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REVIEW ARTICLE

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Ceftriaxone versus β-lactams with antipseudomonal activity for empirical, combined antibiotic therapy in febrile neutropenia: a meta-analysis

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Abstract The object of this work was to compare the efficacy of antibiotic combinations including ceftriaxone with that of combinations including an antipseudomonal β-lactam for the empirical treatment of febrile neutropenia in cancer patients. We identified all published randomised trials comparing two antibiotic combinations differing only in the β-lactam, being ceftriaxone in one treatment group and an antipseudomonal β-lactam in the other. The quality of individual trials was formally evaluated. A meta-analysis was performed using the Peto-modified Mantel-Haenszel method for combining binary data. Primary analysis was done, for both febrile episodes and bacteraemic episodes, using failure of empirical antibiotic treatment defined as modification of the initial allocated regimen or death during treatment. Secondary analysis was done using death from any cause in the two treatment groups. Data relating to 1,537 febrile neutropenic episodes recorded in eight randomised clinical trial were pooled s. Overall, there were 256 treatment failures out of 782 febrile episodes treated with ceftriaxone-containing combinations (32.7%), and 243 out of 755 treated with antipseudomonal β-lactam regimens (32.1%). The pooled odds ratio of failure for ceftriaxone-containing combinations for febrile episodes was 1.04, with the 95% confidence interval ranging from 0.84 to 1.29, and that for bacteraemic episodes was 0.93 (95% confidence interval 0.58–1.49). With regard to overall mortality, there were 54 deaths among 782 febrile episodes treated with ceftriaxone-containing combinations (6.9%) and 62 deaths among 755 febrile episodes treated with antipseudomonal β-lactam-containing regimens (8.2%). The pooled odds ratio of death for ceftriaxone regimens was 0.84 (95% confidence interval 0.57–1.24). Results of this meta-analysis show that in the empirical treatment of febrile neutropenia, antibiotic combinations containing ceftriaxone are as effective as those in which the β-lactam has specific activity against *Pseudomonas aeruginosa*, such as ureidopenicillin or ceftazidime.

Key words Meta-analysis · Ceftriaxone · Fever · Neutropenia · Antipseudomonal β-lactam

Introduction

Infections are the main cause of death in neutropenic patients with onco-haematological malignancies undergoing chemotherapy with or without bone marrow transplantation. Empirical antibiotic treatment at the onset of fever has been shown to decrease the rate of morbidity and mortality attributable to infections [21].

Several antibiotic combination regimens have been used to provide a broad spectrum of coverage, a synergistic effect and high bactericidal serum antibiotic levels and to avoid the emergence of resistant organisms. A combination of an aminoglycoside and an antipseudomonal beta-lactam has usually been selected to provide adequate coverage against life-threatening gram-negative infections, particularly those caused by *Pseudomonas aeruginosa* [11, 13]. However, in recent years, a decrease of gram-negative infections and a concurrent increase in gram-positive infections in neutropenic patients has been reported worldwide. Consequently, the possibility of modifying the antibiotic regimen for empirical treatment has arisen [10, 14, 20].

Ceftriaxone (CRO) is a third-generation cephalosporin with good activity against many gram-negative bacteria, but limited activity against *Pseudomonas aeruginosa*. It has been used for febrile neutropenic patients in combination with an aminoglycoside and/or a glycopeptide, and these combinations were shown to have good efficacy and be well tolerated in randomised clinical trials [4, 8, 9, 12, 17, 18, 24, 27]. However, in these studies the samples were generally small, leaving some doubt about the feasibility of using CRO instead of an antipseudomonal β-lactam.

The considerable decrease in the number of *Pseudomonas aeruginosa* infections in many onco-haematological institutions, the ease of once-daily administration of CRO and its lower acquisition cost compared with antipseudomonal β-lactams make CRO a very attractive alternative drug for empirical therapy of febrile neutropenic patients. These considerations prompted us to perform a systematic review (meta-analysis) of published studies to evaluate and compare the efficacy of antibiotic combinations containing CRO and those containing an antipseudomonal β-lactam for the empirical treatment of febrile neutropenic patients.

Methods

Overview

We developed a working protocol for the systematic review of all published randomised clinical trials in which patients with febrile neutropenia were allocated to receive either an antibiotic combination containing ceftriaxone as β-lactam or an antibiotic combination containing an antipseudomonal β-lactam. We assessed the quality of the relevant trials, pooled data across trials to assess comparative efficacy, and examined the effect of some characteristics of study design and patient population on relative efficacy [5, 16, 23].

Literature search strategy

Several strategies were used to identify all published studies of interest. We scanned the literature by a formal computer-assisted search of Medline from 1966 to 1997. The principal keywords and subject headings used were: ceftriaxone, ceftriaxon, granulocytopenia, neutropenia, fever, controlled, randomised, clinical trial, antipseudomonal, β-lactam, antibiotic and bacteraemia.

The drug manufacturer was also requested to provide all published studies and unpublished files from the central internal product information database on ceftriaxone that would be relevant to the subject of this meta-analysis. We also performed a manual search of bibliographies of pertinent studies and reviews.

Inclusion criteria

The features required for a study to be included in our meta-analysis were: controlled randomised design, a combination of antibiotics containing CRO as the β-lactam for the experimental group and an antibiotic combination containing an antipseudomonal β-lactam for the control group, patient population with fever ($\geq 38\,^{\circ}C$) and neutropenia (< 1000 cells/mm^3). Some individual trials allowed patients to enroll in the given study more than once during multiple neutropenic febrile episodes, and all episodes were then included in the meta-analysis.

Data extraction

Data of each study were gathered independently by two people familiar with the clinical topic and blinded to author, title and journal; their reports were cross-checked to avoid possible errors. The items of information extracted from each study were: number and ages of patients enrolled, drugs, dose and schedule of administration in the control and experimental groups, type of underlying disease, definition of neutropenia (degree and duration), adverse effects, number of failures and successes in each treatment group, number of deaths, number of exclusions or withdrawals.

Outcome measure

The outcome measure we considered was failure of antibiotic treatment. Different analyses of the data set were performed according to two different definitions of treatment failure.

First, we analysed failure of empirical therapy without modification, that is an inadequate clinical response requiring a change or addition of antibiotics to the initial regimen, whatever the eventual outcome (primary outcome measure). Then we analysed failures defined as overall deaths with or without modification of the initial therapy (secondary outcome measure).

Quality assessment

We evaluated the quality of randomised clinical trials, modifying a widely known method of quality assessment previously used by others [3, 22]. A total of 20 items, 9 on study design and 11 on data analysis and results presentation, were considered. Two re-

viewers independently assigned a score to each item. When the two reviewers disagreed, their disagreement was discussed and a consensus was reached. The maximum possible score achievable by each study was 75 points; 64%, 28% and 8% of this total score was for study design, data analysis and results presentation, respectively. A score was assigned to each item when the item was applicable. Then the total score gained in each study was divided by the maximum possible score applicable for the given study. Scores of non-applicable items were not counted in the denominator. Table 1 shows the items of quality assessment and points attributed to each item.

Statistical methods

The statistical method used to assess the relative efficacy of CRO combinations versus antipseudomonal β-lactam combinations was the Peto-modified Mantel-Haenszel fixed-effect method for combining binary data [1, 19, 28]. For each trial the number of failures observed (O) in the CRO group was contrasted with the number of failures that would have been expected (E), on the assumption that the two treatments being compared were equally effective. Consequently, if the CRO combination was superior to the control treatment the O–E value would have tended to be negative. The variance (V) of the difference between the observed number and the expected number was also computed. For each trial the odds ratio (OR) of failure for the CRO regimen (CRO/control) was estimated as exp [(O–E)/V]. To combine results from individual trials without bias the values of O–E were summed over the whole set of trials to obtain the grand total (GT). The overall variance (V_t) of this GT was obtained likewise by summing the separate variances of individual trials. A "typical odds ratio" of failure for the CRO regimen was estimated in the trials that contributed to the grand total as exp (GT/V_t) with a 95% confidence interval (CI) estimated as $\exp(GT/V_t \pm 1.96/\sqrt{V_t})$. With these definitions a point estimate of $OR < 1.0$ favours CRO-containing combinations and the observed difference is statistically significant when its CI does not include 1.0, the point of equal efficacy. A Chi-square test for heterogeneity of treatment effects between different trials was also performed to assess the appropriateness of pooling [1]. A subgroup analysis was performed to examine how the pooled OR of failure of CRO combinations might change when calculated for specific subsets of trials according to selected characteristics of the study population, study design and treatment regimens, such as age of patients (older than 14 years), bacteraemic episodes, severity of neutropenia (less than 500 neutrophils/mm^3), high quality of trials (only trials with quality score equal to or above the mean for all trials), aminoglycoside-containing regimens.

Table 1 Selected items and maximum possible score of the study quality assessment instrument

Item description	Maximum possible score
Study design	
1. Selection criteria	3
2. List of patients excluded	3
3. Description of therapeutic regimens	3
4. Blinding of randomisation	10
5. Blinding of patients to treatment	8
6. Blinding of physicians to treatment	8
7. Blinding of physicians and patients to ongoing results	4
8. Prior sample size estimation	3
9. Testing of randomisation	3
Data analysis and presentation	
10. Statistical significance of major endpoints	3
11. Confidence intervals	2
12. Mention of power post hoc	3
13. Overall statistical methods	4
14. Listing of withdrawals	3
15. Handling of withdrawals	4
16. Dates of study	2
17. Statistical analysis of randomisation testing	2
18. Tabulation of events employed as endpoints	2
19. Side effect discussion	3
20. Retrospective analysis of subgroups	2

Results

Description of the trials included

We identified eight published studies fulfilling our inclusion criteria, involving 1537 evaluable febrile episodes in neutropenic patients (range per trial from 17 to 694) [4, 8, 9, 12, 17, 18, 24, 27].

Table 2 describes the characteristics of the studies on which this meta-analysis was based. The studies were published between 1989 and 1997; for only five of the eight studies is the patients' enrollment period reported (between 1988 and 1992). All but two trials were conducted in a single centre. All trials had one or more concurrent control groups and a randomised assignment of treatment regimens. In no case was the allocated regimen administered in a blinded fashion. Inclusion and exclusion criteria and outcome measures were similar across the studies: in five of the eight studies patients were eligible with a neutrophil count of 500/mm^3 or less, whereas a neutrophil count of 1000/mm^3 or less was required for enrollment in the remaining three studies. The age of patients enrolled in overall studies ranged from 1 to 84 years; only three trials allowed enrollment of patients younger than 14 years of age. All trials included patients with both leukaemias and solid tumours; in four studies bone marrow-transplanted patients were included. In all trials, the assessment of pretreatment characteristics of the patient population failed to find any significant imbalance suggestive of possible biases in treatment allocation. In the eight studies there were 298 febrile episodes not evaluable for response to treatment, out of a total of 1,835 originally randomised to receive study drugs (global drop-out rate: 16%, range per trial from 0% to 22%); in one trial all the febrile episodes included were judged evaluable. The antibiotic combination regimens to be compared were CRO plus amikacin versus ceftazidime plus amikacin in six out of eight studies, CRO plus tobramycin versus azlocillin plus tobramycin in one study, and CRO plus teicoplanin versus ceftazidime plus teicoplanin in the remaining study (see Table 2). A standard dosage schedule of antibiotics was adopted in all trials

Table 2 Characteristics of trials included in the meta-analysis. In all studies treatment regimen was assigned randomly; in no study was treatment regimen administered in a blinded fashion (*CRO/Control* ceftriaxone combination / antipseudomonal β-lactam combination, *CRO* ceftriaxone, *CAZ* ceftazidime, *AMK* amikacin, *TOB* tobramycin, *AZL* azlocillin, *TEICO* teicoplanin, *neut* neutrophil count, *L* leukaemia, *L&BMT* leukaemia, including bone marrow-transplanted patients, *Ly* lymphoma, *ST* solid tumour, *O* other)

Reference	Age		Criteria for inclusion	Febrile episodes pooled (*n*)	Exclusions or withdrawals, CRO/control (*n*)	Ceftriaxone combination	Antipseudomonal β-lactam combination	Quality score
	Mean	Range						
[18]	51.5	16–76	38.5 °C, neut. <500/mmc	17 (2 of 3 arms)	0/1	CRO 2 g/day + AMK 7.5 mg/kg every 12 h	CAZ 2 g every 8 h + AMK 7.5 mg/kg every 12 h	0.23
[27]	50.6	17–76	38 °C, neut. <500/mmc	50	0/0	CRO 2 g/day + AMK 500 mg every 12 h	CAZ 2 g every 12 h + AMK 500 mg every 12 h	0.18
[24]	49.4	14–84	38 °C, neut. <1000/mmc	83	10/7	CRO 3 g/day + AMK 7.5 mg/kg every 12 h	CAZ 1.5 g every 6 h + AMK 7.5 mg/kg every 12 h	0.31
[9]	51	17–79	38 °C, neut. <1000/mmc	92	0/3	CRO 2 g/day + TOB 5 mg/kg per day	AZL 4 g every 6 h + TOB 1.5 mg/kg every 6 h	0.36
[17]	50	11–79	38 °C, neut. <500/mmc	138	4/2	CRO 2 g/day + AMK 20 mg/kg per day, single or three divided doses	CAZ 2 g every 8 h + AMK 20 mg/kg per day, three divided doses	0.24
[12]	28.7	1–84	38 °C, neut. <1000/mmc	694	77/87	CRO 30 mg/kg per day or 80 mg/kg per day (children) + AMK 20 mg/kg per day	CAZ 33 mg/kg q8 h + AMK 20 mg/kg per day, three divided doses	0.68
[8]	42.6	16–74	38 °C, neut. <500/mmc age>16 years	99	1/2	CRO 2 g/day + TEICO 400 mg/day	CAZ 2 g every 8 h + TEICO 400 mg/day	0.43
[4]	6.5	1–17	38 °C, neut. <500/mmc	364	51/53	CRO 80 mg/kg per day (max. 2 g) + AMK 20 mg/kg per day	CAZ 50 mg/kg every 8 h (max. 2 g daily) + AMK 6.5 mg/kg every 8 h	0.46

but one, in which ceftazidime 2 g was given every 12 h.

Quality assessment

A total of 160 items were scored by two reviewers independently. The agreement in their initial score was complete in 86% of the items, whereas in 13% there was an agreement within one grading level. After discussion a consensus was reached in all items. Study quality scores ranged from 0.18 to 0.68 (Table 2); the mean score was 0.36. Table 3 shows the global quality score gained for each item relative to study design, data analysis and results presentation in the eight studies considered. Most of the studies achieved the maximum possible score in only four items: selection criteria, listing of withdrawals, dates of study and tabulation of events employed as endpoints. There were three items for which all studies achieved the minimum possible score: list of patients excluded, blinding of patients to treatment and blinding of physicians to treatment.

Pooled ORs of meta-analysis

Figure 1 shows the individual ORs of failure defined as death or modification of the initially allocated regimen (primary outcome measure) of CRO combinations compared with antipseudomonal β-lactam combinations for each of the eight published studies included in the meta-analysis. The ORs for individual studies varied fairly widely, ranging from 0.51 to 1.37 and favouring CRO combinations in three of the eight trials and the comparator in the remaining five trials. Confidence intervals (95% CI) were wide, with the lower value ranging from 0.05 to 0.86 and the upper value ranging from 0.99 to 11.69. All but one of the CIs of individual trials encompassed the point of efficacy equivalence. When data from individual trials were pooled, the point estimate of the typical OR of CRO combination failure was 1.04, with an estimated 95% CI ranging from 0.84 to 1.29, showing no significant difference in efficacy of CRO regimens compared with antibiotic combinations containing an antipseudomonal β-lactam. The suitability of combining data across individual trials was corroborated by a non-significant Chi-square test for heterogeneity of treatment effects (χ^2 6.1, 7 *df*, $P>0.3$). Figure 2 shows the pooled OR of failure of CRO combinations when failure was redefined as eventual mortality (secondary outcome measure) disregarding any modification of the empirical antibiotic treatment. Although the point estimate of the pooled OR slightly favoured CRO combinations (OR 0.84) the difference was not significant, since the 95% CI ranging from 0.57 to 1.24, included the point of equal efficacy. A heterogeneity

Table 3 Performance of studies on selected quality items

Item description	No. of clinical trials achieving		
	Highest score for item	Intermediate score for item	Lowest score for item
Study design			
1. Selection criteria	6	2	0
2. List of patients excluded	0	0	8
3. Description of therapeutic regimens	3	5	0
4. Blinding of randomisation	2	0	6
5. Blinding of patients to treatment	0	0	8
6. Blinding of physicians to treatment	0	0	8
7. Blinding of physicians and patients to ongoing results	2	0	6
8. Prior sample size estimation	2	0	6
9. Testing of randomisation	3	5	0
Data analysis and presentation			
10. Statistical significance of major endpoints	3	3	2
11. Confidence intervals	4	0	4
12. Mention of power post hoc	0	1	7
13. Overall statistical methods	1	5	2
14. Listing of withdrawals	5	3	0
15. Handling of withdrawals [a]	1	6	0
16. Dates of study	5	0	3
17. Statistical analysis of randomisation testing	1	7	0
18. Tabulation of events employed as endpoints	8	0	0
19. Side effect discussion	1	7	0
20. Retrospective analysis of subgroups	1	6	1

[a] No withdrawals in one study

test for treatment effects across individual trials was not significant (χ^2 6, 6 *df*, $P>0.3$).

Subgroup analysis

Results of meta-analysis of subgroups of studies are shown in Fig. 3.

Only the primary endpoint was analysed in these subgroups. When the analysis was done on either the studies enrolling exclusively adult patients, or on studies with baseline neutropenia less than 500 cells/mm^3, or on studies comparing aminoglycoside containing combinations, or on studies of higher quality, or on bacteraemic episodes exclusively, the pooled ORs of failure of CRO combinations for all these subgroups of studies ranged from 0.89 to 1.12. However, 95% CIs always included the point of equal efficacy between the two regimens. These findings suggest no influence of the variables considered above on the overall result of this meta-analysis. The impact of other prognostic factors well known to be relevant to the outcome of febrile neutropenia, such as duration of neutropenia, profound bacteraemic neutropenia less than 100/mm^3 and the use of antimicrobial prophylaxis could not be assessed since disaggregated data were not uniformly reported in individual clinical trials and therefore could not be meaningfully combined. The exclusion from analysis of the EORTC trial, which was the largest individual study, did not modify the results substantially (pooled OR 0.94; 95% CI 0.71–1.25).

Discussion

Empirical antibiotic treatment of fever in cancer patients who become neutropenic due to chemotherapy has been found to reduce morbidity and mortality from infections. As an increasing number of cancer patients is likely to receive aggressive antineoplastic therapies in the near future, interest in defining an effective, safe and possibly less costly empirical antibacterial regimen is substantial. A combination of an aminoglycoside with an antipseudomonal β-lactam (e.g. piperacillin or ceftazidime) has been widely considered the standard empirical antimicrobial therapy for febrile neutropenia during the last two decades, affording as it does a broad-spectrum coverage and an additive or synergistic bactericidal effect against *Pseudomonas aeruginosa*, the most life-threatening gram-negative pathogen. However, in recent years a new epidemiological picture of possibly less severe bacterial infections has emerged in neutropenic cancer patients. This consists of a substantially lower incidence of gram-negative infections, including those caused by *Pseudomonas aeruginosa*, and an increase in the frequency of gram-positive infections, in particular those caused by staphylococci and streptococci. Taking into consideration this epidemio-

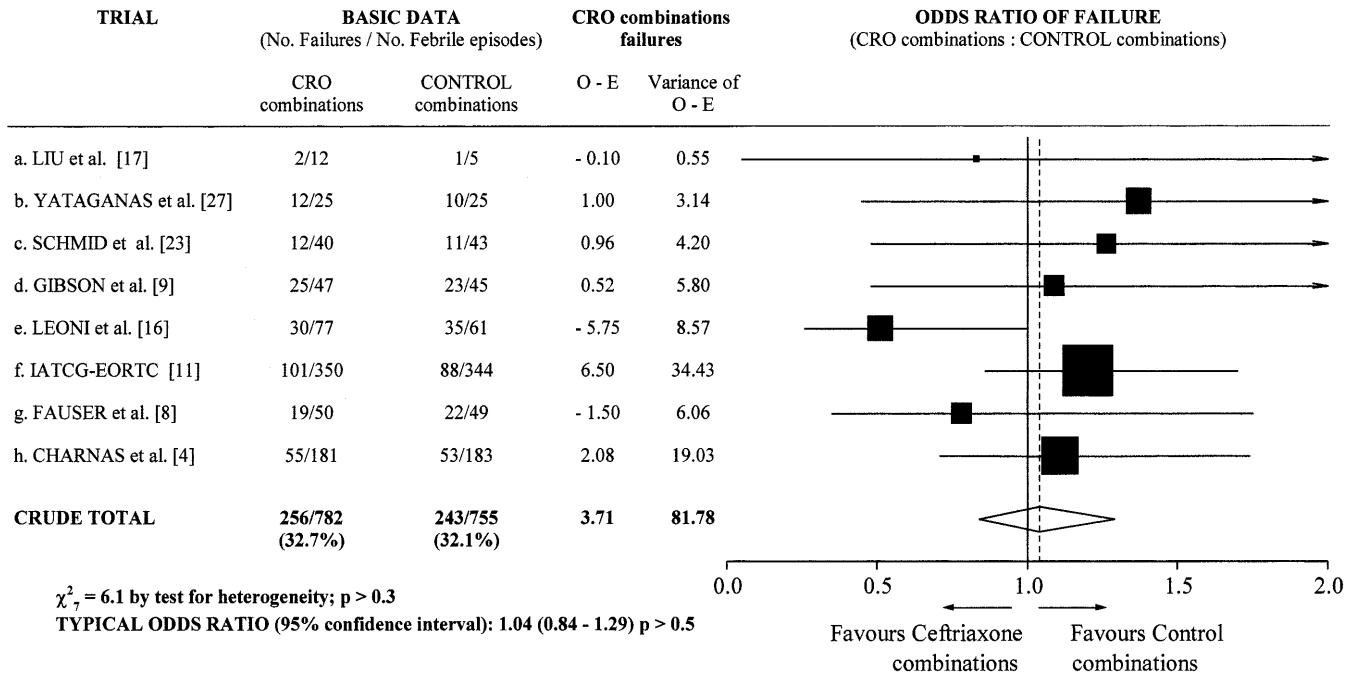

Fig. 1 Odds ratios of treatment failure (defined as death or modification of the initial allocated antibiotic regimen) between patients receiving a CRO combination and patients receiving an antipseudomonal β-lactam combination for individual trials (*a–h*) and for pooled trials. Each trial is described by one line of information: reference no., basic data (no. of failures/no. of febrile episodes) and statistical calculation. For each trial *O–E*, that is, observed minus expected events for the CRO group, and its variance have been printed; the odds ratio (CRO/control) and its 95% confidence interval have been plotted as a *black square* and a *horizontal segment*. The area of each *black square* is proportional to the amount of information contributed by the corresponding trial. This way, large trials involving many events are represented by *large black squares* and *short horizontal segments*. *The vertical solid line* denotes the point of no difference in treatment failure between CRO combinations and antipseudomonal β-lactam combinations, which means that results plotted to the *left* of this *line* favour CRO combinations. On the *bottom line* the grand total of O–E and its variance are printed (see statistical method section for more detail). The pooled odds ratio of meta-analysis and its 95% confidence interval are plotted as a *vertical broken line* and *diamond shape*

logical change, two approaches to empirical antibacterial therapy that could be seen as alternatives to the above-mentioned "standard" regimens and are aimed at preserving efficacy and reducing costs appear to be reasonable. One option is to use an empirical single-drug regimen, such as ceftazidime or a carbapenem. Large randomised clinical trials have shown that these monotherapy regimens provide a success rate equivalent to that obtained with a "standard" combination such as ceftazidime plus an aminoglycoside, but they are nevertheless very expensive [6]. A second option is the use of the combination of CRO with an aminoglycoside. This regimen seems very attractive, as it combines a good coverage of gram-positive pathogens (especially streptococci, the second most frequent isolate in bacteraemic neutropenic patients) with a satisfactory spectrum of activity against most gram-negative pathogens (with the exception of *Pseudomonas aeruginosa*) and with a favourable pharmacokinetic profile, which allows once-daily administration, and low cost. Both approaches need the best possible evidence from clinical trials. Several randomised clinical trials have addressed this issue, but lack of statistical power in most, and contradictory reporting of treatment effect directions or magnitude between them make their results difficult to interpret. Reasonable certainty of detecting statistically a moderate treatment effect in favour of either regimen would require enrollment of a larger number of patients than has generally been accomplished in these trials. Furthermore, the between-study difference in design and patient characteristics and in the criteria adopted to define and report outcomes of the empirical treatment contributes to the difficulty experienced with the overall interpretation of the merits and of the limitations of the regimens being compared. The best way to address the above-mentioned limitations is to perform a definitive, well-designed randomised, controlled clinical trial of adequate size, but a well-conducted meta-analysis of studies can be a useful tool yielding a meaningful summary of the differences in treatment effect observed in several individual trials, increasing statistical power by carrying out an overall statistical test of treatment efficacy, allowing a quantitative estimate of the size of treatment effect, and allowing subgroup analyses with sufficiently large numbers when appropriate attention is paid to control

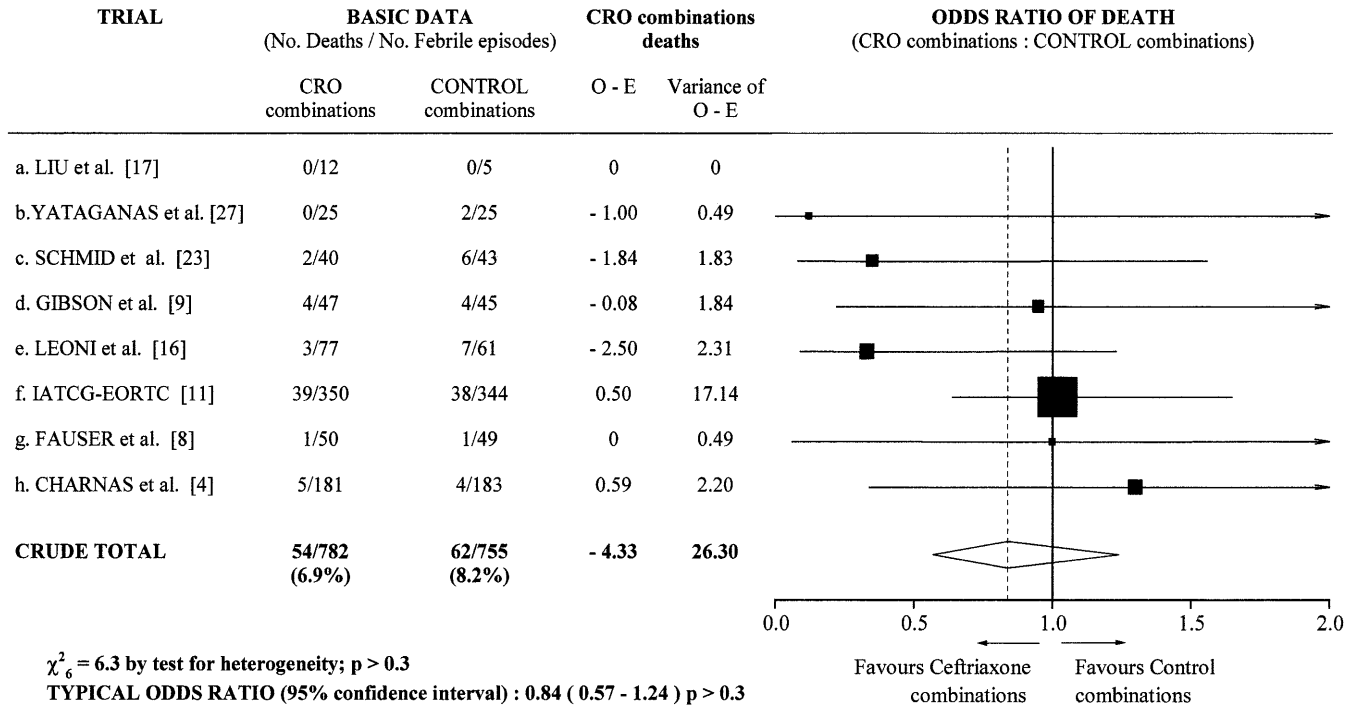

Fig. 2 Odds ratios of death (defined as overall number of deaths from any cause) between patients receiving a CRO combination and patients receiving an antipseudomonal β-lactam combination for individual trials (*a–h*) and for pooled trials. Each trial is described by one line of information: author, basic data (no. of deaths/no. of febrile episodes) and statistical calculation. For each single trial O–E, that is, observed minus expected events for CRO group, and its variance have been printed; the odds ratio (CRO/control) and its 95% confidence interval have been plotted as a *black square* and a *horizontal segment*. The area of each *black square* is proportional to the amount of information contributed by the corresponding trial. This way, large trial involving many events are represented by large black squares and short horizontal segments. *Vertical solid line* denotes the point of no difference in mortality between CRO combinations and antipseudomonal β-lactam combinations, so that results plotted to the left of this line favour CRO combinations. On the *bottom line* the grand total of O–E and its variance are printed (see statistical method section for more detail). The pooled odds ratio of meta-analysis and its 95% confidence interval are plotted as a *vertical broken line* and *diamond shape*

for excessive clinical heterogeneity of the studies to be included [7, 16, 23, 25, 26]. Our meta-analysis, pooling data from 1,537 febrile episodes and 280 bacteraemic episodes during neutropenia, shows point estimates of ORs for CRO combination failure of 1.04 (<1.29) and 0.93 (<1.49) respectively. The overall mortality in febrile episodes turned out to be comparable, at being 0.84 (<1.24) for the point estimate of OR for CRO combination deaths, even though the lower event rate of death as an outcome compared with the primary outcome makes the sample size in the meta-analysis less adequate to detect a significant difference between treatment groups in terms of deaths, if such a difference actually exists. These results suggest that, in terms both of the necessity of empirical regimen modification and of eventual deaths, in the empirical treatment of febrile neutropenia antibiotic combinations containing CRO are as effective as conventionally used antibiotic combinations in which the β-lactam, such as ceftazidime or one of the ureidopenicillins, has specific activity against *Pseudomonas aeruginosa*. The same conclusion is valid when treatment failure is assessed in the following specific subgroups: studies with combinations containing an aminoglycoside, studies with adult patients exclusively, studies with neutropenia below 500 cells/mm^3, and studies with higher quality. The secondary outcome measure of this meta-analysis, overall mortality, could not be evaluated in the subset of bacteraemic episodes because the disaggregated data were not uniformly reported across individual trials. However, owing to the small number of events and their even distribution in the overall patient population, it is unlikely that any significant difference would have been found in the bacteraemia subset.

As well as outcome measure, other characteristics of individual trials, such as patient population, treatments, and study design, were sufficiently consistent to avoid substantial clinical heterogeneity. Moreover, on formal testing, no significant statistical heterogeneity of treatment effects across individual studies was found, corroborating the suitability of combining data. The relative similarity of trials pooled in this meta-analysis may be

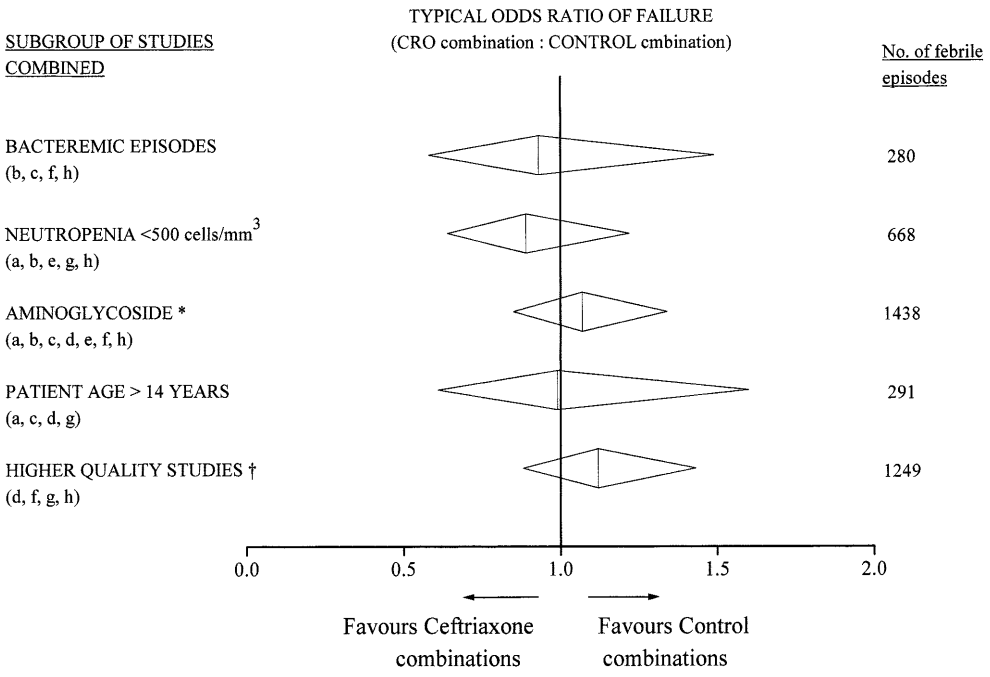

Fig. 3 Pooled odds ratios of failure of CRO combinations compared with antipseudomonal β-lactam combinations for subgroups of studies. Each *line* describes a subgroup analysis. *Vertical thin lines* and *diamond shapes* denote the pooled odds ratios of failure of CRO combination and their 95% confidence intervals; *vertical thick line* denotes the point of no difference in treatment failure between CRO combinations and antipseudomonal β-lactam combinations; results plotted to the *left* of this line favour CRO combinations. *a–h* study reference; *aminoglycoside + β-lactam combinations; † studies with quality score equal to or above the mean value

partly due to the fairly strict criteria used to select studies for inclusion, according to a predefined protocol consistent with the objective of assessing the comparative efficacy of the two combined antibiotic regimens of interest in febrile neutropenia. The need for the best available evidence from the literature prompted us to consider only randomised controlled clinical trials published as full papers [16]. Although publication bias (namely the selective publication of studies showing a difference of treatment effect) may be a major potential limitation of meta-analyses in general, this should be a minor problem in the area of comparative trials on antimicrobials in which negative results (i.e. equivalent efficacy) are almost the rule. In any case, no trial published in abstract form was identified, so that the inclusion criteria for this overview were met. Inclusion of data from poor-quality studies may also have the potential for biasing results of meta-analyses, but our results were very similar when only data from studies with the quality score equal to or above the mean were reanalysed.

Before any firm conclusions are drawn it is worth stressing some limitations to the generalisability of the findings of our study. This meta-analysis could not address treatment effect in one subset of neutropenic patients at high risk of empirical therapy failure, namely bacteraemic patients with very profound neutropenia below 100 cells/mm^3, since no single study report gave the outcome for this subset in a disaggregated form allowing data extraction and pooling [2, 15]. Similarly, lack of uniform reporting on the duration of neutropenia, the presence of central venous catheter, antibacterial prophylaxis and *Pseudomonas aeruginosa* infections in relation to outcome prevented the assessment of the impact of these important variables on treatment effect. However, in the selected studies *Pseudomonas aeruginosa* infections ranged from 0% to 10.8% of febrile episodes, and the rates of the individual studies in the CRO group and in the comparator group were respectively 2.6% and 3.3% [17], 12.5% and 9.3% [24], 4% and 8% [27], 0% and 2.2% [4], 4% and 0% [8], 8% and 0% [18], 1.4% and 1.4% (bacteraemias only) [12], and 0% and 0% [9]. With regard to the type of antibiotic combinations being compared, in seven of the eight studies CRO or an antipseudomonal β-lactam was combined with another antibiotic that is potentially active against *Pseudomonas aeruginosa*, namely an aminoglycoside. In one of the eight studies pooled in this meta-analysis only, the antibiotic combined with the β-lactam, teicoplanin, did not provide additional coverage against gram-negative bacilli and particularly *Pseudomonas aeruginosa* [8], but this study accounted for only 6.4% of the overall febrile episodes pooled. Another limitation might stem from the absence of an intent-to-treat analysis or information about the outcome of withdrawals in data reporting from individual trials. However, the rate of drop-outs in the combined trials was generally low and compatible with that usually observed in studies evaluating empirical antibiotic therapies of febrile neutropenia. Data on toxicity could not be combined because adverse events were described in an exhaustive way only in the two largest studies. However, the rate of toxicity was similar for both studies in the two treatment groups.

In conclusion, the results of this meta-analysis provide convincing evidence that antibiotic regimens containing CRO are as effective as combinations in which the β-lactam exerts specific activity against *Pseudomonas aeruginosa*, such as ureidopenicillins or ceftazidime in initial empirical therapy of febrile neutropenic patients. The data presented here are not intended to support the indiscriminate use of CRO-containing combinations as first-line treatment in febrile neutropenia. In making the choice of empirical treatment of febrile neutropenic patients it is wise to consider the individual patient's risk factors, the local epidemiology and possible modification of the initially selected regimen on the basis of frequent and careful reassessment of clinical response in these critically ill patients.

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