Empiric antibiotic therapy for suspected ventilator-associated pneumonia: A systematic review and meta-analysis of randomized trials

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Objective: **To compare specific antibiotic regimens, and monotherapy vs. combination therapy, for the empirical treatment of ventilator-associated pneumonia (VAP).**

Design: **Meta-analysis.**

Data Source: **Medline, Embase, Cochrane register of controlled trials, study authors, and review articles.**

Study Selection: **We included randomized controlled trials that evaluated empirical parenteral antibiotic regimens for adult patients with clinically suspected VAP.**

Data Selection: **Two independent review groups searched the literature, extracted data, and evaluated trial quality. The primary outcome was all-cause mortality; secondary outcomes included treatment failure. Relative risks were pooled using a random effects model.**

Results: **We identified 41 trials randomizing 7,015 patients and comparing 29 unique regimens. Methodological quality was low, reflecting low rates of complete follow-up (43.9%), use of a double-blinded interventional strategy (14.6%), and randomization concealment (48.6%). Overall mortality was 20.3%; treatment failure occurred in 37.4% of patients who could be evaluated microbiologically. No mortality differences were observed between any of the regimens compared. Only one of three pooled comparisons yielded a significant difference for treatment failure: The combination of ceftazidime/aminoglycoside was inferior to meropenem (two trials, relative risk 0.70, 95% confidence interval 0.53–0.93). Rates of mortality and treatment failure for monotherapy compared with combination therapy were similar (11 trials, relative risk for mortality of monotherapy 0.94, confidence interval 0.76–1.16; and relative risk of treatment failure for monotherapy 0.88, confidence interval 0.72–1.07).**

Conclusions: **Monotherapy is not inferior to combination therapy in the empirical treatment of VAP. Available data neither identify a superior empirical regimen nor conclusively conclude that available regimens result in equivalent outcomes. Larger and more rigorous trials evaluating the choice of, and even need for, empirical therapy for VAP are needed. (Crit Care Med 2008; 36:108–117)**

KEY WORDS: antibiotics; ventilator-associated pneumonia; randomized control trial; meta-analysis; empirical therapy; critical care; cross-infection

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection acquired in the intensive care unit (ICU). VAP develops in 10% to 20% of patients who undergo mechanical ventilation >24 hrs (1–3) and is associated with an excess ICU stay of 5–7 days, increased costs (4), and an attributable mortality ranging from 0% to 50% (5–8).

The diagnosis of VAP is notoriously difficult (9). Clinical criteria are nonspecific (10), and results of cultures and sensitivity testing are only available several days later. Published guidelines recommend early empirical antimicrobial therapy—the administration of antibiotics before a microbiological diagnosis of infection is established (11)—targeted to the most likely infecting pathogens based on the timing of the episode, the severity of illness, and previous antibiotic exposure (12, 13). Early VAP results from organisms commonly seen in community-acquired pneumonia—*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. Late VAP or VAP in a patient previously exposed to antibiotics is more likely to be caused by multiresistant organisms such as *Pseudomonas* spp, *Acinetobacter*, and methicillin-resistant *S. aureus* (14–16). Recommendations for empirical treatment of early VAP are single agent ceftriaxone, ampicillin/sulbactam, or a fluoroquinolone. In contrast, recommended regimens for late VAP include a carbapenem with or without vancomycin, or combination therapy comprising an aminoglycoside or ciprofloxacin with an antipseudomonal penicillin, a β-lactam/β-lactamase inhibitor combination, ceftazidime, or cefepime (13).

Combination therapy is believed to increase the likelihood of therapeutic suc-

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Supported, in part, by the physicians of Ontario through a grant from the Physician's Services Incorporated Foundation of Ontario.

Dr. Aarts was the recipient of the Wyeth-Ayerst Fellowship in Clinical and Evaluative Sciences of the Surgical Infection Society. Dr. Heyland has received honoraria and grant funding from Astra Zeneca and Bayer. Dr. Marshall is a consultant to Wyeth, Astra Zeneca, LEO Pharma, Hutchinson, Eisai, and Becton-Dickinson. He has also received speaking fees from Pfizer and grant funding from GlaxoSmithKline. The remaining authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/01.CCM.0000297956.27474.9D

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cess through an extended spectrum of activity (17), antimicrobial synergy (18), and a decreased potential for promoting resistant microorganisms (19). However, studies in critically ill patients suggest that combination therapy is expensive and associated with greater toxicity and that broad-spectrum therapy is a risk factor for the later emergence of multiresistant organisms, increased rates of superinfections, and death (14, 15, 20–22).

Published guidelines that recommend combination empirical therapy for late-onset VAP are based on the expected microbial spectra, narrative reviews, and expert opinion (12–14, 23). We undertook this systematic review to synthesize the available evidence from randomized controlled trials that evaluate the effectiveness of parenteral antibiotic regimens, and monotherapy vs. combination therapy, in the empirical treatment of suspected VAP.

MATERIALS AND METHODS

Process of the Review. Two groups independently conducted the literature search, reviewing all potential abstracts regardless of language or publication status up to January 2007. We searched Medline (1966 to January 2007), EMBASE (1980 to January 2007), and the Cochrane Central Register of Controlled Trials using the following strategy: Explode "ventilator associated pneumonia," "ventilators, mechanical," or "respiration, artificial" combined with "cross-infection," or "pneumonia," and crossed with "anti-bacterial agents." The associated text/title words were similarly searched. Standard limiters were used to identify randomized controlled trials and review articles. Bibliographies of all reviews and studies were searched for additional studies, and unpublished trials were sought by contacting experts in the field and authors of identified trials.

We included randomized controlled trials of empirical treatment for VAP if they compared a parenteral antibiotic regimen with a placebo or comparison parenteral antibiotic. A suspicion of VAP was defined as a new or progressive infiltrate, in association with fever, leukocytosis, and/or purulent secretions in patients ventilated >48 hrs. Trials were excluded if <50% of patients were ventilated or if culture results were available before initiation of antibiotics.

Our primary outcome was 28- or 30-day all-cause mortality. Secondary outcomes included treatment failure, defined as lack of improvement in signs or symptoms of pneumonia; serious attributable adverse events (seizures, pseudomembranous colitis, nonreversible end organ damage); and superinfections (new, persistent, or worsening signs of infection associated with the isolation of a new pathogen or similar pathogen with a different antibiotic susceptibility profile or site of infection).

Data Abstraction and Quality. The two review groups extracted data and assessed quality in duplicate, resolving discrepancies through consensus. For each trial identified, we recorded the number and description of participants, the country, the number of participating sites, the experimental and control antibiotic regimens, the length of hospitalization before enrollment, the duration of therapy and strategy to alter antibiotics based on microbiological evaluation, the definition of clinical response, and the source of trial financial support. Unless otherwise specified, we assumed that the experimental therapy included the antibiotic that was produced by the pharmaceutical company supporting the trial. For studies including patients with community-acquired pneumonia or other types of nosocomial infection, only outcomes reported for the subgroup of patients with VAP were included. When outcomes for this cohort were not adequately reported in the study, additional information was requested from the authors.

The quality of trials was assessed by evaluating whether physicians and patients were blinded to treatment assignment (double-blinded) and, if not, whether the allocation of patients to treatment groups was concealed and the outcome was evaluated by a blinded assessor. We also evaluated whether all patients initially enrolled were accounted for and whether an intention-to-treat (ITT) analysis was applied. In addition, we noted whether a sample size calculation was included in the report.

Data Synthesis and Analysis. We used outcome data from the ITT analysis or per protocol analysis (when ITT data were not available) to evaluate the clinical efficacy of the empirical antibiotic regimens. We conducted a subgroup analysis of patients with positive cultures of sputum, endotracheal aspirate, bronchial alveolar lavage, and/or blood to determine the impact of therapy on microbiologically confirmed infection.

Primary and secondary outcomes were combined for trials comparing antibiotics from the same class of agents, grouped as follows: 1 = penicillins; 2 = cephalosporins; 3 = carbapenems; 4 = aminoglycosides; 5 = quinolones; 6 = metronidazole; 7 = clindamycin; 8 = vancomycin; 9 = linezolid; 10 = quinupristin/dalfopristin; 11 = aztreonam.

A further analysis compared studies of monotherapy with combination therapy. For this analysis, we included trials that compared a single broad-spectrum agent to any combination therapy. Two sensitivity analyses were conducted for these pooled trials. The first evaluated only high-quality trials that employed at least two of double-blinded methodology, blinded assessment of outcome, concealed group allocation, or complete follow-up of enrolled patients. The second analysis was limited to trials that exclusively enrolled ventilated patients.

Dichotomous outcomes were expressed as relative risks (RR) with 95% confidence intervals (CI). A RR <1.0 suggests a reduced risk of mortality, treatment failure, superinfections, and adverse events with the experimental treatment, compared with the control treatment, and with monotherapy compared with combination therapy. A random effects model

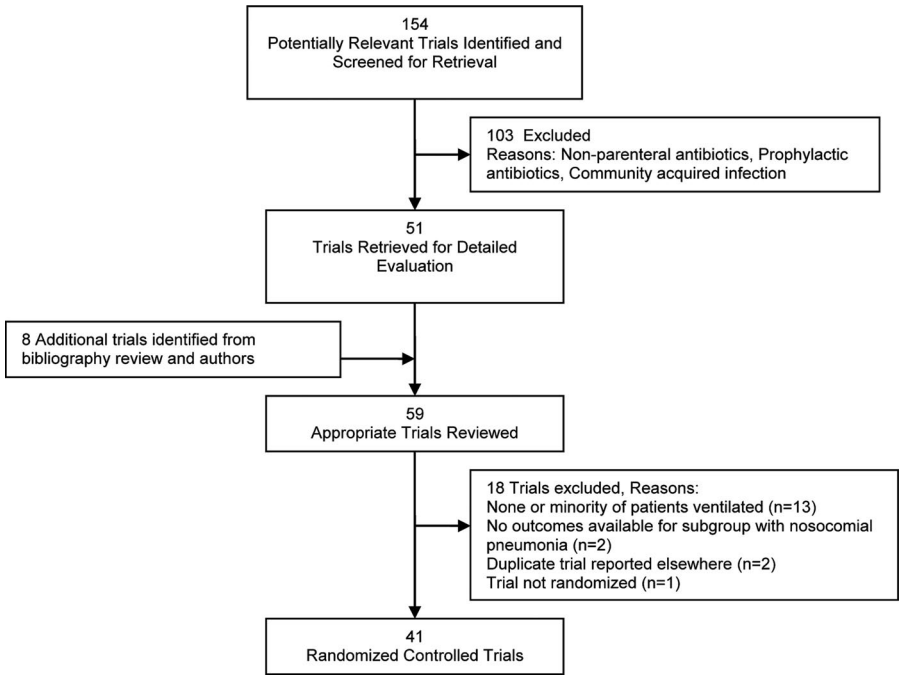

Figure 1. Study flow diagram of the process for identifying the 41 studies included in this review.

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Table 1. Characteristics and quality of trials comparing antibiotic therapies for ventilator-associated pneumonia (VAP)

Reference	Experimental vs. Control Therapy	Additional Antibiotic Both Groups	No.	Patients Ventilated, %	*Pseudomonas* Species, %	Group Assignment Concealed	Double Blind	Blind Outcome Assessment	ITT Analysis	Comple Follow-Up
Gram-positive coverage										
Cepeda 2004 (67)	Linezolid vs. teicoplonin		50[a]	84	NA	Yes	Yes	Yes	Yes	No
Wunderink 2003 (57)[b] Rubinstein 2001 (44)	Linezolid vs. vancomycin	Aztreonam	544	100	NA	Not stated	Yes	Yes	Yes	No
Grudinina 2002 (46)	Linezolid vs. vancomycin		69	100	NA	Not stated	Not stated	Not stated	No	No
Fagon 2000 (61)	Quinupristen/dalfopristin vs. vancomycin	Aztreonam	298	74	NA	Yes	No	No	Yes	Yes
Monotherapy vs. combination therapy										
Damas 2006 (43)	Cefepime vs. cefepime/ amikacin or cefepime/ levofloxacin		74	100	13.5	No	No	No	Yes	Yes
Muscedere 2005 (45)	Meropenem vs. meropenem/ciprofloxacin		739	100	6.2	Yes	No	No	Yes	Yes
Alvarez 2001 (48)	Meropenem vs. ceftazidime/amikacin		140	100	23	Not stated	No	Yes	Yes	Yes
Manhold 1998 (16)	Ciprofloxacin vs. ceftazidime/gentamicin		51	100	NA	Not stated	Not stated	No	Yes	Not clear
Sieger 1997 (69)	Meropenem vs. ceftazidime/tobramycin		211	70	22	Not stated	No	No	Yes	Yes
Rubinstein 1995 (74)[c]	Ceftazidime vs. ceftriaxone/tobramycin	Metronidazole[d]	297	60	16	Yes	No	Yes	Yes	Yes
Mouton 1995 (64)[c]	Meropenem vs. ceftazidime/amikacin		84	50	22	Not stated	No	No	No	No
Cometta 1994 (70)[c,e]	Imipenem vs. imipenem/ netilmicin		177[a]	55	19	Yes	Yes	Yes	No	Yes
Kljucar 1987 (54)[f]	Ceftazidime vs. ceftazidime/tobramycin		33	100	6	Not stated	No	Not stated	Yes	No
Brown 1984 (63)	Moxalactam vs. carbenicillin/tobramycin		48	85	21	No	No	No	No	Yes
Rapp 1984 (81)[c]	Ceftazidime vs. ticarcillin/ tobramycin		35	NA	23	Not stated	No	No	No	No
Carbapenem vs. carbapenem										
Garau 1997 (79)	Meropenem vs. imipenem		79	84	15	Yes	No	No	No	No
Colardyn 1996 (78)[c]	Meropenem vs. imipenem		80	59	12	Not stated	No	No	No	Not clear
Cephalosporin vs. carbapenem										
Zanetti 2003 (76)	Cefipime vs. imipenem		281	66	25	Yes	No	Yes	No	Yes
Norrby 1993 (62)[c]	Ceftazidime vs. imipenem		254[a]	50	12	Yes	No	Yes	No	No
Cephalosporin vs. cephlasporin										
Beaucaire 1999 (50)	Cefepime vs. ceftazidime	Amikacin	275	100	19	Not stated	No	Yes	Yes	Yes
Wolff 1998 (77)	Cefpirome vs. ceftazidime		400	69	12	Not stated	No	Yes	Yes	Yes
Thomas 1994 (55)	Cefotaxime vs. ceftriaxone		142	100	4	Not stated	Yes	Yes	No	No
Croce 1993 (53)[c]	Cefoperazone vs. ceftazidime	Gentamicin	109	100	NA	Not stated	No	No	No	Not clear
Reeves 1989 (73)	Cefotaxime vs. ceftriaxone		51	90	4	Not stated	No	No	Yes	Not clear
Fluoroquinolone vs. cephlasporin										
Saginur 1997 (56)[c]	Ciprofloxacin vs. ceftazidime	Clindamycin[d]	77[g]	100	4	Yes	No	No	No	No
Rapp 1991 (65)[c]	Ciprofloxacin vs. ceftazidime	Metronidazole	32	66	6	Yes	No	Yes	No	Yes
Fluoroquinolone vs. carbapenem										
West 2003 (66)	Levofloxacin vs. imipenem	Ceftazidime Amikacin	438	60	8	No	No	No	Yes	Yes
Torres 2000 (75)	Ciprofloxacin vs. imipenem		152	99	35	Yes	No	No	No	No
Fink 1994 (59)	Ciprofloxacin vs. imipenem	Vancomycin Metronidazole[d]	402	76	23	Yes	Yes	Yes	Yes	Not clear
Giamarellou 1990 (91)	Pefloxacin vs. imipenem		71	72	35	No	No	No	No	No

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Table 1.—*Continued*

Reference	Experimental vs. Control Therapy	Additional Antibiotic Both Groups	No.	Patients Ventilated, %	*Pseudomonas* Species, %	Group Assignment Concealed	Double Blind	Blind Outcome Assessment	ITT Analysis	Comple Follow-Up
Antipseudomonal penicillin vs. cephalosporin										
Alvarez-Lerma 2001 (68)	Pip/tazobactam vs. ceftazidime	Amikacin	124	86	21	Not stated	No	Yes	Yes	Yes
Brun-Buisson 1998 (47)	Pip/tazobactam vs. ceftazidime	Amikacin	207	100	31	Not stated	No	Yes	Yes	Yes
Aztreonam vs. aminoglycoside										
Torres 1989 (51)[c]	Aztreonam vs. amikacin	Cefotaxime	33	100	33	Not stated	No	No	No	No
Schentag 1985 (60)	Aztreonam vs. tobramycin	Gram positive coverage[d]	47	68	28	Yes	No	No	No	No
Other										
Baker 2003 (42)	Delayed culture directed antibiotic vs standard therapy[h]		100	100	4	Not stated	No	Yes	No	Yes
Singh 2000 (7)	Ciprofloxacin vs. standard therapy[h]		81	58	NA	Not stated	No	No	Yes	Yes
Jaccard 1998 (72)	Pip/tazobactam vs. imipenem		154[a]	50	29	Yes	No	No	No	Not clear
Polk 1997 (52)	Aztreonam/vancomycin vs. imipenem		122	100	NA	Not stated	No	No	Yes	Not clear
Beaucaire 1995 (49)	Isepamicin vs. amikacin	Ceftazidime	86	100	NA	Not stated	No	No	Yes	Yes
Beuscart 1989 (58)[c]	Pefloxacin vs. amikacin	Ceftazidime	352	90	25	Not stated	Not stated	Not stated	No	No
Kljucar 1987 (54)[f]	Ceftazidime vs. azlocillin	Tobramycin	32	100	14	Not stated	No	Not stated	Yes	No
Total, 41 trials			7,015	77	18					

ITT, study employed an intention-to-treat analysis; NA, not available.

[a]Subgroup with nosocomial pneumonia; [b]the VAP subgroup data were reported in a retrospective review paper (92); [c]only clinical cure or improvement reported; [d]additional therapy optional; [e]outcomes of subgroup communicated from author; [f]the trial by Kljucar 1987 had three treatment arms and is reported as two separate comparisons; [g]subgroup with ventilator-dependent pneumonia; [h]standard therapy (defined by the attending physician, usually combination therapy).

was used to analyze the pooled outcomes using the DerSimonian-Laird method (24). Outcomes were weighted by inverse variance. Analysis was conducted using Review Manager (RevMan, version 4.2 for Windows Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003).

RESULTS

Study Identification. We screened 154 trials for inclusion in this review. We excluded 18 of 59 potentially eligible trials, as outlined in Figure 1 (4, 25–41). The 41 trials included in the review were conducted in >30 countries and were published between 1984 and 2006; they enrolled a total of 7,015 patients. Twenty-nine different regimens of antibiotics were compared (Table 1); no antibiotic was consistently used as the comparator in the control arm of these studies. Most regimens included sufficient coverage for Gram-positive, Gram-negative, and anaerobic organisms. Five studies evaluated the best coverage for Gram-positive agents, with linezolid being the experimental therapy in three of these trials. No placebo-controlled trials were identified; however, one trial compared early empirical therapy with delayed culture-directed therapy based on bronchoscopic specimens (42). Twenty-six studies enrolled ICU patients exclusively. Seventeen trials restricted entry to patients with suspected VAP (16, 42–57); only two of these compared the same regimens—linezolid and vancomycin (46, 57). Late-onset pneumonia, with hospitalization or ICU stay >96 hrs, was evaluated in only two trials (16, 45). Two trials recruited only trauma patients (42, 53). Four of the included studies were reported in languages other than English, specifically German (54), French (50, 58), and Russian (46).

All trials initiated antibiotics empirically before the availability of culture results. Four studies required a positive sputum Gram stain before initiation of treatment (53, 59–61). A strategy to alter antibiotics following the availability of culture results was described in 19 trials (46.3%). In eight trials, antibiotics were added or changed if the patient was failing or a resistant organism was identified (43, 49, 50, 53, 62–65). In two trials, Gram-positive coverage or Gram-negative coverage could be added as required (66, 67). Criteria for discontinuation of therapy were specified in nine trials: In four trials, the aminoglycoside was discontinued if the culture results were negative for infection with *Pseudomonas* (47, 48, 68, 69); in a single trial, antibiotics were discontinued if there was no clinical improvement by day 3 (54); and in four trials, discontinuation of all antibiotic therapy was mandated if eventual culture results were negative (7, 42, 45, 58).

Study Quality. The overall quality of the included studies was low (Table 1). A double-blinded methodology was employed in only six trials (14.6%) (44, 55, 57, 59, 65, 67). Of the nonblinded trials, allocation to study group was concealed in 17 of 35 trials (48.6%) (45, 54, 56, 57, 59–62, 65–67, 70–76), and outcomes were evaluated by a blinded assessor in only 9 of 35 trials (25.7%) (42, 47, 48, 50, 62, 68, 74, 76, 77). Only 18 of 41 trials (43.9%) had complete follow-up of en-

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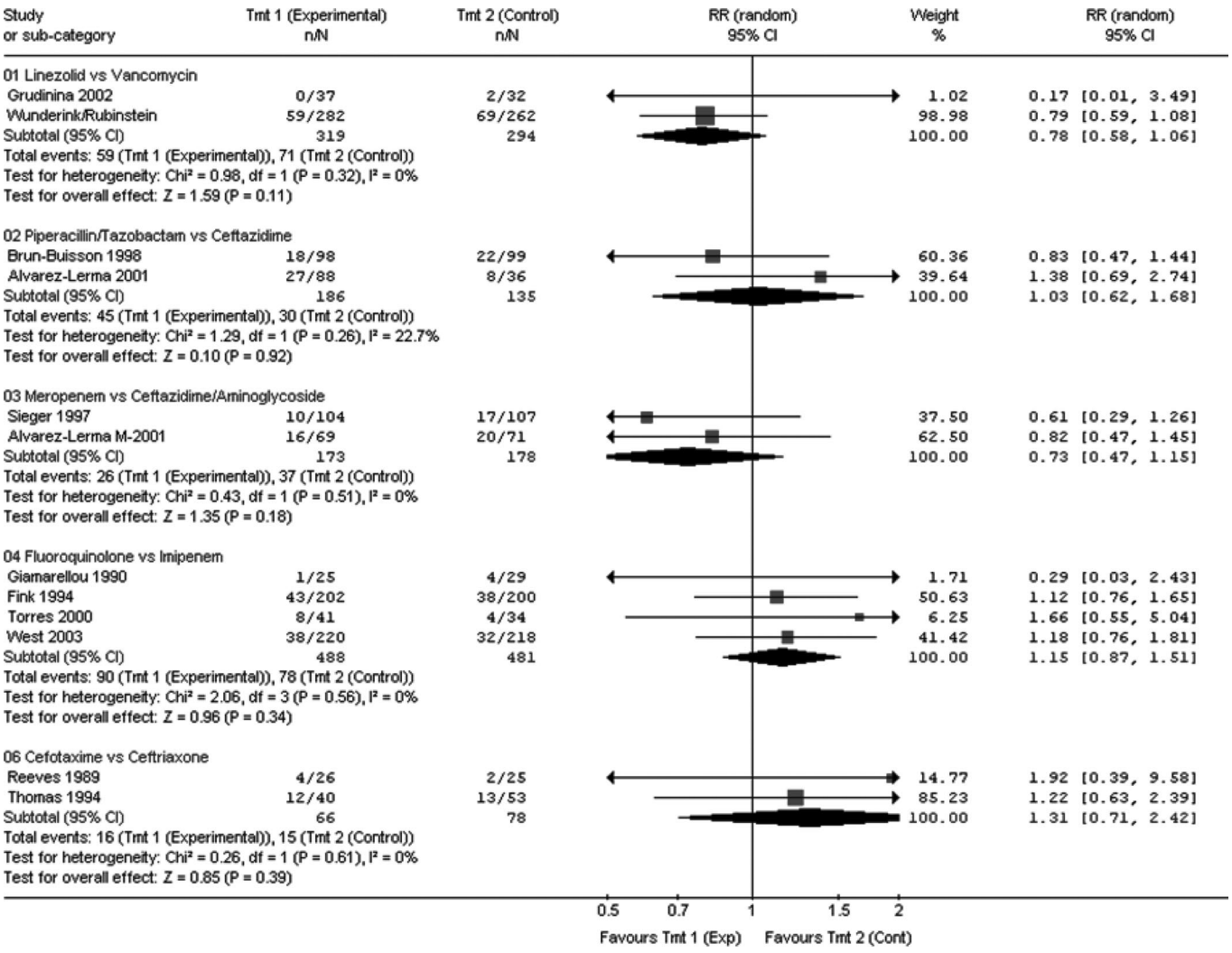

Figure 2. Mortality in pooled trials comparing specific antibiotic regimens. Unless otherwise specified in the report, we assumed that the experimental therapy was the therapy produced by the pharmaceutical company supporting the trial; the first-named regimen is the experimental regimen. No regimen demonstrated superiority for a particular regimen. *Tmt*, treatment; *RR*, relative risk; *CI*, confidence interval.

rolled patients. A power calculation was included in the report of 19 trials (46.3%) (7, 42, 45, 48, 56, 57, 59, 61, 62, 66–70, 74, 76–79). Most of these were powered to detect a 15% to 20% difference in clinical outcome (12 of 19); five were powered to detect a 10% difference in clinical cure (62, 74, 77), bacteriologic response (59), or renal toxicity (70); and only two were powered to detect a difference in mortality—10% in 28-day mortality (45) or 25% in hospital mortality (42).

Mortality. There was no evidence that any particular regimen improved survival. Mortality was reported in 30 of the trials, analyzing an ITT or per protocol population was reported in 26, and only patients with a pathogen sensitive to the study drug were reported in four (55, 60, 63, 75). The overall reported mortality rate was 20.3% (1,072 of 5,277). No significant differences in survival were identified between any study regimens, even with pooling of trial results (Fig. 2). Importantly, the CIs also remained wide for most comparisons. Among the pooled comparisons the narrowest CI spanned from 0.58 to 1.06 for the comparison of linezolid to vancomycin, and in the unpooled comparisons it spanned from 0.70 to 1.27 with an RR of 0.94 for meropenem vs. meropenem and ciprofloxacin (45). Worse, 13 of 18 unpooled comparisons were not able to exclude effect sizes greater than RR = 2.0 (or less than RR = 0.5), indicating that large clinical differences could exist between regimens.

Treatment Failure. Nineteen studies reported rates of treatment failure in patients with clinically suspected pneumonia (ITT or per protocol analysis). Six trials could be pooled in three comparisons (Fig. 3) and showed meropenem to be superior to combination ceftazidime/aminoglycoside (RR 0.70, 0.53–0.93). Another 13 trials could not be pooled because the treatment regimens compared differed. Only one of these studies yielded a significant difference; short-course ciprofloxacin (discontinued if cultures were negative and the Clinical Pulmonary Infection Score was <6) was superior to standard therapy (determined by the treating physician) (RR 0.64, 0.41–0.99) (7). The overall failure rate in these studies was 42.2% (1,775 of 4,211).

Thirty-three trials reported treatment failure rates for the subgroup of patients with microbiologically confirmed infection. The overall failure rate was 37.4% (1,328 of 3,548). Twenty of the 33 trials could be pooled in nine comparisons.

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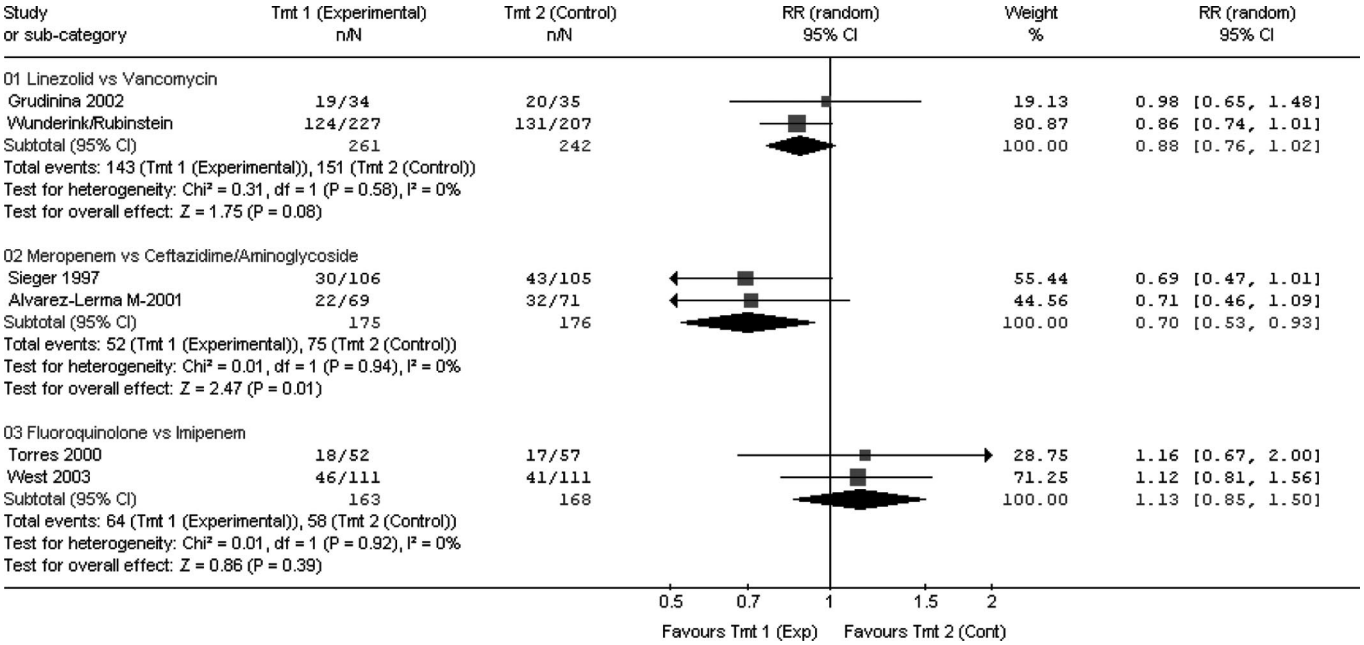

Figure 3. Rates of treatment failure in pooled trials comparing specific antibiotic regimens. The only evidence of superior efficacy was seen in studies comparing meropenem to a combination of ceftazidime and an aminoglycoside. *Tmt,* treatment; *RR,* relative risk; *CI,* confidence interval.

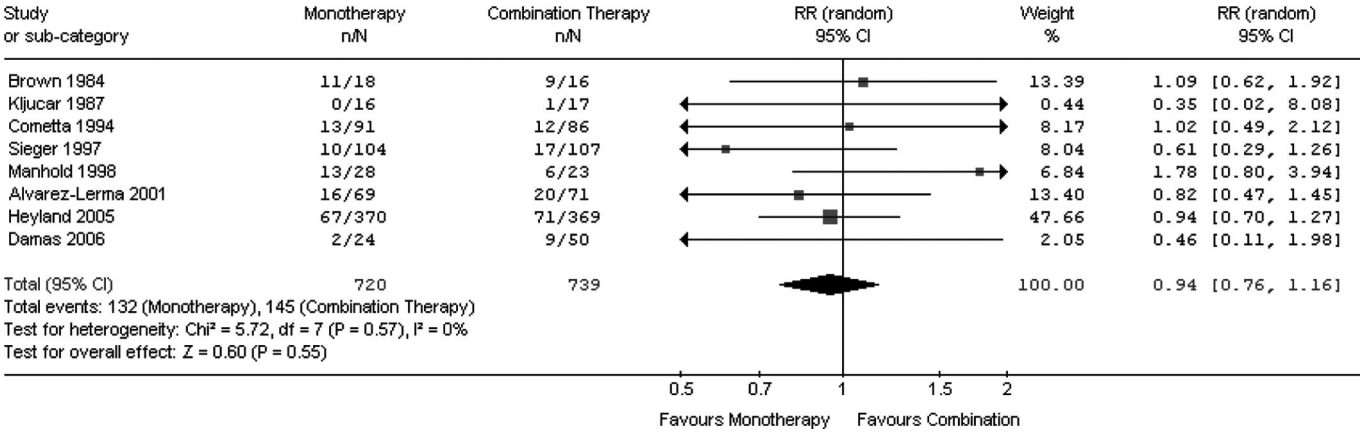

Figure 4. Mortality in pooled trials comparing monotherapy to combination therapy. There is no evidence that combination therapy improves survival when compared with monotherapy. *RR,* relative risk; *CI,* confidence interval.

Pooled results of three trials showed meropenem to be superior to combined ceftazidime/aminoglycoside, RR 0.51 (0.33–0.80) (48, 64, 69), while linezolid was superior to vancomycin for suspected Gram-positive infection when two trials were pooled (RR 0.75, 0.59–0.96) (46, 57). Pefloxacin was found inferior to amikacin, with an RR of 2.07 (1.09–3.93); however, this trial was of very poor quality and did not report mortality (58).

Superinfections and Adverse Events. Superinfection occurred in 564 of 4,217 patients (13.3%) in the 26 trials that reported this outcome. Only one trial found a significantly different superinfection rate between treatment strategies. Ciprofloxacin, discontinued at 48 hrs if culture results were negative and the Clinical Pulmonary Infection Score was <6, was associated with a significantly lower rate of superinfection than standard therapy as directed by the attending physician—5 of 39 (13%) vs. 14 of 42 (33%) (RR 0.38, 0.15–0.97) (7). The average rate of serious side effects across the 26 studies that reported this outcome was 6.3% (356 of 5,655). The only trial to find a significant difference in rates of adverse events compared ciprofloxacin (3 of 202; 1.5%) to imipenem (11 of 200; 5.5%) (RR 0.27, 0.08–0.95) (59).

Combination Therapy Vs. Monotherapy. Eleven trials compared monotherapy with combination therapy (16, 43, 45, 48, 54, 63, 69, 70, 74, 80, 81). Of the 1,805 patients in these trials, 85.1% were ventilated and 13.8% were infected with *Pseudomonas* spp. (Table 1); only five trials exclusively enrolled ventilated patients (16, 43, 45, 48, 54). Monotherapy consisted of a carbapenem (n = 5), ceftazidime (n = 3), cefepime (n = 1), ciprofloxacin (n = 1), or moxalactam (n = 1). Combination therapy consisted of ciprofloxacin combined with meropenem (n = 1); cefepime combined with levofloxacin or amikacin (n = 1); or an aminoglycoside combined with one of ceftazidime (n = 5), ceftriaxone (n = 1), an antipseudomonal penicillin (n = 2), or a carbapenem (n = 1).

Eight of these trials, enrolling 1,459 patients, reported mortality (Fig. 4).

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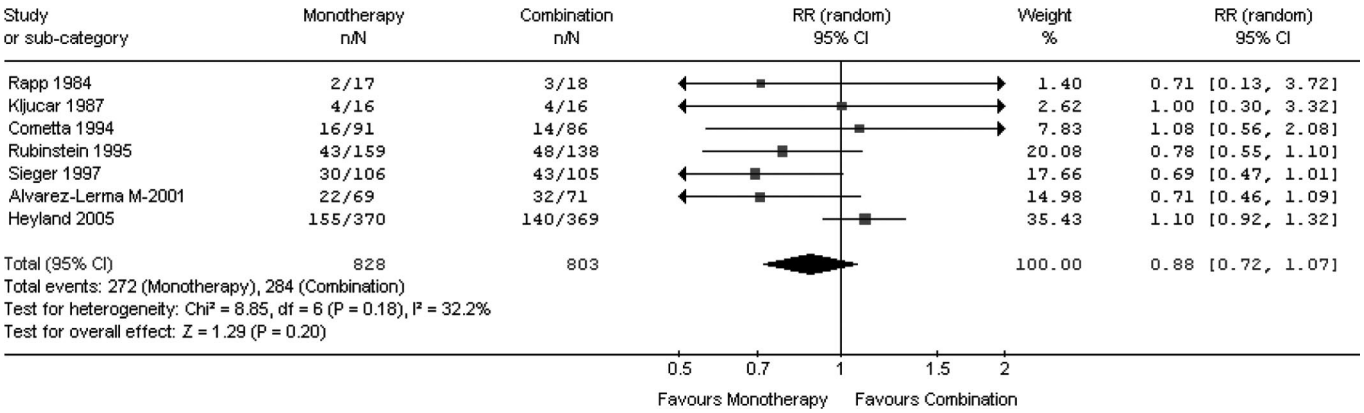

Figure 5. Treatment failure in pooled trials comparing monotherapy with combination therapy. There was no evidence that combination therapy results in lower rates of treatment failure but rather a statistically nonsignificant trend to higher rates of treatment failure when combination therapy is used. *RR*, relative risk; *CI*, confidence interval.

There was no mortality difference for patients receiving monotherapy in comparison to combination therapy (RR 0.94, 0.76–1.16). Based on this narrow 95% confidence interval, with a maximum RR of 1.16, it does not appear likely that combination therapy is clinically superior to monotherapy. Similarly there was no significant difference in treatment failure in patients with clinically suspected pneumonia (RR 0.88, 0.72–1.07; Fig. 5) or microbiologically proven pneumonia (RR 0.86, 0.63–1.16) (45, 48, 63, 64, 69, 70, 74). Outcomes did not change in the sensitivity analyses of high-quality trials (45, 48, 70, 74) (mortality, RR 0.93, 0.72–1.19; treatment failure, RR 0.92, 0.72–1.17) or in the five trials exclusively enrolling ventilated patients (16, 43, 45, 48, 54) (mortality, RR 0.95, 0.74–1.22; treatment failure, RR 0.95, 0.68–1.32). There were no significant differences in rates of superinfections (RR 0.77, 0.48–1.22) or serious adverse events (RR 0.84, 0.48–1.49).

DISCUSSION

More than 7,000 patients were enrolled in the 41 different trials included in this meta-analysis, yet the results do not permit robust conclusions regarding the selection of optimal empirical antimicrobial therapy for patients with suspected VAP. We found no mortality benefit for any of the regimens evaluated. Moreover, we found no evidence that combination therapy is superior to monotherapy in reducing the 37.4% rate of treatment failure or in altering rates of superinfection and adverse events. These findings are similar to those of a recent meta-analysis which found no difference in outcomes with β–lactam-aminoglycoside combination therapy compared with β -lactam monotherapy in patients with severe sepsis (82).

The only significant difference observed between any specific empirical regimens was that meropenem was associated with a decreased treatment failure rate when compared with ceftazidime and aminoglycoside combination therapy. This treatment effect, however, did not translate into a difference in mortality. The two trials pooled in this analysis were of low quality. In addition, in light of the multiple comparisons made in this analysis evaluating treatment failure (19 comparisons), it could be expected that roughly 5% of these differences could be explained by chance alone (type I error) using $\alpha = .05$.

There are several plausible explanations for the overall lack of proven differential therapeutic efficacy. The individual trials are generally small and lack the power to detect modest but clinically important differences in outcome between the treatment groups. The objective of most studies was to demonstrate equivalence, but almost all were underpowered to detect an absolute difference of 10% between the two study arms. Even when we pooled patients from trials employing the same antibiotic interventions, the resulting sample sizes were still too small to conclude with confidence that there is no clinically important difference in patient outcomes.

The efficacy of the initial empirical antibiotic regimen is at least partly dependent on the therapeutic strategy employed once the results of cultures are available. Two studies evaluating the utility of bronchoscopic methods to rule out infection found that discontinuing antibiotics when cultures are demonstrated to be negative not only is safe but may actually increase survival (83, 84); however, a third randomized controlled trial included in this meta-analysis did not support this conclusion (45). All trials in this review initiated treatment based on a clinical suspicion of pneumonia; however, the strategy for altering agents once microbiological data were available was neither consistent nor explicitly defined. Only one study specified that the empirical regimen (ciprofloxacin) be discontinued if culture results were negative in the absence of clinical deterioration (7); this study reported a reduction in rates of superinfection and an improvement in clinical outcomes when antibiotics were stopped.

The heterogeneity of patients enrolled into these trials may have diluted the impact of particular antibiotic regimens in patients with a specific diagnosis of VAP. The concept of VAP first appeared in 1978 (85), but only in the past decade has it has received widespread attention as a distinct condition. However, even in the 17 trials that exclusively recruited patients with VAP, no significant differences in outcomes were observed between treatment arms.

Variability in the accuracy and completeness of the outcomes measured may also have influenced the conclusions of this review. The primary outcome for all but two of these studies was "cure" or "improvement" of pneumonia. This outcome is subjective and observer-dependent; however, in only 13 trials (32%) was the assessor blinded to treatment group.

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All-cause mortality was reported in only 26 of the 41 trials.

Finally, it is possible that the administration of empirical antibiotics to patients suspected of having VAP does not significantly improve clinical outcome or that the selection of agent is much less important than the timing of administration. The impact of delayed culture-guided therapy was evaluated in a single trial that found no difference in mortality rates but was underpowered to exclude a clinically important difference (42). The conclusion that early empirical therapy for VAP is beneficial is derived from studies of patients with community-acquired infections or from retrospective analyses of observational studies of patients with VAP (86–88). In the absence of a rigorous comparison, it is unclear whether the equivalence of active treatments reflects true therapeutic equivalence or the lack of utility of a strategy of empirical therapy (89, 90).

This meta-analysis synthesizes the best evidence from randomized controlled trials regarding empirical antibiotic therapy for VAP and demonstrates that we are forced to choose among potentially inferior alternatives because research is lacking that would either identify a superior regime or demonstrate that available choices are effectively equivalent. Although we cannot recommend a particular antibiotic regimen, in the absence of strong evidence of safety for delayed therapy, we recommend that patients with a high clinical suspicion of VAP be started on empirical antibiotic therapy. We found no benefit for combination empirical therapy over monotherapy, even in the two studies specific to late-onset pneumonia (16, 45). However, the percentage of episodes of VAP caused by multi-drug-resistant or difficult-to-treat organisms was low in the trials we reviewed, and the initial selection of agent or agents must be guided by consideration of local microbial ecology. Our data do not permit specific recommendations regarding the additional utility of empirical coverage against methicillin-resistant *S. aureus*, as all studies evaluating linezolid or vancomycin included methicillin-resistant *S. aureus* coverage in the comparator arm.

Finally, this review underlines the need for high-quality adequately powered trials to determine the best treatment for suspected VAP. Contemporary concerns about the adverse consequences of antibiotic overuse highlight a need for randomized controlled trials to address the appropriate timing of initiation, duration, and de-escalation of therapy following identification of a pathogen and the overall utility of early and aggressive empirical antibiotic therapy (91, 92).

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