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Papers

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

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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 unit[16] 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.

P+ *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, endocarditis in four (table 1).[21 32 48 63 69] Combined relative risks for fatality and failure favoured monotherapy, although differences were non-significant.

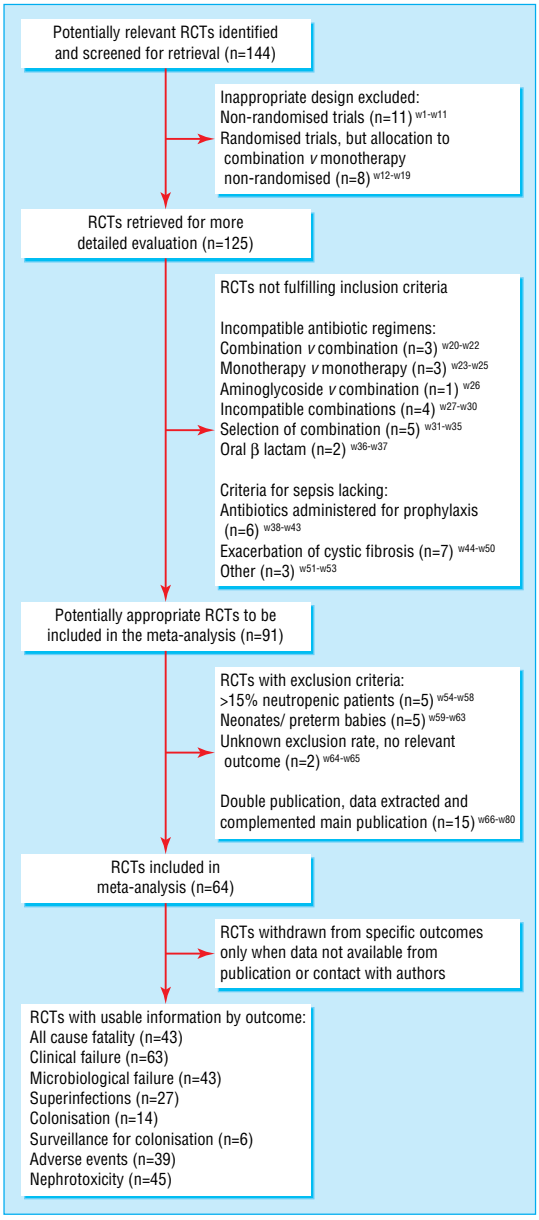

Fig 1 Detail of trial selection. The list of excluded references (w1-w80) can be found on bmj.com

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 *Staphylococcus aureus* 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	Endomyoparametritis 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[31] 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 *S aureus* 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* azloclillin + 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 *S aureus* 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-clavulonic 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 $\log_{10}$ or

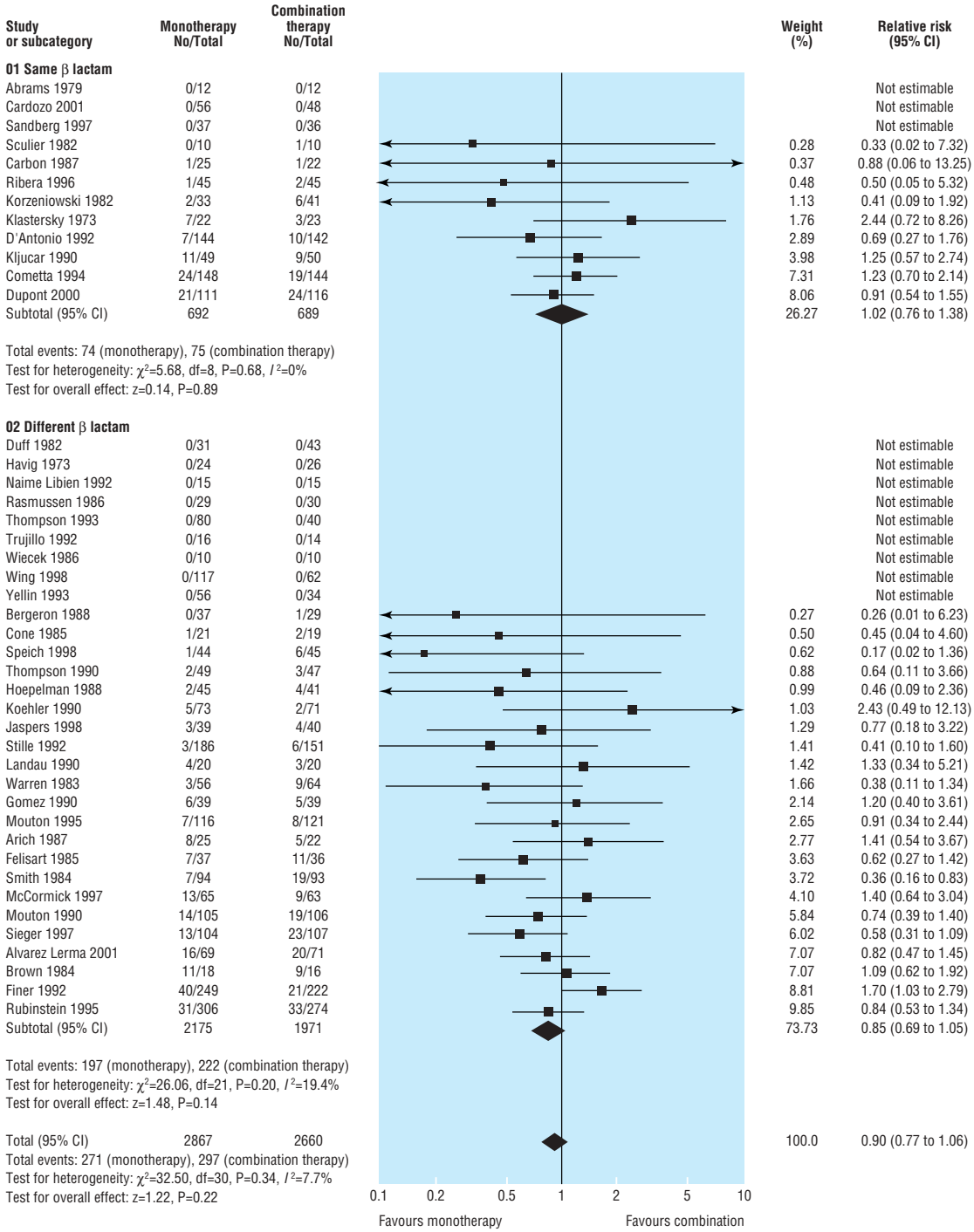

Fig 2 All cause fatality in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

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

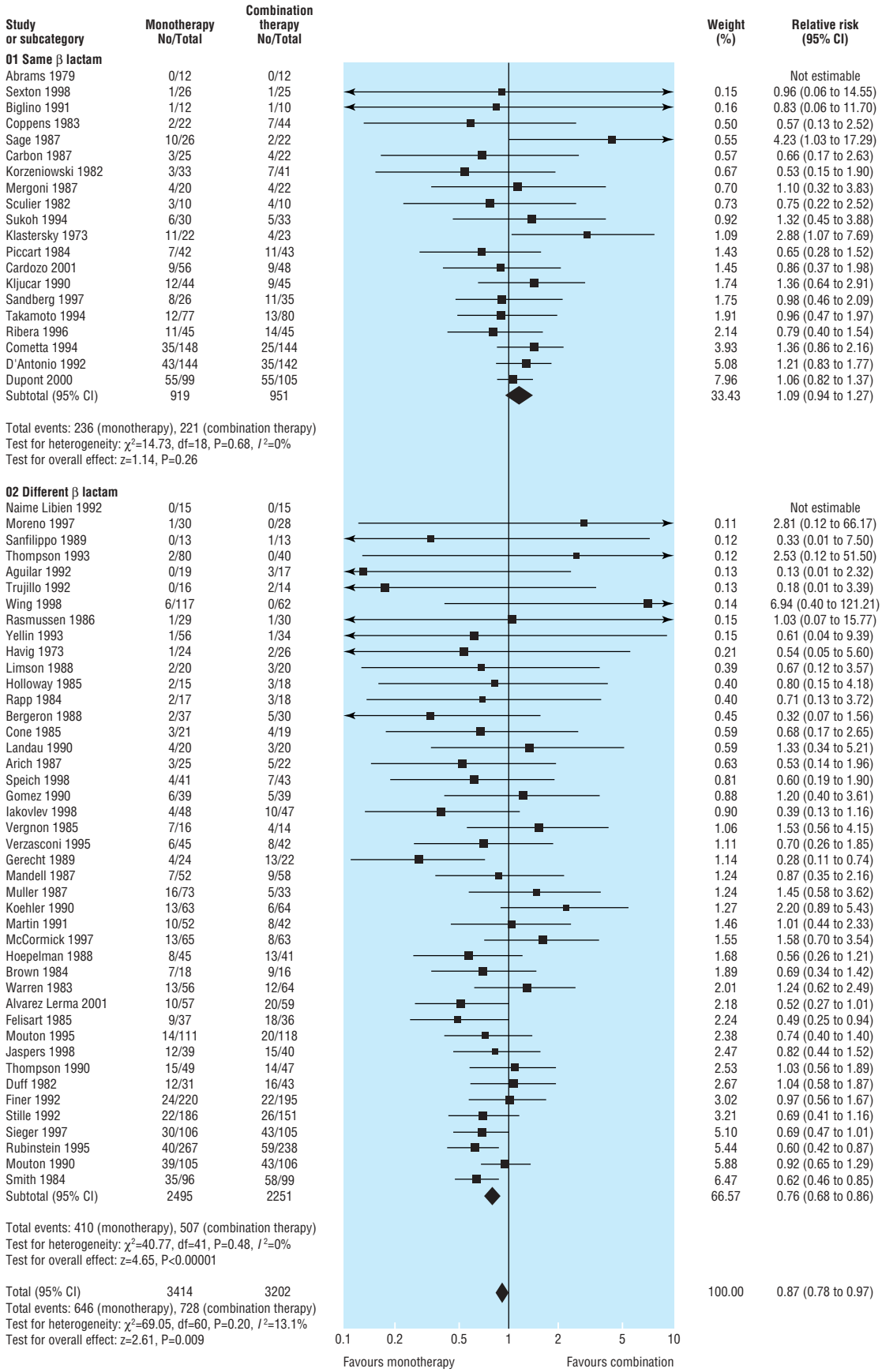

Fig 3 Clinical failure in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

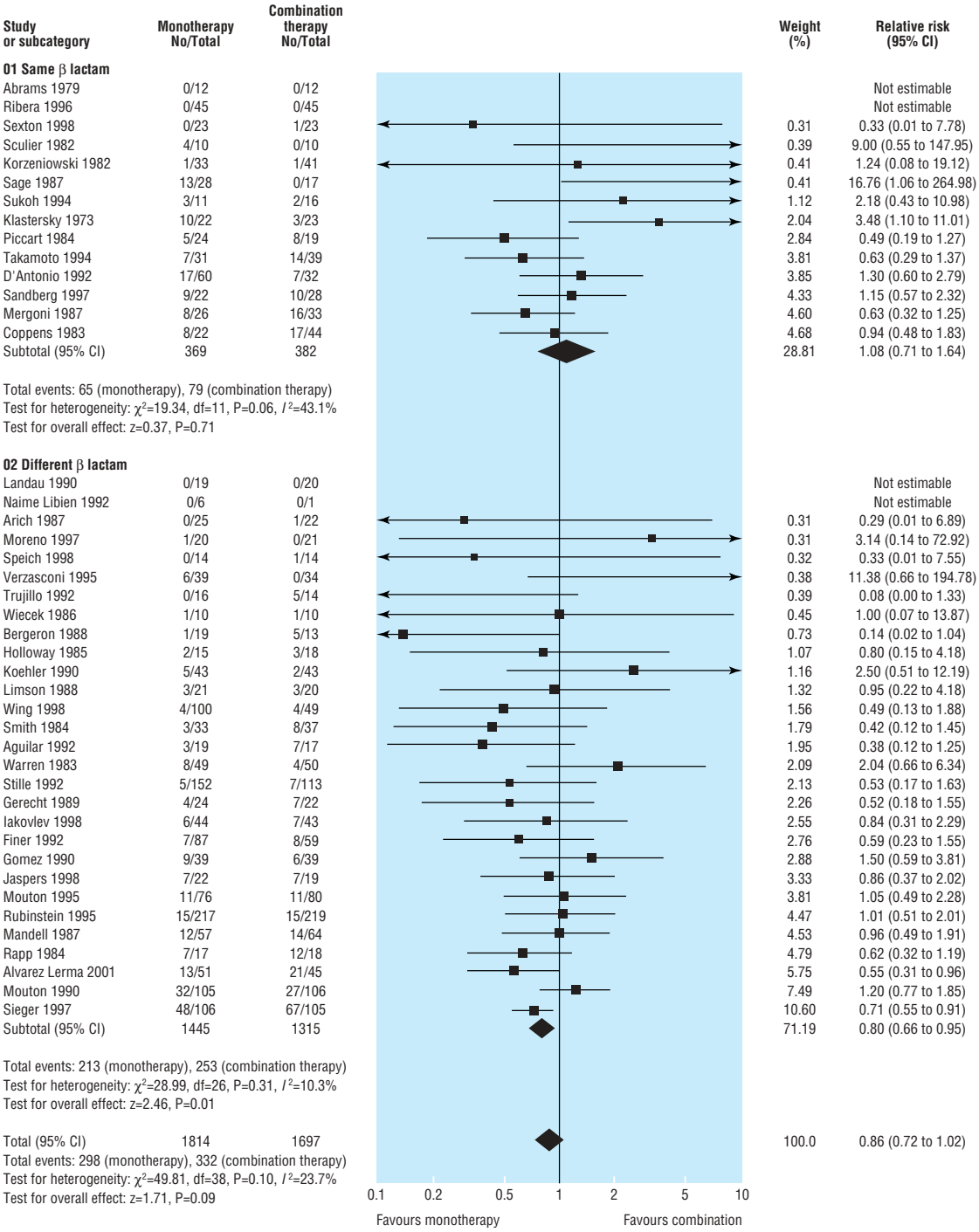

Fig 4 Bacteriological failure in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

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)
Pseudomonas aeruginosa 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)
Staphylococcus aureus 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 aminglycoside 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)
Pseudomonas aeruginosa 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.

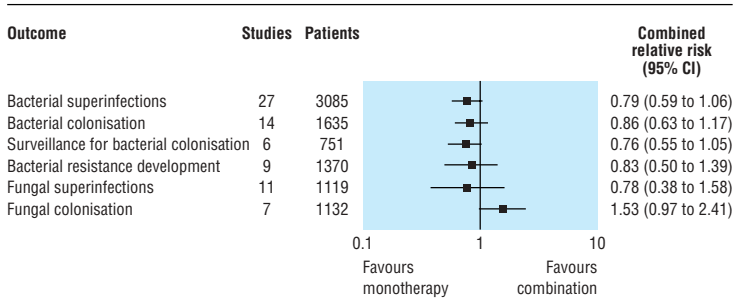

Fig 5 Summary relative risks for outcome relating to resistance development in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

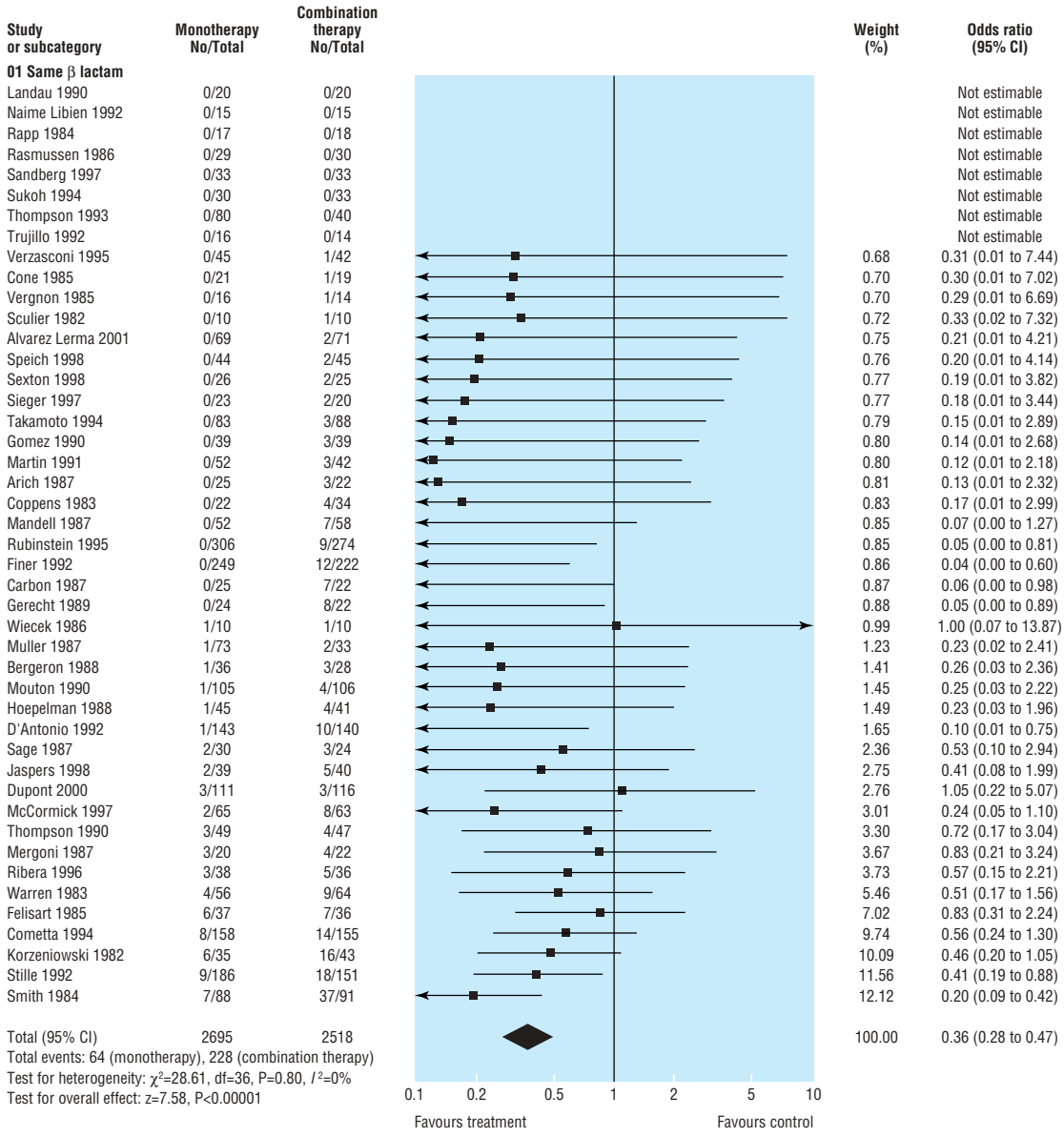

Fig 6 Adverse events: nephrotoxicity in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

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.

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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.

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Competing interests: None declared.

Ethical approval: Not required.

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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	Multicetre, 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.

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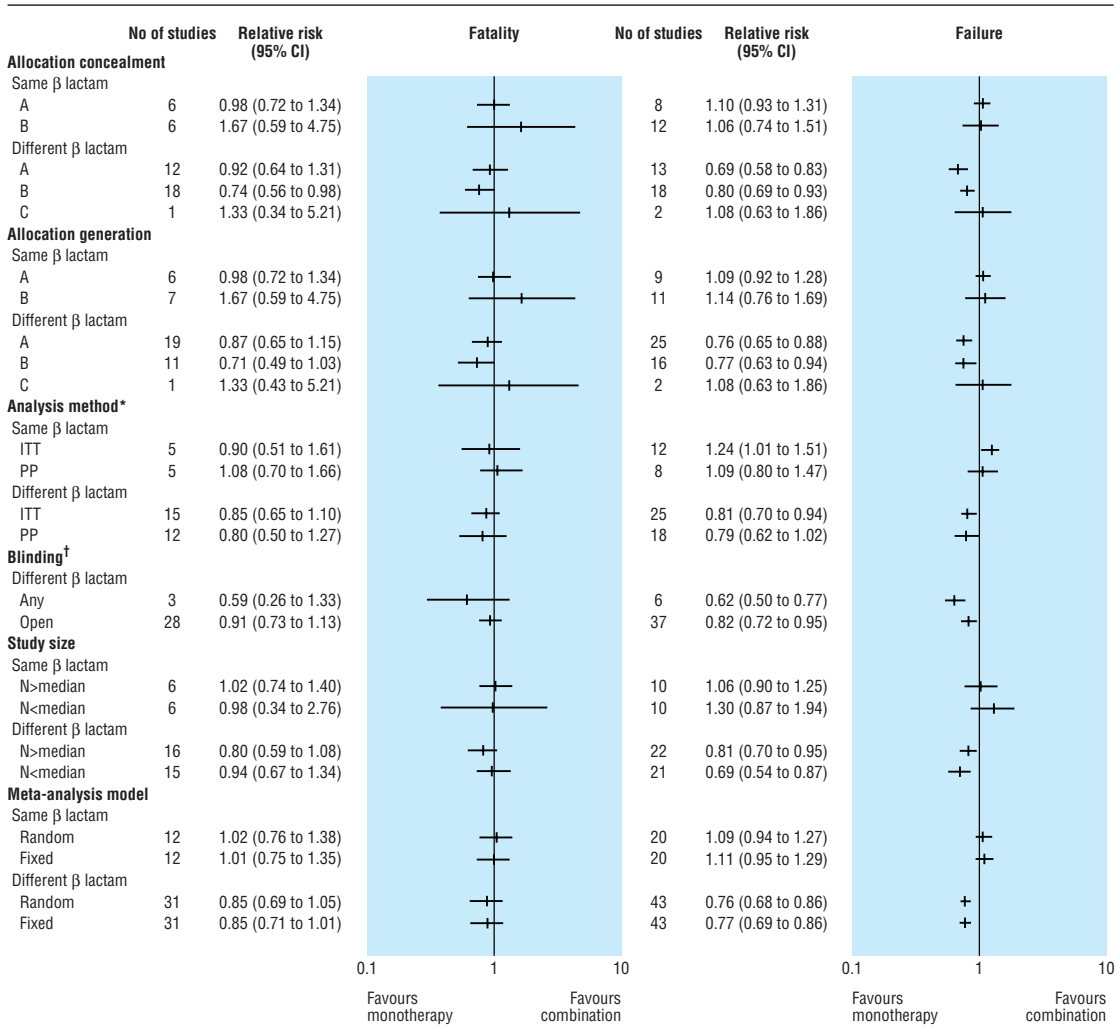

Fig 7 Sensitivity analyses Randomisation methods were classified as A=adequate; B=unknown; C=inadequate.[85] Central randomisation, inaccessible computer randomisation, and sealed opaque envelopes were considered adequate for allocation concealment. Table of random numbers, computer generated lists, 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

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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 aminogoycoside

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.

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