue 2. Oxford: Update Software, 2003.

(Accepted 22 December 2003)

doi 10.1136/bmj.38028.520995.63

Department of Medicine E and Infectious Diseases Unit, Rabin Medical Centre, Beilinson Campus, Petah-Tikva 49100, Israel
Mical Paul consultant

Department of Medicine E, Rabin Medical Centre, Beilinson Campus, Petah-Tikva
Ishay Benuri-Silbiger researcher
Karla Soares-Weiser coordinator of clinical research
Leonard Leibovici associate professor

Correspondence to: M Paul mica@zahav.net.il