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

Mical Paul, Karla Soares-Weiser, Leonard Leibovici

Abstract

Objective To compare the effectiveness of β lactam monotherapy versus β lactam-aminoglycoside combination therapy in the treatment of patients with fever and neutropenia.

Data sources Medline, Embase, Lilacs, the Cochrane Library, and conference proceedings to 2002. References of included studies and contact with authors. No restrictions on language, year of publication, or publication status.

Study selection All randomised trials of β lactam monotherapy compared with β lactam-aminoglycoside combination therapy as empirical treatment for patients with fever and neutropenia.

Data selection Two reviewers independently applied selection criteria, performed quality assessment, and extracted data. An intention to treat approach was used. Relative risks were pooled with the random effect model.

Main outcome measure All cause fatality.

Results Forty seven trials with 7807 patients met inclusion criteria. Nine trials compared the same β lactam. There was no significant difference in all cause fatality (relative risk 0.85, 95% confidence interval 0.72 to 1.02). For success of treatment there was a significant advantage with monotherapy (0.92, 0.85 to 0.99), though there was considerable heterogeneity among trials. There was no significant difference between monotherapy and combination treatment in trials that compared the same β lactam, whereas there was major advantage with monotherapy in trials that compared different β lactams (0.87, 0.80 to 0.93). Rates of superinfection were similar. Adverse events, including those associated with severe morbidity, were significantly more common in the combination treatment group. Detected flaws in methods did not affect results.

Conclusions For patients with fever and neutropenia there is no clinical advantage in treatment with β lactam-aminoglycoside combination therapy. Broad spectrum β lactams as monotherapy should be regarded as the standard of care for such patients.

Introduction

Patients with fever and neutropenia can be treated with a single β lactam (third or fourth generation anti-pseudomonal cephalosporins or carbapenems) or β lactam-aminoglycoside combination therapy.[1] So far studies that have compared monotherapy with combination therapy have not been large enough to compare survival. Comparative data regarding high risk subgroups are needed,[2 3] and thus far conclusions regarding superinfections are contradictory.[4 5]

We performed a systematic review and meta-analysis of β lactam monotherapy and β lactam-aminoglycoside combination therapy to compare all cause fatality.

Methods

We searched Medline, Embase, Lilacs, the Cochrane Library, and the Interscience Conference on Antimicrobial Agents and Chemotherapy up to the year 2002. The terms "neutropenia" and similar and "aminoglycoside" or specific aminoglycosides were crossed. References of all included trials and reviews identified were scanned for additional studies. We put no restrictions on language, year of publication, or publication status.

We included all randomised trials that compared treatment with any β lactam alone with any combination of a β lactam and an aminoglycoside, for the empirical treatment of patients with fever and neutropenia. We excluded studies with a dropout rate above 30%, unless intention to treat analysis was carried out for mortality or failure outcomes.

Two reviewers independently applied inclusion and exclusion criteria and extracted the data. Allocation generation and concealment,[6 7] blinding, method of analysis (intention to treat or per protocol), number of dropouts, randomisation unit (patient or episode), follow up, and publication status were recorded. Authors of all included trials were contacted for complementary information.

Our primary outcome was all cause fatality at the end of follow up and up to 30 days after treatment was stopped. Our secondary outcomes included failure of treatment (defined as death, persistence, recurrence, or worsening of presenting infection, and any modifica-

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A list of all identified studies can be found on bmj.com

tions to the assigned antibiotic treatment); bacterial and fungal superinfections; colonisation; and adverse events. Predefined subgroups were patients with haematological cancer, severe neutropenia (<100/mm^3), bacteraemia, documented infections, and *Pseudomonas aeruginosa* infections.

We pooled relative risks using a random effect model and compared them with a fixed effect model.[8] Analyses were performed by intention to treat, unless data were given only for those patients who could be evaluated. We assessed heterogeneity with χ^2 test. As we anticipated heterogeneity between studies comparing the same β lactam and studies comparing different β lactams[9] we separated analysis of these trials. The effect of measures of quality was examined through sensitivity analysis. A funnel plot of log of the relative risk against the sample size was examined to estimate potential selection bias (such as publication bias) and to assess whether effect estimates were associated with study size. We used the inverse of the variance to calculate pooled means for all studies and tested correlations for significance with a non-parametric test (Spearman).

Results

We evaluated 72 eligible randomised trials (see bmj.com for full list of references) and included 47 in the review (fig 1). The trials included 7807 patients and 8803 febrile episodes (28 to 1034 patients per trial) and took place from 1981 to 2000. Nine trials compared the same β lactam, while all other trials compared one β lactam with a different, narrower spectrum β lactam combined with an aminoglycoside.

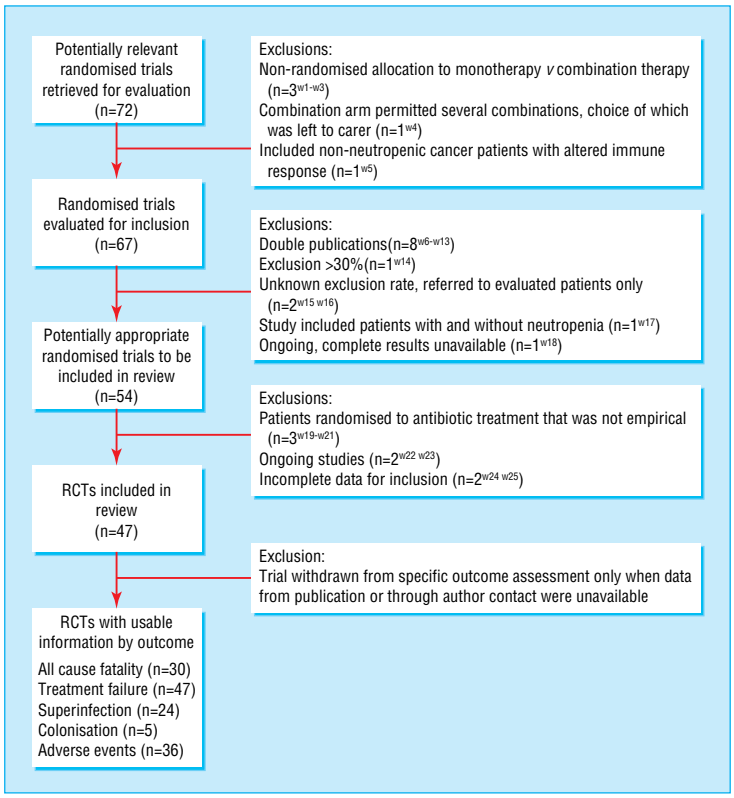

Fig 1 Trials identified for study and exclusions

In 21 trials (45%) randomisation procedures were adequate, and eight (17%) were blinded (table 1). Intention to treat analysis for failure was possible in 17 of the 47 trials and for fatality in 18 of 30 trials. The median dropout rate was 9%. In 31 trials episodes of fever were the unit of randomisation. and the number of participating patients was given in 25 (81%), and the episode to patient ratio varied from 1.03 to 1.63 among trials.

Many patients (89%) had haematological malignancies, and 61% had severe neutropenia (<100/mm^3) on admission. Eight trials included children, five being restricted to children below 16 years. The adjusted mean percentage of documented infections was 56%, with rates varying from 24% to 94%. Bacteraemia was present in 24% of patients (4-57%). *P aeruginosa* was isolated in less than 2% (0-13%) of included patients, constituting 15% (0-44%) of all documented Gram negative isolates. Gram positive bacteria were identified more commonly than Gram negative bacteria in two third of the trials.

Eighteen studies compared resistance rates of pathogens isolated on admission in the two treatment arms. In 12 of these studies, resistance to the β lactam in the combination therapy was more common than resistance to the β lactam in monotherapy (when these differed). Resistance was similar in two studies. However, when we considered the combined coverage offered by the aminoglycoside and the β lactam of the combination arm, resistance rates were similar for both arms.

All cause fatality

The average all cause fatality was 6.2%, with a decline in fatality correlating with advancing year of the study (r_s=−0.43, P=0.03). Comparative fatality data were obtained for 30 trials (fig 2). When all studies were combined there was no significant difference between monotherapy and combination therapy (relative risk 0.85, 95% confidence interval 0.72 to 1.02). Five trials compared the same β lactam (0.73, 0.49 to 1.08), and 24 studies compared different β lactams (0.89, 0.73 to 1.08). No significant differences in fatality were present among all subgroups tested (table 2).

Treatment failure

When we combined all studies we found an advantage with monotherapy (0.92, 0.85 to 0.99, 47 trials), but there was significant heterogeneity among trials (χ^2 73.28, df=46, P=0.0064, fig 3). There was no significant difference between monotherapy and combination therapy in trials that compared the same β lactam in both arms (nine trials, 1.12, 0.96 to 1.29), whereas there was a significant benefit with monotherapy in trials that compared different β lactams (0.87, 0.80 to 0.93, 38 trials). Among subgroups, there was a significant advantage with monotherapy for patients with documented infections and those with haematological malignancy. No correlation was observed between treatment failure and fatality in the studies (r_s=0.03, P=0.9, 29 trials). Rates of treatment failures did not decline in recent years nor was the variance between studies reduced.

Superinfections and colonisation

Superinfections developed with similar frequencies after combination or monotherapy (0.97, 0.82 to 1.14,

Table 1 Characteristics of included studies

	Monotherapy	Combination therapy	Patients/ episodes	Neutropenia (/mm³)	Haematological cancer (%)	Documented infection (%)	Bacteraemia (%)	Allocation concealment*	Allocation generation (blinding)†
Adults									
Akova 1999§[w26]	Meropenem	Ceftazidime-amikacin OD	NS/83	500	78	63.9	16.9	A	A
Alanis 1983[w27]	Moxalactam	Nafcillin-tobramycin	86/108	1000	85	73.1	NS	A	A
Au 1994[w28]	Imipenem	Ceftriaxone-gentamicin	56	1000	NS	28	14	B	B
Behre 1998§[w29]	Meropenem	Ceftazidime-amikacin	71/78	500	55	41	28.2	A	B
Bezwoda 1985[w30]	Moxalactam	Cephradine-tobramycin	63	1000	65	100	30	B	B
Cornelissen 1992[w31]	Imipenem	Cefuroxime or cephalotin-gentamicin	93/100	500	75	81.9	30.9	B	B
De la Camara 1997§[w32]	Meropenem	Ceftazidime-amikacin	103	500	100	54.8	44.1	A	A
De Pauw 1983[w33]	Ceftazidime	Cefotaxime-gentamicin	87	1000	100	NS	NS	B	B
De Pauw 1994§[w34]	Ceftazidime	Piperacillin-tobramycin	1012/1086	500	83	58.7	33.5	A	A
Del Favero 200[w35]	Piperacillin/ tazobactam	Piperacillin/ tazobactam-amikacin	760	500	81	49.2	37.8	A	A (DB)
Dincol 1998§[w36]	Imipenem	Cefoperazone/ sulbactam-amikacin OD	97/150	500	43	73.3	10	B	A
Doyen 1983‡[w37]	Ceftazidime	Ceftazidime-amikacin	83/104	500	100	93.8	41.2	B	B
Erjavec 1994[w38]	Imipenem	Cefuroxime-tobramycin	127/179	500	100	54.5		B	B
Gibson 1989[w39]	Ceftazidime	Azlocillin- amikacin	102	1000	100		24.5	A	A
Glasmacher 1999‡[w40]	Piperacillin/ tazobactam	Ceftriaxone-gentamycin OD	130/212	500	100	51.9	19.1	A	A
Gribble 1983[w41]	Piperacillin	Carbenicillin-gentamicin	NS/30	1000	NS	NS	NS	B	A
Hansen 1986[w42]	Latamoxef	Carbanicillin-gentamicin	NS/40	1500	0	NS	12.1	B	B
Hess 1998[w43]	Piperacillin/ tazobactam	Ceftazidime-amikacin OD	83/107	500	67	80.4	36.4	A	A
Kojima 1994§[w44]	Imipenem	Imipenem-amikacin	60/70	1000	0	67	7.5	A	B
Leyland 1992[w45]	Imipenem	Piperacillin-gentamicin	234/312	1000	100	44	33	A	B (SB)
Lieschke 1990‡[w46]	Imipenem	Piperacillin-tobramycin	150/182	1000	55	26.9	16.5	A	B
Liu 1989[w47]	Imipenem	Ceftriaxone-amikacin or ceftazidime-amikacin	28	500	67	55.6	23.3	B	B
Marie 1991[w48]	Ceftazidime	Ceftazidime-amikacin	NS/146	500	NS	NS	NS	A	A
Matsui 1991§[w49]	Imipenem	Moxalactam-tobramycin	98/101	1000	0	100	4	A	A (SB)
Norrby 1987§[w50]	Imipenem	Piperacillin-amikacin	210	1000	93	57.1	14.3	A	B
Novakova 1990[w51]	Ceftazidime	Piperacillin-amikacin	83/90	500	100	NS	30	A	A
Novakova 1991[w52]	Ceftazidime	Ceftazidime-amikacin	82/90	1000	100	100	23.3	A	A
Ozyilkan 1999§[w53]	Imipenem	Cefoperazone/ sulbactam-amikacin	30	1000	93	70	56.7	A	A (DB)
Pegram 1984‡[w54]	Moxalactam	Ticarcillin-tobramycin	NS/140	1000	NS	70	32.1	B	B
Pellegrin 1988[w55]	Ceftazidime	Cefotaxime-tobramycin	157	500	100	77.7	27.4	B	A
Perez 1995[w56]	Imipenem	Ceftazidime-amikacin	52/60	500	88	68.3	48.3	B	A
Piccart 1984[w57]	Cefoperazone	Cefoperazone-amikacin	49	1000	55	67.3	55.1	B	B
Pickard 1982‡[w58]	Moxalactam	Ticarcillin-tobramycin	NS/80	1000	54	72.5	45	A	A
Piguet 1988[w59]	Ceftazidime	Cefotaxime-amikacin	NS/174	500	100	56	30.2	B	B
Rodjer 1987[w60]	Ceftazidime	Cefuroxime-tobramycin	52/61	1000	90	44.8	37.9	B	B
Rolston 1992[w61]	Ceftazidime imipenem	Ceftazidime-amikacin Imipenem-amikacin	NS/908	1000	67	46.5		B	A (SB)
Tamura 2002[w62]	Cefepime/ carbapenem	Cefepime-aminoglycoside	165	1000	89	24	8.5	B	B
Wade 1987¶[w63]	Imipenem	Piperacillin-amikacin	NS/460	1000	NS	64.6	14.3	B	B (DB)
Yamamura 1997§[w64]	Cefepime	Piperacillin-gentamicin	111	1000	65	49.5	23.4	A	A
Adults and children									
Borbolla 2001[w65]	Cefepime	Ceftriaxone-amikacin OD	40	500	100		15	B	B
Cometta 1996[w66]	Meropenem	Ceftazidime-amikacin OD	1034	1000	72	47.5	22	A	A (SB)
Kinsey 1990[w67]	Ceftazidime	Ceftazidime-gentamicin	139/205	500	100		46.2	B	B
Children									
Agaoglu 2001§[w68]	Meropenem	Cefepime-netilmicin or ceftazidime-amikacin	82/87	1000	85	39.1	26.4	B	B
Duzova 2001§[w69]	Meropenem	Piperacillin-amikacin OD	NS/90	500	62	NS	23.3	B	B (SB)
Jacobs 1993[w70]	Ceftazidime	Ceftazidime-tobramycin	92/107	500	NS	32.2	23.3	B	B
Morgan 1983[w71]	Ceftazidime	Azlocillin-tobramycin	34/50	1000	68	44	28	B	B
Smith 1990§[w72]	Ceftriaxone	Azlocillin-netilmicin	63/100	500	87	NS	34	B	B

OD=once daily aminoglycoside treatment; NS=not stated; SB=single blind; DB=double blind.
*A=adequate (central randomisation, inaccessible computer randomisation, sealed envelopes); B=uncertain (no details concerning randomisation procedure, or methods unclear) C=inadequate (alternation, case record numbers, dates of birth or day of the week, open list of random numbers).
†A=any method resulting in adequate randomisation; B=uncertain procedure.
‡Conference proceedings, additional data/manuscripts obtained from authors.
§Complementary data from authors included in review.
¶Conference proceeding describes trial design, outcomes obtained from subsequent authors' reviews.[w72 w73]

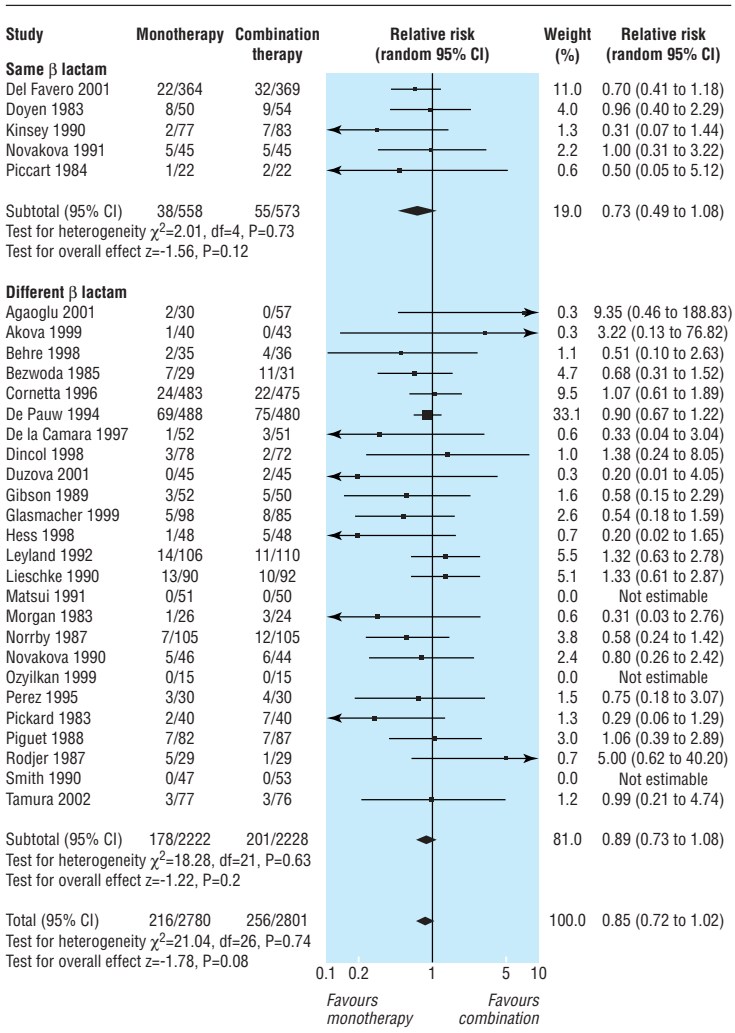

Fig 2 All cause fatality

for bacterial superinfections, 24 trials (fig 4); and 0.75, 0.51 to 1.10 for fungal super infections, 18 trials;). Only five studies compared colonisation, and none found any differences.[10]

Adverse events

Adverse events were significantly more common in the combination treatment group (figs 5 and 6). The difference was most remarkable for development of renal failure (0.49, 0.36 to 0.65) and was not influenced by single daily administration of the aminoglycoside. Likewise, discontinuation of study medication due to adverse events occurred was more common in the combination group (0.57, 0.36 to 0.91).

Compared with smaller trials, larger trials had relative risks closer to equivalence. When we looked at treatment failure, in trials that compared different β lactams and in which the number of randomised patients was below the median, monotherapy showed a highly significant advantage (0.73, 0.64 to 0.84), while larger studies showed no such advantage (0.94, 0.89 to 1.00, P=0.025 for the difference). The corresponding funnel plot for treatment failure generated a nearly symmetrical "funnel distribution." Sensitivity analyses by all quality measures did not reveal any effect on our results (fig 7).[10]

Discussion

Our results support the use of broad spectrum β lactam monotherapy in the empirical treatment of patients with fever and neutropenia. Most studies in our meta-analysis compared a new broad spectrum β lactam (carbapenem, ceftazidime, cefepime, piperacillin-tazobactam) with a combination of an "older" β lactam (usually an ureidopenicillin or a cephalosporin drug) and an aminoglycoside. In the comparisons the advantages of monotherapy were clear: a non-significant trend toward better survival, a significant advantage in preventing treatment failures, and fewer adverse effects. Fewer trials compared one β lactam with a combination of the same β lactam and an aminoglycoside. In these trials there were no significant benefits and more adverse effects, including severe ones, with the combination therapy. The shift of treatment failure risk-ratio towards combination therapy in these studies translates to some 20 patients who would have to be given an additional aminoglycoside to prevent one failure, which most commonly implies merely an antibiotic modification. Superinfections occurred equally with the two regimens. These results were consistent among all subgroups tested.

Synergism, proved in vitro, is usually the major reason given for combination therapy.[11–15] We found no clinical benefit associated with synergism. Combination treatment may provide broader spectrum coverage. Yet single aminoglycoside treatment, or combination treatment where pathogens are covered by the aminoglycoside alone, is inadequate.[16–18] Indeed, combination therapy was less effective than monotherapy in studies that compared different β lactams, although the spectrum of coverage was similar for both arms of these trials. Finally, combination therapy may prevent emergence of resistant pathogens.[19 20] We have

Table 2 Subgroup analysis, showing number of studies and episodes included in analysis with relative risk (RR) and 95% confidence intervals

	All cause fatality			Treatment failure (same β lactam)			Treatment failure (different β lactam)		
	Studies	Episodes	RR (95% CI)	Studies	Episodes	RR (95% CI)	Studies	Episodes	RR (95% CI)
All	30	5581	0.85 (0.72 to 1.02)	9	2178	1.12 (0.96 to 1.29)	38	5920	0.87 (0.80 to 0.93)
Documented infections	12	1158	0.78 (0.52 to 1.15)	7	1006	1.05 (0.89 to 1.23)	23	2614	0.88 (0.82 to 0.96)
Bacteraemia	11	583	0.69 (0.39 to 1.22)	5	384	1.04 (0.89 to 1.21)	18	1054	0.87 (0.74 to 1.02)
Gram negative infections	13	328	0.67 (0.35 to 1.27)	7	261	1.50 (0.80 to 2.79)	21	603	0.68 (0.50 to 0.93)
Pseudomonas infections	7	58	0.78 (0.24 to 2.56)	3	49	1.46 (0.23 to 9.41)	12	90	0.87 (0.54 to 1.41)
Haematological cancer	13	2188	0.78 (0.58 to 1.06)	4	361	0.92 (0.76 to 1.12)	13	2287	0.83 (0.73 to 0.96)
Severe neutropenia	5	677	0.66 (0.35 to 1.26)	2*	237	1.49 (1.13 to 1.97)	6	757	0.94 (0.75 to 1.18)
Adults >16 years	21	3205	0.88 (0.72 to 1.08)	6	1173	1.21 (1.07 to 1.37)	25	3503	0.83 (0.75 to 0.92)
Children	4	327	0.75 (0.08 to 7.11)	1*	91	2.74 (1.08 to 6.98)	4	327	0.94 (0.64 to 1.39)

*Significant advantage to combination therapy.

shown that superinfection rates after combination or monotherapy were similar. Information regarding colonisation was scarce. In a recent review that compared single versus combination therapy for patients with cystic fibrosis, monotherapy was associated with an increased risk of carriage of resistant *P aeruginosa* at follow up, but duration of treatment was longer.[9] As we could assess only superinfections, we can conclude that for the individual patient, during a specific episodes of infection, differences in development of resistance are clinically non-significant. Adverse events, as expected, were more common with combination therapy, and the risk was not reduced by the use of once daily aminoglycoside dosing.

The European Organisation for Research and Treatment of Cancer's EORTC IV trial is often quoted in support of combination therapy. It showed a significant advantage, for failure only, with combination therapy given for longer than 72 hours among a subgroup of patients with Gram negative bacteraemia.[21] These findings are not supported by our subgroup analyses, which included 1438 episodes of bacteraemia and 864 documented Gram negative infections.

Limitations of study

We detected a sample size bias for treatment failure, with smaller studies exaggerating the beneficial effect of monotherapy. As smaller studies did not consistently differ from larger trials with respect to severity of disease, methods, or therapy, this may reflect publication bias. Most studies used febrile episodes as the unit of randomisation, allowing patients to re-enter the trial. As outcomes for re-entering patients are not independent, results may have been affected. Intention to treat analysis was possible in just over half the included trials, and adequate randomisation procedures were used in less than half of these trials. Sensitivity analyses did not detect an effect of these measures on our results.

The major caveat with respect to the interpretation of our results is the lack of data on fatality in some of the trials. Survival should be the primary outcome as it is ultimately the objective of treatment for these patients.[22] Admittedly, only a small part of the variance in fatality is explained by infection. Appropriate randomisation, however, should ensure similar distribution of risk factors for death not related to infection between the study groups. Treatment failure, whether defined as modifications to treatment or delayed resolution of fever, is subjective and clinically less meaningful. Finally, for failure to have some prognostic importance it should correlate with fatality, and we have shown that in these studies a correlation did not exist.

Implications for practice and research

From our results we consider that broad spectrum monotherapy should be the standard treatment for patients with fever and neutropenia. Studies of antibiotic treatment in these patients should adhere to better standards of methods and reporting. Specifically, the unit of randomisation should be the patient not the episode. Future trials of combination treatment should be performed only to address issues where doubt still exists. Synergism should be specifically assessed by comparing the same β lactam in both arms of the study.

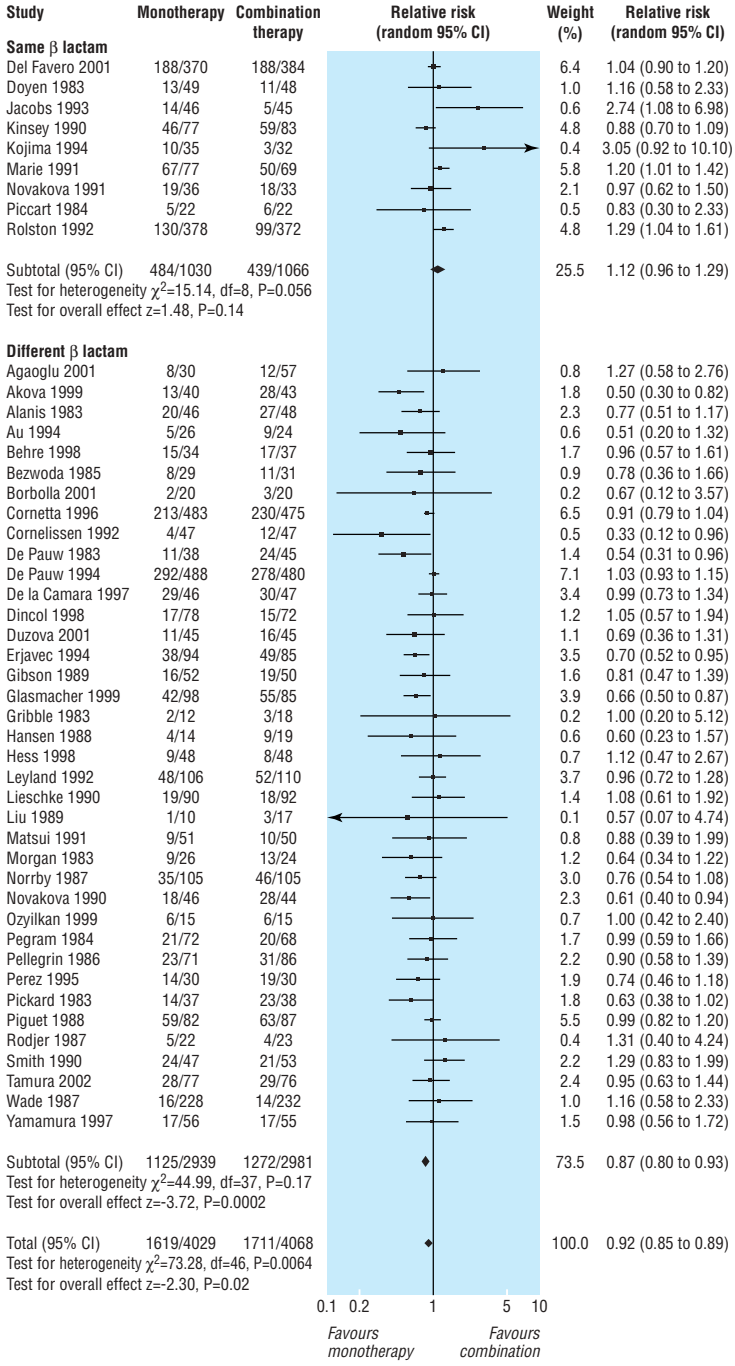

Fig 3 Treatment failure

Studies should use all cause fatality as the primary outcome. The low fatality (lower in recent years) translates into a large sample size. Survival of patients, however, is the underlying reason for empirical treatment with antibiotics for fever with neutropenia.

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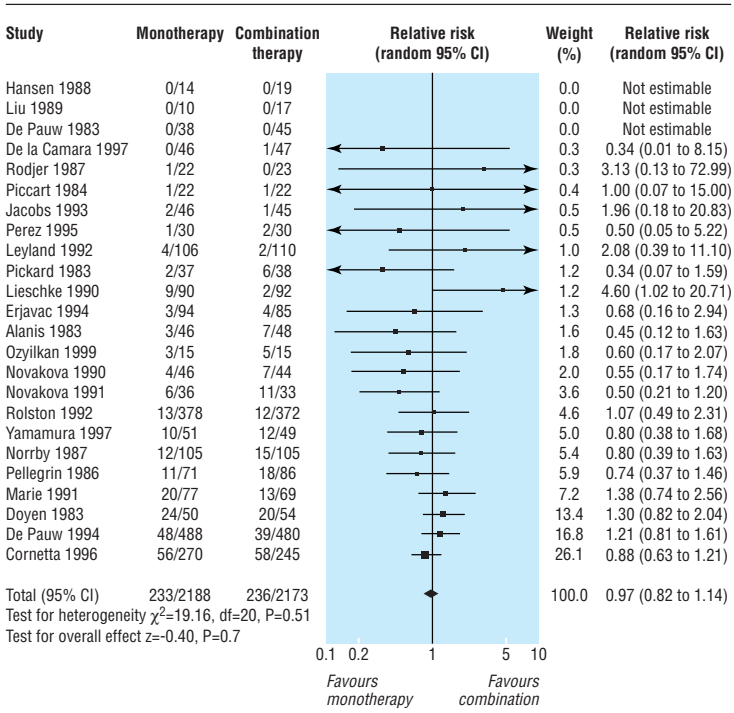

Fig 4 Bacterial superinfections

What is already known on this topic

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

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

What this study adds

There is no survival advantage with combination therapy

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

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

S W Hansen); A Glasmacher and G J Lieschke who supplied their full unpublished manuscripts; G Keddie and B Wilks of AstraZeneca for supplying their available data; and G P Bodey for his response and comments. Partial results were presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, December 2001, Chicago. A more detailed version of this review is also published in the Cochrane Library where it will be updated if further data become available.[10]

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 in 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.

1 Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730-51.
2 Paesmans M. Risk factors assessment in febrile neutropenia. *Int J Antimicrob Agents* 2000; 16: 107-11.
3 Elting LS, Rubenstein EB, Rolston KV, Bodey GP. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997;25:247-59.
4 Pizzo PA, Hathorn JW, Hiemenz J, Browne M, Commers J, Cotton D, et al. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986;315:552-8.
5 Kramer BS, Ramphal R, Rand KH. Randomized comparison between two ceftazidime-containing regimens and cephalothin-gentamicin-carbenicillin in febrile granulocytopenic cancer patients. *Antimicrob Agents Chemother* 1986;30:64-8.
6 Clarke M, Oxman AD, eds. *Cochrane reviewers' handbook 4.1.4*. Oxford: Update Software, 2001.
7 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.
8 Der Simonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
9 Elphick HE, Tan A. Single versus combination intravenous antibiotic therapy for people with cystic fibrosis. *Cochrane Database Syst Rev* 2003;(1):CD002007.
10 Paul M, Soares-Weiser K, Grozinsky S, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropaenia. *Cochrane Database Syst Rev* 2003;(1):CD003038.
11 Giamarellou H, Zissis NP, Tagari G, Bouzos J. In vitro synergistic activities of aminoglycosides and new beta-lactams against multiresistant Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1984;25:534-6.
12 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.
13 Klastersky 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.
14 Klastersky J, Zinner SH. Synergistic combinations of antibiotics in gram-negative bacillary infections. *Rev Infect Dis* 1982;4:294-301.
15 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.
16 Leibovici L, Paul M, Poznanski O, Drucker M, Samra Z, Konigsberger H, et al. Monotherapy versus beta-lactam-aminoglycoside combination treatment for gram-negative bacteremia: a prospective, observational study. *Antimicrob Agents Chemother* 1997;41:1127-33.
17 Bodey GP, Middleman E, Umsawadi T, Rodriguez V. Infections in cancer patients. Results with gentamicin sulfate therapy. *Cancer* 1972; 29:1697-701.
18 Klastersky J, Glauser MP, Schimpff SC, Zinner SH, Gaya H. Prospective randomized comparison of three antibiotic regimens for empirical therapy of suspected bacteremic infection in febrile granulocytopenic patients. *Antimicrob Agents Chemother* 1986;29:263-70.
19 Mouton JW. Combination therapy as a tool to prevent emergence of bacterial resistance. *Infection* 1999;27:S24-8.
20 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.
21 EORTC. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. The EORTC International Antimicrobial Therapy Cooperative Group. *N Engl J Med* 1987;317:1692-8.
22 Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *N Engl J Med* 1971;284:1061-5.

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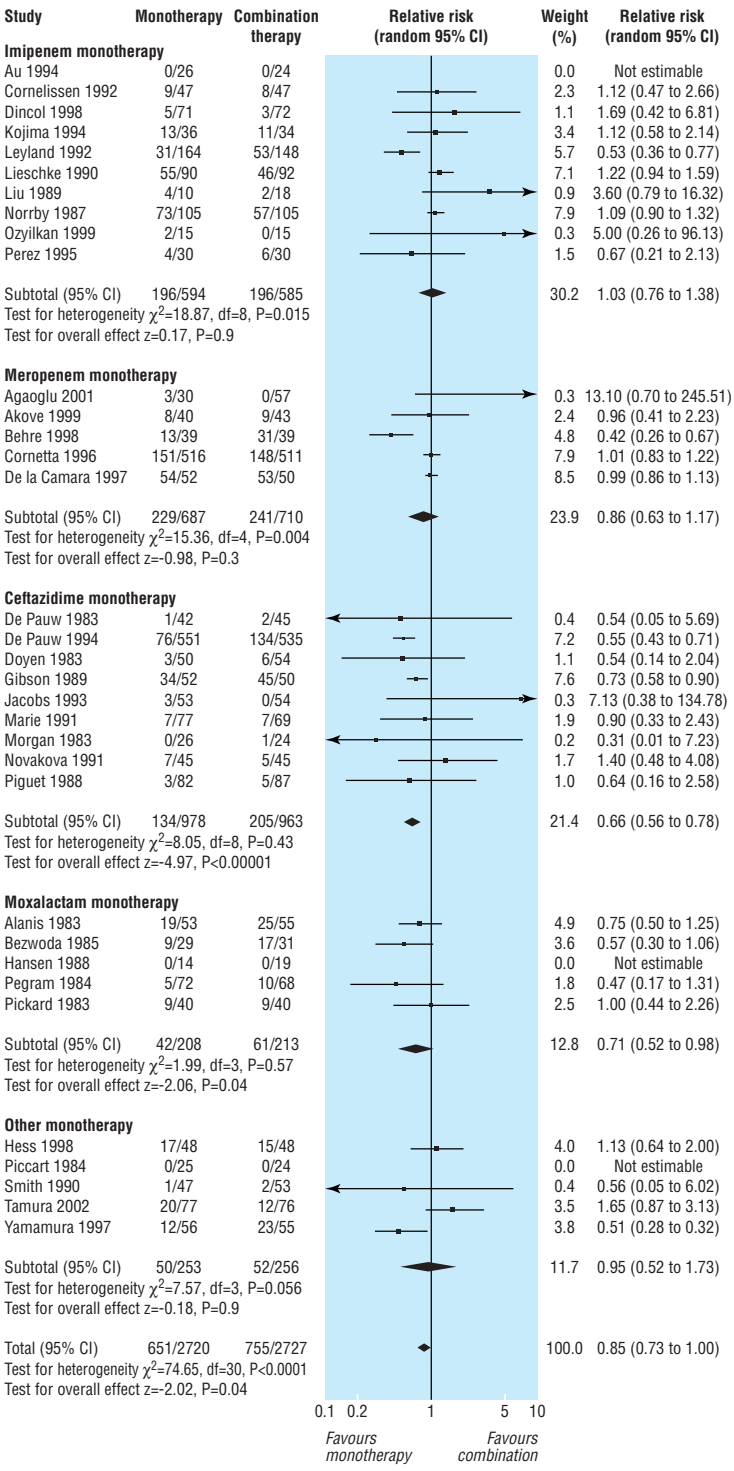

Fig 5 Any adverse event

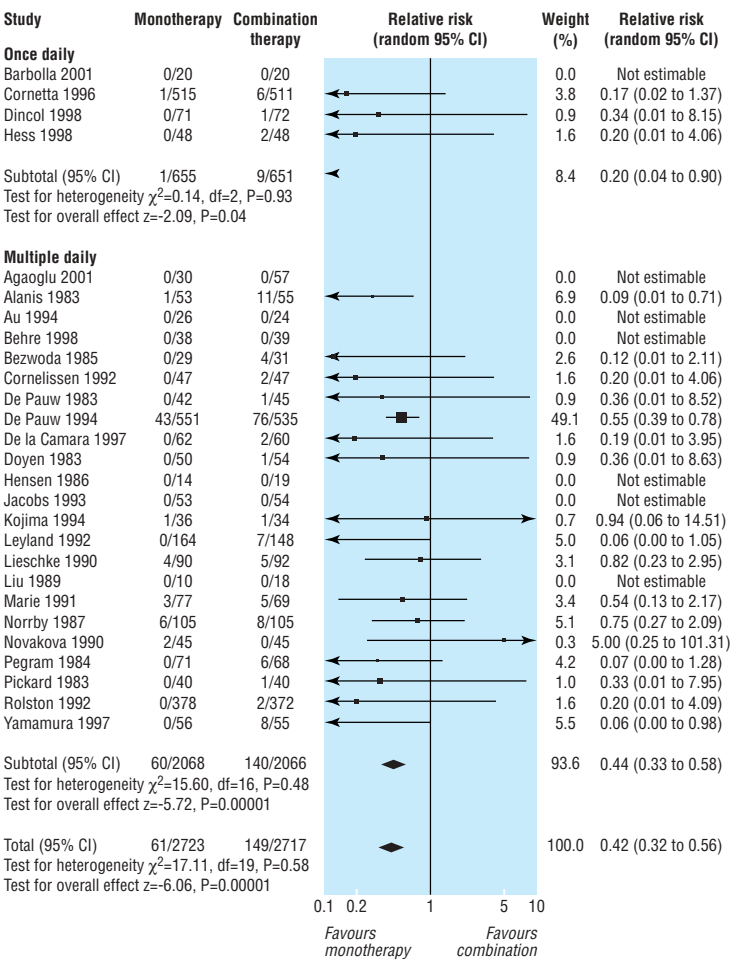

Fig 6 Nephrotoxicity

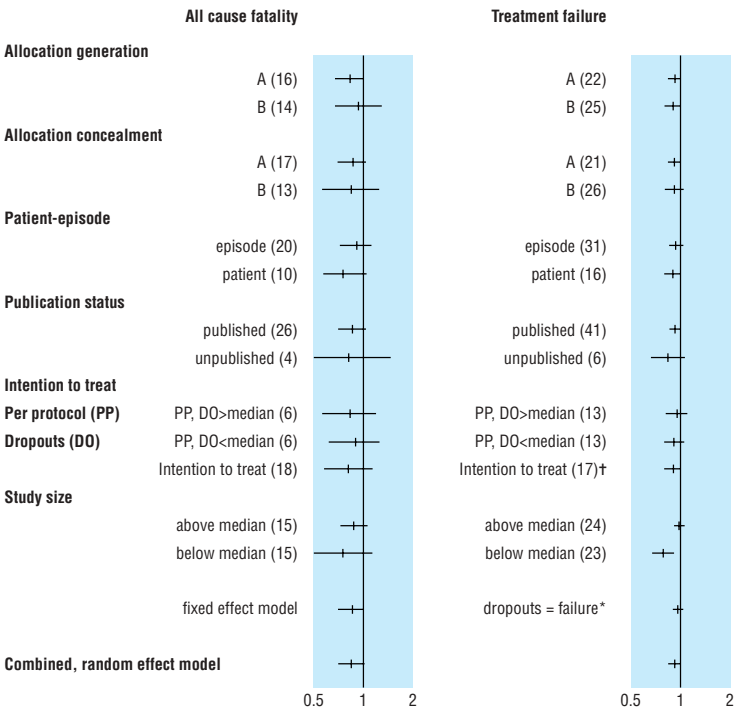

Fig 7 Sensitivity analysis. Number in parenthesis refers to number of studies included in analysis. Studies in which number of dropouts for failure analysis was not specified are not included. †Analysis performed counting all dropouts as treatment failures