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Monotherapy with meropenem versus combination therapy of ceftazidime plus amikacin for empirical treatment of cancer patients with Febrile Neutropenic (FN): systematic review and meta-analysis

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Summary. *Background:* Combination therapy has traditionally been recommended for cancer patients with Febrile Neutropenia (FN), but the results remain controversial. *Objective:* To evaluate the safety and effectiveness of the two methods in clinical practice. *Methods:* We performed a meta-analysis of randomized controlled trials (RCT) to compare monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin for empirical treatment of cancer patients with FN. Data on interventions, participants' characteristics and the outcomes of therapy, were extracted for statistical analysis. Seven trials fulfilled the inclusion criteria. *Results:* The treatment with ceftazidime plus amikacin was more effective than meropenem (OR = 1.17; 95% CI 0.94 -1.45; 1471 participants). Likewise, the failure rate of meropenem was higher than ceftazidime plus amikacin (OR = 0.87; 95% CI 0.7 -1.08; 1471 participants). A total of five articles mentioned adverse effects in detail. Drug-related adverse effects affliction more patients treated with ceftazidime plus amikacin (OR = 1.06; 95% CI 0.83 -1.35; 1336 participants). The common responses were nausea, diarrhea, rash, and increase in SGOT, SGPT and bilirubin. The treatment effects of the two therapy methods were almost parallel in adults (OR = 1.04; 95% CI 0.64 - 1.67; 378 participants older than 16). Only trials on adults mentioned adverse effects in this review. The use of monotherapy for FN is associated with higher failure than ceftazidime plus amikacin and should be cautiously considered pending further analysis. However empirical use of ceftazidime plus amikacin entails more adverse effects. *Conclusions:* Ceftazidime plus amikacin should be the first choice, and meropenem may be chosen as a last defense against pathogenic bacteria.

Key words: febrile neutropenia, meropenem, ceftazidime, amikacin, meta-analysis

«Confronto tra terapia con meropenem e terapia combinata con ceftazidime e amikacin per il trattamento empirico di pazienti malati di cancro con Neutropenia Febbrile (FN): revisione sistematica e meta-analisi»

Riassunto. *Background*: La terapia combinata viene tradizionalmente raccomandata per i pazienti malati di cancro con Neutropenia Febbrile (FN), anche se i risultati rimangono controversi. *Obiettivo*: Valutare la sicurezza e l'efficacia dei due metodi terapeutici nella pratica clinica. *Metodi:* Dopo aver effettuato una meta-analisi di studi randomizzati controllati (RCT) sono state messe a confronto la monoterapia con meropenem e la terapia combinata con ceftazidime ed amikacin per il trattamento empirico dei pazienti malati di cancro con FN. A fini statistici, sono stati presi in considerazione i dati sull'intervento, sulle caratteristiche dei partecipanti e sui risultati della terapia Sette prove hanno soddisfatto i criteri di inclusione. *Risultati:*

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Il trattamento con ceftazidime associato ad amikacin è stato più efficace rispetto al trattamento con solo meropenem (OR = 1.17; 95% CI 0.94 – 1.45; 1471 partecipanti). Allo stesso modo il tasso di fallimento del meropenem è stato superiore rispetto al trattamento con ceftazidime associato ad amikacin (OR =0.87; 95% CI 0.7 – 1.08; 1471 partecipanti). In cinque articoli si è parlato in dettaglio degli effetti avversi. Molti pazienti trattati con ceftazidime e amikacin hanno subito gli effetti avversi correlati al farmaco (OR = 1.06; 95% CI 0.83 – 1.35; 1336 partecipanti). Le risposte comuni erano nausea, diarrea, rash cutaneo ed aumento dei valori SGOT, SGPT e bilirubina. Gli effetti scaturiti dai due metodi terapeutici sono da considerarsi quasi identici negli adulti (OR = 1.04; 95% CI 0.64 – 1.67; 378 partecipanti di età superiore a 16 anni). In questa revisione sono stati esposti gli effetti avversi solo su pazienti adulti. L'utilizzo della monoterapia per la FN è associata ad un più elevato fallimento rispetto al trattamento con ceftazidime ed amikacin, anche devono ancora essere attentamente valutate ulteriori analisi in sospeso. In ogni caso, l'utilizzo empirico di ceftazidime e amikacin comporta maggiori effetti negativi. *Conclusioni:* Ceftazidime ed amikacin dovrebbero essere la prima scelta ed il meropenem dovrebbe essere scelto come ultima difesa contro batteri patogeni.

Parole chiave: neutropenia febbrile, meropenem, ceftazidime, amikacin, meta-analisi.

Introduction

Febrile Neutropenia (FN), an important complication, is common in patients receiving chemotherapy for hematological malignancy or cancer (1). Over the last decades, the survival rate of patients with malignancy has considerably increased as a result of aggressive cytotoxic chemotherapy and improvements in anticancer and supportive therapy (2, 3). However, aggressive chemotherapy has been found to induce severe neutropenia, which will make patients vulnerable to bacteria, fungi and commonly encountered viruses (4). Reports indicated that patients with profound neutropenia were at high risk (approximately 90%) of acquiring life-threatening infectious complications (5), which were significant causes of morbidity and mortality (6).

Taylor and co-workers have systematically shown that outpatient management is a well tolerated and cost-effective strategy for low-risk febrile neutropenia in children with cancer, although parental preferences are highly variable for outpatient versus inpatient management (8). However, in clinical management, prompt antimicrobial therapy, especially broad-spectrum antibiotic therapy, tends to be applied at the onset of fever before the nature and susceptibility of the pathogen is detected in such infection. Following the NICE guidance (the National Institute for Health and Clinical Excellence) in treating cancer patients for neutropenic sepsis, piperacillin with tazobactam is recommended as the initial empirical antibiotic therapy (http://www.nice.org.uk/guidance/cg151/resources). As the use of antimicrobial agents in neutropenic patients with cancer, clinical guideline updated by the Infectious Diseases Society of America (IDSA) in 2010 recommend monotherapy with a cefepime (CFPM), a carbapenem (imipenemecilastatin (IPM/CS) or meropenem (MEPM)) (2).

Considering the advantages of decreased toxicity and cost as compared to multidrug regimens in many researches (9, 10), monotherapy with a broad-spectrum cephalosporin, such as ceftazidime (CFZ) and cefepime (CFP), or a carbapenem, is reported to be an effective treatment (11-13) and suggested as a successful monotherapy (14, 15). On the beta-lactam side, Rejin Kebudi and co-workers found that both cefepime and ceftazidime were effective and safe for the empirical treatment of febrile episodes in neutropenic patients (16). As an ultra-broad spectrum antibiotic of the carbapenem group, meropenem is highly active *in vitro* against most of the gram-positive and gram-negative bacteria and anaerobes responsible for infections in neutropenic patients (17). Unlike imipenem, meropenem may be given without concomitant addition of cilastatin. It is a possible last line of defense against multidrug-resistant gram-negative infections. It must be pointed out that meropenem should be used with

caution and discretion, as there are not many drugs in the pipeline in the near future. Thus, combination therapy with a beta-lactam and an aminoglycoside has been traditionally recommended for febrile episodes in neutropenic patients.

Despite the picture outlined above, there is still confusion as to the curative effect and safety of traditional combination therapy with ceftazidime plus amikacin versus monotherapy with meropenem. Collecting and analyzing newly published articles since 1995, we performed a systematic review with meta-analysis of randomized controlled trials alternating combination therapy with ceftazidime plus amikacin or/and monotherapy with meropenem in the treatment of cancer patients with febrile neutropenia.

Materials and methods

Information sources and search strategy

The Cochrane Library, PubMed, Sciencedirect, Wiley Online, Science Citation Index (SCI), Google (scholar), National Center for Biotechnology Information (NCBI), and China National Knowledge Infrastructure (CNKI) were searched for clinical trials on ceftazidime plus amikacin, or/and monotherapy with meropenem for the treatment of cancer patients with FN. This search was performed using the following keywords: monotherapy, combination therapy, ceftazidime plus amikacin, meropenem, and febrile neutropenia in cancer. The publication language was limited to English.

Eligibility criteria

The inclusion criteria were the following: (1) randomized controlled trials (RCTs); (2) clinical trials on therapy for cancer patients with FN; (3) published from 1995 to now; (4) randomization procedure performed; (5) interventions conducted in trials with meropenem or ceftazidime plus amikacin ; (6) scientific standard for curative effect; (7) reasonable exclusion criteria for participant selection.

Exclusion criteria were: (1) overlapping data; (2) not randomized studies; (3) only relevant to monotherapy or combination therapy; (4) reviews, abstracts, animal studies or letters; (5) *in vitro* activity only.

Data Extraction

Titles and abstracts were scanned by reviewers, independently, to filter out reviews, unavailable full articles and irrelevant ones. Then full texts of studies included were assessed for final quality eligibility on the basis of consolidated standards of reporting trials (CONSORT) (18). The methodological quality of the trials was assessed with the Cochrane Collaboration Risk of Bias Tool (CCRBT) in RevMan 5.1 for bias risk analysis.

Data from the trials included were extracted independently for qualitative analysis, and any disagreement was resolved by discussion subsequently. The primary information was collected on study ID, year of publication, drug regimen and adverse effects. The quantitative data included patient characteristics, such as average age, sample size, sex ratio, assessment of successful cases and failure cases at the end of therapy.

Statistical analysis

Statistical analysis was performed using RevMan version 5.1 (Nordic Cochrane Centre, Copenhagen, Denmark). Heterogeneity was explored using a Chi-square test, and the quantity of heterogeneity was measured using the I^2 statistic with Review Manager. $P \leq 0.10$ or $I^2 \geq 50$ % suggests that there is heterogeneity and a random-effect model should be chosen (19). In the experimental group, the first outcome was comparison of the success rates of meropenem versus control (ceftazidime plus amikacin) for empirical treatment of cancer patients with FN; the second was comparison of the failure rate; the third regarded adverse effects. Pooled odds ratios (ORs) and 95 % confidence intervals (CIs) for all outcomes were calculated with the Mantel-Haenszel fixed-effects (20). For all analyses, results from the fixed-effect models are presented only when there was no heterogeneity between studies; otherwise, results from random-effect models are presented. The reported results of outcomes of the studies analyzed were weighted by the inverse of their variance from fixed-effect models.

Results

Characteristics of eligible studies

Relevant publications were retrieved from databases (PubMed, Google scholar, and SCI). As the assessment outcome, Figure 1 shows review authors' judgments about each risk of bias item, presented as percentages across all studies included. A total of 16 relevant publications were adopted through reading records. After full-text scanning, 10 were excluded for various reasons: two were single clinical trials about combination therapy in febrile neutropenic patients with cancer (21, 22); three studied monotherapy with meropenem only (23-25); while two compared meropenem versus ceftazidime as empirical monotherapies (14, 26); Oguz *et al.* (27) dealt with cefepime versus meropenem; one of the full-text articles was not available (25, 28) (Figure 2).

Eventually, seven papers were available for data extraction and assessment (28-34) (Table 1). Inventions performed in six RCTs were all divided into two groups: a meropenem group and a ceftazidime plus amikacin group. The drug regimen with these three antibiotics varied according to verified empirical therapy s[illegible]hat the dose differences between groups were n[illegible]igible. All but one trial reported the adverse effects mor[illegible]less.

Quantitative synthesis

In this analysis, participants treated by meropenem were considered as experimental cases, while those on ceftazidime plus amikacin were seen as controls. In order to estimate the pharmaceutical effects of meropenem versus ceftazidime plus amikacin for empirical treatment of cancer patients with FN, only the cured or improved cases were considered, while und[illegible]table or unchanged outcomes were cons[illegible]red as "eve[illegible]" in terms of analysis.

No heterogeneity bet[illegible]ween studie[illegible]as identified in these three outco[illegible]s (Ch^2 = 3.00, [illegible] = 6 (P = 0.81); I^2 = 0 %). The outco[illegible]on com[illegible]ring the success rate indicated that ceftazi[illegible]e plus amikacin was more effective [illegible] meropenem monotherapy (OR = 1.17; 95% C[illegible] 0.94 [illegible]5; 1471 participants) (Figure 3). Agai[illegible]ilure rate o[illegible]ropenem was higher than ceftaz[illegible]dime plus amikacin (OR = 0.87; 95% CI 0.7 -1.08[illegible] 1471 partic[illegible]pants) (Figure 4). Analyzing the adver[illegible]effects [illegible]ntioned in detail in the five articles (28, [illegible]), more patients suffered drug-related a[illegible]e effects when treated with ceftazidime plus a[illegible]kac[illegible] (OR = 1.06; 95% CI 0.83 -1.35; 1336 participants) (Figure 5), (Table 2). Common responses w[illegible]re nausea, diarrhea, rash, and increase of SGOT, SGPT, and bilirubin. For further understanding of

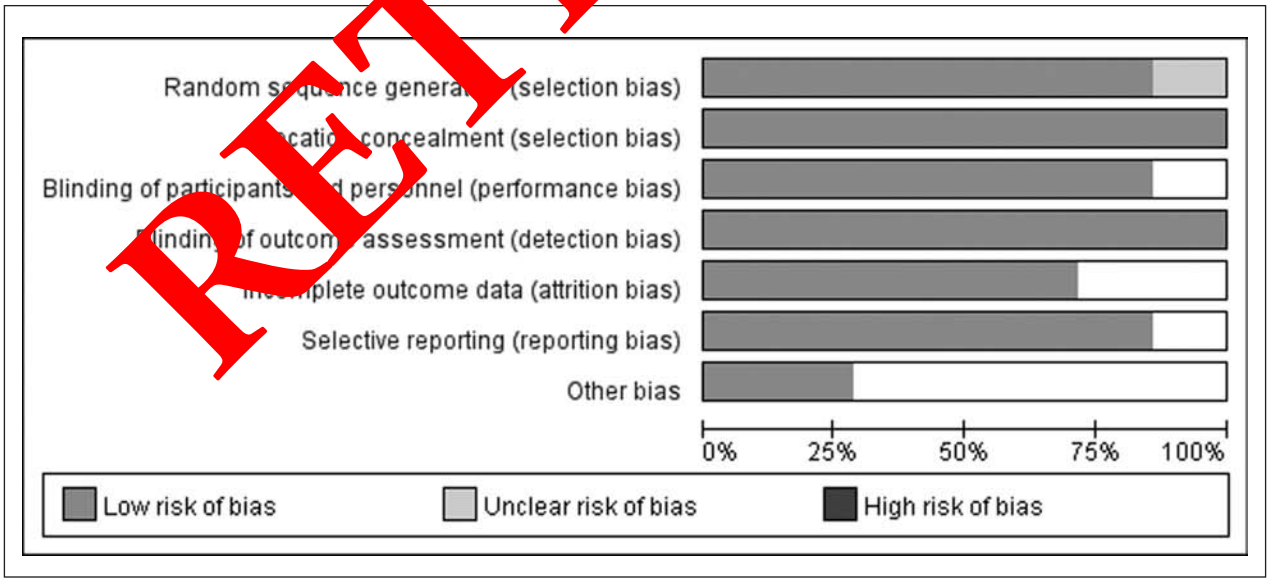

Figure 1. Risk of bias graph.

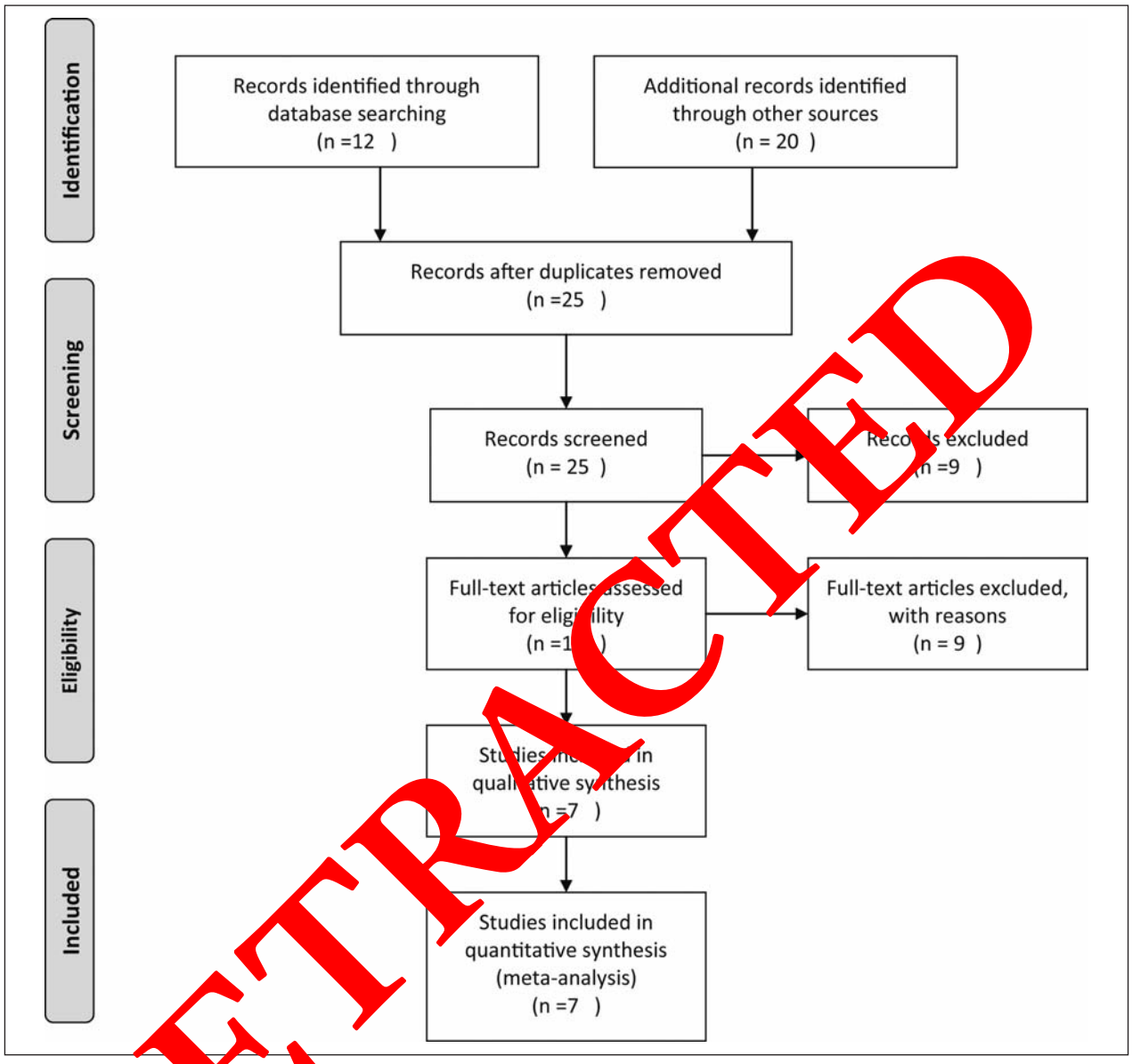

Figure 2. Flow diagram showing studies processed for inclusion in the meta-analysis.

the drug responses by children and adults, data were sub-grouped by age (Table 3). Theata of Cometta (32) were not included in the adult group due to the existence of children without final treatment data. In the sub-grouped outcome of success cases, however, the treatment effects of the two therapy methods ran almost parallel in adults (OR = 1.04; 95% CI 0.64 -1.67; 378 participants older than 16) (Figure 6). No differences were identified in subgroup analysis of failure cases (Figure 7). The articles mentioning adverse effects were all trials on adults.

Tests for publication bias and sensitivity analyses

Given that the number of studies (N=7) was too small to test for small study effects, publication bias analysis consisted only in a funnel plot performed by Review Manager as shown in Figure 8.

Table 1. Characteristics of all included studies in the meta-analysis.

Study IDs	Years	Interventions	Participants	M:F Ratio	Mean Ages (years)	Success Numbers	Failure	Adverse Effects
Hung-2003 (23)	2003	meropenem (40 mg/kg/dose max 1 g/dose q 8h)	39	21/18	4.2 (0.7±16.3)	28	10	not mentioned
		ceftazidime (50 mg/kg/dose max 2 g/dose q 8h) plus amikacin (5 mg/kg/dose max 0.25 g/dose q 8 h)	37	24/13	3.6 (0.6±12.4)	21	14	[illegible]entioned
Agaoglu-2001 (29)	2001	meropenem alone (60 mg/kg/d i.v. in 3 doses)	30	1/8	6	[illegible]	8	In the meropenem arm, 3 patients had vomiting but no seizures
		ceftazidime (100 mg/kg/d i.v. in 3 doses) plus amikacin (15 mg/kg/d i.v. in 2 doses)	29		7	23	6	
		cefepime (100 mg/kg/d i.v. in 3 doses) plus netilmicin (5 mg/kg[illegible].v. in 2-3 dos[illegible]	28		9	22	6	
Akova-1999 (30)	1999	mero[illegible]m (1 g[illegible])	40	25/15	36 (39±17)	24	13	5.5% hypersensitivity; 11% transient increase in transaminases; 1% nausea and 1% diarrhoea
		ceftazidim[illegible] (2 g tds) plu[illegible] amikacin (1 g[illegible]ngle daily)	43	25/18		22	18	17.5% transient increase in transaminases; 5% diarrhoea
Beh[illegible]8 (31)	1998	Meropenem (1 g every 8 h by intravenous infusion for 20±30 min)	34	22/12	46 (18±76)	20	14	13% drug-related effects like nausea, diarrhoea and rash
		Ceftazidime (2 g every 8 h by intravenous infusion) plus Amikacin (15 mg/kg per day in 2 or 3 equally divided doses)	37	24/13	50 (22±70)	23	14	15% drug-related effects like diarrhoea and increase on SGOT, SGPT, Bilirubin

(continued)

Table 1. Characteristics of all included studies in the meta-analysis.

Study IDs	Years	Interventions	Participants	M:F Ratio	Mean Ages (years)	Success Numbers	Failure	Adverse Effects
de la Camara-1997 (33)	1997	meropenem (1 g/8 h)	46	22/24	42.2 (17±71)	17	29	Erythema multiforme; Alkaline phosphatase increase; SGOT/ T increase
		ceftazidime (2 g/8 h) plus amikacin (15 mg/kg/day)	47	27/20	41.6 (16±66)	17	30	Rena nction alterati ; Rash; Deafn ss
Cometta-1996 (32)	1996	meropenem (1g every 8 h [q8 h] for adults and children weighing more than 50 kg, 20 mg/kg q8h for children weighing less than 50 kg) infused over a period of 20 to 30 min	483	275/208	38 (1±8)		190	151 of 516 (29%) only 19 patients (all adults) in the mono-therapy arm and 31 (30 adults and 1 child) in the combination arm experienced an adverse event considered related or probably related to the study drug
		ceftazidime (2 g q8 h for adults, 35 mg/kg q8 h for children) pl amikacin (2 mg/ day given in le daily ose)	47	266/209	39 (1±77)	245	206	148 of 511 (29%)
Solberg-1995 (28)	1995	m nem (500 m intrav sly every 8 h)	61	42/29	60.1±19.0	56	5	18 meropenem-treated patients (25%) and 12 patients (15%) in the ceftazidime/ amikacin group experienced at least one adverse event. A single patient in the ceftazidime/amikacin group was withdrawn from the study because of drug-induced rash.
		ceftazidi e (2 g every 8 h) plus an kacin (15 mg/kg/day)	70	51/31	63.6±17.8	66	4	

Discussion

Patients with malignancy are at high risk of suffering chemotherapy-induced neutropenia, a significant dose-limiting toxicity in cancer treatment, leading to infection-related morbidity and mortality (35). During a neutropenic period, physicians must be keenly aware of the infection risks, diagnostic methods, and antimicrobial therapies required for management of febrile patients. Accordingly, researchers were keenly interested in algorithmic approaches to fever and neutropenia, infection prophylaxis and treatment (36).

Prompt empirical antibiotic therapy using the new broad-spectrum antibiotics, such as the carbapenems,

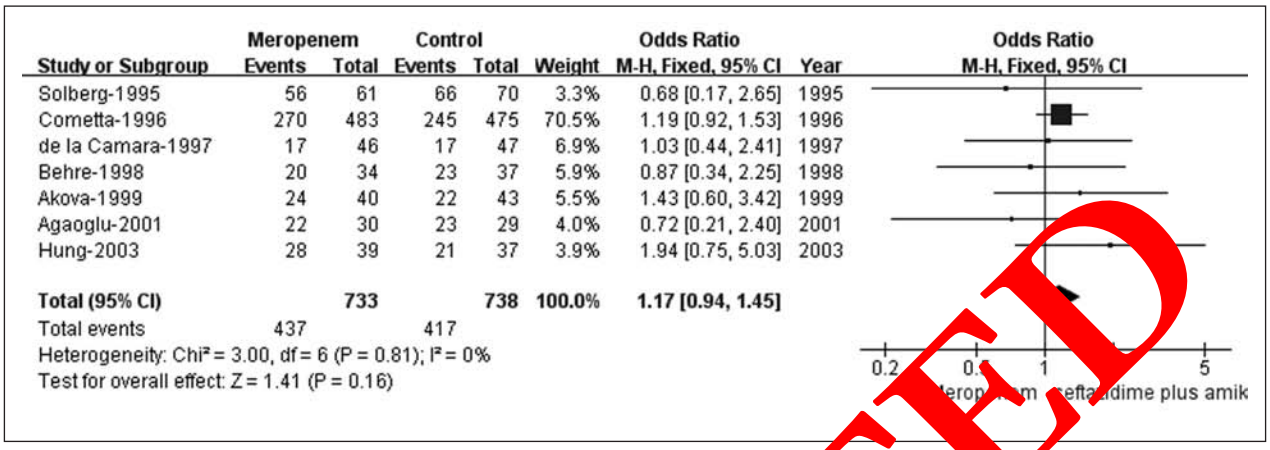

Figure 3. Comparison of the success rate of meropenem versus combined therapy with ceftazidime plus amikacin. The size of each square denotes the proportion of information given by each trial. Vertical line, "no difference" point in emergence of success cases treated by meropenem and ceftazidime plus amikacin; horizontal lines, 95% CIs; squares, ORs; diamond, pooled OR for all studies.

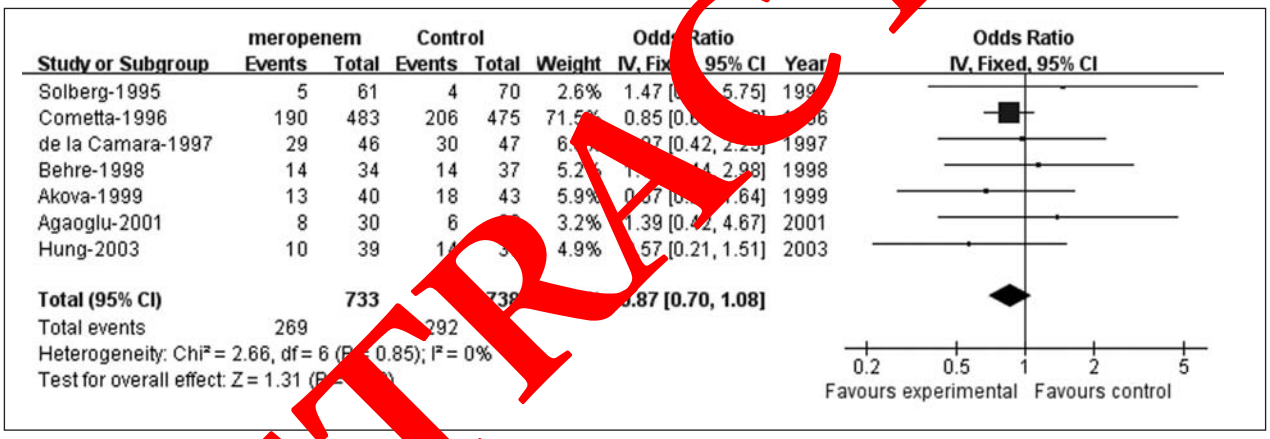

Figure 4. Failure rate of meropenem vs ceftazidime plus amikacin. The size of each square denotes the proportion of information given by each trial. Vertical line, "no difference" point in emergence of failure cases treated by meropenem and ceftazidime plus amikacin; horizontal lines, 95% CIs; squares, ORs; diamond, pooled OR for all studies.

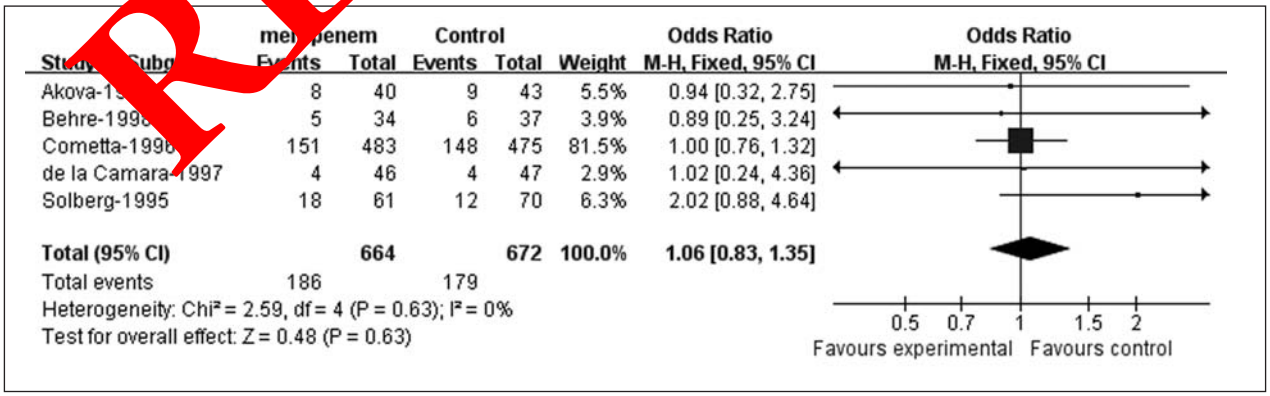

Figure 5. Outcomes of drug-related adverse effects from the two treatments. The size of each square denotes the proportion of information given by each trial. Vertical line, "no difference" point in emergence of adverse effects treated by meropenem and ceftazidime plus amikacin; horizontal lines, 95% CIs; squares, ORs; diamond, pooled OR for all studies.

Table 2. Outcomes without subgroup of analysis on treatment effects.

Outcome without subgroup	Studies	Participants	Statistical method	Effect estimate
Success case	7	1471	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.94, 1.45]
Failure case	7	1471	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.70, 1.08]
Adverse effect	5	1336	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.83, 1.35]

Table 3. Outcomes with subgroup of analysis on treatment effects

Outcome and subgroup	Studies	Participants	Statistical method	Effect estimate
Success case	6	513	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.74, 1.67]
adult	4	378	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.64, 1.67]
children	2	135	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.48, 3.33]
Failure case	6	513	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.61, 1.37]
adult	4	378	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.59, 1.55]
children	2	135	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.38, 1.72]

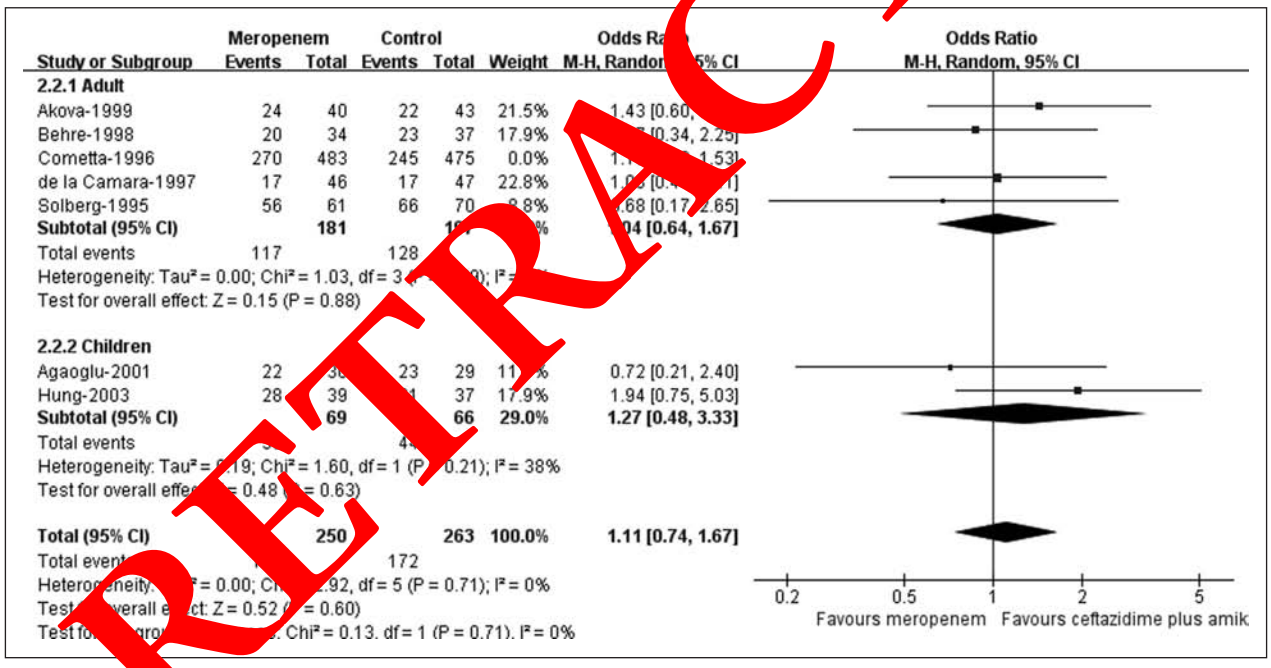

Figure 6. Sub- d outcome of the success cases. The size of each square denotes the proportion of information given by each trial. Vertical line, no difference" point in emergence of success cases treated by meropenem and ceftazidime plus amikacin; horizontal lines, 95% CIs; squares, ORs; diamond, pooled OR for all studies. Grouped by age, adult and children.

is becoming common even in patients with high-risk neutropenia or fever, replacing the traditional combination therapy (30, 31, 37-39). As the newest member of this group of antibiotics, meropenem also is reportedly as safe and effective as a combination of antibiotics (e.g., an aminoglycoside plus an anti-pseudomonal beta-lactam such as ceftazidime) in large comparative trials. Considering this controversy, we designed this review to assess which method was better in terms of treatment effect.

Since 1995, there have not been many articles on clinical trials evaluating monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin for the empirical treatment of cancer

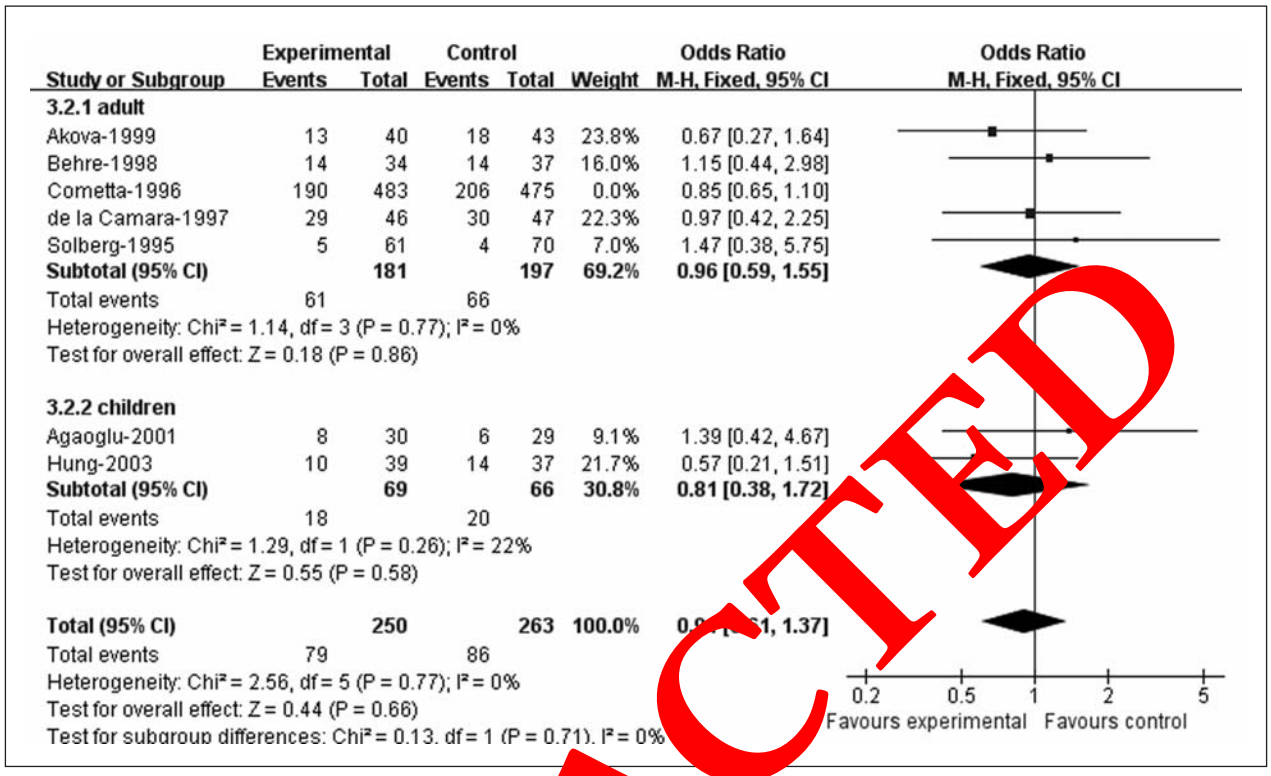

Figure 7. Subgroup analysis of failure cases. The size of each square notes the proportion of information given by each trial. Vertical line, "no difference" point in emergence of failure cases treated by meropenem and ceftazidime plus amikacin; horizontal lines, 95% CIs; squares, ORs; diamond, pooled OR for all studies. Grouped by age, adult and children.

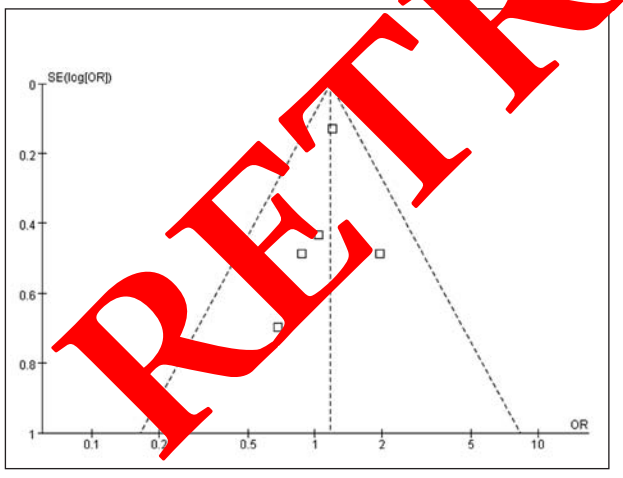

Figure 8. Publication bias analysis consisted only in a funnel plot performed by Review Manager.

patients with FN. With a small data sample, we applied Mantel-Haenszel fixed-effects for analysis. Considering treatment effect and failure rate, meropenem proved less than ideal compared with ceftazidime plus amikacin, especially in children. In contrast, previous studies had reported meropenem to be effective and well-tolerated when used for the treatment of neutropenic cancer children unlike most beta-lactamases produced from gram-negative bacteria (24). Although there was no review on the effect of meropenem versus ceftazidime plus amikacin in this disease, this result was still a valuable reference for clinical management. Monotherapy does indeed possess significant advantages in preventing treatment failure and giving rise to fewer adverse effects. Researchers have suggested that the high activity of meropenem could be explained by its ease of entry into bacteria combining to essential penicillin-binding proteins, including those associated with cytolysis. Although meropenem has a broad antibacterial spectrum due to stability vis-à-vis all serine-based β-lactamases, it is slightly less active against staphylococci and enterococci (17). In this respect, a combined therapy proves superior. In subgroup analy-

sis, the superiority was not so significant in the case of adults. One explanation was that a slight change in dosage for children might have a dramatic effect on the pharmacological action and pharmacokinetics. Moreover, it has been observed that the duration of FN is significantly longer in patients with an absolute neutrophil count (ANC) of less than 100/mm^3 and even in those with an ANC of less than 200/mm^3, as well as in children who are not in remission for malignant disease (23).

Drug-related effects like diarrhea, increase in SGOT, SGPT and bilirubin, nausea, vomiting, abdominal pain, headache, rash and vertigo are established side effects of therapy with both methods, but they are well tolerated. In review, the observed toxicity in combined therapy was higher than in meropenem, but did not lead to withdrawal from therapy.

In conclusion, the efficacy of monotherapy with meropenem seems less than that of combined therapy with ceftazidime plus amikacin for empirical treatment of cancer patients with FN. However, meropenem is safer to use with fewer adverse effects. As a clinical reference, we suggest combination therapy as first priority, while meropenem may be chosen as the last defense against pathogenic bacteria. However, considering the small sample size of included trials, more studies and analysis are still called for.

Acknowledgements

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