A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent on the risk of death: A meta-analytic/meta-regression study

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Objective: **To assess whether a potential benefit with combination antibiotic therapy is restricted to the most critically ill subset of patients, particularly those with septic shock.**

Data Sources: **OVID MEDLINE (1950–October 2009), EMBASE (1980–October 2009), the Cochrane Central Register of Controlled Trials (to third quarter 2009), the ClinicalTrial.gov database, and the SCOPUS database.**

Study Selection: **Randomized or observational studies of antimicrobial therapy of serious bacterial infections potentially associated with sepsis or septic shock. Fifty studies met entry criteria.**

Data Extraction: **Study design, mortality/clinical response, and other variables were extracted independently by two reviewers. When possible, study datasets were split into mutually exclusive groups with and without shock or critical illness.**

Data Synthesis: **Although a pooled odds ratio indicated no overall mortality/clinical response benefit with combination therapy (odds ratio, 0.856; 95% confidence interval, 0.71–1.03; $p = .0943$; $I^2 = 45.1\%$), stratification of datasets by monotherapy mortality risk demonstrated substantial benefit in the most severely ill subset (monotherapy risk of death >25%; odds ratio, 0.51; 95% confidence interval, 0.41–0.64; $I^2 = 8.6\%$). Of those datasets that could be stratified by the presence of shock/critical illness, the more severely ill group consistently demonstrated increased efficacy of a combination therapy strategy (odds ratio, 0.49; 95% confidence interval, 0.35–0.70; $p < .0001$; $I^2 = 0\%$). An increased risk of death was found in low-risk patients (risk of death <15% in the monotherapy arm) exposed to combination therapy (odds ratio, 1.53; 95% confidence interval, 1.16–2.03; $p = .003$; $I^2 = 8.2\%$). Meta-regression indicated that efficacy of combination therapy was dependent only on the risk of death in the monotherapy group.**

Conclusion: **Combination therapy is optimal for management of high-risk, life-threatening infections, particularly those associated with septic shock but may be detrimental to low-risk patients. (Crit Care Med 2010; 38:000–000)**

KEY WORDS: sepsis; septic shock; outcome; serious infection; combination therapy; infectious diseases; antibiotic; critically ill

Combination antimicrobial therapy is commonly used for the treatment of sepsis and septic shock. The most accepted rationale for this approach is an increased spectrum of coverage, even though current antimicrobials possess extremely broad activity. Assuming the pathogenic organism is susceptible to one antibiotic, the incremental benefit of combination therapy is uncertain. Although some animal models (1–3) and clinical studies of infection, including endocarditis, Gram-negative bacteremia, and neutropenic infections (4–6), support such combination therapy, the potential clinical benefit in other severe infections associated with sepsis and septic shock has been questioned. Two separate meta-analyses have failed to demonstrate evidence of improvement of outcome with combination therapy in immunocompetent patients with sepsis and/or Gram-negative bacteremia (7, 8).

Meta-regression studies have found that efficacy of some medical therapies, including immunomodulatory therapy of sepsis, can be contingent on the underlying severity of illness and risk of death (9–12). A potential survival benefit with combination antimicrobial therapy may be similarly restricted to high-risk groups. A benefit in the most severely ill patients may be diluted or offset by less severely ill patients in whom no benefit exists or adverse effects of combination therapy dominate.

We report a meta-analysis/meta-regression study undertaken to determine whether combination antimicrobial therapy reduces mortality compared to monotherapy in patients with serious bacterial infections that can cause sepsis/septic shock. The specific hypothesis was that any beneficial effect of combination antimicrobial therapy on mortality of life-threatening infection is restricted to patients with septic shock or otherwise high-risk of death.

MATERIALS AND METHODS

Study Selection and Dataset Derivation

Both randomized and observational studies of antimicrobial therapy of serious bacte-

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The authors have not disclosed any potential conflicts of interest.

Anand Kumar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Shravan Reddy and Anand Kumar served as the reviewers. Nasia Safdar performed the meta-analysis and Dan Chateau performed the meta-regression.

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rial infections potentially associated with sepsis and/or septic shock were included irrespective of causative organism, Gram-negative stain characteristics, presence of bacteremia, or specific clinical infection (as long as the primary cause of mortality in the infection was typically sepsis/septic shock). Sufficient data to calculate an odds ratio (OR) between single vs. combination antibiotic therapy had to be provided. Combination therapy was defined as a combination of two or more antibiotics of different antimicrobial class and mechanism of action (for example, two of three of a β-lactam, an aminoglycoside, or fluoroquinolones). The causative organism was required or, in the case of randomized trials, expected to be sensitive to both antimicrobials. Mortality and infection-related mortality were the primary outcome measures, although "clinical failure" was acceptable when mortality was not provided. Studies published in any language were reviewed.

Excluded were noninferiority studies comparing fixed regimens of a superior primary agent vs. an inferior agent of the same class with a second agent of a different class (because of the intrinsic, structural bias in such studies), investigations of endocarditis or meningitis (because the primary mechanism of death in these conditions is rarely sepsis/septic shock), and trials restricted to neutropenic sepsis. Two independent reviewers performed the literature searches and identified relevant eligible studies. Final selection of studies was performed by consensus.

Data Sources

Relevant human studies were identified from OVID MEDLINE (1950–October 2009). This search strategy was adapted to search EMBASE (1980–October 2009) and the Cochrane Central Register of Controlled Trials (to third quarter 2009). The ClinicalTrial.gov database, the SCOPUS database, SIGLE (System for Information on Gray Literature), and Google Scholar were also utilized to search for relevant studies. Search terms included "sepsis," "septicemia," "septic shock," "severe sepsis," "bacterial pneumonia," "empyema," "bacteremia," "bloodstream infection," "peritonitis," "bowel perforation," "pyelonephritis," "urinary tract infection," "ischemic bowel," "bowel infarction," "entercolitis," "cellulitis," "necrotizing fasciitis," "cholangitis," "cholecystitis," "mediastinitis," and "abscess." These search terms were cross-referenced against "drug therapy, combination," "antibiotic," "monotherapy," or "combination therapy." References from relevant articles were reviewed to identify additional. Meeting abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, the American Society of Microbiology, the Infectious Diseases Society of America, the European Congress of Clinical Microbiology and Infectious Diseases, the Society for Healthcare Epidemiology of America, and the Society of Critical Care Medicine were reviewed from 1990 to 2009.

Data Extraction and Modification

Whenever possible, relevant subgroups were extracted from published data. As a priority, eligible datasets were split into two mutually exclusive groups of septic shock and nonseptic shock or, if necessary, critically ill and noncritically ill. When the published dataset did not include this information, the primary study author of relevant studies was contacted to request these data. When possible, the monotherapy group was limited to β-lactams and/or fluoroquinolones (as the primary agent), and the combination therapy group required the same primary agent as part of the combination (to maximize comparability between the groups). Because of long-standing concerns regarding inferior results with aminoglycoside monotherapy, in particular, in the most severely ill (13, 14), these cases were excluded when the dataset provided sufficient detail to allow extraction. Neutropenic, culture-negative, and atypical organism (mycoplasma, Legionella, viral) sepsis cases were also extracted when possible.

A standard form was used to extract pertinent data. Data were extracted by two independent reviewers. When analyzed data were extracted or modified from the original dataset, calculations were also performed independently by the two reviewers. Any disagreement between the two reviewers was resolved by consensus.

Statistical Analysis

Meta-Analysis. Pooled ORs and 95% confidence intervals (CIs) were calculated for each dataset. Pooled estimates of the OR and 95% CI were obtained using the random-effects model of DerSimonian and Laird (15). Because most prospective clinical studies of severe sepsis inclusive of septic shock have yielded mortality risks of >25% and studies of sepsis without shock have yielded mortality risks of <15% (16–18), eligible datasets were stratified (on an *a priori* basis) into three corresponding monotherapy mortality/clinical failure rate groups of <15%, 15% to 25%, and >25%.

An OR of <1 signifies decreased mortality with combination therapy compared to monotherapy. Results were supported by application of fixed-effects models (15). The analyses were performed using StatsDirect Software (StatsDirect, Cheshire, UK). Testing for heterogeneity was performed using the I^2 statistic (19). This statistic can be interpreted as the proportion of total variation across studies attributable to heterogeneity (min–max, 0%–100%). A funnel plot of the log of the OR against the sample size was performed to assess for potential selection biases, including publication bias (20). Stratified subgroup analyses were also performed.

Meta-Regression. Because the I^2 statistic indicated significant heterogeneity among the entire collection of datasets, meta-regression was performed (21,22). Possible sources for heterogeneity including mortality rate in the reference (monotherapy) group were investigated.

To analyze the relationship between reference (monotherapy) mortality rate and the relative treatment effect, the log OR of death with combination therapy was plotted against the monotherapy mortality rate (x-axis) for each study. A linear meta-regression weighted to reflect the variance of the individual datasets was used to model the data. The mathematical model described the relationship between the log of the OR of death with combination therapy as a function of the mortality rate in the monotherapy arm. Supplemental meta-regressions were performed to examine the interactions of monotherapy mortality risk with major stratification groups. These analyses were performed using SAS PROC MIXED (v9.1.3; SAS Institute, Cary, NC).

RESULTS

Trial Characteristics

Fifty studies were found to be suitable for inclusion in this analysis (23–73) (Fig. 1). Of the 1534 studies identified for initial examination, 59 were determined to potentially fit inclusion criteria after screening of published abstracts. Subsequently, nine studies were excluded after review of the article (4, 74–81). Of the 50 remaining eligible studies (23–73), 12 had data that could be split into mutually exclusive groups with differing severity of illness (25–29, 34, 42, 46, 54–56,60). Subset data for eight of these studies could be found in the original publication (25, 26, 28, 29, 34, 54, 55, 60). The authors of four other published studies provided supplemental data from the original publication to separately analyze shock/nonshock cases (27, 42, 46, 56). As a result, 62 distinct datasets were available for analysis (Fig. 1, Table 1).

Of the 12 split datasets, eight were split by presence or absence of shock (27, 28, 34, 42, 46, 54–56). The other four were split by a severity of illness scoring system (25, 26, 29, 60). In addition, 17 datasets were modified by extraction of cases of aminoglycoside

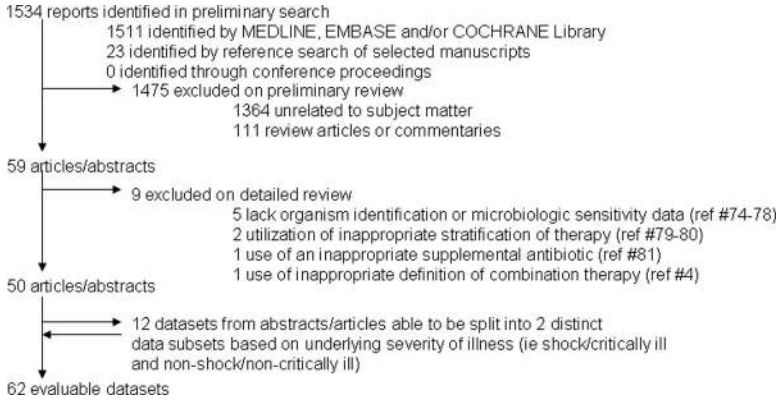

Figure 1. Study selection and dataset derivation.

monotherapy (24, 30, 36, 37, 41, 45, 49–52, 54, 62, 65, 70–73). Six studies and nine total datasets retained or potentially retained some cases of aminoglycoside monotherapy (29, 34, 38, 40, 60, 63). Of the former, two studies had aminoglycoside monotherapy in approximately half the cases (29, 34), with similar mortality outcome with aminoglycoside monotherapy and β-lactam monotherapy; another had a maximum of 15% of monotherapy with aminoglycosides (60), and frequency was undefined in one (63). The inclusion of aminoglycoside treatment as monotherapy was uncertain in two studies (38, 40). Four studies had culture negative and/or atypical organism cases extracted (25, 46, 59, 67). Three studies had cases of neutropenic sepsis extracted (53, 67, 72). Microbiological sensitivity of pathogens to antibacterials was confirmed in all included cases for all but 14 studies (19 datasets), and it was inferred in at least some cases (24–28, 33, 35, 44, 46, 48, 51, 59, 63, 64). Twelve eligible studies (13 datasets) represented randomized, controlled trials (RCTs) (23, 33, 35, 39, 46, 48, 51, 53, 57–59, 62, 67). The remaining studies were either prospective observational or retrospective cohort investigations (Table 1).

Table 1 summarizes the characteristics of the datasets utilized in this analysis. The number of evaluable cases of life-threatening infection in the 50 eligible trials was 8504 patients (4553 monotherapy, 3951 combination therapy). Sample size among the different datasets ranged from 16 to 1111. Most studies primarily involved therapy with a β-lactam with or without an aminoglycoside, fluoroquinolone, or macrolide.

A Cook's D (influence diagnostic) test demonstrated that none of the datasets exceeds the critical value, i.e., none has a disproportionate impact on the results.

Meta-Analyses

Meta-analysis of the 62 eligible datasets demonstrated an estimated pooled OR for death/clinical failure of 0.856 (95% CI, 0.713–1.027) for combination compared to monotherapy regimens (p = .094) (Fig. 2). There was no evidence of a publication bias based on the Egger method (p = .275). The shape of the funnel plot was symmetrical. However, there was statistically significant heterogeneity among the eligible datasets (Breslow-Day chi-square = 125.03; df = 61; $p < .0001$, I^2 = 45.1%).

In Figure 2, datasets are listed in sequential order of increasing monotherapy mortality/clinical failure rate. Although the pooled OR fails to demonstrate a significant advantage of combination therapy, there is a trend of the individual OR positions switching from the right (favoring monotherapy) to the left (favoring combination therapy) as monotherapy mortality/clinical failure rate increases. Stratification of the dataset by monotherapy mortality/clinical failure rate confirms this observation. The pooled OR for datasets when the monotherapy mortality/clinical failure rate is <15% significantly favors monotherapy (OR, 1.53; 95% CI, 1.16–2.03; p = .003; I^2 = 8.2%). The pooled OR for monotherapy mortality/clinical failure rate of 15% to 25% indicates no difference in efficacy of monotherapy or combination therapy (OR, 1.04; 95% CI, 0.81–1.34; p = .7657; I^2 = 30.7%). However, combination therapy demonstrates a significant advantage over monotherapy when the rate of death/clinical failure exceeds 25% (pooled OR, 0.54; 95% CI, 0.45–0.66; $p <$ .0001; I^2 = 0%). Stratification of datasets results in a marked decrease in heterogeneity in all stratified groups, suggesting that variations in mortality/clinical failure risk represents a substantial portion of the heterogeneity in the aggregate meta-analysis. No other stratification resulted in a similar decrease of I^2 in all strata (Table 2).

The 12 studies that were stratified into septic shock/critically ill and nonseptic shock/noncritically ill datasets were examined (Fig. 3). Pooled ORs for the eight studies split by the presence or absence of shock (27,28,34,42,46,54–56) and the four studies split by the presence or absence of critical illness (25,26,29,60) demonstrated a significant advantage to combination therapy in the more ill group but did not demonstrate evidence of a similar trend in the less ill groups. Consolidation of the combined shock and critically ill datasets demonstrated similar results (OR, 0.51; 95% CI, 0.36–0.72; p = .0002; I^2 = 0%). Pooled ORs for the consolidated nonshock/noncritically ill show an absence of any beneficial effect with combination therapy (OR, 1.06; 95% CI, 0.76–1.47; p = .7178; I^2 = 19.1%). Consolidation of all datasets yields a trend toward superiority of combination therapy that fails to reach significance (OR, 0.76; 95% CI, 0.57–1.02; p = .0622; I^2 = 33.8%). The I^2 value for study heterogeneity is substantially reduced by splitting the 12 datasets into shock/critically ill and nonshock/noncritically ill groups. As can be seen by examination of the datasets used in this analysis (25–29, 34, 42, 46, 54–56, 60) in Figure 2, the OR describing mortality/clinical failure with combination therapy for the septic shock or otherwise more critically ill subset of the individual datasets was shifted to the left (i.e., favoring combination therapy) relative to the matching nonseptic shock/noncritically ill dataset in 10 of the 12 datasets excluding only the studies of Harbarth et al (42) and Garnacho-Montero et al (55).

To further examine statistical heterogeneity in the aggregate meta-analysis and potential sources of variation in individual dataset results, additional stratified meta-analyses were performed (Table 2). Observational (non-RCT) studies (49 datasets) demonstrate a high level of heterogeneity and fail to show evidence of a benefit of combination therapy. A similar lack of evidence of efficacy is apparent whether examining prospective observational data (15 datasets) or retrospective

Table 1. Study mortality and characteristics

	Study Design	Monotherapy, Number of Deaths or Clinical Failure/Total (%)	Combination Therapy, Number of Deaths or Clinical Failure/Total (%)	Difference in Combination vs. Monotherapy Mortality/Clinical Failure (%)
Sculier et al 1982	RCT	0/10 (0)	1/10 (10.0)	10
Karnad et al 1985	RCS	0/4 (0)	18/47 (38.3)	38.2
Vazquez et al[a] 2005	RCS	2/45 (4.4)	6/142 (4.2)	−0.2
Dwyer et al[a] 2006	POS	9/195 (4.6)	7/57 (12.3)	7.7
Baddour et al[a,c] 2004	POS	17/279 (6.1)	7/63 (11.1)	5
Rodriguez et al[a] 2007	POS	4/63 (6.3)	14/196 (7.1)	0.8
Chow et al[a] 1991	POS	3/42 (7.1)	2/34 (5.9)	−1.3
Kim et al 2003	RCS	8/90 (8.9)	6/24 (25.0)	16.1
Chokshi et al 2007	RCS	4/42 (9.5)	12/66 (18.2)	8.7
Martinez et al 2003	RCS	17/171 (9.9)	18/238 (7.6)	−2.4
Damas et al 2006	RCT	2/20 (10.0)	8/39 (20.5)	10.5
Korvick et al[a] 1992	POS	11/92 (12.0)	13/83 (15.7)	3.7
Cometta et al 1994	RCT	18/142 (12.7)	13/138 (9.4)	−3.3
Kreger et al 1980	RCS	8/60 (13.3)	35/140 (25.0)	11.7
McCue et al 1985	RCS	19/141 (13.5)	20/81 (24.7)	11.2
Bouza et al 1987	RCS	3/21 (14.3)	2/5 (40.0)	25.7
Carbon et al 1987	RCT	4/25 (16.0)	5/22 (22.7)	6.7
Harbarth et al[a,c] 2005	RCS	10/62 (16.1)	4/19 (21.1)	4.9
McCue et al 1987	RCS	30/185 (16.2)	21/80 (26.3)	10
Kuikka et al 1997	RCS	35/211 (16.6)	5/68 (7.4)	−9.2
Siegman-Igra et al 1998	RCS	7/42 (16.7)	7/15 (46.7)	30
Gullberg et al 1989	RCS	3/18 (16.7)	8/38 (21.1)	4.4
Leibovici et al 1997	POS	134/789 (17.0)	57/322 (17.7)	0.7
Heyland et al[a,c] 2008	RCT	13/76 (17.1)	21/75 (28.0)	10.9
Waterer et al 2001	RCS	18/99 (18.2)	11/126 (8.7)	−9.5
Dupont et al 2000	RCT	21/111 (18.9)	24/116 (20.7)	1.8
Patterson et al 2003	POS	9/47 (19.1)	1/15 (6.7)	−12.5
Kim et al 2002	RCS	12/59 (20.3)	11/42 (26.2)	5.9
Fernandez-Guerrero et al 1991	RCT	58/275 (21.1)	21/91 (23.1)	2
Kuikka et al 1998	RCS	7/32 (21.9)	11/41 (26.8)	4.9
Piccart et al 1984	RCT	5/22 (22.7)	5/26 (19.2)	−3.5
Bodey et al[a] 1985	RCS	18/78 (23.1)	16/104 (15.4)	−7.7
Garnacho-Montero et al[a] 2007	RCS	7/29 (24.1)	7/46 (15.2)	−8.9
Vazquez et al[b] 2005	RCS	4/15 (26.7)	5/53 (9.4)	−17.2
Chamot et al[a,c] 2003	RCS	12/44 (27.3)	8/37 (21.6)	−5.7
Kljucar et al 1990	RCT	14/50 (28.0)	10/50 (20.0)	−8
D'Antonio et al 1992	RCT	17/60 (28.3)	7/32 (21.9)	−6.5
Hilf et al[a] 1989	POS	9/31 (29.0)	20/106 (18.9)	−10.2
Watanakunkorn et al 1993	RCS	17/58 (29.3)	10/38 (26.3)	−3
Harbarth et al[b,c] 2005	RCS	6/20 (30.0)	1/6 (16.7)	−13.3
Klatersky et al 1973	RCT	7/22 (31.8)	3/23 (13.0)	−18.8
Montgomerie et al 1980	RCS	9/28 (32.1)	0/3 (0)	−32.1
Graninger et al 1992	RCS	10/31 (32.3)	4/14 (28.6)	−3.7
Baddour et al[b,c] 2004	POS	11/33 (33.3)	4/36 (11.1)	−22.2
Ko et al 2000	RCS	13/33 (39.4)	3/26 (11.5)	−27.9
Aspa et al 2006	POS	99/251 (39.4)	61/198 (30.8)	−8.6
Fainstein et al 1983	RCT	13/32 (40.6)	10/39 (25.6)	−15
Maki et al 1988	RCS	14/34 (41.2)	18/46 (39.1)	−2
Dwyer et al[b] 2006	POS	11/25 (44.0)	3/8 (37.5)	−6.5
Mendelson et al 1994	RCS	4/9 (44.4)	4/15 (26.7)	−17.8
Garnacho-Montero et al[b] 2007	RCS	11/24 (45.8)	23/44 (52.3)	6.4
Heyland et al[b,c] 2008	RCT	12/24 (50.0)	5/17 (29.4)	−20.6
Chow et al[b] 1991	POS	6/12 (50.0)	8/30 (26.7)	−23.3
Korvick et al[b] 1992	POS	13/26 (50.0)	7/29 (24.1)	−25.9
Bodey et al 1989	RCS	39/72 (54.2)	16/76 (21.1)	−33.1
Rodriguez et al[b] 2007	POS	30/52 (57.7)	100/218 (45.9)	−11.8
Feldman et al 1990	RCS	5/7 (71.4)	0/9 (0)	−71.4
Bodey et al[b] 1985	RCS	9/12 (75.0)	28/52 (53.8)	−21.2
Chamot et al[b,c] 2003	RCS	9/11 (81.8)	4/6 (66.7)	−15.2
Hilf et al[b] 1989	POS	11/12 (91.7)	18/37 (48.6)	−43
Tapper et al 1974	RCS	1/1 (100)	13/20 (65.0)	−35
Hammond et al 1990	RCS	4/4 (100)	12/17 (70.6)	−29.4

CAP, community-acquired pneumonia; VAP, ventilator-associated pneumonia; AG, aminoglycoside; FQ, fluoroquinolones; ESBL, extended-spectrum β-lactamase; RCT, randomized controlled trial; RCS, retrospective cohort study; POS, prospective observational study.

[a]Nonshock or shock or noncritically ill stratified dataset; [b] Shock or critically ill stratified dataset; [c] Modified dataset provided by study authors.

Table 1. —*Continued*

End Point	Clinical Infection	Antimicrobial Regimens	Septic Shock (%)	Neutropenic (%)
Infection-related hospital mortality	Gram-negative pneumonia	Mezlocillin ± sisomycin		
7-day mortality	Gram-negative pneumonia	β-lactam ± amikacin		6
Hospital mortality	Pneumococcal CAP	β-lactam ± macrolide		0
Hospital mortality	Bacteremic pneumococcal CAP	β-lactam ± macrolide		
14-day mortality	Pneumococcal bacteremia	Mixed combinations	0	
28-day mortality	Mixed organism CAP	Mixed combinations (β-lactam dominant as primary agent; FQ/macrolide as secondary)	0	
14-day mortality	Enterobacter bacteremia	β-lactam and/or AG	33	6
14-day mortality	Citrobacter/Serratia/Enterobacter bacteremia	β-lactam/FQ ± FQ/AG	17.3	14
Hospital mortality	Bacteremic pneumococcal CAP	β-lactam or FQ vs. lactam/FQ/macrolide combination	8.3	
Hospital mortality	Bacteremic pneumococcal CAP	β-lactam ± macrolide	9.8	4
28-day mortality	Mixed organism VAP	β-lactam ± AG/levofloxacin		
14-day mortality	Klebsiella bacteremia	β-lactam and/or AG	0	
Hospital mortality	Mixed organism sepsis	Imipenem ± netilmicin		0
7-day mortality	Gram-negative bacteremia	β-lactam ± AG		10
Hospital mortality	Gram-negative bacteremia	β-lactam ± AG		
Mortality after 7 days after of treatment	Serratia bacteremia	Mixed undefined combinations	28	
Hospital mortality	Gram-negative bacteremia	Cefotaxime ± amikacin	15	0
30-day mortality	Pneumococcal sepsis	Mixed combinations (β-lactam dominant as primary agent; FQ/macrolide as secondary)	0	0
Hospital mortality	Gram-negative bacteremia	Mixed undefined combinations		7
30-day mortality	Escherichia coli bacteremia	Primarily β-lactam ± AG	22	13
Infection-related hospital mortality	Pseudomonas aeruginosa bacteremia	Imipenem/cephalsporin/FQ ± AG		6
Hospital mortality	Enterococcal bacteremia	β-lactam/vancomycin ± AG		5
Hospital mortality	Gram-negative bacteremia	β-lactam ± AG	10.2	<10
28-day mortality	Gram-negative VAP	meropenem ± ciprofloxacin	0	0
15-day mortality	Bacteremic pneumococcal CAP	Primarily β-lactam or FQ vs. lactam/FQ/macrolide combination		
Clinical failure, 30 days after treatment	Mixed peritoneal sepsis/peritonitis	Piperacillin/tazobactam ± amikacin		
14-day mortality	ESBL Klebsiella bacteremia	Primarily β-lactam ± AG		<5
30-day mortality	Klebsiella bacteremia	β-lactam/FQ ± AG	18	
Clinical failure, 2 days after treatment completion	Mixed organism hospital-acquired pneumonia	Cefotaxime ± mixed agents (primarily AG)		
30-day mortality	Pseudomonas aeruginosa bacteremia	β-lactam/ciprofloxacin ± AG (or ciprofloxacin for lactam)		28
Clinical failure or death during therapy	Gram-negative bacteremia	Cefoperazone ± amikacin		0
Clinical failure during therapy	Pseudomonas aeruginosa bacteremia	β-lactam ± AG	0	45
Hospital mortality	Pseudomonas aeruginosa VAP	β-lactam/FQ ± AG (or FQ for β-lactam)	0	
Hospital mortality	Pneumococcal CAP	β-lactam ± macrolide		0
30-day mortality	Pseudomonas aeruginosa bacteremia	β-lactam/FQ ± AG (or FQ for β-lactam)	0	30
Clinical failure, 7 days after treatment	Mixed organism hospital-acquired pneumonia	Ceftazidime ± tobramycin		
Clinical failure during therapy	Mixed sepsis	Ceftriaxone ± amikacin		0
10-day mortality	Pseudomonas aeruginosa bacteremia	β-lactam and/or AG		13.5
Hospital mortality	Enterococcal bacteremia	Penicillin drug/vancomycin ± gentamicin		
30-day mortality	Pneumococcal sepsis	Mixed combinations (β-lactam dominant as primary agent; FQ/macrolide as secondary)	10	0
Infection-related hospital mortality	Gram-negative sepsis	Carbenicillin ± gentamicin	20	
Hospital mortality	Klebsiella bacteremia	β-lactam and/or AG		
21-day clinical failure or death	Enterococcal bacteremia	Ampicillin/piperacillin ± gentamicin/netilmicin		
14-day mortality	Pneumococcal bacteremia	Mixed combinations	100	
14-day mortality	Aeromonas bacteremia	β-lactam ± AG		
30-day mortality	Pneumococcal CAP	β-lactam ± macrolide	16	
Clinical failure during therapy	Mixed sepsis	Ceftazidime ± tobramycin	33	0
Hospital mortality	Enterococcal bacteremia	Ampicillin ± AG	19	
Hospital mortality	Bacteremic pneumococcal CAP	β-lactam ± macrolide		
Hospital mortality	Pseudomonas aeruginosa bacteremia	β-lactam ± AG		
Hospital mortality	Pseudomonas aeruginosa VAP	β-lactam/FQ ± AG (or FQ for β-lactam)	100	
28-day mortality	Gram-negative VAP	Meropenem ± ciprofloxacin	100	0
14-day mortality	Enterobacter bacteremia	β-lactam and/or AG	33	6
14-day mortality	Klebsiella bacteremia	β-lactam and/or AG	100	
Clinical failure during therapy	Klebsiella bacteremia	Cephalosporin ± AG	25	41
28-day mortality	Mixed organism CAP	Mixed combinations (β-lactam dominant as primary agent; FQ/macrolide as secondary)	100	
Hospital mortality	Klebsiella bacteremia	β-lactam/ciprofloxacin ± AG	12.8	
Clinical failure during therapy	Pseudomonas aeruginosa bacteremia	β-lactam ± AG	100	45
30-day mortality	Pseudomonas aeruginosa bacteremia	β-lactam/FQ ± AG (or FQ for β-lactam)	100	30
10-day mortality	Pseudomonas aeruginosa bacteremia	β-lactam and/or AG		13.5
Hospital mortality	Pseudomonas aeruginosa bacteremia	Carbenicillin ± gentamicin		0
Hospital mortality	Klebsiella CAP	Third-generation cephalosporin ± AG	83	

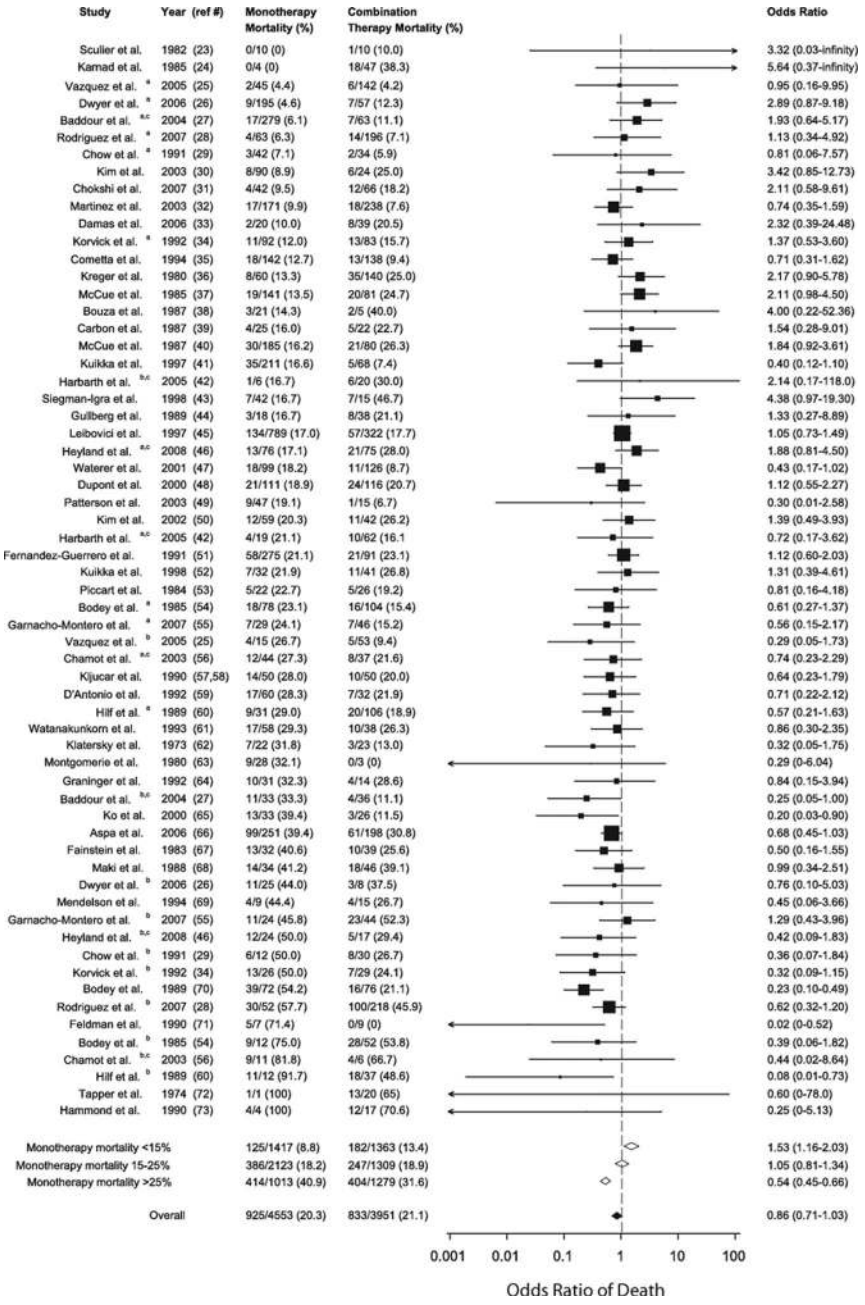

Figure 2. Analysis of studies comparing combination antibiotic therapy with monotherapy for reducing mortality of life-threatening infections associated with sepsis. The size of the squares is proportional to the reciprocal of the variance of the studies. *A*, Nonshock or noncritically ill stratified dataset. *B*, Shock or critically ill stratified dataset. *C*, Modified dataset provided by study authors.

cohort studies (34 datasets) (Tables 1 and 2). RCTs (13 datasets) demonstrate no significant benefit of a combination strategy despite low heterogeneity (Tables 1 and 2). Exploratory subgroup analyses to determine whether findings would differ by limiting the analysis to studies published during or before 1992 (29 datasets) or during or after 1993 (33 datasets), when more potent antimicrobials became available for serious infection demonstrated similar results (Tables 1 and 2).

Stratification by other criteria including use of β-lactam as sole primary therapy, aminoglycosides as the sole secondary agent, clinical syndrome (bacteremia, nonbacteremia, community-acquired pneumonia, hospital-acquired pneumonia/ventilator-associated pneumonia), Gram-negative stain characteristic of pathogen, specific pathogen (*Pseudomonas*, *Klebsiella*, *Streptococcus pneumoniae*), and end point (hospital mortality, 7- to 30-day mortality, clinical failure) also showed no significant reduction in heterogeneity or beneficial effect of combination therapy (Table 2).

Meta-Regression

Figure 4 plots the OR of death with combination therapy (*y*-axis) against the mortality/clinical failure rate with monotherapy in individual datasets (x-axis). There is a significant negative slope (OR, 1.304; 95% CI, 1.205–1.412; $p < .0001$ per 10% increase in reference group mortality), suggesting that the probability of a beneficial effect with combination therapy increases with increasing risk of death/clinical failure in the monotherapy arm. A random-effects meta-regression (OR, 1.318; 95% CI, 1.190–1.460; $p < .0001$ per 10% increase in monotherapy group mortality) and meta-regression using the aggregate mortality of the complete datasets (i.e., both monotherapy and combination therapy groups together) in place of the monotherapy group mortality as the independent variable (OR, 1.173; 95% CI, 1.070–1.285; $p < .0001$ per 10% increase in aggregate mortality) performed to address the issue of regression to the mean yielded similar results (21, 82, 83).

In Figure 4, the intersection of the 95% CI lines with the x-axis shows a statistically significant benefit with combination therapy begins as monotherapy mortality rate exceeds 25% (OR, 0.881; CI, 0.780–0.994; $p = .0447$). In contrast, monotherapy is statistically favored at a monotherapy mortality risk of 15% or lower (OR, 1.180; CI, 1.017–1.3681; $p = .0334$).

A similar trend is seen if the meta-regression is restricted to either observational studies (Fig. 5*A*) or RCTs (Fig. 5*B*). In addition, Table 2 contains a series of meta-regressions for subgroups. In almost every case, there is at least a trend suggesting increasing benefit with combination antimicrobial therapy as the monotherapy mortality rate increases. This effect holds whether hospital mortality, 7- to 30-day mortality, or clinical failure is used as the study end point. Further, Table 3 shows the OR intercepts at 0% and 100% mortality in the monotherapy reference group for each subgroup. Notably, whenever there is a significant meta-regression slope in Table 2, the intercept for 0% and 100% reference group mortality is always more than one and less than one, respectively. This indicates a trend toward harm and benefit,

Table 2. Stratified summary values for meta-analyses and meta-regression

Stratification	Number of Datasets, Meta-Analysis	Meta-Analysis Pooled Random-Effects Odds Ratio (95% Confidence Interval)	Meta-Analysis *P*	I^2, %	Number of Datasets, Meta-Regression	Meta-Regression Odds Ratio (95% Confidence Interval) Per 10% Increment of Reference Mortality[a]	Meta-Regression *P*
All datasets	62	0.856 (0.713–1.027)	.09	45.1	56	1.304 (1.205–1.412)	<.0001
Large datasets[b]	35	0.866 (0.706–1.062)	.17	52.9	35	1.213 (1.091–1.347)	<.0001
All split pair datasets	24	0.760 (0.568–1.018)	.07	34.3	24	1.185 (1.073–1.309)	.0028
Nonsplit pair datasets	38	0.919 (0.727–1.163)	.48	50.6	32	1.713 (1.530–1.918)	<.0001
Randomized controlled trials	13	0.933 (0.720–1.224)	.61	1.7	12	1.425 (1.121–1.811)	.0159
Non-randomized controlled trials (observational studies)	49	0.840 (0.673–1.047)	.12	51.4	44	1.475 (1.385–1.569)	<.0001
Prospective observational studies	15	0.772 (0.553–1.076)	.12	48.8	15	1.289 (1.162–1.430)	.0003
Retrospective cohort studies	34	0.883 (0.654–1.191)	.41	53.5	29	1.345 (1.177–1.537)	.0002
Clinical failure end point	9	0.645 (0.430–0.950)	.02	47.8	9	1.364 (1.123–1.656)	.0166
Hospital mortality end point	24	1.136 (0.860–1.482)	.37	34.9	20	1.380 (1.232–1.546)	<.0001
7-to 30-day mortality end point	29	0.774 (0.585–1.023)	.07	40.9	27	1.389 (1.229–1.568)	<.0001
Proven microbiological sensitivity	43	0.805 (0.639–1.014)	.06	50.8	39	1.336 (1.212–1.473)	<.0001
Inferred microbiological sensitivity	19	0.984 (0.730–1.303)	.86	26.9	17	1.237 (1.078–1.419)	.0085
During or after 1993	33	0.908 (0.728–1.132)	.39	40	33	1.286 (1.185–1.394)	<.0001
During or before 1992	29	0.774 (0.563–1.065)	.11	51.4	23	1.406 (1.252–1.579)	<.0001
Neutropenia in ≤10% of cases	23	1.074 (0.824–1.400)	.59	30.7	20	1.288 (1.150–1.443)	.0002
Neutropenia in >10% of cases	11	0.570 (0.332–0.976)	.04	58.3	11	1.254 (1.135–1.386)	.0016
β-lactam only as primary Rx	32	0.840 (0.671–1.062)	.14	44.7	28	1.227 (1.121–1.343)	<.0001
Mixed agents as primary Rx[c]	30	0.872 (0.647–1.175)	.36	47	28	1.310 (1.160–1.479)	.0002
AG excluded as primary Rx	53	0.867 (0.717–1.049)	.14	43.8	48	1.397 (1.274–1.533)	<.0001
AG only as secondary Rx	29	0.824 (0.642–1.059)	.13	46.9	24	1.413 (1.246–1.604)	<.0001
Non-AG as secondary Rx[d]	33	0.873 (0.661–1.152)	.33	45.6	32	1.268 (1.170–1.373)	<.0001
Macrolides only as secondary Rx	6	0.831 (0.503–1.372)	.47	40.8	6	1.077 (0.870–1.332)	.5335
Mixed agents as secondary Rx[e]	25	0.877 (0.623–1.233)	.45	47.9	24	1.212 (1.104–1.330)	.0004
Bacteremia	40	0.858 (0.660–1.116)	.25	56.6	37	1.391 (1.270–1.523)	<.0001
Nonbacteremia	22	0.820 (0.676–0.994)	.04	2.5	19	1.163 (1.016–1.331)	.0421
Community-acquired pneumonia	11	0.780 (0.555–1.096)	.15	30.9	10	1.286 (1.087–1.521)	.0189
Hospital-acquired pneumonia/ ventilator-associated pneumonia	7	1.043 (0.704–1.546)	.83	17.9	7	1.302 (0.966–1.756)	.1440
All pneumonia	18	0.870 (0.667–1.135)	.31	30.8	17	1.318 (1.143–1.519)	.0018
Gram-negative infection	37	0.829 (0.618–1.113)	.20	56.5	31	1.261 (1.145–1.388)	<.0001
Pseudomonas infection	12	0.747 (0.485–1.144)	.18	28.8	11	1.293 (1.119–1.495)	.0070
Klebsiella infection	8	0.441 (0.194–1.002)	.06	63.3	5	1.533 (1.218–1.930)	.0357
Gram-positive infection	17	0.830 (0.618–1.113)	.21	28.2	17	1.398 (1.169–1.672)	.0023

Table 2. —*Continued*

Stratification	Number of Datasets, Meta-Analysis	Meta-Analysis Pooled Random-Effects Odds Ratio (95% Confidence Interval)	Meta-Analysis *P*	I^2, %	Number of Datasets, Meta-Regression	Meta-Regression Odds Ratio (95% Confidence Interval) Per 10% Increment of Reference Mortality[a]	Meta-Regression *P*
Pneumococcal infection	12	0.780 (0.605–1.063)	.06	47.3	12	1.413 (1.141–1.750)	.0088
Unmodified datasets	29	0.943 (0.736–1.208)	.64	32	27	1.381 (1.235–1.544)	<.0001
Modified datasets	33	0.777 (0.595–1.105)	.06	53.5	29	1.237 (1.140–1.341)	<.0001

Rx, therapy; AG, aminoglycoside.

[a]Change in log of the odds ratio of the probability of benefit with combination therapy with every 10% increase in mortality risk of the reference (monotherapy) group; [b]Datasets with a an n ≤ 25 in either monotherapy or combination therapy arm excluded; [c] Primary agent other than β-lactam (i.e., other than penicillin, cephalosporin, carbapenem, or monobactam); [d] Secondary agent other than only aminoglycoside; [e] Secondary agents not specifically defined (may include aminoglycosides, fluoroquinolones, macrolides, or others). Note that number of datasets for meta-regression may be smaller than those used for meta-analysis because of the fact that meta-regression did not include studies when the estimate effect was infinite (i.e., 0% or 100% mortality in either arm).

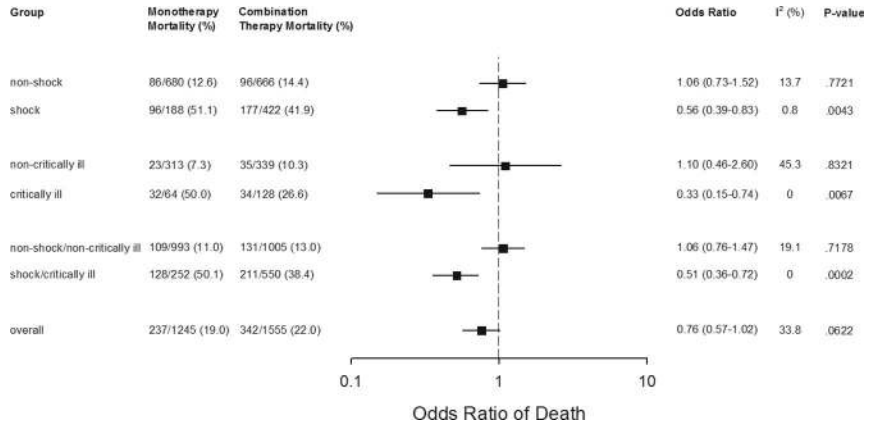

Figure 3. Subset analysis comparing combination antibiotic therapy with monotherapy for reducing mortality of life-threatening infections associated with sepsis in shock/critically ill and nonshock/noncritically ill patient datasets (derived from 12 studies in which groups could be separated; see Table 1).

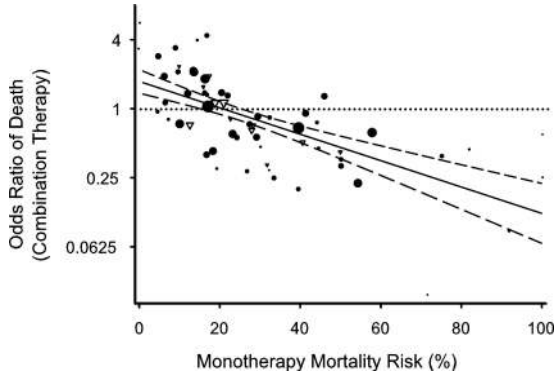

Figure 4. Meta-regression of all datasets. The weighted meta-regression line (with 95% confidence interval) shows the relationship between the log odds ratio of death/clinical failure with combination therapy and the mortality/clinical failure rate in the reference (monotherapy) group for all eligible datasets. Closed circles represent nonrandomized observational datasets (n = 44), whereas open inverted triangles represent randomized, controlled study datasets (n = 12). The size of the symbols is inversely proportional to the variance of each dataset. The negative slope of the regression line indicates a significant positive relationship between the probability of benefit of combination therapy and increasing risk of death/clinical failure in the reference (monotherapy) group (odds ratio, 1.304; 95% confidence interval, 1.205–1.412; $p < .0001$ per 10% increase in reference group mortality). Combination therapy appears to hold a significant advantage at reference group mortality/clinical failure rates of >25% (as indicated by the crossing of the upper 95% confidence interval line through a log odds ratio value of 1). However, combination therapy appears to confer a significant disadvantage at reference group mortality rates of ≤15%.

respectively, at low and high mortality risk in each subgroup (even if the range of the 95% CI included one in some cases).

These analyses indicate that a substantial amount of heterogeneity in the OR of death/clinical failure with combination therapy is accounted for by the mortality rate of the monotherapy group. Addition of variables for other potential sources of heterogeneity and the interaction between these and monotherapy mortality rate were uniformly found to be nonsignificant ($p > .20$). These other variables included, most notably, the presence or absence of an RCT study design. In addition, Gram-negative staining, bacteremia, pulmonary site of infection, >10% patients with neutropenia, microbiological proof of antibiotic sensitivity, use of β-lactam as primary therapy, and use of aminoglycoside as secondary therapy were also not significant in the model. Inclusion in the meta-regression of year of publication and use of mortality vs. clinical failure end point yielded similar negative results. Only monotherapy mortality rate was associated with probability of benefit with combination therapy in these analyses.

DISCUSSION

Our results indicate, in contrast to previous meta-analytic studies (7, 8), that combination anti-infective therapy reduces mortality in patients with serious bacterial infections, but only in those at the highest risk for death (Fig. 2). The analysis of those studies that could be split into septic shock and nonshock strata (27, 28, 34, 42, 46, 54–56) suggests that the beneficial effect may be entirely restricted to septic shock cases (Fig. 3).

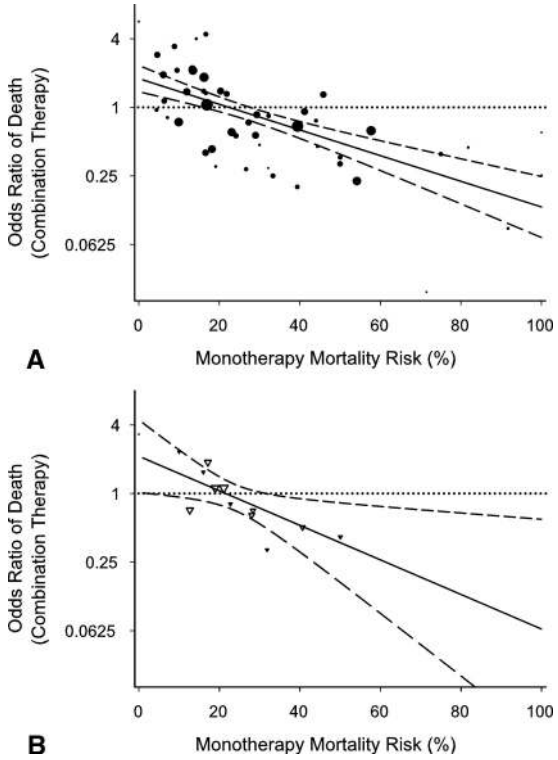

Figure 5. Meta-regression of non-randomized control trial (*RCT*) (*A*) and RCT datasets (*B*). The weighted meta-regression line (with 95% confidence interval) shows the relationship between the log odds ratio of death/clinical failure with combination therapy and the mortality/clinical failure rate in the reference (monotherapy) group for each group of datasets. Closed circles represent nonrandomized observational datasets (n = 44), whereas open inverted triangles represent randomized, controlled study datasets (n = 12). The size of the symbols is inversely proportional to the variance of each dataset. Both datasets show a similar negative slope indicating a significant positive relationship between the probability of benefit of combination therapy and increasing risk of death/clinical failure in the reference (monotherapy) group. For the non-RCT datasets, the negative slope of the regression line indicates a significant positive relationship between the probability of benefit of combination therapy and increasing risk of death/clinical failure in the reference (monotherapy) group (odds ratio, 1.475; 95% confidence interval, 1.385–1.569; $p < .0001$ per 10% increase in reference group mortality). Based on the 95% confidence interval, mortality/clinical failure rates in the reference group of >26% or <15% indicated significant benefit or harm respectively from combination therapy. For the RCT datasets, the regression line indicates a significant positive relationship between the probability of benefit of combination therapy and increasing risk of death/clinical failure in the reference (monotherapy) group (odds ratio, 1.425; 95% confidence interval, 1.121–1.811; $p < .0001$ per 10% increase in reference group mortality. Mortality/clinical failure rates of ≥35% suggested significant benefit with combination therapy, but a trend toward harm at lower risk levels did not reach significance.

Our conclusions regarding the importance of mortality risk in relation to the potential benefit of combination therapy is strongly supported by the meta-regression results (Fig. 4, Table 2). The data clearly suggest that there is a statistically significant benefit of combination therapy at mortality/clinical failure risk of approximately >25%, but that this benefit disappears in the 15% to 25% risk range. In fact, combination therapy appears to be associated with worse survival if the reference (monotherapy) risk is 15% or less. The meta-regression also confirms that no assessed factor other than monotherapy mortality risk makes a statistically significant contribution to the model. Notably, our meta-regression results held individually in both RCT and non-RCT subgroups (Fig. 5, Table 2).

Several potential explanations for a differential impact of combination and monotherapy at varying mortality risks exist. The underlying hypothesis driving this analysis was that the evolution of septic shock is based, in part, on an increasing microbial burden relative to less severe illness (84, 85) and that persistence of shock results in a marked time-dependent increased risk of death (86, 87). Accelerated pathogen clearance in septic shock should presumably result in more rapid establishment of hemodynamic stability and improved survival. Combination therapy, particularly with β-lactams in combination with aminoglycosides (88–91), fluoroquinolones (92–98), and macrolides (99–102), has demonstrated evidence of synergism (i.e., accelerated pathogen clearance) in experimental studies. Given the larger proportion of septic shock cases likely to exist in the high-risk mortality groups, any benefit of combination therapy would be expected to be disproportionately high in such groups.

Immunomodulatory effects of the supplemental agent could also provide a greater benefit to sicker patients in view of the greater inflammatory responses seen in septic shock patients (103, 104). Potentially salutary immunomodulatory activity has been suggested with macrolides (105–109) but has also been described with fluoroquinolones (106, 110, 111). Despite this, clinically relevant immunomodulatory activity of the secondary agent would seem to be less likely because beneficial effects would not be expected to be seen with several different antibiotic groups, particularly aminoglycosides.

The design of this study removes the potential benefit of providing a broader range of coverage for microbial pathogens with combination therapy by excluding or eliminating culture-negative cases (when possible) and retaining only studies with inferred or confirmed pathogen sensitivity to utilized antimicrobials. Notably, restriction of the dataset to studies with confirmed microbiological sensitivity (Table 2) showed the same variation in impact of combination therapy with mortality risk patients as the overall group.

The mechanism underlying the apparent survival disadvantage in lower-risk patients treated with combination therapy is unknown. Drug toxicity (13, 110) would seem to be most likely, but possible antibiotic antagonism (112) and the development of resistant organisms (113) could each play a role.

Because the individual studies encompassed in our study are substantially identical to those in earlier meta-analyses indicating an absence of any benefit of combination therapy (7, 8), the reason for the divergent conclusions must be addressed. The basis of the divergence appears to be differences in handling of the individual datasets. Previous meta-analytic investigations have attempted to minimize heterogeneity by focusing on specific clinical syndromes, organism groups, and study designs. We opted to maximize our sample size by including a

Table 3. Stratified odds ratio intercept values for 0% and 100% projected mortality

Stratification	Number of Datasets (Meta-Regression)	Meta-Regression Odds Ratio (95% Confidence Interval) Intercept at 0% Mortality	0% Mortality Intercept *P*	Meta-Regression Odds Ratio (95% Confidence Interval) Intercept at 100% Mortality	100% Mortality Intercept *P*
All datasets	56	1.710 (1.358–2.155)	<.0001	0.124 (0.068–0.225)	<.0001
Large datasets[a]	35	1.913 (1.448–2.528)	<.0001	0.058 (0.025–0.134)	<.0001
All split pair datasets	24	1.169 (0.796–1.717)	.4339	0.217 (0.107–0.440)	.0003
Nonsplit pair datasets	32	2.955 (2.121–4.117)	<.0001	0.026 (0.011–0.057)	<.0001
Randomized controlled trials	12	2.911(1.578–5.371)	.0066	0.020 (0.004–0.118)	.0016
Non-randomized controlled trials (observational studies)	44	2.318 (1.844–2.914)	<.0001	0.085 (0.051–0.141)	<.0001
Prospective observational studies	15	1.325 (1.001–1.755)	.0498	0.108 (0.046–0.250)	.0002
Retrospective cohort studies	29	1.927 (1.351–2.748)	.0012	0.107 (0.038–0.303)	.0002
Clinical failure end point	9	1.911 (1.026–3.557)	.0482	0.072 (0.020–0.258)	.005
Hospital mortality end point	20	2.335 (1.496–3.644)	.0015	0.071 (0.028–0.185)	<.0001
7- to 30-day mortality end point	27	1.042 (0.747–1.454)	.8110	0.098 (0.040–0.244)	<.0001
Proven microbiological sensitivity	39	1.447 (1.083–1.934)	.0170	0.179 (0.103–0.310)	<.0001
Inferred microbiological sensitivity	17	2.057 (1.329–3.183)	.0055	0.047 (0.014–0.163)	.0002
During or after 1993	33	1.340 (1.011–1.777)	.0405	0.151 (0.059–0.383)	.0008
During or before 1992	23	2.078 (1.389–3.110)	.0019	0.075 (0.033–0.169)	<.0001
Neutropenia in ≤10% of cases	20	1.939 (1.264–2.976)	.0072	0.067 (0.017–0.256)	.0009
Neutropenia in >10% of cases	11	1.497 (0.867–2.585)	.1815	0.102 (0.047–0.221)	.0003
β-lactam only as primary Rx	28	1.449 (1.024–2.051)	.0460	0.151 (0.059–0.383)	.0005
Mixed agents as primary Rx[b]	28	1.481 (1.125–1.949)	.0095	0.075 (0.041–0.136)	<.0001
AG excluded as primary Rx	48	1.944 (1.507–2.508)	<.0001	0.066 (0.033–0.134)	<.0001
AG only as secondary Rx	24	2.424 (1.713–3.429)	<.0001	0.060 (0.023–0.152)	<.0001
NonAG as secondary Rx[c]	32	1.470 (1.138–1.899)	.0061	0.140 (0.076–0.261)	<.0001
Macrolides only as secondary Rx	6	0.840 (0.509–1.387)	.5330	0.404 (0.071–2.296)	.3646
Mixed agents as secondary Rx[d]	24	1.800 (1.293–2.506)	.0019	0.142 (0.073–0.275)	<.0001
Bacteremia	37	1.750 (1.304–2.348)	0.0007	0.115 (0.055–0.242)	<.0001
Nonbacteremia	19	1.070 (0.734–1.561)	.7277	0.278 (0.112–0.694)	.0139
Community-acquired pneumonia	10	1.474 (1.042–2.086)	.0419	0.225 (0.073–0.693)	.0317
Hospital-acquired pneumonia/ventilator–assisted pneumonia	7	2.842 (1.397–5.784)	.0345	0.062 (0.013–0.290)	.0324
All pneumonia	17	1.477 (1.065–2.047)	.0336	0.121 (0.042–0.345)	.0013
Gram-negative infection	31	1.239 (1.186–1.294)	.0221	0.100 (0.052–0.192)	<.0001
Pseudomonas infection	11	3.014 (2.941–3.088)	.0124	0.133 (0.060–0.294)	.0008
Klebsiella infection	5	1.454 (0.554–3.819)	.4927	0.052 (0.012–0.232)	.0304
Gram-positive infection	17	1.505 (1.377–1.644)	.0451	0.175 (0.046–0.667)	.0221
Pneumococcal infection	12	0.866 (0.258–2.903)	.6171	0.135 (0.024–0.774)	.0484
Unmodified datasets	27	2.251 (2.251–2.252)	.0001	0.092 (0.040–0.213)	<.0001
Modified datasets	29	1.217 (0.919–1.613)	.1825	0.153 (0.085–0.274)	<.0001

Rx, therapy; AG, aminoglycoside.

[a]Datasets with an n ≤ 25 in either monotherapy or combination therapy arm excluded; [b] Primary agent other than a β-lactam (i.e., other than a penicillin, cephalosporin, carbapenem, or monobactam); [c] Secondary agent other than only aminoglycoside; [d] Secondary agents not specifically defined (may include aminoglycosides, fluoroquinolones, macrolides, or others).

wide variety of organisms, clinical syndromes, and types of studies. However, heterogeneity was limited by excluding most noninferiority studies because of their intrinsic structural bias toward regimen equivalence. In addition, when possible, datasets were modified to focus on β-lactam and/or fluoroquinolone monotherapy in comparison to a similar regimen supplemented with the addition of a secondary agent (aminoglycoside, fluoroquinolones, or macrolides). To further

minimize heterogeneity, we extracted or excluded culture-negative and neutropenic cases when that was an option. Perhaps most importantly, we were able to split 12 of the study datasets into mutually exclusive shock/critically ill and nonshock/noncritically ill components. This had the effect of increasing the potential underlying signal. The result of these maneuvers was apparent in the monotherapy mortality stratified meta-analysis in which the benefit of combination antibiotic therapy is shown to be highly dependent on baseline (monotherapy) mortality risk and in the split studies that demonstrate that combination therapy benefits those groups of patients with septic shock or critical illness based on severity scoring.

Our analysis has significant limitations. Few of the included studies were randomized trials; most studies were observational, using varying anti-infectives for varying durations in nonstandardized schedules. In these observational studies, the effect of unidentified confounding factors or residual confounding for known factors cannot be ruled out. Although we attempted to use an alternate indicator of severity of illness in monotherapy mortality, most studies did not stratify outcome by severity of illness. This may be important because combination therapy may more likely to be administered in either the sickest patients who are more likely to die or, alternately, less likely to be administered to such patients because of concurrent organ failure, which may increase risk of drug toxicity. For example, Paul et al (78) have demonstrated that an apparent advantage of combination therapy (β-lactam with or without macrolides) in unadjusted data for hospitalized community-acquired pneumonia is eliminated in a propensity-adjusted analysis. The inability to adjust for confounding covariates in most of the nonrandomized cohort studies precludes drawing strong conclusions regarding our findings. However, the fact that meta-regression results held in the RCT subset of studies (Table 2) supports the validity of the central observation across the entire study dataset.

In conclusion, our study suggests that a survival benefit of combination antibiotic therapy in serious bacterial infections associated with sepsis is restricted to the most severely ill subset of patients with septic shock and/or a projected mortality/clinical failure rate of >25% (in the absence of combination therapy). Notably, our data also suggest the possibility that combination therapy may be associated with increased risk of death in patients with low mortality risk (≤15%). The presence of septic shock may be a simple prospective method to identify patients who may benefit from combination therapy. Alternately, severity of illness scoring systems could be used to identify patients most likely to benefit.

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