Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis

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The use of combination antimicrobial therapy for bacteraemia caused by Gram-negative bacilli is controversial. We did a meta-analysis of published studies to determine whether a combination of two or more antimicrobials reduces mortality in patients with Gram-negative bacteraemia. Criteria for inclusion were: analytic studies of patients with documented Gram-negative bacteraemia that included patients receiving a single antibiotic (monotherapy) and patients receiving two or more antibiotics (combination therapy). Data on mortality (outcome) had to be provided. A pooled odds ratio was calculated with the random effects model of DerSimonian and Laird. Assessment of heterogeneity was done with the Breslow-Day test and reasons for heterogeneity were explored. 17 studies met the inclusion criteria, five prospective cohort studies, two prospective randomised trials, and ten retrospective cohort studies. Most studies used beta-lactams or aminoglycosides alone and in combination. The summary odds ratio was 0·96 (95% CI 0·70–1·32), indicating no mortality benefit with combination therapy. Subgroup analyses adjusting for year of publication, study design, and severity of illness did not change the results. Considerable heterogeneity was present in the main analyses. Analysis of only *Pseudomonas aeruginosa* bacteraemias showed a significant mortality benefit (OR 0·50, 95% CI 0·30–0·79). Our analysis does not support the routine use of combination antimicrobial therapy for Gram-negative bacteraemia, beyond settings where infection by *P aeruginosa* is strongly suspected or more than one drug would be desirable to assure in-vitro efficacy.

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The late 20th century witnessed a rapidly growing crisis in antimicrobial resistance, especially among microorganisms that cause nosocomial infection.[1–4] In particular, multidrug-resistant Gram-negative bacteria are re-emerging as a major threat, especially to critically ill intensive care unit (ICU) patients.[5–8] Data from the National Nosocomial Infection Surveillance Study at the US Centers for Disease Control and Prevention show that by June 2002, nosocomial infections in ICU patients caused by Gram-negative bacilli resistant to third-generation cephalosporins accounted for 26·4% of all enterobacter infections, 14% of all *Pseudomonas aeruginosa* infections, and 6·1% of all *Klebsiella* spp infections.[9] Of all *P aeruginosa* isolates, 36% were fluoroquinolone-resistant and 20% were resistant to carbapenems. Data from the Surveillance Network Database (TSN Focus technologies) has shown a 62% increase in isolates of multidrug-resistant *P aeruginosa* (resistant to >3 drugs) from 1998 to 2000.[10] These infections greatly increase length of stay, hospital costs, and mortality.[4,11–17]

Since many species of Gram-negative bacilli have frequent intrinsic and acquired resistance, which cause serious infections and high mortality,[10,18] combination antimicrobial therapy, most commonly with two agents, has been advocated for Gram-negative bacteraemia.[19,20] The added benefits of this approach besides its intuitive appeal, assuming the organism or organisms are susceptible in vitro to the agents chosen, are unclear. Moreover, there are potential disadvantages to using combination antiinfective therapy, including a greater risk of drug toxicity, increased cost, and superinfection with even more resistant bacteria or fungi.

We report the findings of a systematic review and meta-analysis undertaken to determine whether combination antimicrobial therapy reduces mortality in patients with bacteraemia caused by Gram-negative bacilli.

Methods

Search strategy and selection criteria

We searched the following databases: Medline (Jan 1 1966–Aug 1 2003), Current Contents (Jan 1 1993–Aug 1 2003), Pubmed (Jan 1 1966–Aug 1, 2003), CancerLit, and the Cochrane Network. The following MeSH keywords were used alone and in combination: "Gram-negative bacteraemia", "combination antibiotic", "antibiotic", "antimicrobial", "mortality", "*Pseudomonas aeruginosa*", "*Serratia*", "*Klebsiella*", "*Escherichia coli*", "bloodstream infection", and "neutropenic fever". The term Gram-negative bacteraemia was exploded and crossed with the term antibiotic or antimicrobial. The related articles of each relevant citation in Pubmed were also reviewed. Meeting abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, the American Society of Microbiology, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America, the American Cancer Society, and the Society of Critical

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Care Medicine were reviewed. References from recent published reviews,[21–27] and two meta-analyses of the effect of combination therapy for neutropenic fever[28,29] were also reviewed to identify relevant studies. Authorities in the field, including the authors of the included studies, were contacted by email to identify additional published or unpublished studies. Only studies published in English were reviewed.

Inclusion criteria

For a study to be included it had to be an analysis of patients of Gram-negative bacteraemia, with mortality as an outcome measure, and provide sufficient data on single versus combination antibiotic therapy to calculate an odds ratio between treatment groups.

Case reports, review articles, and non-English language studies were excluded. Studies that used outcome measures other than mortality, such as "cure", or "emergence of resistance" were excluded.

Outcome measures

The primary outcome measure was mortality.

Data extraction

We used a standard form to extract relevant data from the included articles, including study design, patient population, characteristics of bacteraemia (organism, nosocomial or community acquired, portal of entry) and data relevant to therapy (antimicrobials used).

Statistical analysis

Odds ratios and 95% confidence intervals (CIs) were calculated using data provided in each study. Pooled estimates of the odds ratio and 95% CI were obtained using the random-effects model of DerSimonian and Laird[30] and testing for heterogeneity was done using the Breslow-Day test,[31] with EasyMA statistical software (2000, Cucherat, France). Publication bias was assessed by the funnel plot method.[32] We did subgroup analyses to assess the effect of year of publication, study design, and pseudomonas bacteraemia alone on the findings.

Results

Of the 471 studies identified by the initial search strategy, 17 met the inclusion criteria, encompassing 3077 patients.[19,20,33–47] The remainder were excluded because they did not adequately compare combination and single antimicrobial therapy (326), were not studies of bacteraemia (76), did not use mortality as an outcome measure (50), did not provide sufficient data to calculate an odds ratio for mortality (1),[48] or had no fatal outcomes in either treated group (1).[49] Five were prospective cohort studies, two were prospective randomised trials and ten were retrospective cohort studies. Three studies included only patients with cancer; 14 looked at general hospitalised patients, although most included a disproportionate number of patients with malignancy. The characteristics of included studies are shown in table 1.[19,20,33–47]

11 studies focused on a particular organism, five with *P aeruginosa*, four with *Klebsiella* spp, one with *Serratia* sp, and one with *Enterobacter* spp. The remainder included multiple species of Gram-negative bacilli.

53% of bacteraemias were nosocomially acquired; the most common source was the respiratory or urinary tract.

Several different antimicrobial classes were used in the included studies for treatment of Gram-negative bacteraemia; however, the detail provided in each study regarding the specific antimicrobial used varied greatly.

In the prospective study of *P aeruginosa* bacteraemia by Hilf et al,[19] the most commonly used antimicrobials were piperacillin plus tobramycin, or ticarcillin plus tobramcyin in the patients receiving combination antimicrobial therapy. Drugs used for monotherapy were either antipseudomonal penicillin or an aminglycoside. In the study by Tapper et al,[35] patients received either gentamicin alone or carbenicillin alone or the two in combination. Piccart et al[37] compared cefoperazone with cefoperazone and amikacin in a randomised trial. In the retrospective study by Mendelson et al,[43] most patients received either a third-generation antipseudomonal penicillin (ceftazidime) alone or an aminoglycoside alone or in combination. Kim et al[47] defined monotherapy as a beta-lactam, carbapenem, aminoglycoside, or ciprofloxacin. Any combination of two of the above antimicrobials was defined as combination therapy.

In the prospective study of enterobacter bacteraemia by Chow et al,[40] 42% of patients received monotherapy, either an aminoglycoside, co-trimoxazole, or ciprofloxacin. Of the 54% of patients receiving combination therapy, 89% were given a beta-lactam plus an aminoglycoside; the rest received trimethoprim-sulfamethoxazole plus an aminoglycoside or ciprofloxacin plus an aminoglycoside.

In the studies by McCue et al[33,34] and Bouza et al,[39] combination therapy consisted of a beta-lactam plus an aminoglycoside but no further detail was provided regarding the specific antimicrobials used; patients treated with a single agent received either a beta-lactam or an aminoglycoside.

Kuikka et al[46] reported that although the most commonly used combination regimen in their study was an antipseudomonal beta-lactam (piperacillin, ceftazidime, imipenem, carbenicillin) plus an aminoglycoside, a fluoroquinolone with a beta-lactam was also used in some patients. Monotherapy was defined as therapy with an antipseudomonal beta-lactam, fluoroquinolone, or aminoglycoside. Leibovici et al[41] reported that combination therapy consisted of a beta-lactam and an aminoglycoside; the beta-lactams used were mainly cefuroxime, ceftazidime, or other third-generation cephalosporins. Monotherapy consisted of a beta-lactam alone or an aminoglycoside alone.

Igra et al[45] explicitly defined monotherapy as a fluoroquinolone or a third-generation cephalosporin or imipenem; any one of the above drugs or a ureidopenicillin plus an aminoglycoside was considered combination therapy. Several different antimicrobial classes were used singly and in combination in the study by Kreger et al,[36] including chloramphenicol, tetracycline, kanamycin, gentamicin, penicillins, or cephalosporins. de Pauw[44] compared ceftazidime with piperacillin and tobramycin in a randomised trial. Garcia de la Torre[38] provided the susceptibility pattern in

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

Author, year, reference	Type of study	Organisms studied	Number of patients	Portal of entry	Nosocomial cases (%)	Patient population	Assessment of severity of illness	Regimens	Underlying diseases
Tapper et al, 1974[35]	Retrospective cohort	*P aeruginosa*	50	Majority respiratory/ urinary	44 (88)	Haeme malignancy	No	ESbL, AG	Neutropenia
Kreger et al, 1980[36]	Retrospective cohort	Multiple species	612	NR	NR	General	Yes	ESbL, AG	CHF, diabetes, malignancy
Piccart et al, 1984[37]	Prospective, randomised trial	Multiple species	23	NR	NR	Haeme malignancy	No	ESbL, AG	Neutropenia
McCue et al, 1985[34]	Retrospective cohort	*Escherichia coli* (51%) *Pseudomonas* spp (11%)	319	Urinary tract (51%) GI/biliary (24%)	122 (38)	General	No	ESbL, AG	Malignancy, diabetes, neutropenia
de la Torre et al, 1985[38]	Retrospective cohort	*Klebsiella* spp	100	Urinary tract	77 (77)	General inpatients	Yes	NR	Malignancy, heart disease
McCue, 1987[33]	Retrospective cohort	*Escherichia coli* (51%) Proteus spp (16%)	315	Urinary tract (50%)	129 (41)	General patients	Yes	ESbL, AG	NR
Bouza et al, 1987[39]	Retrospective cohort	*Serratia* spp	50	Urinary tract (50%)	46 (92)	General patients	Yes	ESbL, AG	COPD, cancer
Hilf et al, 1989[19]	Prospective cohort	*P aeruginosa*	200	Urinary tract (29%), respiratory tract (34%)	154 (77)	General inpatients	Yes	ESbL, AG	Malignancy, critically ill, neutropenia
Feldman et al, 1990[20]	Prospective cohort	*Klebsiella* spp	47	Respiratory tract (60%)	25 (53)	General inpatients	No	ESbL, AG, FQ	Alcoholism, neoplastic disease
Chow et al, 1991[40]	Prospective cohort	*Enterobacter* spp	129	GI (39%), urinary tract (11%)	108 (84)	General inpatients	Yes	ESbL, AG, FQ	Malignancy, transplantation
Leibovici et al, 1997[41]	Prospective cohort	*Escherichia coli* (39%) *K pneumonia* (17%) *P aeruginosa* (16%)	2165	Urinary tract (44%)	821 (38)	General patients	Yes	ESbL, AG,	Malignancy, CHF, renal failture
Korvick et al, 1992[42]	Prospective cohort	*Klebsiella* spp	230	Urinary tract (28%), biliary tract (12%)	122 (53)	General inpatients	Yes	ESbL, AG	Malignancy, diabetes
Mendelson et al, 1994[43]	Retrospective cohort	*P aeruginosa*	21	Respiratory tract (51%)	8 (38)	HIV/AIDS	No	ESbL, FQ	PCP
De Pauw et al, 1994[44]	Pospective, randomised trial	Multiple species	23	NR	NR	NR	Yes	ESbL, AG	Haeme malignancy
Igra et al, 1998[45]	Retrospective cohort study	*P aeruginosa*	57	Majority urinary tract	46 (80)	General patients	No	ESbL, AG, FQ	Malignancy
Kuikka et al, 1998[46]	Retrospective cohort	*P aeruginosa*	132	Respiratory tract (48%)	120 (90)	General patients	Yes	ESbL, AG, FQ	Surgery, renal disease
Kim et al, 2002[47]	Retrospective cohort	*Klebsiella oxytoca* (34%)	125	Biliary tract (44%), primary bacteraemia	65 (52)	General patients	Yes	ESbL, AG, FQ	Malignancy

ESbL=extended-spectrum beta-lactam; AG=aminoglycoside; FQ=fluoroquinolone; CHF=congestive heart failure; GI=gastrointestinal; PCP=*Pneumocystis carinii* pneumonia; COPD=chronic obstructive pulmonary diseases; NR=not reported; Haeme=haematology.

a study of klebsiella bacteraemia but did not provide information on the actual antimicrobials used, beyond noting whether monotherapy or combination therapy was used.

Feldman et al[20] reported that the most commonly used antimicrobials used singly were beta-lactams, aminoglycosides, or fluoroquinolones; they defined combination therapy as a beta-lactam plus an aminoglycoside. Korvick et al[42] defined monotherapy as any agent to which the infecting strain (in their study, *Klebsiella* spp) was susceptible in vitro; most patients received either a beta-lactam or an aminolygocoside singly or in combination.

11 studies reported severity of illness and only four adjusted for it in multivariable analyses[19,37,41,44] assessing the outcome of antimicrobial therapy.

Overall, in the 17 studies we included in our analysis only two studies, both prospective cohort analyses,[19,20] reported a significant beneficial effect of combination antimicrobial therapy on mortality. One, a retrospective cohort study found an increased mortality risk in patients treated with combination therapy.[34] In the remaining 14, no statistically significant superiority of combination therapy could be shown (table 2). The summary odds ratio was 0·96 (95% CI

Table 2. Mortality in patients with Gram-negative bacteraemia receiving combination or mono-anti-infective therapy

Author, year, reference	Proportion of patients who died		Odds ratio (95% CI)
	Combination therapy	*Monotherapy*	
Tapper et al, 1974[35]	30/44	27/34	0·56 (0·17– 1·75)
Kreger et al, 1980[36]	43/260	37/231	1·04 (0·63–1·73)
Piccart et al, 1984[37]	3/12	2/11	1·50 (0·13–21·72)
de La Torre, 1985[38]	9/45	9/41	0·89 (0·27–2·88)
McCue et al, 1985[34]	20/81	21/169	2·31 (1·10–4·82)
Bouza et al, 1987[39]	2/40	3/14	0·19 (0·01–1·98)
McCue et al, 1987[33]	10/33	10/74	2·78 (0·90–8·48)
Hilf et al, 1989[19]	38/143	20/43	0·42 (0·19–0·90)
Feldman et al, 1990[20]	0/9	12/16	0·00 (0·00–0·29)
Chow et al, 1991[40]	10/54	9/54	1·14 (0·37–3·49)
Korvick et al, 1992[42]	23/117	20/113	1·14 (0·56–2·34)
Mendelson et al, 1994[43]	4/15	4/9	0·45 (0·06–3·66)
De Pauw et al, 1994[44]	3/15	1/8	1·75 (0·11–104·80)
Leibovici et al, 1997[41]	62/327	131/789	1·18 (0·83–1·66)
Igra et al, 1998[45]	2/15	6/42	0·92 (0·08–6·08)
Kuikka et al, 1998[46]	11/41	28/70	0·55 (0·21–1·36)
Kim et al, 2002[47]	11/42	13/66	1·45 (0·52–3·98)

0·70–1·32), indicating no mortality benefit with the use of combination therapy (figure 1).

We did exploratory subgroup analyses to determine whether our findings would differ by limiting the analysis to studies published during or after 1990, when more potent antimicrobials were available for serious Gram-negative infections. Analysis of the eight studies published before 1990 did not change our results; the summary odds ratio was 0·97 (0·56–1·69) for studies published before 1990 and 0·97 (0·67–1·41) for studies published after 1990 (figure 2 and figure 3).

To ascertain the effect of study design on our findings, we analysed retrospective and prospective studies separately. The odds ratios for prospective and retrospective studies were 0·85 (0·50–1·48) and 1·03 (0·67–1·57), respectively (figure 4 and figure 5), suggesting no survival benefit with combination antimicrobial therapy.

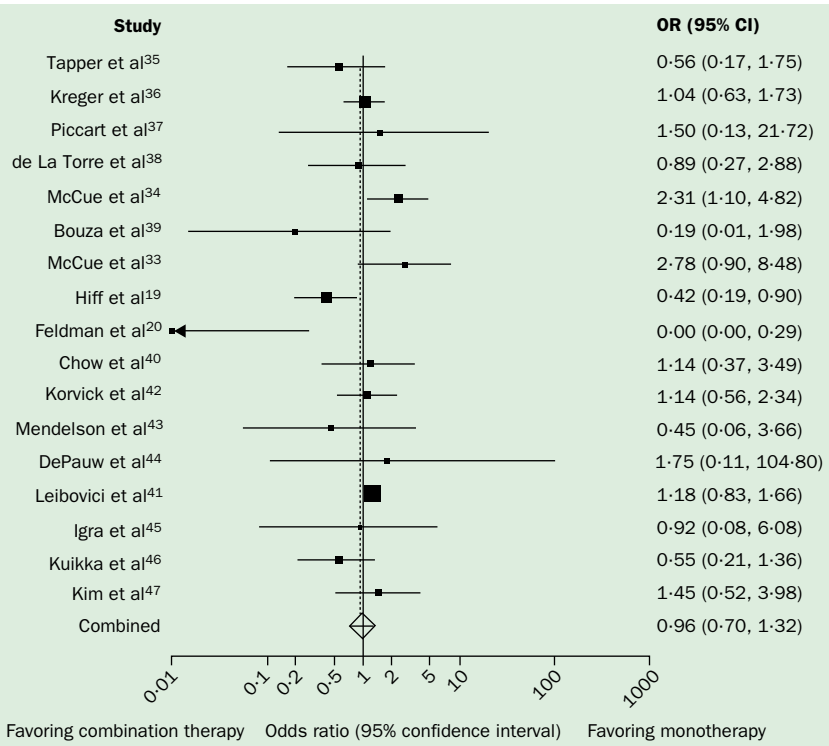

Figure 1. Analysis of studies comparing combination anti-infective therapy with monotherapy for reducing mortality of Gram-negative bacteraemia. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 0.96 (95% CI 0·70–1·32), indicating no mortality benefit with combination antimicrobial therapy.

Analysis restricted to studies of *P aeruginosa* bacteraemia was done. The studies of *P aeruginosa* bacteraemia did not show statistical heterogeneity and all the included studies showed a trend towards reduced mortality with combination therapy, which reached statistical significance in the study by Hilf et al.[19] In the five studies included, the summary odds ratio was 0·50 (0·32–0·79, p=0·007), suggesting a 50% relative reduction in mortality with the use of combination therapy (figure 6). The underlying populations however, varied considerably in the included studies; one study was limited to HIV-infected patients, one to patients with underlying malignancy, and three included general medical patients, a considerable proportion of whom were immunocompromised.

Substantial statistical heterogeneity was present in the main and subgroup analyses (p<0·01), except for

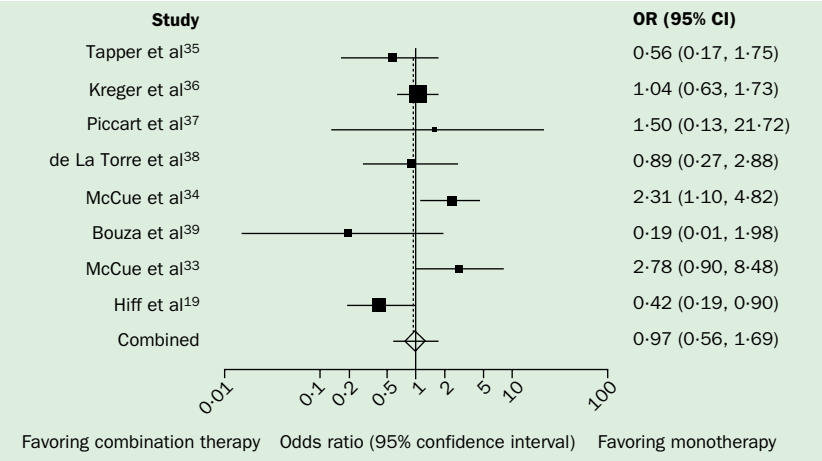

Figure 2. Analysis of studies done before 1990 comparing combination anti-infective with monotherapy for reducing mortality of Gram-negative bacteraemia. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 0·97 (95% CI 0·56–1·69), indicating no mortality benefit with combination antimicrobial therapy.

the studies of *P aeruginosa* bacteraemia, reflecting the widely varying study designs, different organisms analysed, and varying antimicrobials studied. Since most of the studies included were observational studies, the effect of unidentified confounding factors or residual confounding for known factors cannot be ruled out; it is possible that underlying disease and severity of illness had a role in determining the outcome of bacteraemia, beyond the antimicrobial treatment used.

We were not able to detect publication bias, as tested using the Egger method.[32] The shape of the funnel plot was symmetrical (figure 7).

Adverse events of monotherapy and combination therapy

Only one study[44] reported the adverse effects of combination or monotherapy among the 17 included studies. In a randomised trial, de Pauw et al[44] found that, overall, adverse events were 2·9 times more frequent in patients treated with the combination of piperacillin with tobramycin than in patients treated only with ceftazidime. The adverse effects consisted of renal toxicity, skin rash, and ototoxicity.

Discussion

Gram-negative bacilli cause serious, life-threatening infections, especially in neutropenic or critically ill patients. Several studies have convincingly shown that appropriate antimicrobial therapy, defined as the use of at least one antibiotic active in vitro against the causative organism, leads to lower mortality rates in Gram-negative bacteraemia. A landmark study by McCabe and Jackson[50] in the early 1960s reported a reduction in mortality associated with Gram-negative bacteraemia in 173 patients from 48% to 22% with the use of early appropriate antiinfective therapy. More recent studies have confirmed these results, which seem to be most pronounced for the most critically ill patients.[51–53] However, there is no consensus regarding the need to use combination as opposed to single-agent antimicrobial therapy.[21–27,53,54]

There are three potential advantages to using combination therapy: (1) an increased likelihood that the infecting pathogen will be susceptible to at least one of the components of the regimen; (2) prevention of emergence of resistance;[55,56] and (3) reduced mortality, perhaps because of an additive or even synergistic effect of the combination.[57–60] We chose to use mortality in our meta-analysis as the most objective of these three possible outcomes.

Our results indicate that combination anti-infective therapy does not reduce mortality in patients with Gram-negative bacteraemia. Patients with multiple comorbidities who are severely ill are at highest risk of developing Gram-negative sepsis, and it is clear that mortality in these patients is influenced at least as much by their underlying condition as by the Gram-negative bacteraemia itself; such patients may also be more likely to receive combination therapy. In recent years, more potent antimicrobials have become available, and hence therapy with a second antimicrobial may not be necessary.

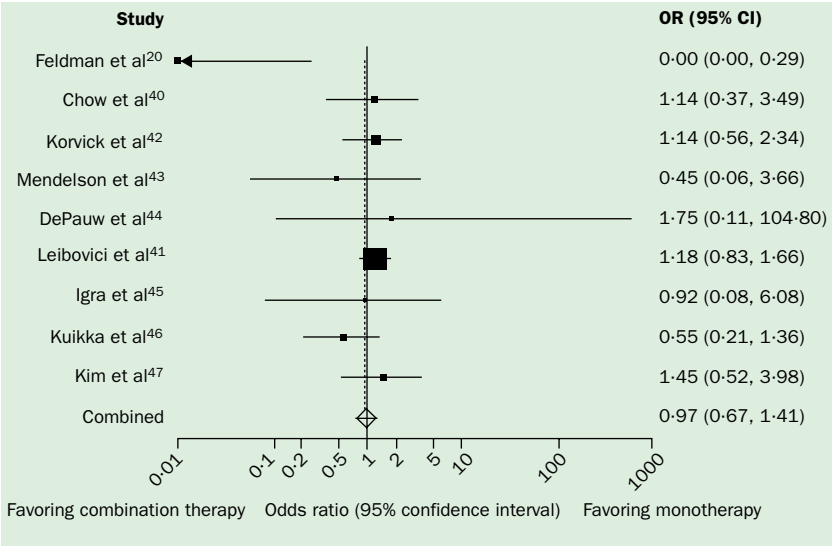

Figure 3. Analysis of studies done in or after 1990 comparing combination anti-infective therapy with monotherapy for reducing mortality of Gram-negative bacteraemia. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 0·97 (95% CI 0·67–1·41), indicating no mortality benefit with combination antimicrobial therapy.

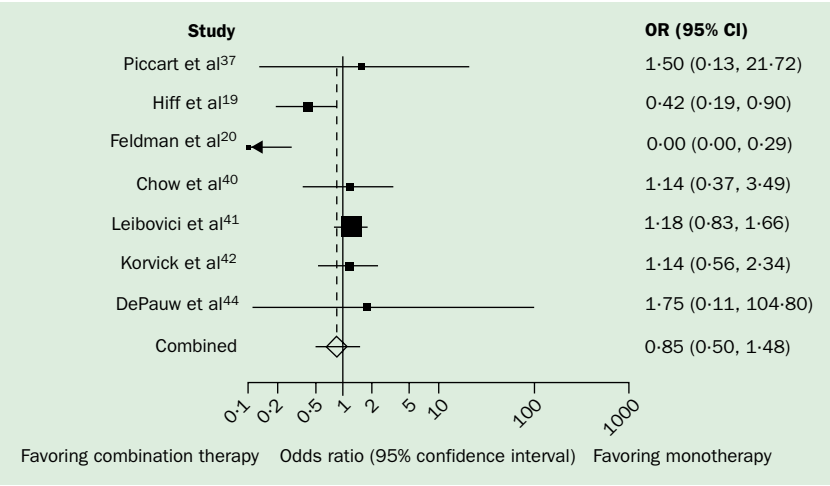

Figure 4. Analysis of prospective studies comparing combination anti-infective therapy with monotherapy for reducing mortality of Gram-negative bacteraemia. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 0·85 (95% CI 0·50–1·48), indicating no mortality benefit with combination antimicrobial therapy.

P aeruginosa is a major cause of nosocomial infection, particularly in critically ill, immunocompromised patients and is associated with greatly prolonged hospitalisation, increased costs and 20–40% mortality.[14,15,48,61] Among the 17 studies included in our analysis, five evaluated combination therapy with *P aeruginosa* bacteraemia. We found a survival benefit with the use of combination therapy for *P aeruginosa* bacteraemia, with an approximately 50% mortality reduction, based on the five studies that addressed this issue. However, despite the lack of statistical heterogeneity, the pooled results should be viewed with caution, since the studies varied considerably in the types of antimicrobial used and there is considerable clinical heterogeneity. In the largest of these studies, a prospective cohort study of 200 consecutive patients with *P aeruginosa* bacteraemia, 77% of which were nosocomial, Hilf et al[19] compared monotherapy versus combinations for reducing mortality at 10 days. Combination therapy was substantially superior (27% *vs* 47%, p<0·02); however, most patients in the monotherapy group received aminoglycosides alone.

A recent meta-analysis of randomised trials involving 7462 patients to assess the efficacy of combination antimicrobial therapy (beta-lactam and aminoglycoside) compared with monotherapy (beta-lactam alone) for patients with cancer and neutropenic fever reported that monotherapy with a broad-spectrum beta-lactam provided similar, if not slightly better, survival (RR 1·17, 95% CI 0·98–1·38). Bacterial and fungal superinfections developed with similar frequencies in the monotherapy and combination treatment groups. Adverse effects, particularly renal toxicity, were more common in patients receiving combination regimens.[62] Nor did a subgroup analysis done for patients with *P aeruginosa* infections find a benefit with combination therapy; however, the study included all types of pseudomonas infections, not only bacteraemias.

There is ample in vitro evidence for synergy against *P aeruginosa* with aminoglycoside–beta-lactam combinations.[63–65] This in vitro synergy is variably present, is strain dependent and varies with different aminoglycoside-beta-lactam combinations.[66] Animal studies have also confirmed the *in vitro* synergy of this combination of antimicrobials.[67]

Although far less evidence exists for synergy between beta-lactams and fluoroquinolones, in-vitro time-kill studies have shown variable synergy between various beta-lactams and fluoroquinolones.[68–71] In time-kill studies with ciprofloxacin in combination with aztreonam, ceftazidime, piperacillin/tazobactam, and ticarcillin/clavulanic acid against three isolates each of *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, and *P aeruginosa*, Pohlman et al[71] found that synergy was most likely to occur when ciprofloxacin and the beta-lactam were tested at concentrations equal to their respective minimum inhibitory concentrations (MICs). However, antagonism was noted in several instances, particularly when ciprofloxacin and the beta-lactam were combined at one-quarter of their respective MICs.

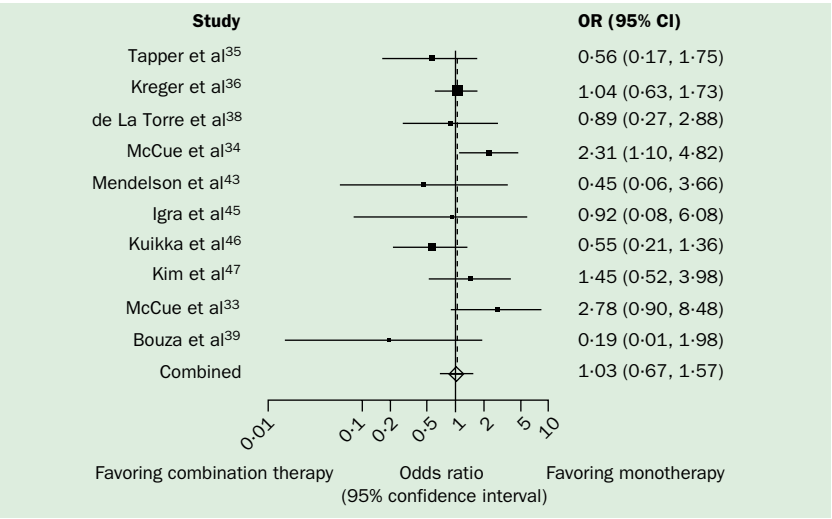

Figure 5. Analysis of retrospective studies comparing combination antiinfective therapy with monotherapy for reducing mortality of Gram-negative bacteraemia. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 1·03 (95% CI 0·67–1·57), indicating no mortality benefit with combination antimicrobial therapy.

Enterobacter spp are the most common Gram-negative health-care-associated pathogens. They are responsible for 5–7% of nosocomial bacteraemias and are the second most common Gram-negative pathogens causing intensive-care-unit-associated pneumonia.[9,16] Enterobacter isolates have an almost unique capacity to become resistant to broad-spectrum beta-lactams during therapy, owing largely to their chromosomal group 1 beta-lactamase gene, which facilitates the emergence, under antibiotic pressure, of highly resistant, stably derepressed mutants.[7,72,73] These strains are resistant to broad-spectrum cephalosporins, a feature that complicates treatment of infections caused by *Enterobacter* spp and is associated with adverse outcomes.[11,40] We were not able to identify a sufficient number of studies to do a subgroup analysis for bacteraemia caused by this organism.

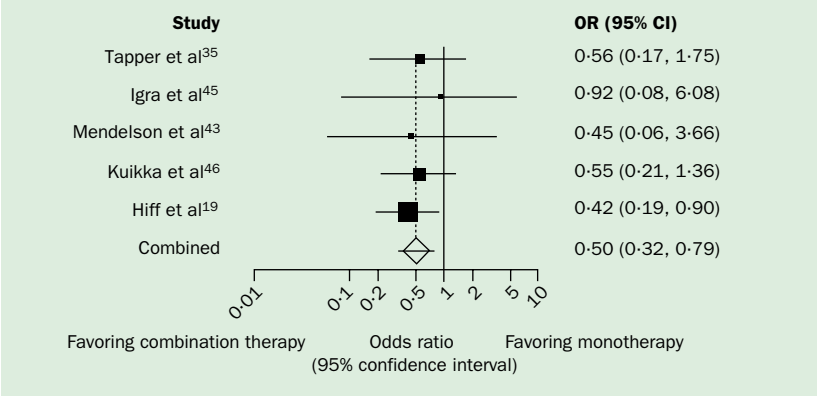

Figure 6. Analysis of studies comparing combination anti-infective therapy with monotherapy for reducing mortality of Pseudomonas *spp bacteraemia. The size of the squares is proportional to the reciprocal of the variance of the studies. The summary odds ratio is 0·50 (95% CI 0·32–0·79), indicating a mortality benefit with combination antimicrobial therapy.*

Whether combination therapy prevents the emergence of resistance in Gram-negative bacteria has been the subject of intense debate. The emergence of resistance during single-drug therapy is well documented, especially with third generation cephaloporins for infections caused by *Enterobacter* spp.[7,73] The resistant organisms are generally thought to be naturally occurring mutants selected by drug exposure. Because mutations frequencies seem to vary from 10^{-6} to 10^{-8}, it is not surprising that emergence of resistant organisms occurs primarily at sites of high organism density such as the lower respiratory tract.[16] In a comprehensive review of 173 studies encompassing more than 14 000 patients with infection (70% of the infecting organisms were Gram-negative bacilli), Fish et al[74] found that emergence of resistance occurred in 5·0% of all infections; while combination therapy was associated with a significantly reduced rate of resistance developing (3·1% with combination therapy versus 4·4% with cephalosporins alone), the dosing regimens used could not be analysed. Resistance emerged more frequently with *Pseudomonas aeruginosa* (38/252, 15%), *Enterobacter* spp (35/517, 6·8%) and *Serratia* spp (24/308, 7·7%) than *Escherichia coli* (18/2715, 0·7%, $p<0·001$). Intensive care unit patients were at highest risk for emergence of a resistant strain during treatment of infection.

A recent study that attempted to relate pharmacodynamics to the emergence of resistance in organisms, most of which were Gram-negative bacilli causing nosocomial pneumonia, found that the probability of developing resistance during therapy increased significantly when antimicrobial exposure was at an area under the curve (AUC)/MIC ratio of less than 100.[75] Since combination therapy was more likely to achieve higher AUC/MIC values, emergence of resistance was less likely with combination therapy (27% resistance in all organisms with ciprofloxacin monotherapy as opposed to 0% with ciprofloxacin and piperacillin combined therapy). Since most studies in our analysis did not provide details of dosing regimens and duration, we are not able to correlate these factors with survival. It is highly likely that suboptimal dosing schedules are a major factor leading to emergence of resistance and clinical failure.

Our analysis has significant limitations stemming from the design of the available studies. Few of the studies were prospective; most studies were retrospective, used varying antiinfectives, for varying durations, in non-standardised schedules. Moreover, most did not stratify outcome by severity of illness, which is important because combination therapy is most likely to be given to the sickest patients who are more likely to die. As such, the inability to adjust for confounding covariates in most of the non-randomised cohort studies precludes drawing strong conclusions regarding our findings and point to the need for large, multicentre prospective randomised trials to determine whether antimicrobial combinations significantly improve

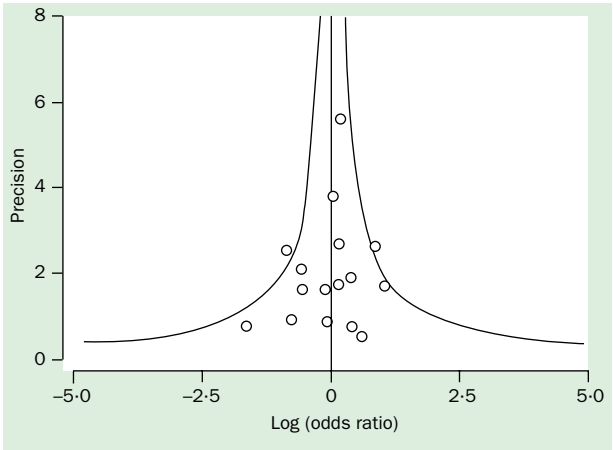

Figure 7. Funnel plot to assess the effect of publication bias in studies comparing monotherapy with combination anti-infective therapy for Gram-negative bacteraemia. Each circle represents a study. The shape of the funnel plot is symmetrical, indicating lack of publication bias.

Search strategy and selection criteria

These are described in detail in the Methods section on page 519.

outcome in patients with life threatening infections caused by Gram-negative bacilli.

In this analysis, we did not assess other important outcomes of Gram-negative bacteraemia such as microbiological cure or emergence of resistance, both of which are less precise outcomes, and thus we cannot draw any conclusions regarding the effect of combination therapy on these outcomes.

In conclusion, our study suggests that there may be no survival benefit of combination antiinfective therapy in Gram-negative bacteraemia, except in the setting of suspected infection by *P aeruginosa* or other multiresistant Gram-negative bacilli where more than one drug would be desirable to assure susceptibility to at least one antimicrobial agent.

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Conflicts of interest

We have no conflict of interest to declare.

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