Antibiotic Combination

REASONS TO USE ANTIBIOTIC COMBINATIONS

- **Broader coverage**
- **Antimicrobial synergism**
- **Increased bacterial killing**
- **Decrease in antimicrobial resistance**

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Empiric Combination Antibiotic Therapy Is Associated with Improved Outcome against Sepsis Due to Gram-Negative Bacteria: a Retrospective Analysis▽

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The optimal approach for empirical antibiotic therapy in patients with severe sepsis and septic shock remains controversial. A retrospective cohort study was conducted in the intensive care units of a university hospital. The data from 760 patients with severe sepsis or septic shock associated with Gram-negative bacteremia was analyzed. Among this cohort, 238 (31.3%) patients received inappropriate initial antimicrobial therapy (IIAT). The hospital mortality rate was statistically greater among patients receiving IIAT compared to those initially treated with an appropriate antibiotic regimen (51.7% versus 36.4%; $P < 0.001$). Patients treated with an empirical combination antibiotic regimen directed against Gram-negative bacteria (i.e., β-lactam plus aminoglycoside or fluoroquinolone) were less likely to receive IIAT compared to monotherapy (22.2% versus 36.0%; $P < 0.001$). The addition of an aminoglycoside to a carbapenem would have increased appropriate initial therapy from 89.7 to 94.2%. Similarly, the addition of an aminoglycoside would have increased the appropriate initial therapy for cefepime (83.4 to 89.9%) and piperacillin-tazobactam (79.6 to 91.4%). Logistic regression analysis identified IIAT (adjusted odds ratio [AOR], 2.30; 95% confidence interval [CI] = 1.89 to 2.80) and increasing Apache II scores (1-point increments) (AOR, 1.11; 95% CI = 1.09 to 1.13) as independent predictors for hospital mortality. In conclusion, combination empirical antimicrobial therapy directed against Gram-negative bacteria was associated with greater initial appropriate therapy compared to monotherapy in patients with severe sepsis and septic shock. Our experience suggests that aminoglycosides offer broader coverage than fluoroquinolones as combination agents for patients with this serious infection.

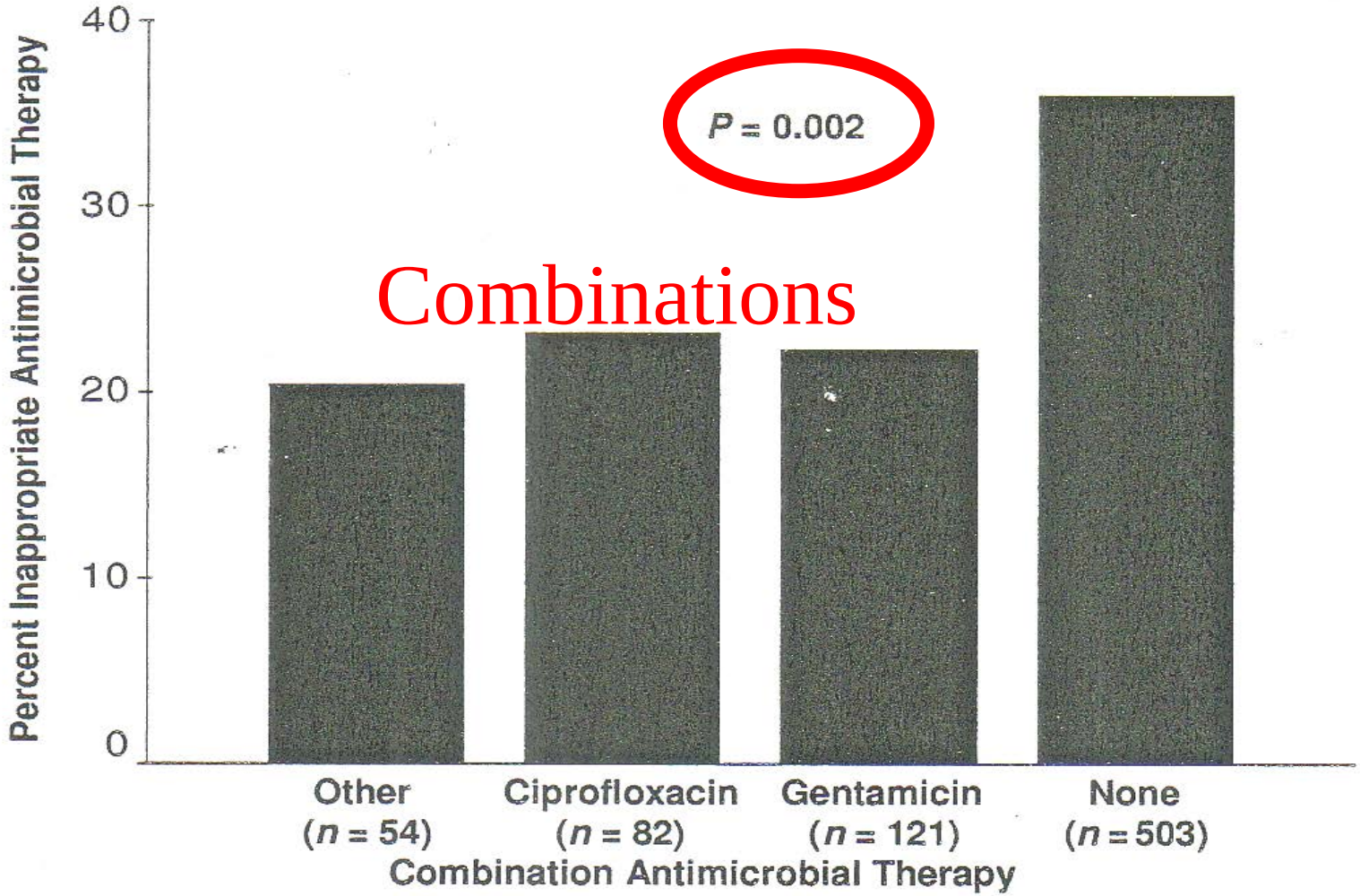
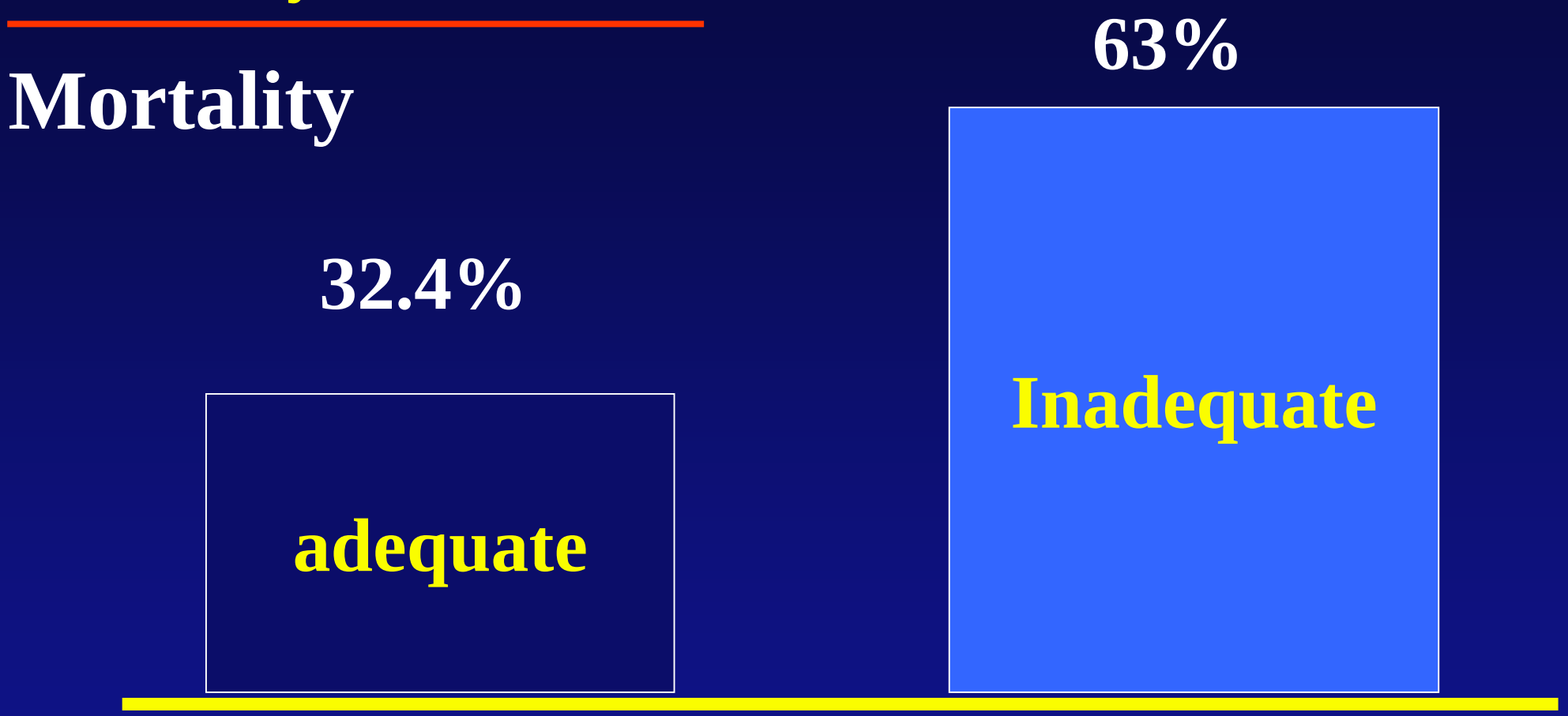


FIG. 1. Percent of patients receiving inappropriate initial antimicrobial therapy (IIAT) according to combination antimicrobial treatment. Other combination antimicrobial therapy included double β-lactam (non-carbapenem) combinations ($n = 33$), β-lactam carbapenem combinations ($n = 16$), and combinations including either tigecycline or colistin ($n = 5$).

Inadequate Empirical Antibiotic Therapy and Mortality



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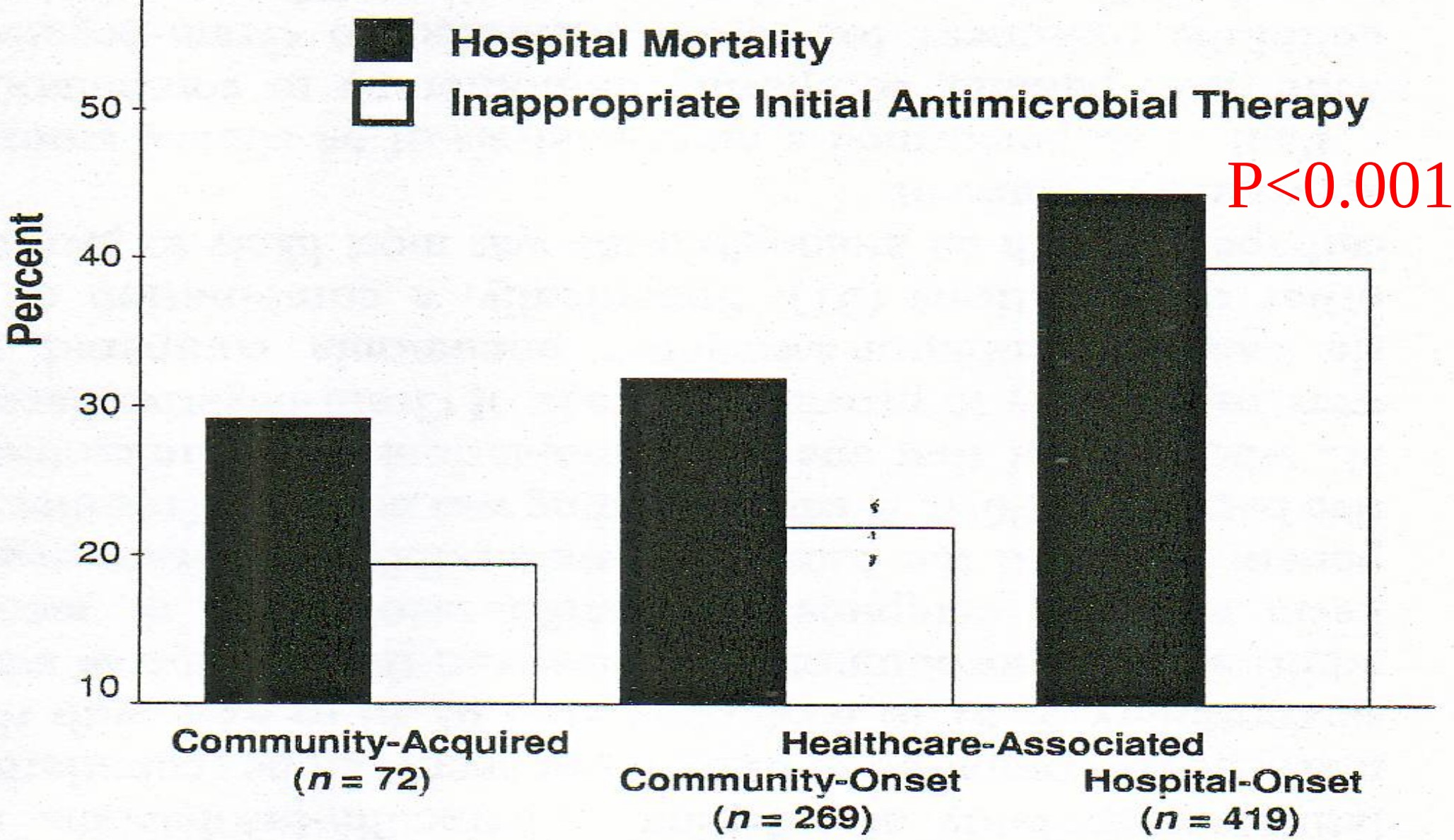

FIG. 2. Hospital mortality and inappropriate initial antimicrobial therapy (IIAT) according to classification of infection source. ($P < 0.001$ for differences in hospital mortality and IIAT).

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- Combination for all ?
- Or for selected patients ??????

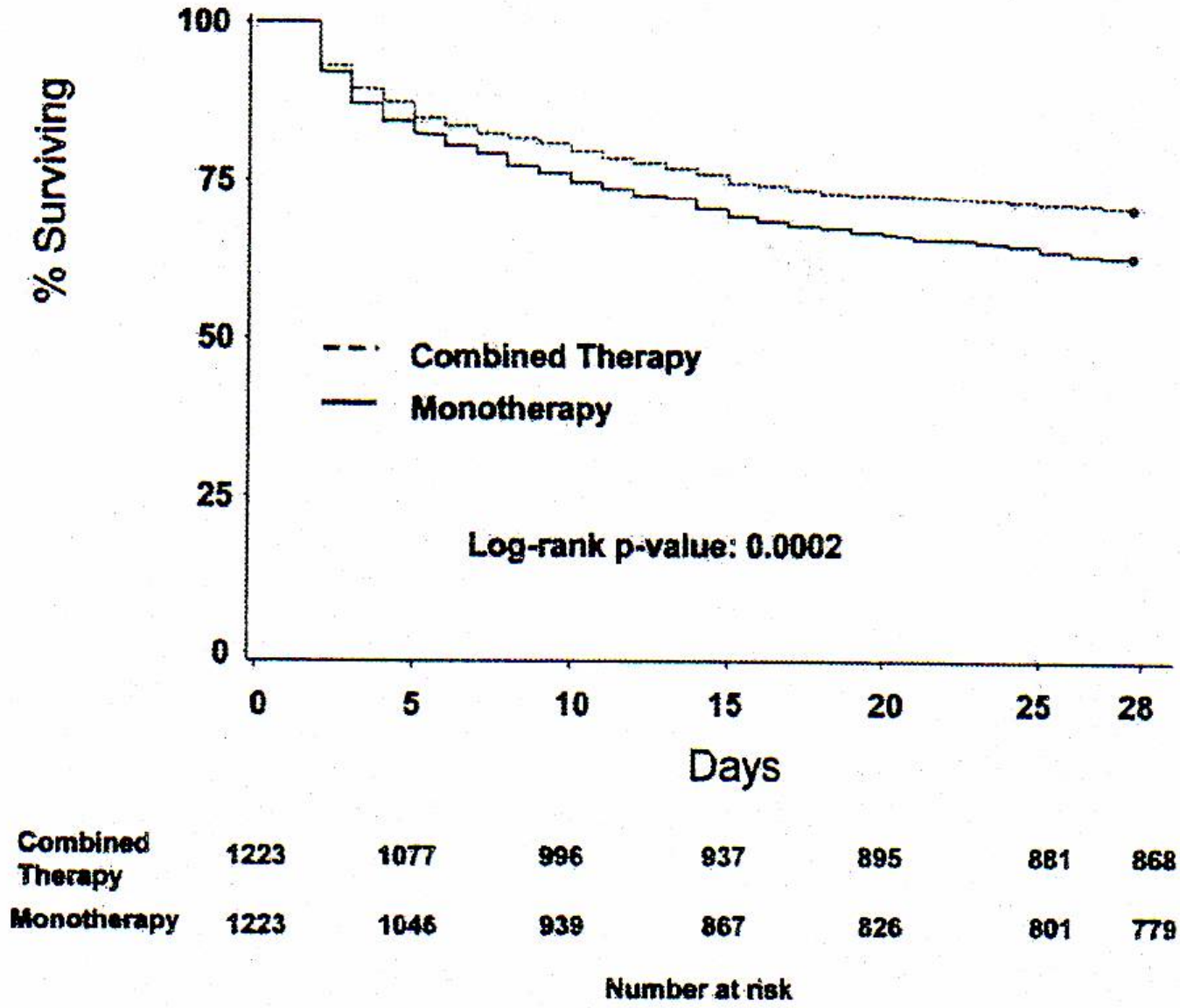


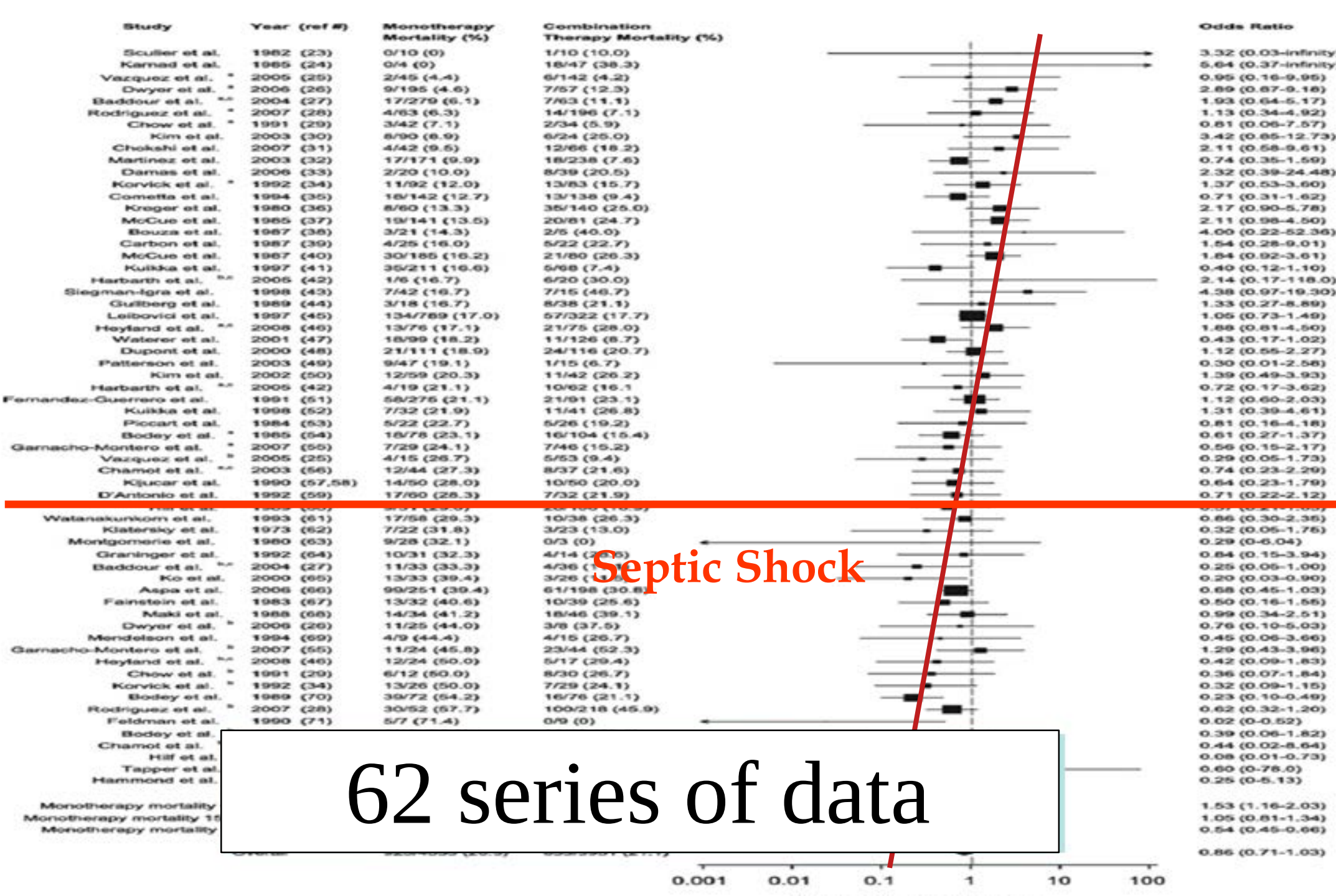
Figure 2. Adjusted Cox proportional hazards of mortality associated with combination antibiotic therapy of septic shock.

Continuing Medical Education Article

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

Anand Kumar, MD; Nasia Safdar, MD; Shravan Kethireddy, MD; Dan Chateau, PhD

62 series of data


Study
Year (ref #)
Monotherapy Mortality (%)
Combination Therapy Mortality (%)
Odds Ratio
Sculier et al. 1982 (23) 0/10 (0) 1/10 (10.0) 3.32 (0.03-infinity)
Karnad et al. 1985 (24) 0/4 (0) 18/47 (38.3) 5.64 (0.37-infinity)
Vazquez et al. * 2005 (25) 2/45 (4.4) 6/142 (4.2) 0.95 (0.16-9.95)
Dwyer et al. * 2006 (26) 9/195 (4.6) 7/57 (12.3) 2.89 (0.87-9.16)
Baddour et al. b,c 2004 (27) 17/279 (6.1) 7/63 (11.1) 1.93 (0.64-5.17)
Rodriguez et al. * 2007 (28) 4/63 (6.3) 14/196 (7.1) 1.13 (0.34-4.92)
Chow et al. * 1991 (29) 3/42 (7.1) 2/34 (5.9) 0.81 (0.06-7.57)
Kim et al. 2003 (30) 8/90 (8.9) 6/24 (25.0) 3.42 (0.85-12.73)
Chokshi et al. 2007 (31) 4/42 (9.5) 12/66 (18.2) 2.11 (0.58-9.61)
Martinez et al. 2003 (32) 17/171 (9.9) 18/238 (7.6) 0.74 (0.35-1.59)
Damas et al. 2006 (33) 2/20 (10.0) 8/39 (20.5) 2.32 (0.39-24.48)
Korvick et al. * 1992 (34) 11/92 (12.0) 13/83 (15.7) 1.37 (0.53-3.60)
Cometta et al. 1994 (35) 18/142 (12.7) 13/138 (9.4) 0.71 (0.31-1.62)
Kreger et al. 1980 (36) 8/60 (13.3) 35/140 (25.0) 2.17 (0.90-5.78)
McCue et al. 1985 (37) 19/141 (13.5) 20/81 (24.7) 2.11 (0.98-4.50)
Bouza et al. 1987 (38) 3/21 (14.3) 2/5 (40.0) 4.00 (0.22-52.36)
Carbon et al. 1987 (39) 4/25 (16.0) 5/22 (22.7) 1.54 (0.28-9.01)
McCue et al. 1987 (40) 30/185 (16.2) 21/80 (26.3) 1.84 (0.92-3.61)
Kuikka et al. 1997 (41) 35/211 (16.6) 5/68 (7.4) 0.40 (0.12-1.10)
Harbarth et al. b,c 2006 (42) 1/6 (16.7) 6/20 (30.0) 2.14 (0.17-118.0)
Siegman-Igra et al. 1998 (43) 7/42 (16.7) 7/15 (46.7) 4.38 (0.97-19.30)
Gullberg et al. 1989 (44) 3/18 (16.7) 8/38 (21.1) 1.33 (0.27-8.89)
Leibovici et al. 1997 (45) 134/789 (17.0) 57/322 (17.7) 1.05 (0.73-1.49)
Heyland et al. b,c 2008 (46) 13/76 (17.1) 21/75 (28.0) 1.88 (0.81-4.50)
Waterer et al. 2001 (47) 18/99 (18.2) 11/126 (8.7) 0.43 (0.17-1.02)
Dupont et al. 2000 (48) 21/111 (18.9) 24/116 (20.7) 1.12 (0.55-2.27)
Patterson et al. 2003 (49) 9/47 (19.1) 1/15 (6.7) 0.30 (0.01-2.58)
Kim et al. 2002 (50) 12/59 (20.3) 11/42 (26.2) 1.39 (0.49-3.93)
Harbarth et al. b,c 2005 (42) 4/19 (21.1) 10/62 (16.1 0.72 (0.17-3.62)
Fernandez-Guerrero et al. 1991 (51) 58/276 (21.1) 21/91 (23.1) 1.12 (0.60-2.03)
Kuikka et al. 1998 (52) 7/32 (21.9) 11/41 (26.8) 1.31 (0.39-4.61)
Piccart et al. 1984 (53) 5/22 (22.7) 5/26 (19.2) 0.81 (0.16-4.18)
Bodey et al. * 1985 (54) 18/78 (23.1) 16/104 (15.4) 0.61 (0.27-1.37)
Garnacho-Montero et al. * 2007 (55) 7/29 (24.1) 7/46 (15.2) 0.56 (0.15-2.17)
Vazquez et al. b 2005 (25) 4/15 (26.7) 5/53 (9.4) 0.29 (0.05-1.73)
Chamot et al. b,c 2003 (56) 12/44 (27.3) 8/37 (21.6) 0.74 (0.23-2.29)
Kjucar et al. 1990 (57,58) 14/50 (28.0) 10/50 (20.0) 0.64 (0.23-1.79)
D'Antonio et al. 1992 (59) 17/60 (28.3) 7/32 (21.9) 0.71 (0.22-2.12)
Watanakunkorn et al. 1993 (61) 17/58 (29.3) 10/38 (26.3) 0.86 (0.30-2.35)
Klatersky et al. 1973 (62) 7/22 (31.8) 3/23 (13.0) 0.32 (0.05-1.76)
Montgomerie et al. 1980 (63) 9/28 (32.1) 0/3 (0) 0.29 (0-6.04)
Graninger et al. 1992 (64) 10/31 (32.3) 4/14 (28.6) 0.84 (0.15-3.94)
Baddour et al. b,c 2004 (27) 11/33 (33.3) 4/36 (11.1) 0.25 (0.06-1.00)
Ko et al. 2000 (65) 13/33 (39.4) 3/26 (11.5) 0.20 (0.03-0.90)
Aspa et al. 2006 (66) 99/251 (39.4) 61/198 (30.8) 0.68 (0.45-1.03)
Fainstein et al. 1983 (67) 13/32 (40.6) 10/39 (25.6) 0.50 (0.16-1.55)
Maki et al. 1988 (68) 14/34 (41.2) 18/46 (39.1) 0.99 (0.34-2.51)
Dwyer et al. b 2006 (26) 11/25 (44.0) 3/8 (37.5) 0.76 (0.10-5.03)
Mendelson et al. 1994 (69) 4/9 (44.4) 4/15 (26.7) 0.45 (0.06-3.66)
Garnacho-Montero et al. b 2007 (55) 11/24 (45.8) 23/44 (52.3) 1.29 (0.43-3.96)
Heyland et al. b,c 2008 (46) 12/24 (50.0) 5/17 (29.4) 0.42 (0.09-1.83)
Chow et al. b 1991 (29) 6/12 (50.0) 8/30 (26.7) 0.36 (0.07-1.84)
Korvick et al. b 1992 (34) 13/26 (50.0) 7/29 (24.1) 0.32 (0.09-1.15)
Bodey et al. 1989 (70) 39/72 (54.2) 16/76 (21.1) 0.23 (0.10-0.49)
Rodriguez et al. b 2007 (28) 30/52 (57.7) 100/218 (45.9) 0.62 (0.32-1.20)
Feldman et al. 1990 (71) 5/7 (71.4) 0/9 (0) 0.02 (0-0.52)
Bodey et al. 0.39 (0.06-1.82)
Chamot et al. 0.44 (0.02-8.64)
Hilf et al. 0.08 (0.01-0.73)
Tapper et al. 0.60 (0-78.0)
Hammond et al. 0.25 (0-5.13)
Monotherapy mortality 1.53 (1.16-2.03)
Monotherapy mortality 1 1.05 (0.81-1.34)
Monotherapy mortality 0.54 (0.45-0.66)
0.86 (0.71-1.03)
0.001
0.01
0.1
1
10
100
Septic Shock
62 series of data

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

Combination or Monotherapy ?

Beneficial if Mortality > 25 %

Desadvantage if Mortality < 15 %

Odds Ratio of Death (Combination Therapy)

4
1
0.25
0.0625

0 20 40 60 80 100

Monotherapy Mortality Risk (%)

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Antibiotic with resistance	No. of resistant isolates	No. of isolates (%) susceptible to:	
		Ciprofloxacin	Gentamicin
Cefepime	126	23 (18.3)	49 (38.9)
Imipenem or meropenem	78	20 (25.6)	34 (43.6)
Piperacillin-tazobactam	155	56 (36.1)	90 (58.1)

Aminoglycoside > Fluoroquinolone

↑ Renal toxicity (aminoglycoside)

RRT similar rate

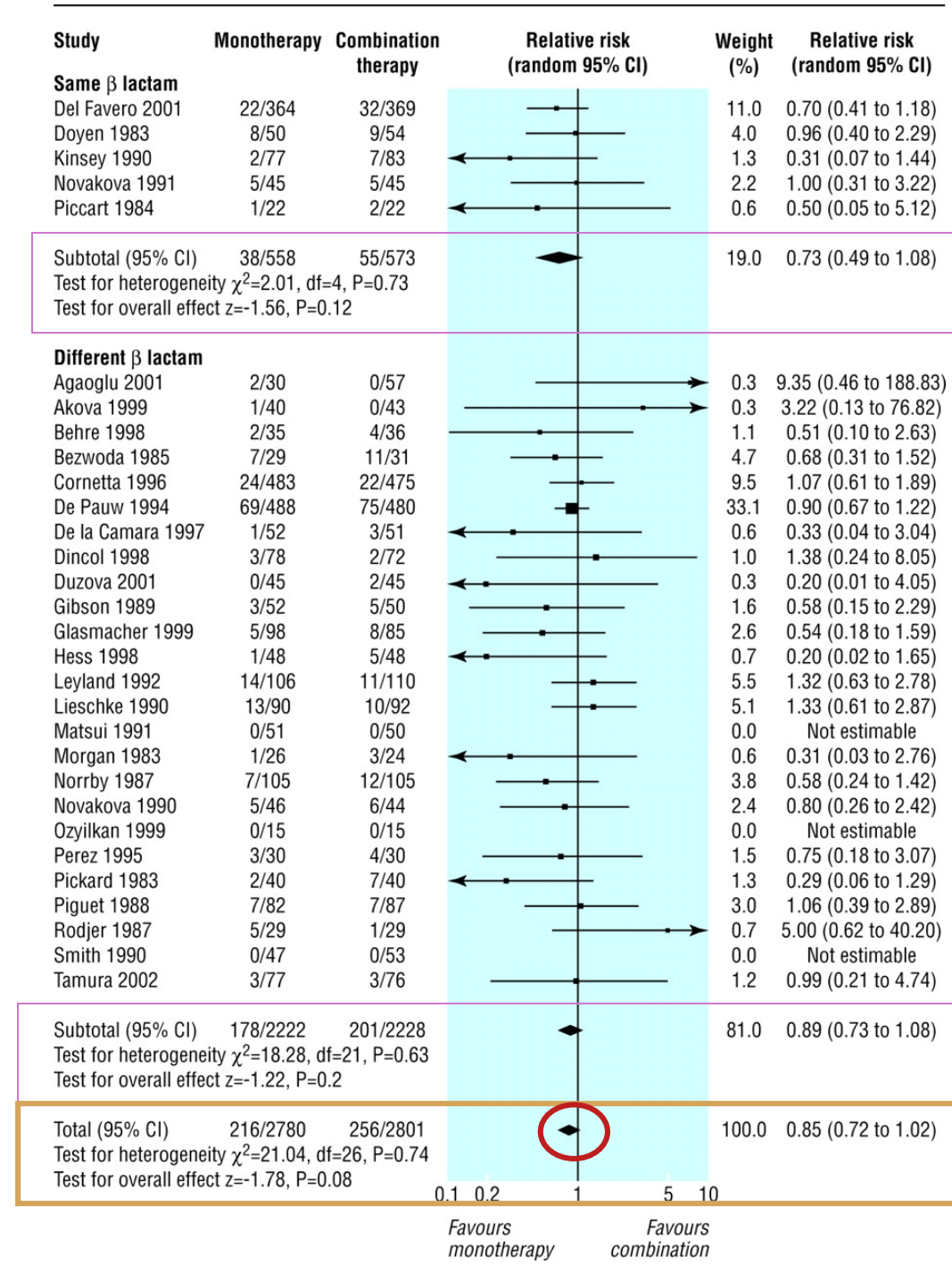
Antibiotic Combination: Broader coverage

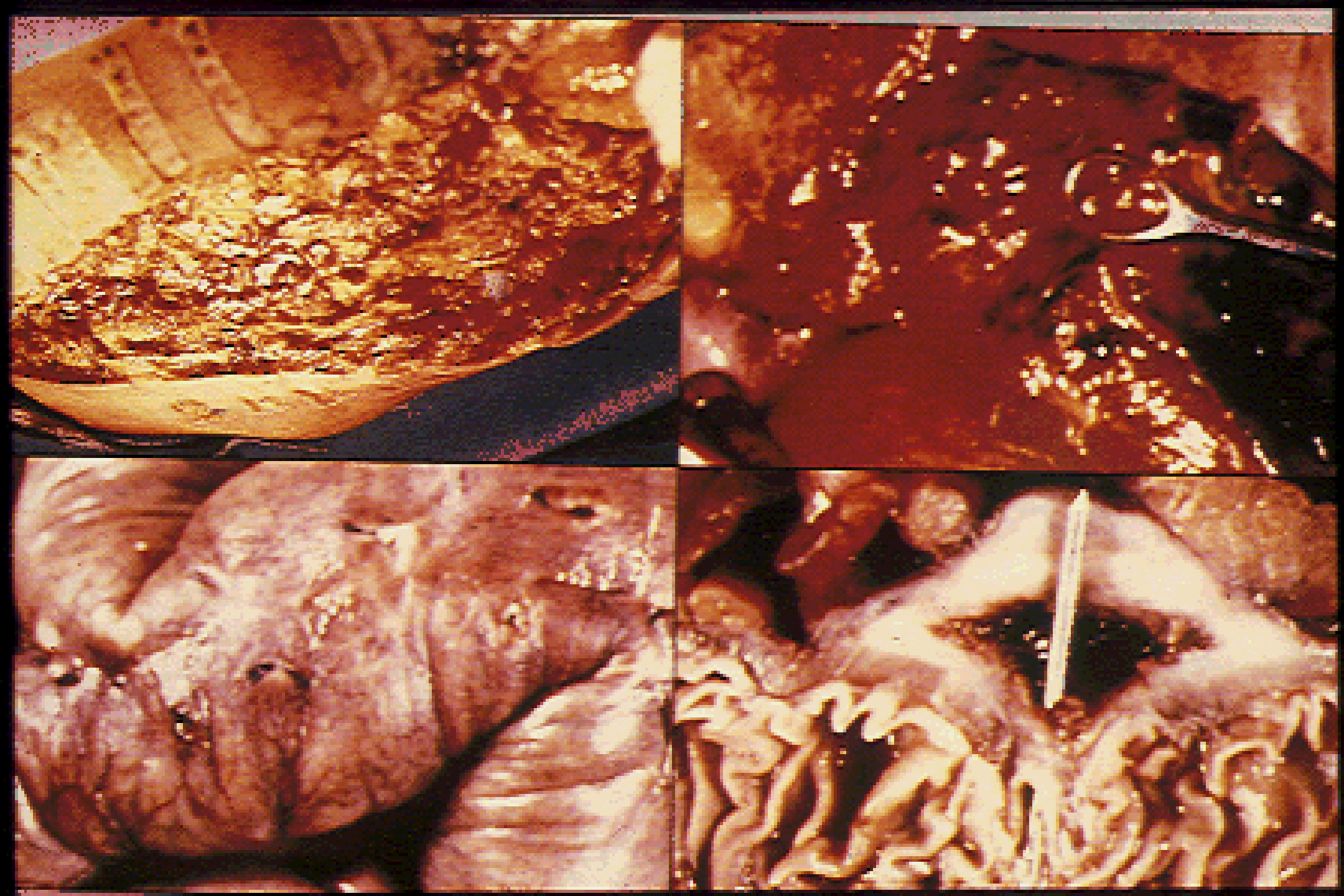
Immunodepression

?????

Febrile Neutropenia

(Paul, BMJ 2003)





TARGET BACTERIA ?

Microbiology of Peritoneal Infections

Facultative GNB	
E. coli	60%
Klebsiella	15%
Proteus	15%
Enterobacter	5%
Morganella	5%
Other...	

Anaerobes	
B. fragilis	50%
Other Bacter.	40%
Fusobacterium	5%
Clostridium	25%
Peptococcus	30%
Lactobacillus	15%

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CID 2010,50 133 - 164

Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America

Joseph S. Solomkin,[1] John E. Mazuski,[2] John S. Bradley,[3] Keith A. Rodvold,[7,8] Ellie J. C. Goldstein,[5] Ellen J. Baron,[6] Patrick J. O'Neill,[9] Anthony W. Chow,[16] E. Patchen Dellinger,[10] Soumitra R. Eachempati,[11] Sherwood Gorbach,[12] Mary Hilfiker,[4] Addison K. May,[13] Avery B. Nathens,[17] Robert G. Sawyer,[14] and John G. Bartlett[15]

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Table 2. Agents and Regimens that May Be Used for the Initial Empiric Treatment of Extra-biliary Complicated Intra-abdominal Infection

Regimen	Community-acquired infection in pediatric patients	Community-acquired infection in adults	
		Mild-to-moderate severity: perforated or abscessed appendicitis and other infections of mild-to-moderate severity	High risk or severity: severe physiologic disturbance, advanced age, or immunocompromised state
Single agent	Ertapenem, meropenem, imipenem-cilastatin, ticarcillin-clavulanate, and piperacillin-tazobactam	Cefoxitin, ertapenem, moxifloxacin, tigecycline, and ticarcillin-clavulanic acid	Imipenem-cilastatin, meropenem, doripenem, and piperacillin-tazobactam
Combination	Ceftriaxone, cefotaxime, cefepime, or ceftazidime, each in combination with metronidazole; gentamicin or tobramycin, each in combination with metronidazole or clindamycin, and with or without ampicillin	Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole[a]	Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole[a]

[a] Because of increasing resistance of *Escherichia coli* to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibility should be reviewed.

REASONS TO USE ANTIBIOTIC COMBINATIONS

- **Broader coverage**
- **Antimicrobial synergism**
- **Increased bacterial killing**
- **Decrease in antimicrobial resistance**

- **Synergism :**
  Combination of two antibiotics targeting the same germ(s)

- **Synergism :**
  - **Decrease treatment failure**
  - **Increase survival**

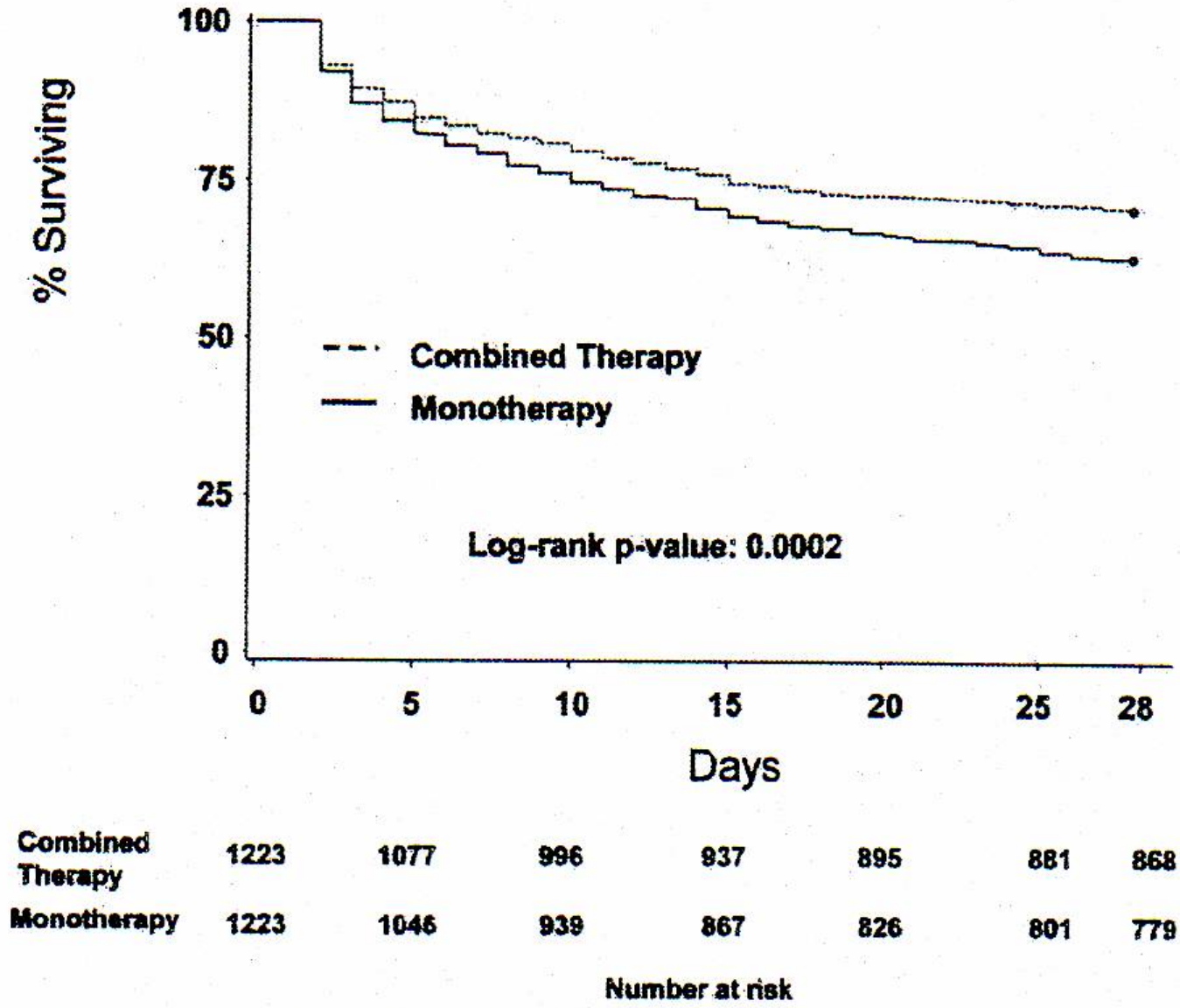

Figure 2. Adjusted Cox proportional hazards of mortality associated with combination antibiotic therapy of septic shock.

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Carbapenemase-Producing *Klebsiella pneumoniae* Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems

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First Department of Propaedeutic Medicine, University of Athens, Athens, Greece[a]; Fifth Department of Internal Medicine, University of Athens, Athens, Greece[b]; Department of Microbiology, University of Athens, Athens, Greece[c]; Department of Clinical Microbiology, Evangelismos General Hospital, Athens, Greece[d]; Depart Clinical Microbiology, Laiko General Hospital, Athens, Greece[e]; Department of Hygiene and Epidemiology, University of Athens, Athens, Greece[f]; Laboratory of Bacteriology, Hellenic Pasteur Institute, Athens, Greece[g]; Department of Pharmacy, Laiko General Hospital, Athens, Greece[h]

Carbapenemase-producing *Klebsiella pneumoniae* strains (CP-Kps) are currently among the most important nosocomial pathogens. An observational study was conducted during 2009 to 2010 in two hospitals located in a high-prevalence area (Athens, Greece). The aims were (i) to evaluate the clinical outcome of patients with CP-Kp bloodstream infections (BSIs), (ii) to identify predictors of mortality, and (iii) to evaluate the various antibiotic schemes employed. A total of 205 patients with CP-Kp BSIs were identified: 163 (79.5%) were infected with KPC or KPC and VIM, and 42 were infected with VIM producers. For definitive treatment, 103 patients received combination therapy (two or more active drugs), 72 received monotherapy (one active drug), and 12 received therapy with no active drug. The remaining 18 patients died within 48 h after the onset of bacteremia. The all-cause 28-day mortality was 40%. A significantly higher mortality rate was observed in patients treated with monotherapy than in those treated with combination therapy (44.4% versus 27.2%; $P = 0.018$). The lowest mortality rate (19.3%) was observed in patients treated with carbapenem-containing combinations. In the Cox proportion hazards model, ultimately fatal disease (hazards ratio [HR], 3.25; 95% confidence interval [CI], 1.51 to 7.03; $P = 0.003$), the presence of rapidly fatal underlying diseases (HR, 4.20; 95% CI, 2.19 to 8.08; $P < 0.001$), and septic shock (HR, 2.15; 95% CI, 1.16 to 3.96; $P = 0.015$) were independent predictors of death. Combination therapy was strongly associated with survival (HR of death for monotherapy versus combination, 2.08; 95% CI, 1.23 to 3.51; $P = 0.006$), mostly due to the effectiveness of the carbapenem-containing regimens.

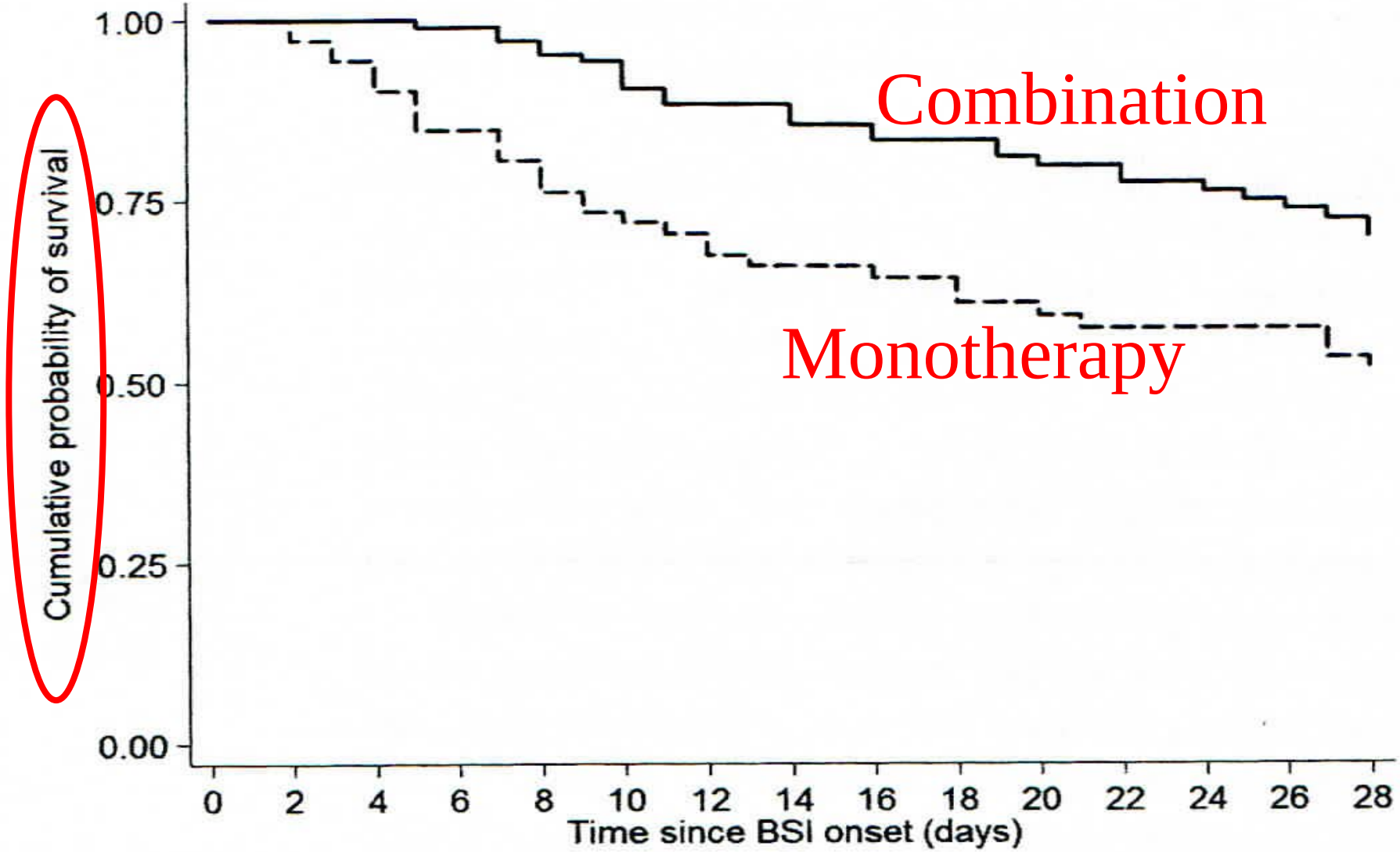

FIG 1 Kaplan-Meier survival estimates of patients with carbapenemase-producing *K. pneumoniae* bloodstream infections according to treatment regimen: combination therapy (continuous line) versus monotherapy (dotted line). $P = 0.003$ (log rank test).

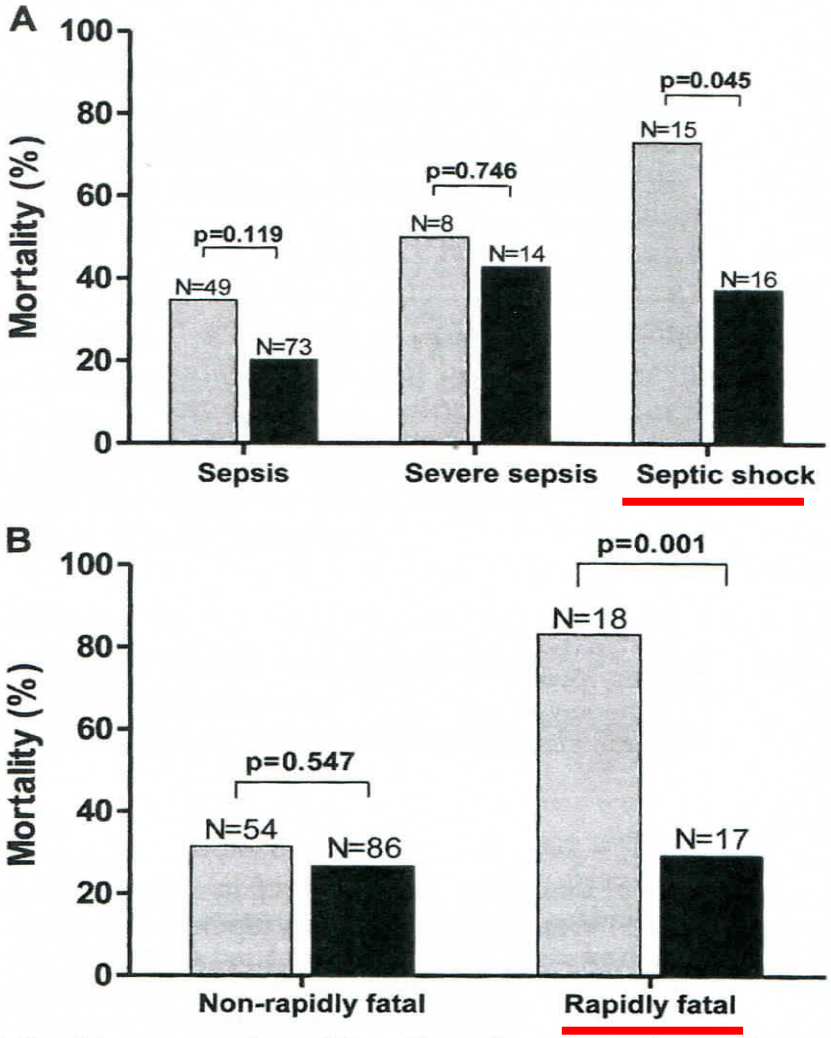

FIG 2 Graphic presentation of the effect of treatment (monotherapy [gray bars] versus combination therapy [black bars]) by severity of underlying disease (A) and by severity of sepsis (B). Numbers above columns indicate the number of patients.

TABLE 5 Cox proportional hazards model of factors associated with all-cause 28-day mortality in 175 patients with carbapenemase-producing *K. pneumoniae* bloodstream infections

Variable	HR (95% CI)	*P*
Age (per 1-yr increase)	1.01 (0.99–1.03)	0.198
Gender (female/male)	1.45 (0.82–2.55)	0.198
Severity of underlying disease		
Ultimately fatal/nonfatal	3.25 (1.51–7.03)	0.003
Rapidly fatal/nonfatal	4.20 (2.19–8.08)	<0.001
Charlson comorbidity index	1.01 (0.85–1.20)	0.879
Severity of sepsis		
Severe sepsis/sepsis	1.63 (0.74–3.59)	0.227
Septic shock/sepsis	2.15 (1.16–3.96)	0.015
Polymicrobial bacteremia		
Yes/no	1.29 (0.74–2.23)	0.371
Ward at onset of bacteremia		
ICU/non-ICU	1.36 (0.72–2.57)	0.342
Monotherapy/combination therapy	2.08 (1.23–3.51)	0.006

Influence of Empiric Therapy with a β-Lactam Alone or Combined with an Aminoglycoside on Prognosis of Bacteremia Due to Gram-Negative Microorganisms[▽]

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Evidence supporting the combination of aminoglycosides with β-lactams for Gram-negative bacteremia is inconclusive. We have explored the influence on survival of empirical therapy with a β-lactam alone versus that with a β-lactam-aminoglycoside combination by retrospectively analyzing a series of bacteremic episodes due to aerobic or facultative Gram-negative microorganisms treated with single or combination therapy. The outcome variable was a 30-day mortality. Prognostic factors were selected by regression logistic analysis. A total of 4,863 episodes were assessed, of which 678 (14%) received combination therapy and 467 (10%) were fatal. Factors independently associated with mortality included age greater than 65 (odds ratio [OR], 2; 95% confidence interval [CI], 1.6 to 2.6), hospital acquisition (OR, 1.5; 95% CI, 1.2 to 1.9), a rapidly or ultimately fatal underlying disease (OR, 2.5; 95% CI, 2 to 3.2), cirrhosis (OR, 1.9; 95% CI, 1.4 to 2.6), prior corticosteroids (OR, 1.5; 95% CI, 1.1 to 2), shock on presentation (OR, 8.8; 95% CI, 7 to 11), pneumonia (OR, 2.8; 95% CI, 1.9 to 4), and inappropriate empirical therapy (OR, 1.8; 95% CI, 1.3 to 2.5). Subgroup analysis revealed that combination therapy was an independent protective factor in episodes presenting shock (OR, 0.6; 95% CI, 0.4 to 0.9) or neutropenia (OR, 0.5; 95% CI, 0.3 to 0.9). Combination therapy improved the appropriateness of empirical therapy in episodes due to extended-spectrum β-lactamase (ESBL)- or AmpC-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa*. In patients with Gram-negative bacteremia, we could not find an overall association between empirical β-lactam-aminoglycoside combination therapy and prognosis. However, a survival advantage cannot be discarded for episodes presenting shock or neutropenia, hence in these situations the use of combination therapy may still be justified. Combination therapy also should be considered for patients at risk of being infected with resistant organisms, if only to increase the appropriateness of empirical therapy.

TABLE 4. Appropriateness of antibiotic therapy in patients receiving or not receiving aminoglycosides as empirical therapy

Microorganism	No./total no. (%) receiving:		OR (95% CI)	*P*
	Combination	β-Lactam		
Non-ESBL *E. coli*	242/248 (98)	2,454/2,489 (99)	0.6 (0.2–1.7)	0.3
ESBL *E. coli*	21/28 (75)	62/122 (51)	2.9 (1.07–8.2)	0.02
Non-ESBL *K. pneumoniae*	62/63 (98)	393/420 (94)	4 (0.7–177)	0.2
ESBL *K. pneumoniae*	18/20 (90)	38/63 (60)	2 (1.2–4.2)	0.01
P. mirabilis	10/10 (100)	116/118 (98)		1
Salmonella spp.	15/15 (100)	108/109 (99)		1
AmpC organisms	78/82 (95)	258/326 (79)	5.1 (1.8–20)	0.001
P. aeruginosa	133/143 (93)	201/319 (63)	7.8 (3.8–16)	<0.0001
Other nonfermenters	24/51 (47)	53/105 (51)	0.9 (0.4–1.8)	0.7
Miscellaneous	18/18 (100)	105/114 (92)		0.4

TABLE 7. Multivariate analysis of factors associated with 30-day mortality in selected subgroups

Characteristic	OR (95% CI) for mortality subgroup:				
	Non-UTI, non-i.v. catheter sources	Neutropenia	Shock	ESBL or AmpC	*P. aeruginosa*
Age >65 yr	1.8 (1.4–2.4)		2.1 (1.4–3.1)		2.6 (1.4–5)
Place of acquisition					
Community	1			1	
Hospital	1.6 (1.1–2.2)			1.7 (1–3.2)	
Health care situation	0.9 (0.6–1.4)			0.5 (0.2–1.4)	
Ultimately or rapidly fatal disease	2.6 (1.9–3.4)		2.3 (1.6–3.4)	4.8 (2.5–9.1)	2.1 (1.1–4)
Hematological cancer		0.5 (0.3–1)			
Cirrhosis			1.7 (1–2.9)		
Renal insufficiency	1.6 (1.01–2.6)	5.5 (1.3–23)			
Prior surgery	0.3 (0.2–0.5)				0.4 (0.2–1)
Bladder catheter	1.5 (1.02–2.2)				
Shock	7.9 (6–11)	10 (5.5–19)		8 (5–14)	6.4 (3.5–12)
Source of infection					
Unknown	1		1	1	1
Urinary tract			0.3 (0.2–0.6)	1.3 (0.5–2.4)	0.2 (0.1–0.9)
i.v. catheter			0.3 (0.1–0.7)	0.8 (0.3–1.8)	0.7 (0.3–1.8)
Pneumonia	2.9 (2–4.3)		2.3 (1.3–4.2)	5 (1.6–13)	3.3 (1.5–7)
Intraabdominal	2 (1.3–3)		1 (0.5–1.6)	1.2 (0.5–3.2)	2.8 (0.7–12)
Biliary	0.5 (0.3–0.8)		0.3 (0.2–0.7)	0.4 (0.1–1.4)	0.6 (0.1–2.4)
Skin/soft tissues	1.6 (0.9–2.7)		1.4 (0.5–3.6)	0.8 (0.2–3.8)	1 (0.3–3.6)
Other	1.3 (0.7–2.4)		0.9 (0.3–2.4)	2 (0.4–9)	2.8 (0.7–12)
Combination therapy		0.5 (0.3–0.9)	0.6 (0.4–0.9)		

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Clinical Experience of Colistin-Glycopeptide Combination in Critically Ill Patients Infected with Gram-Negative Bacteria

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A colistin-glycopeptide combination (CGC) has been shown *in vitro* to be synergistic against multidrug-resistant Gram-negative bacteria (MDR GNB), especially *Acinetobacter baumannii*, and to prevent further resistance. However, clinical data are lacking. We carried out a retrospective multicenter study of patients hospitalized in intensive care units (ICUs) who received colistin for GNB infection over a 1-year period, to assess the rates of nephrotoxicity and 30-day mortality after treatment onset among patients treated with and without CGC for ≥48 h. Of the 184 patients treated with colistin, GNB infection was documented for 166. The main causative agents were MDR *A. baumannii* (59.6%), MDR *Pseudomonas aeruginosa* (18.7%), and carbapenem-resistant *Klebsiella pneumoniae* (14.5%); in 16.9% of patients, a Gram-positive bacterium (GPB) coinfection was documented. Overall, 68 patients (40.9%) received CGC. Comparison of patients treated with and without CGC showed significant differences for respiratory failure (39.7% versus 58.2%), ventilator-associated pneumonia (54.4% versus 71.4%), MDR *A. baumannii* infection (70.6% versus 52%), and GPB coinfection (41.2% versus 0%); there were no differences for nephrotoxicity (11.8% versus 13.3%) and 30-day mortality (33.8% versus 29.6%). Cox analysis performed on patients who survived for ≥5 days after treatment onset showed that the Charlson index (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.01 to 1.44; $P = 0.001$) and MDR *A. baumannii* infection (HR, 2.51; 95% CI, 1.23 to 5.12; $P = 0.01$) were independent predictors of 30-day mortality, whereas receiving CGC for ≥5 days was a protective factor (HR, 0.42; 95% CI, 0.19 to 0.93; $P = 0.03$). We found that CGC was not associated with higher nephrotoxicity and was a protective factor for mortality if administered for ≥5 days.

TABLE 6 Cox regression analysis of risk factors for 30-day mortality[a]

Factor	Univariate analysis		Multivariate analysis[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.01 (0.99–1.03)	0.18		
Male sex	1.34 (0.71–2.50)	0.36		
Charlson index	**1.30 (1.14–1.48)**	**<0.001**	**1.26 (1.01–1.44)**	**0.001**
APACHE II score	1.05 (1.00–1.09)	0.03		
VAP	1.28 (0.66–2.49)	0.46		
BSI	0.80 (0.35–1.82)	0.60		
MDR *A. baumannii*	**2.20 (1.10–4.41)**	**0.03**	**2.51 (1.23–5.12)**	**0.01**
MDR *P. aeruginosa*	0.42 (0.15–1.18)	0.10		
CR *K. pneumoniae*	0.73 (0.28–1.87)	0.52		
Coinfection with GPB	0.63 (0.24–1.60)	0.33		
Colistin alone	0.95 (0.49–1.82)	0.87		
Colistin plus a glycopeptide	0.93 (0.45–1.99)	0.84		
Colistin plus other anti-GNB drugs	0.99 (0.46–2.15)	0.98		
Colistin plus other anti-GNB drugs plus a glycopeptide	1.19 (0.55–2.59)	0.65		
Combination including a glycopeptide for ≥48 h	1.05 (0.56–1.96)	0.86		
Days of combination with a glycopeptide	0.95 (0.89–1.01)	0.09		
Combination with a glycopeptide for ≥5 days	**0.47 (0.22–1.02)**	**0.05**	**0.42 (0.18–0.93)**	**0.03**
Nephrotoxicity	0.63 (0.22–1.77)	0.38		

[a] Abbreviations: VAP, ventilator-associated pneumonia; BSI, bloodstream infection; MDR, multidrug resistant; CR, carbapenem resistant; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria. Data in bold are statistically significant.

[b] The multivariate analysis was adjusted for all variables with *P* values of ≤0.1 in the univariate analysis and for age, sex, and the presence of coinfection with GPB.

TABLE 7 Cox regression analysis of risk factors for 30-day mortality among patients with infection due to MDR *A. baumannii*[a]

Parameter	Univariate analysis		Multivariate analysis[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.01 (0.99–1.03)	0.16		
Male sex	1.55 (0.75–3.23)	0.24		
Charlson index	**1.27 (1.08–1.48)**	**0.003**	**1.18 (0.99–1.39)**	**0.06**
APACHE II score	**1.06 (1.01–1.11)**	**0.01**	**1.05 (0.99–1.11)**	**0.97**
VAP	0.92 (0.42–2.03)	0.84		
BSI	1.56 (0.65–3.93)	0.31		
Coinfection with a GPB	0.46 (0.17–1.21)	0.12		
Colistin alone	1.34 (0.61–2.95)	0.46		
Colistin plus a glycopeptide	0.90 (0.41–1.98)	0.79		
Colistin plus other anti-GNB drugs	0.67 (0.23–1.92)	0.45		
Colistin plus other anti-GNB drugs plus a glycopeptide	1.11 (0.47–2.60)	0.81		
Combination including a glycopeptide for ≥48 h	0.98 (0.47–2.05)	0.97		
Days of combination with a glycopeptide	0.94 (0.88–1.01)	0.09		
Combination with a glycopeptide for ≥5 days	**0.44 (0.19–0.99)**	**0.05**	**0.41 (0.17–0.98)**	**0.04**
Nephrotoxicity	0.61 (0.18–2.02)	0.42		

[a] Abbreviations: VAP, ventilator-associated pneumonia; BSI, bloodstream infection; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria. Data in bold are statistically significant.

[b] The multivariate analysis was adjusted for age, sex, Charlson index, APACHE II score, coinfection with GPB, and combination with a glycopeptide for ≥5 days.

ONLINE FIRST

Effect of Empirical Treatment With Moxifloxacin and Meropenem vs Meropenem on Sepsis-Related Organ Dysfunction in Patients With Severe Sepsis

A Randomized Trial

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Context Early appropriate antimicrobial therapy leads to lower mortality rates associated with severe sepsis. The role of empirical combination therapy comprising at least 2 antibiotics of different mechanisms remains controversial.

Objective To compare the effect of moxifloxacin and meropenem with the effect of meropenem alone on sepsis-related organ dysfunction.

Design, Setting, and Patients A randomized, open-label, parallel-group trial of 600 patients who fulfilled criteria for severe sepsis or septic shock (n=298 for monotherapy and n=302 for combination therapy). The trial was performed at 44 intensive care units in Germany from October 16, 2007, to March 23, 2010. The number of evaluable patients was 273 in the monotherapy group and 278 in the combination therapy group.

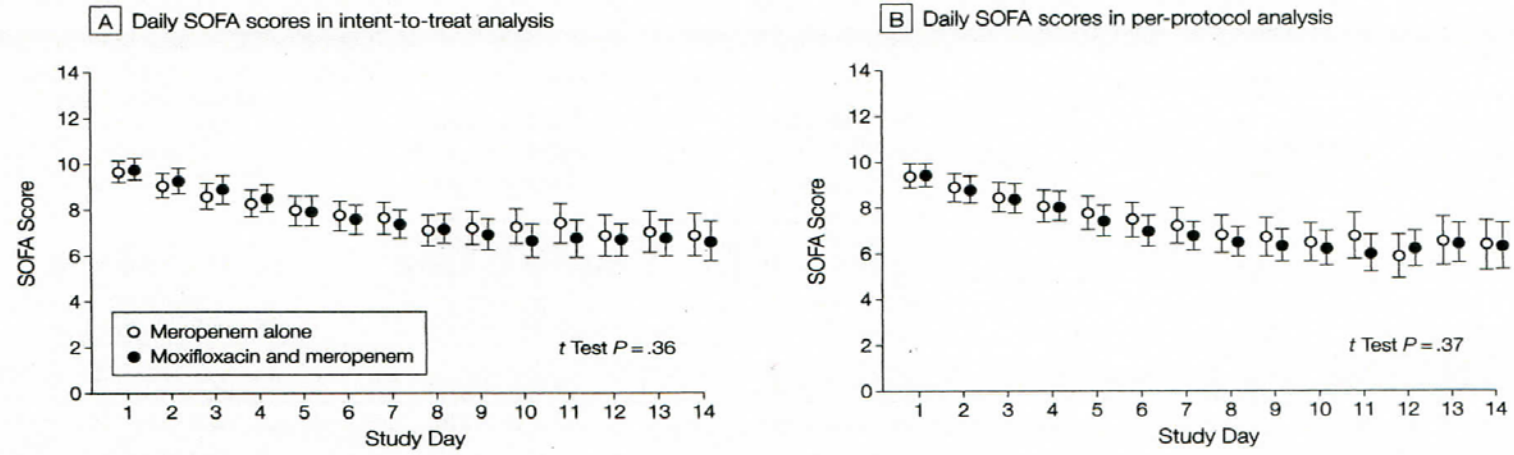
Interventions Intravenous meropenem (1 g every 8 hours) and moxifloxacin (400 mg every 24 hours) or meropenem alone. The intervention was recommended for 7 days and up to a maximum of 14 days after randomization or until discharge from the intensive care unit or death, whichever occurred first.

Main Outcome Measure Degree of organ failure (mean of daily total Sequential Organ Failure Assessment [SOFA] scores over 14 days; score range: 0-24 points with higher scores indicating worse organ failure); secondary outcome: 28-day and 90-day all-cause mortality. Survivors were followed up for 90 days.

Results Among 551 evaluable patients, there was no statistically significant difference in mean SOFA score between the meropenem and moxifloxacin group (8.3 points; 95% CI, 7.8-8.8 points) and the meropenem alone group (7.9 points; 95% CI, 7.5-8.4 points) (P=.36). The rates for 28-day and 90-day mortality also were not statistically significantly different. By day 28, there were 66 deaths (23.9%; 95% CI, 19.0%-29.4%) in the combination therapy group compared with 59 deaths (21.9%; 95% CI, 17.1%-27.4%) in the monotherapy group (P=.58). By day 90, there were 96 deaths (35.3%; 95% CI, 29.6%-41.3%) in the combination therapy group compared with 84 deaths (32.1%; 95% CI, 26.5%-38.1%) in the monotherapy group (P=.43).

Conclusion Among adult patients with severe sepsis, treatment with combined meropenem and moxifloxacin compared with meropenem alone did not result in less organ failure.

Figure 2. Daily Sequential Organ Failure Assessment (SOFA) Scores

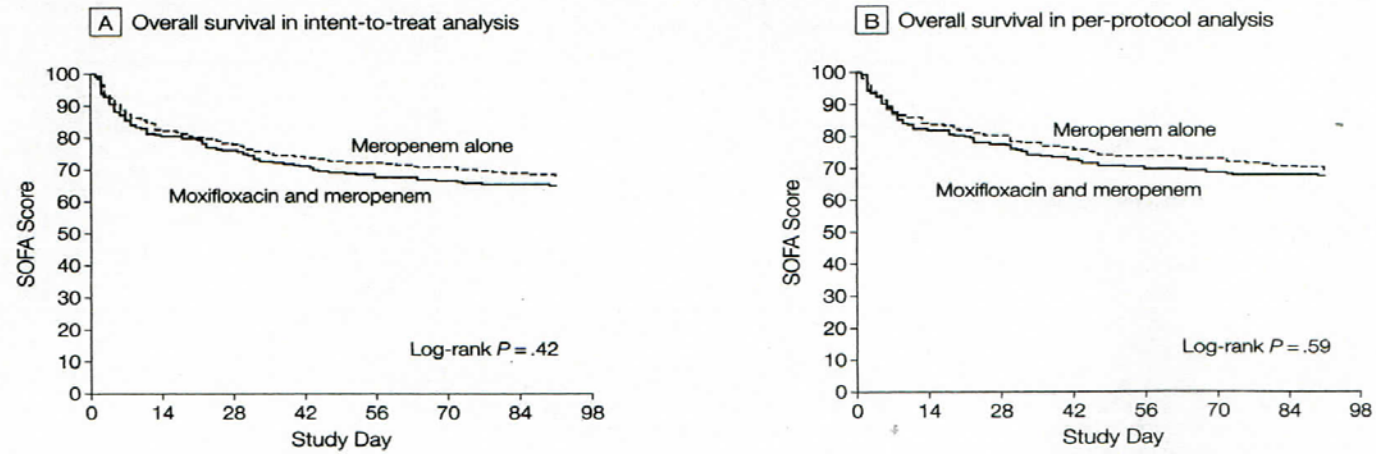


No. of evaluable patients							
Meropenem alone	249	212	167	137	124	103	89
Moxifloxacin and meropenem	255	209	179	153	125	95	81

181	156	122	96	88	71	63
198	165	141	119	96	71	57

The data markers indicate means and the error bars indicate 95% CIs.

Figure 3. Overall Survival



No. of patients at risk							
Meropenem alone	273	222	211	193	188	184	179
Moxifloxacin and meropenem	276	224	210	193	186	180	177

199	164	156	143	138	137	132
214	176	166	155	150	146	144

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

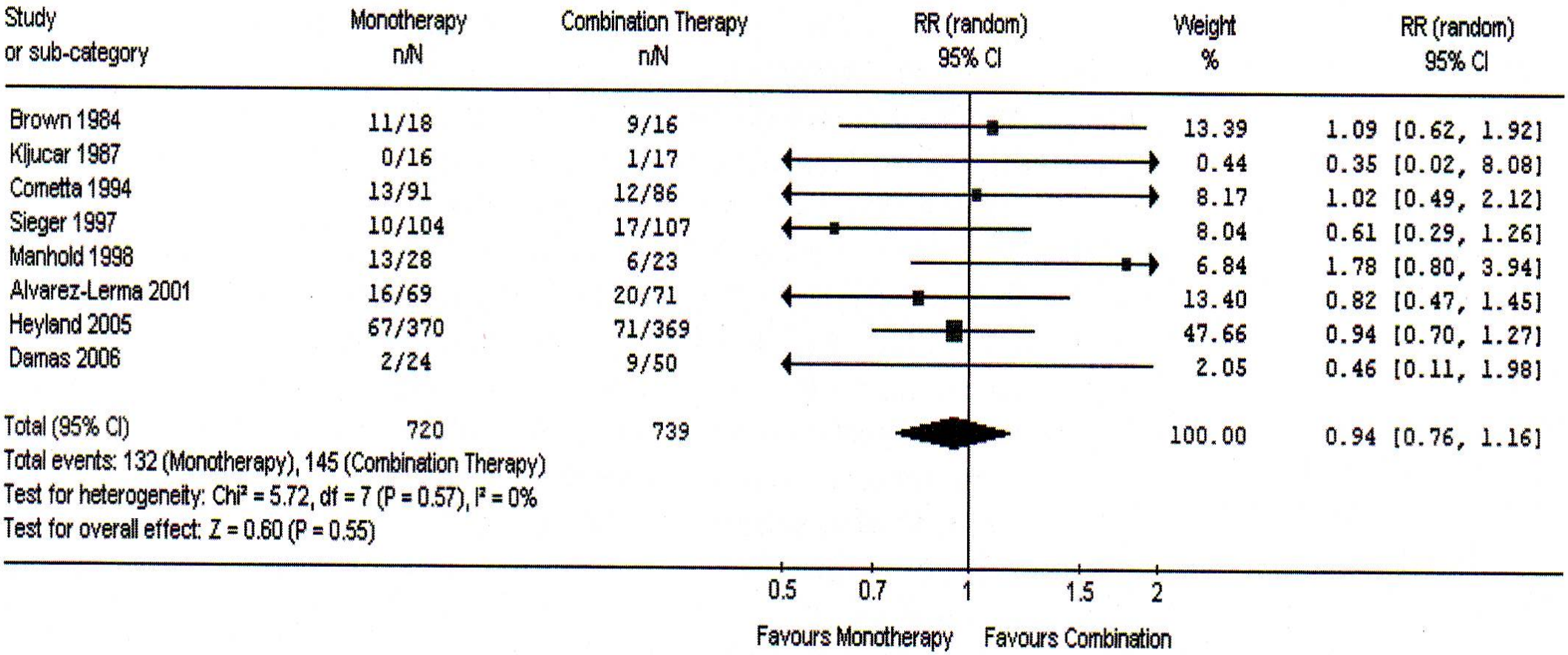


Figure 4. Mortality in pooled trials comparing monotherapy to combination therapy. There is no evidence that combination therapy improves survival when compared with monotherapy. *RR*, relative risk; *CI*, confidence interval.

Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia*

Daren K. Heyland, MD; Peter Dodek, MD; John Muscedere, MD; Andrew Day, MSc; Deborah Cook, MD; for the Canadian Critical Care Trials Group

Objective: To compare a strategy of combination therapy with a strategy of monotherapy with broad-spectrum antibiotics for suspected late ventilator-associated pneumonia.

Design: Randomized trial.

Setting: Twenty-eight intensive care units in Canada and the United States.

Patients: The study included 740 mechanically ventilated patients who developed suspected ventilator-associated pneumonia after 96 hrs in the intensive care unit. Patients known to be colonized or infected with *Pseudomonas* or methicillin-resistant *Staphylococcus aureus* or who were immunocompromised were excluded from the study.

Interventions: As initial unblinded therapy, patients were allocated to receive meropenem (1 g every 8 hrs) and ciprofloxacin (400 mg every 12 hrs) or meropenem alone. Before starting antibiotics, patients were also randomized to bronchoalveolar lavage with quantitative cultures or endotracheal aspirates. When culture results were available, physicians were encouraged to adjust antibiotics. Adequacy of antibiotics was defined as the organism present in the enrollment culture having *in vitro* susceptibility to one or more of the study antibiotics.

Measurements and Main Results: Baseline characteristics and etiologies of ventilator-associated pneumonia were similar in the two groups. There was no difference in 28-day mortality between the combination and monotherapy groups (relative risk = 1.05, 95% confidence interval 0.78–1.42, $p = .74$). Duration of intensive care unit and hospital stay, clinical and microbiological treatment response, emergence of antibiotic-resistant bacteria, isolation of *Clostridium difficile* in stool, and fungal colonization were also similar in the two groups. In a subgroup of patients who had infection due to *Pseudomonas* species, *Acinetobacter* species, and multidrug-resistant Gram-negative bacilli at enrollment (n = 56), the adequacy of initial antibiotics (84.2% vs. 18.8%, $p < .001$) and microbiological eradication of infecting organisms (64.1% vs. 29.4%, $p = .05$) was higher in the combination group compared with the monotherapy group, but there were no differences in clinical outcomes.

Conclusions: For critically ill patients who have suspected late ventilator-associated pneumonia and who are at low risk for difficult-to-treat Gram-negative bacteria, monotherapy is associated with similar outcomes compared with combination therapy. For those patients at high risk of difficult-to-treat Gram-negative bacteria, combination therapy is safe and may be associated with better microbiological and clinical outcomes. (Crit Care Med 2008; 36:737–744)

KEY WORDS: ventilator-associated pneumonia; antibiotics; empirical therapy; combination therapy; randomized controlled trial; outcomes; broad spectrum antimicrobials

Table 4. Effect of study interventions on 28-day mortality

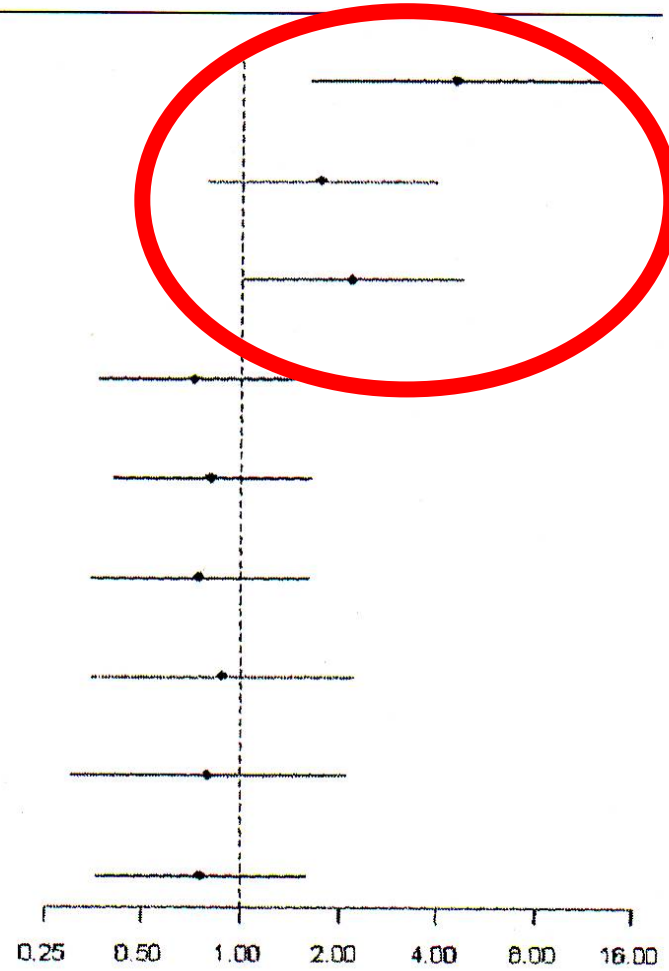
	Combination Therapy	Monotherapy	RR Combination Therapy vs. Monotherapy Conditional on Diagnostic Approach	Overall RR Combination Therapy vs. Monotherapy
Bronchoscopy with BAL	38/182 (20.9%)	31/183 (16.9%)	1.23 (0.80–1.89)	1.05 (0.78–1.42)[a]
ETA	33/187 (17.6%)	36/187 (19.3%)	0.92 (0.60–1.40)	
RR BAL vs. ETA conditional on antibiotics given	1.18 (0.78–1.80)	0.88 (0.57–1.36)		
Overall RR BAL vs. ETA	1.01 (0.75–1.37)[b]			

RR, relative risk; BAL, bronchoalveolar lavage; ETA, endotracheal aspirates.

[a]Stratified by enrollment Acute Physiology and Chronic Health Evaluation (APACHE) II score diagnostic strategy (ETA or BAL); [b]stratified by enrollment APACHE II score and antibiotic therapy (monotherapy or combination therapy). Interaction ratio between interventions: 1.34 ($p = .37$).

Table 6. Subgroup analysis of patients with difficult-to-treat Gram-negative bacilli on enrollment (*Pseudomonas* species, *Acinetobacter* species, and other multidrug-resistant Gram-negative bacilli)

	Combination Therapy (n = 39)	Monotherapy (n = 17)	Combo/Mono RR (95% CI)[a]
Adequacy of empiric therapy, n (%)[b]	32 (84.2)	3 (18.8)	
Clinical resolution at 28 days, n (%)	20 (51.3)	5 (29.4)	
Microbiological resolution at 28 days, n (%)[c]	25 (64.1)	5 (29.4)	
Duration of mechanical ventilation[d]	10.7 (3.3, .)	15.0 (9.3, .)	
Duration of ICU stay[d]	14.2 (8.1, .)	21.2 (14.1, .)	
Duration of hospital stay[d]	55.0 (33.0, .)	111.4 (27.8, .)	
28-day mortality, n (%)	10 (25.6)	5 (29.4)	
ICU mortality, n (%)	9 (23.1)	5 (29.4)	
Hospital mortality, n (%)	13 (33.3)	7 (41.2)	



RR, relative risk; CI, confidence interval; ICU, intensive care unit.

[a]RR and 95% CI are adjusted for Acute Physiology and Chronic Health Evaluation II score and diagnostic technique by the stratified Mantel-Haenszel method for binary outcomes and the proportional hazards model for duration outcomes; [b]adequacy of therapy not available for one patient in each group, n = 38 for combination group, n = 16 for monotherapy group ($p < .001$); [c]$p = .014$; [d]median (interquarile range): The upper quartile range of the time to discharge is undefined for both groups because >25 of patients did not achieve the particular event.

Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia*

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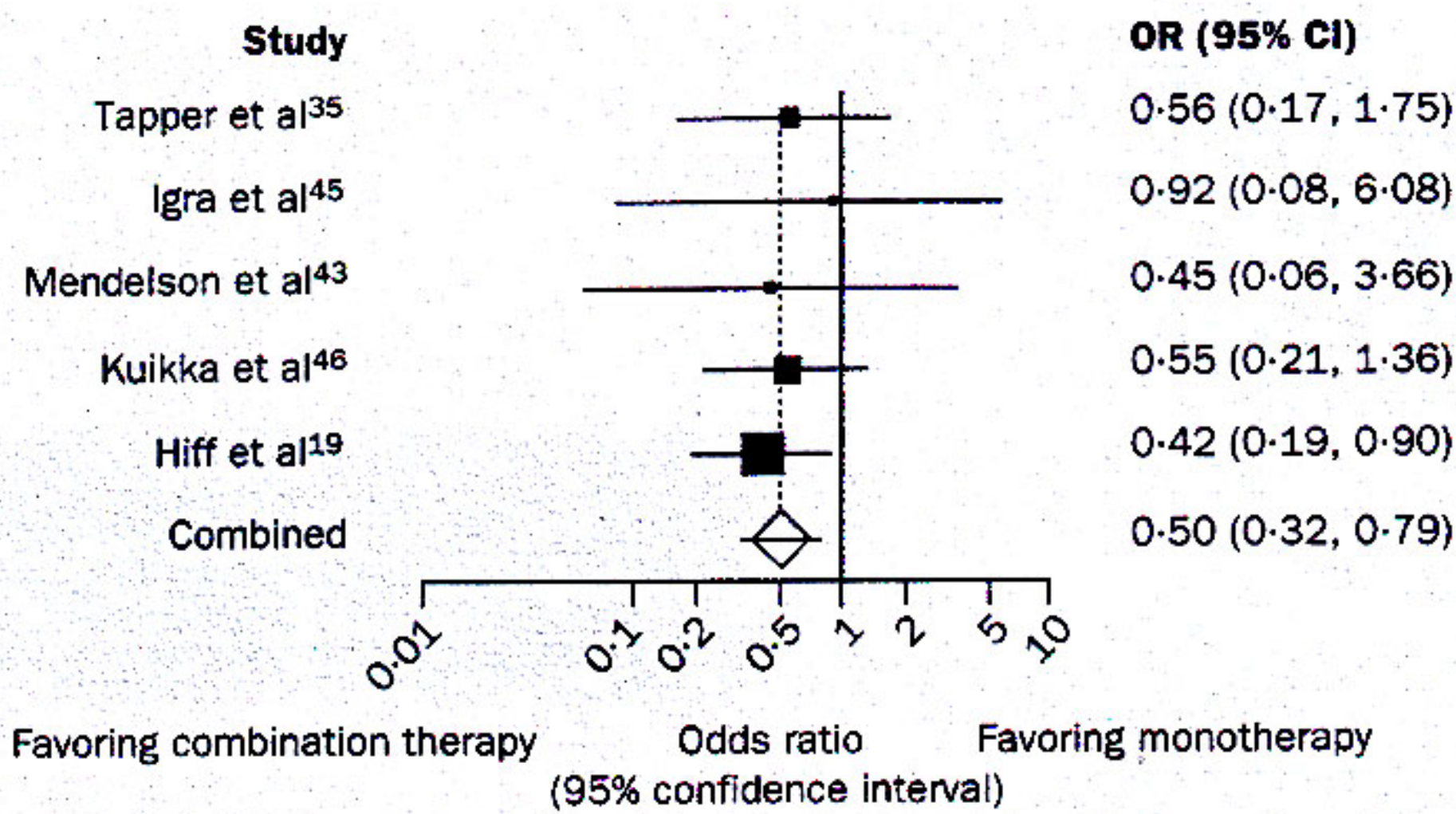
Key Words: ventilator-associated pneumonia; antibiotics; empirical therapy; combination therapy; randomized controlled trial; outcomes; broad spectrum antimicrobials

Pseudomonas

Pseudomonas Bacteremia



Safdar et al Lancet ID 2004 , 4 , 519-527

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Outcomes of Appropriate Empiric Combination versus Monotherapy for *Pseudomonas aeruginosa* Bacteremia

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Pseudomonas aeruginosa **bacteremia is associated with high hospital mortality. Empirical combination therapy is commonly used to increase the likelihood of appropriate therapy, but the benefits of employing >1 active agent have yet to be established. The purpose of this study was to compare outcomes of patients receiving appropriate empirical combination versus monotherapy for *P. aeruginosa* bacteremia. This was a retrospective, multicenter, cohort study of hospitalized adult patients with *P. aeruginosa* bacteremia from 2002 to 2011. The primary endpoint (30-day mortality) was assessed using multivariate logistic regression, adjusting for underlying confounding variables. Secondary endpoints of hospital mortality and time to mortality were assessed by Fisher's exact test and the Cox proportional hazards model, respectively. A total of 384 patients were analyzed. Thirty-day mortality was higher for patients receiving inappropriate therapy than for those receiving appropriate empirical therapy (43.8% versus 21.5%; $P = 0.03$). However, there were no statistical differences in 30-day mortality following appropriate empirical combination versus monotherapy after adjusting for baseline APACHE II scores and lengths of hospital stay prior to the onset of bacteremia ($P = 0.55$). Observed hospital mortality was 36.6% for patients administered combination therapy, compared with 28.7% for monotherapy patients ($P = 0.17$). After adjusting for baseline APACHE II scores, the relationship between time to mortality and combination therapy was not statistically significant ($P = 0.59$). Overall, no significant differences were observed for 30-day mortality, hospital mortality, and time to mortality between combination and monotherapy for *P. aeruginosa* bacteremia. Empirical combination therapy did not appear to offer an additional benefit, as long as the isolate was susceptible to at least one antimicrobial agent.**

TABLE 2 Risk factor analysis of 30-day mortality

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.01 (0.99–1.03)	0.24		
Male gender	1.28 (0.77–2.13)	0.34		
Combination therapy	1.14 (0.63–2.04)	0.67		
Length of stay prior to culture	1.01 (1.00–1.01)	0.01	1.01 (1.00–1.02)	0.01
Infection-related APACHE II score	1.10 (1.07–1.15)	<0.01	1.12 (1.08–1.17)	<0.01
Comorbidities				
Cardiovascular conditions	0.41 (0.23–0.73)	<0.01		
Respiratory conditions	1.46 (0.73–2.94)	0.29		
Central nervous system disease	0.63 (0.27–1.48)	0.29		
Renal disease	1.21 (0.72–2.03)	0.48		
Diabetes mellitus	1.51 (0.85–2.67)	0.16		
Immunosuppression	0.80 (0.45–1.42)	0.44		
Liver disease	2.09 (1.05–4.14)	0.04		
Source of bacteremia				
Line	0.63 (0.31–1.31)	0.22		
Lung	1.54 (0.84–2.82)	0.16		
Urine	0.55 (0.27–1.14)	0.11		
Wound	0.97 (0.46–2.06)	0.94		
Abdomen	1.75 (0.86–3.56)	0.12		
Unknown	0.97 (0.52–1.82)	0.94		

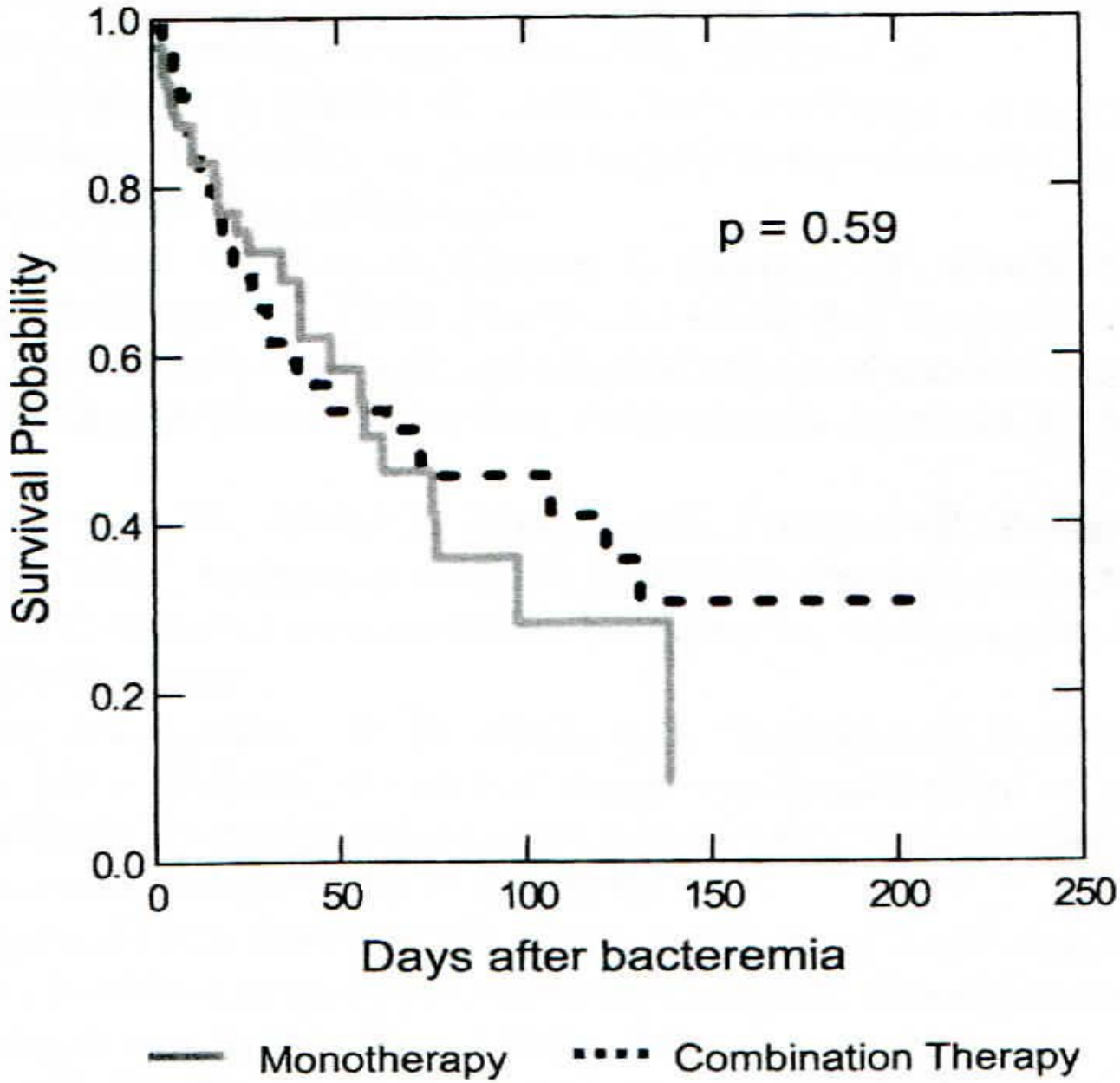

FIG 1 Comparison of times to mortality.

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Outcomes of Appropriate Empiric Combination versus Monotherapy for *Pseudomonas aeruginosa* Bacteremia

Dana R. Bowers,[a,b] Yi-Xin Liew,[c] David C. Lye,[d,e] Andrea L. Kwa,[c] Li-Yang Hsu,[e] Vincent H. Tam[a,b,e]

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MAJOR ARTICLE

CID 2013 57 208

Effect of Adequate Single-Drug vs Combination Antimicrobial Therapy on Mortality in *Pseudomonas aeruginosa* Bloodstream Infections: A Post Hoc Analysis of a Prospective Cohort

Carmen Peña,[1] Cristina Suarez,[1] Alain Ocampo-Sosa,[2] Javier Murillas,[3] Benito Almirante,[4] Virginia Pomar,[5] Manuela Aguilar,[6] Ana Granados,[7] Esther Calbo,[8] Jesús Rodríguez-Baño,[9] Fernando Rodríguez,[10] Fe Tubau,[1] Antonio Oliver,[3] and Luis Martínez-Martínez[2,11]; for the Spanish Network for Research in Infectious Diseases (REIPI)

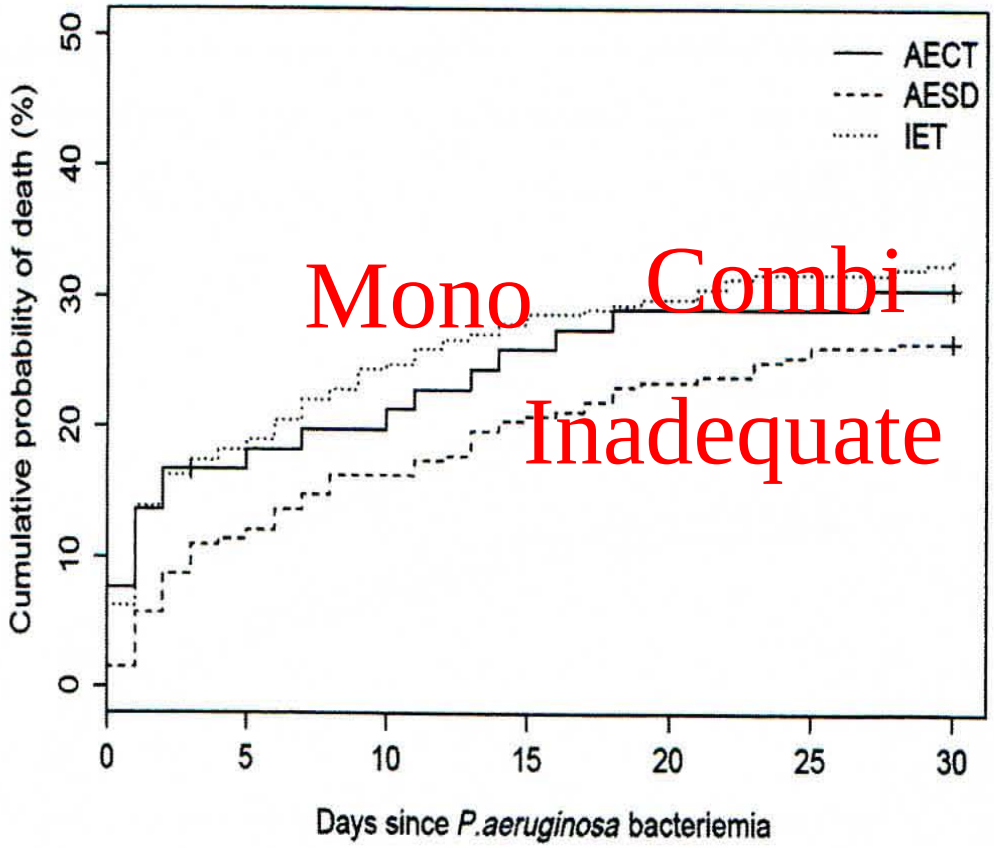

Figure 1. Cumulative risk of death for patients receiving adequate empirical antimicrobial therapy. Abbreviations: AECT, adequate empirical combination therapy; AESD, adequate empirical single-drug therapy; IET, inadequate empirical therapy.

Table 3. Cox Regression Analysis of Relation Between Empirical and Definitive Antimicrobial Therapy and 30-Day Mortality

Characteristic	AHR	95% CI	*P* Value
Empirical antimicrobial therapy			
AECT	1.0 (reference)		
AESD	1.17	.70–1.96	.54
IET	1.70	.99–2.92	.052
Definitive antimicrobial therapy			
ADCT	1.0 (reference)		
ADSD	1.34	.73–2.47	.35
IDT	0.86	.36–2.02	.73

Abbreviations: ADCT, adequate definitive combination therapy; ADSD, adequate definitive single-drug therapy; AECT, adequate empirical combination therapy; AESD, adequate empirical single-drug therapy; AHR, adjusted hazard ratio; CI, confidence interval; IDT, inadequate definitive therapy; IET, inadequate empirical therapy.

Background. Empirical combination therapy is recommended for patients with known or suspected *Pseudomonas aeruginosa* (PA) infection as a means to decrease the likelihood of administering inadequate antimicrobial treatment, to prevent the emergence of resistance, and to achieve a possible additive or even synergistic effect.

Methods. We performed a post hoc analysis of patients with PA bloodstream infections from a published prospective cohort. Mortality was compared in patients treated with adequate empirical and definitive combination therapy (AECT, ADCT), and adequate empirical and definitive single-drug therapy (AESD, ADSD). Confounding was controlled by Cox regression analysis, and a propensity score for rečeiving AECT or ADCT was also used.

Results. The final cohort comprised 593 patients with a single episode of PA bacteremia. The 30-day mortality was 30% (176 patients); 76 patients (13%) died during the first 48 hours. The unadjusted probabilities of survival until day 30 were 69.4% (95% confidence interval [CI], 59.1–81.6) for the patients receiving AECT, 73.5% (95% CI, 68.4%–79.0%) for the AESD group, and 66.7% (95% CI, 61.2%–72.7%) for patients who received inadequate empirical therapy ($P = .17$, log-rank test). After adjustment for confounders, the AESD group (adjusted hazard ratio [AHR], 1.17; 95% CI, .70–1.96; $P = .54$) and patients who received ADSD (AHR, 1.34; 95% CI, .73–2.47; $P = .35$) showed no association with 30-day mortality compared with the AECT and ADCT groups, respectively.

Conclusions. These results suggests that treatment with combination antimicrobial therapy did not reduce the mortality risk compared with single-drug therapy in PA bloodstream infections.

Keywords. bloodstream infections; *P. aeruginosa*; combination antimicrobial therapy; mortality.

EDITORIAL COMMENTARY

Combination Therapy for *Pseudomonas aeruginosa* Bacteremia: Where Do We Stand?

Mical Paul[1,2] and Leonard Leibovici[2,3]

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(See the Major Article by Peña et al on pages 208–16.)

Study or Subgroup	Combination therapy Events	Total	Monotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Igra 1998	7	15	7	42	2.9%	4.38 [1.19, 16.04]
Mendelson 1994	1	7	2	5	2.9%	0.25 [.02, 4.00]
Kuikka 1998	11	41	6	21	8.5%	0.92 [.28, 2.96]
Bliziotis 2011	6	31	8	19	11.7%	0.33 [.09, 1.18]
Chamot 2003	10	46	9	33	12.0%	0.74 [.26, 2.09]
Micek 2005	13	59	14	92	12.5%	1.57 [.68, 3.64]
Leibovici 1997	16	77	20	95	20.7%	0.98 [.47, 2.06]
Peña 2013	13	71	70	339	28.9%	0.86 [.45, 1.66]
Total (95% CI)		**347**		**646**	**100.0%**	**0.99 [.70, 1.38]**
Total events	77		136			

Heterogeneity: $\chi^2 = 10.50$, $df = 7$ ($P = .16$); $I^2 = 33\%$

Test for overall effect: $Z = 0.08$ ($P = .94$)

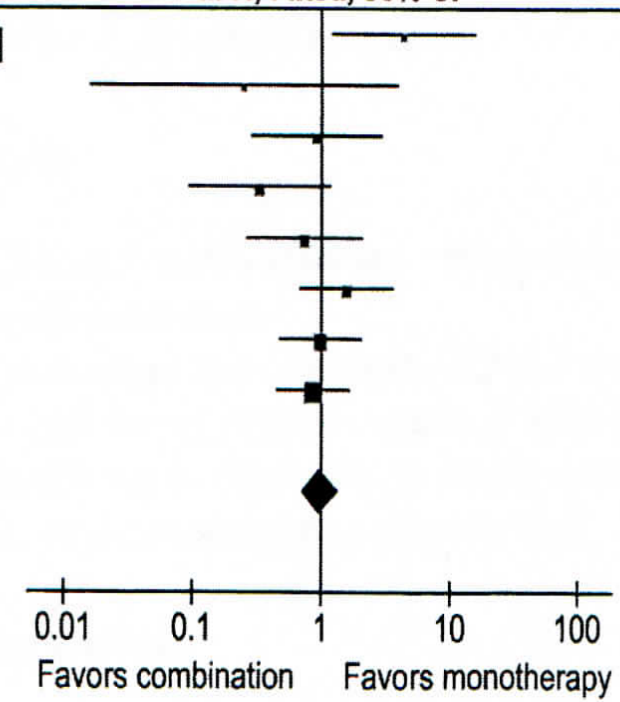

Figure 2. All-cause mortality with definitive combination versus monotherapy, unadjusted results. Studies are labeled by name of first author and year of publication. Odds ratios are pooled using the fixed-effect model. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

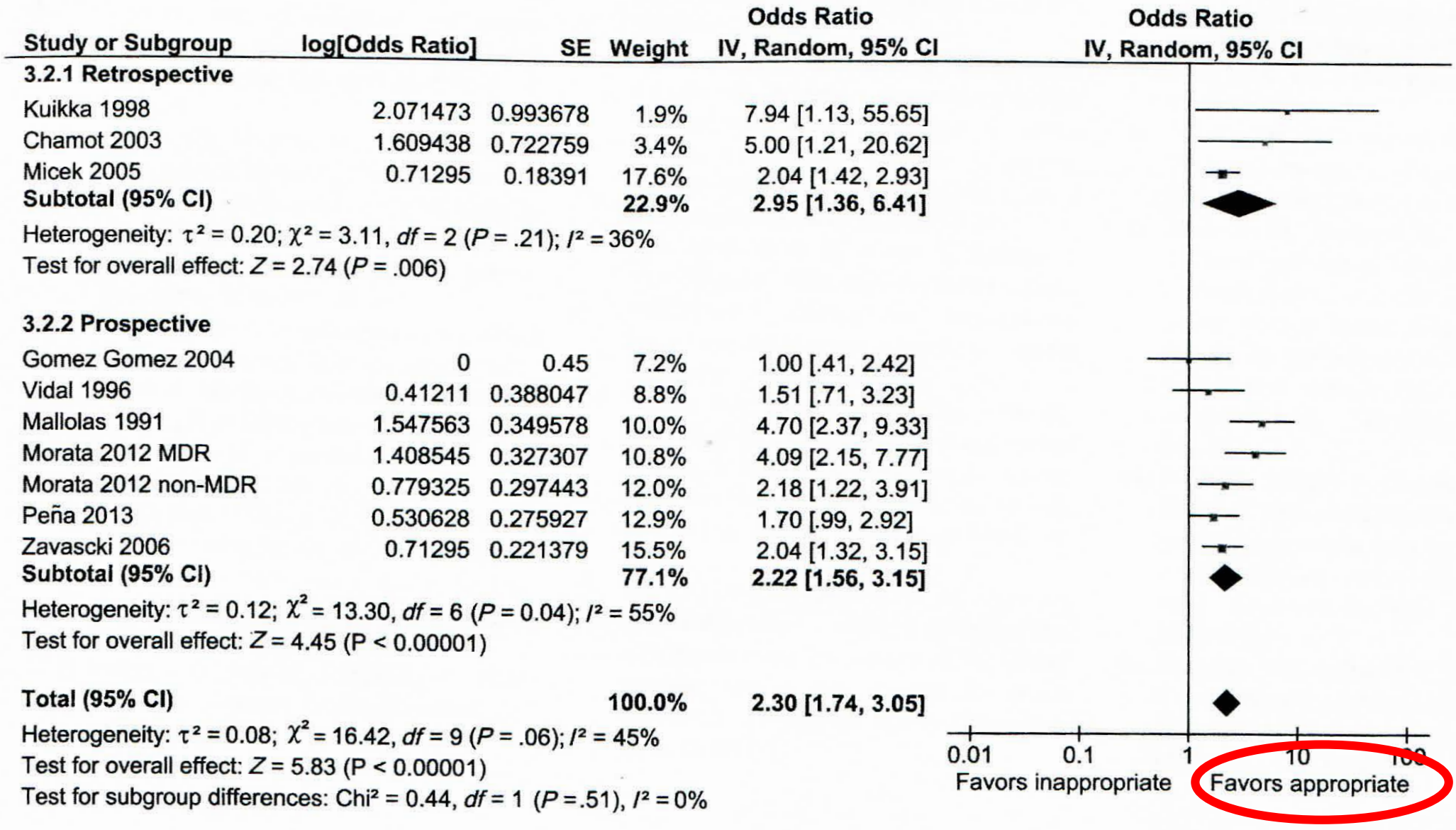

Figure 3. All-cause mortality with inappropriate versus appropriate empiric antibiotic treatment, adjusted results. Studies are labeled by name of first author and year of publication. Odds ratios are pooled using the random-effects model, due to heterogeneity present in the analysis. Abbreviations: CI, confidence interval; IV, inverse variance; MDR, multi-drug resistant; SE, standard error.

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0066-4804/10/$12.00 doi:10.1128/AAC.01365-09

Empiric Combination Antibiotic Therapy Is Associated with Improved Outcome against Sepsis Due to Gram-Negative Bacteria: a Retrospective Analysis▽

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The optimal approach for empirical antibiotic therapy in patients with severe sepsis and septic shock remains controversial. A retrospective cohort study was conducted in the intensive care units of a university hospital. The data from 760 patients with severe sepsis or septic shock associated with Gram-negative bacteremia was analyzed. Among this cohort, 238 (31.3%) patients received inappropriate initial antimicrobial therapy (IIAT). The hospital mortality rate was statistically greater among patients receiving IIAT compared to those initially treated with an appropriate antibiotic regimen (51.7% versus 36.4%; $P < 0.001$). Patients treated with an empirical combination antibiotic regimen directed against Gram-negative bacteria (i.e., β-lactam plus aminoglycoside or fluoroquinolone) were less likely to receive IIAT compared to monotherapy (22.2% versus 36.0%; $P < 0.001$). The addition of an aminoglycoside to a carbapenem would have increased appropriate initial therapy from 89.7 to 94.2%. Similarly, the addition of an aminoglycoside would have increased the appropriate initial therapy for cefepime (83.4 to 89.9%) and piperacillin-tazobactam (79.6 to 91.4%). Logistic regression analysis identified IIAT (adjusted odds ratio [AOR], 2.30; 95% confidence interval [CI] = 1.89 to 2.80) and increasing Apache II scores (1-point increments) (AOR, 1.11; 95% CI = 1.09 to 1.13) as independent predictors for hospital mortality. In conclusion, combination empirical antimicrobial therapy directed against Gram-negative bacteria was associated with greater initial appropriate therapy compared to monotherapy in patients with severe sepsis and septic shock. Our experience suggests that aminoglycosides offer broader coverage than fluoroquinolones as combination agents for patients with this serious infection.

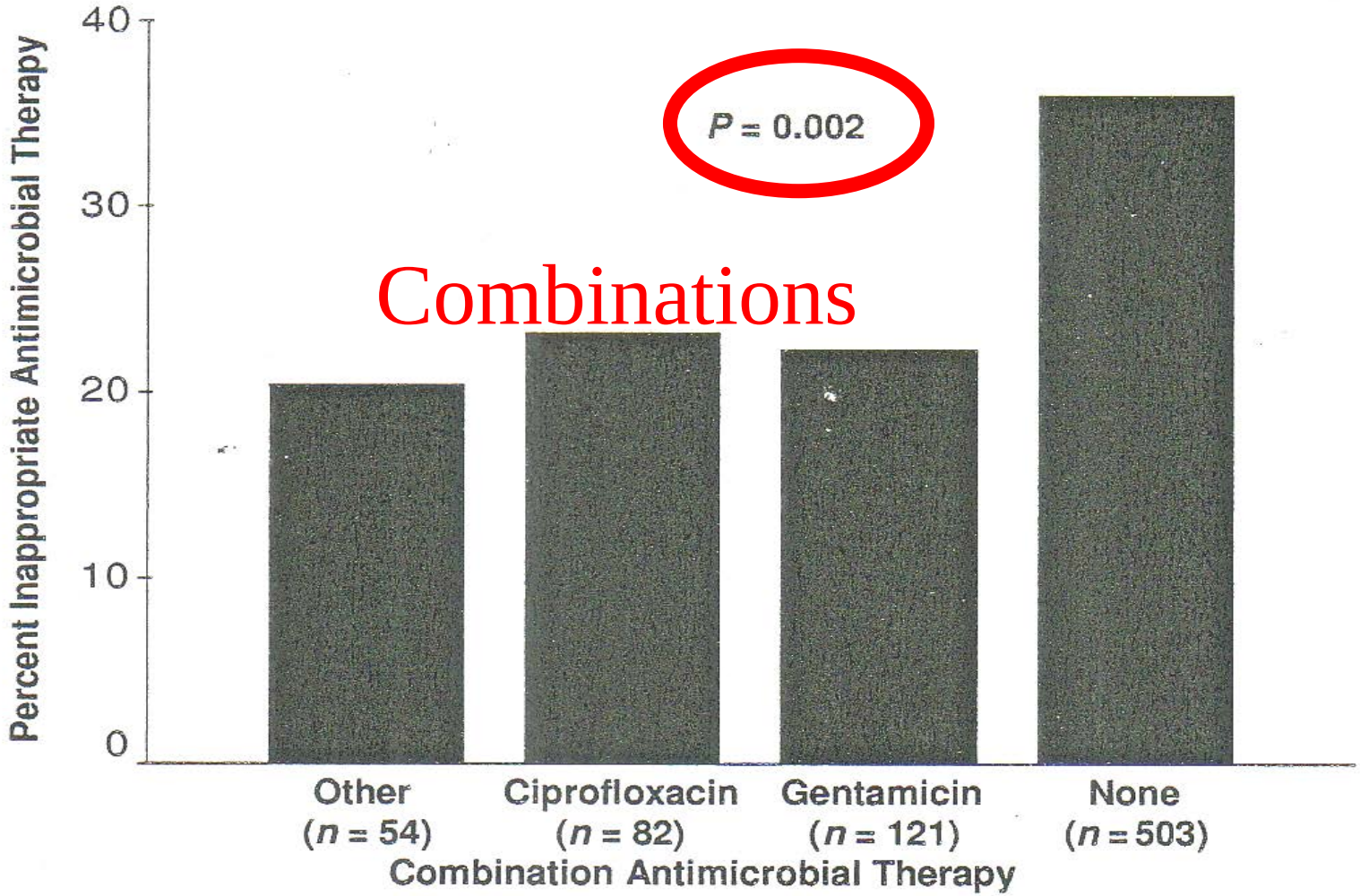

FIG. 1. Percent of patients receiving inappropriate initial antimicrobial therapy (IIAT) according to combination antimicrobial treatment. Other combination antimicrobial therapy included double β-lactam (non-carbapenem) combinations ($n = 33$), β-lactam carbapenem combinations ($n = 16$), and combinations including either tigecycline or colistin ($n = 5$).

REASONS TO USE ANTIBIOTIC COMBINATIONS

- **Broader coverage**
- **Antimicrobial synergism**
- **Increased bacterial killing**
- **Decrease in antimicrobial resistance**

Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia*

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Objective: To compare a strategy of combination therapy with a strategy of monotherapy with broad-spectrum antibiotics for suspected late ventilator-associated pneumonia.

Design: Randomized trial.

Setting: Twenty-eight intensive care units in Canada and the United States.

Patients: The study included 740 mechanically ventilated patients who developed suspected ventilator-associated pneumonia after 96 hrs in the intensive care unit. Patients known to be colonized or infected with *Pseudomonas* or methicillin-resistant *Staphylococcus aureus* or who were immunocompromised were excluded from the study.

Interventions: As initial unblinded therapy, patients were allocated to receive meropenem (1 g every 8 hrs) and ciprofloxacin (400 mg every 12 hrs) or meropenem alone. Before starting antibiotics, patients were also randomized to bronchoalveolar lavage with quantitative cultures or endotracheal aspirates. When culture results were available, physicians were encouraged to adjust antibiotics. Adequacy of antibiotics was defined as the organism present in the enrollment culture having *in vitro* susceptibility to one or more of the study antibiotics.

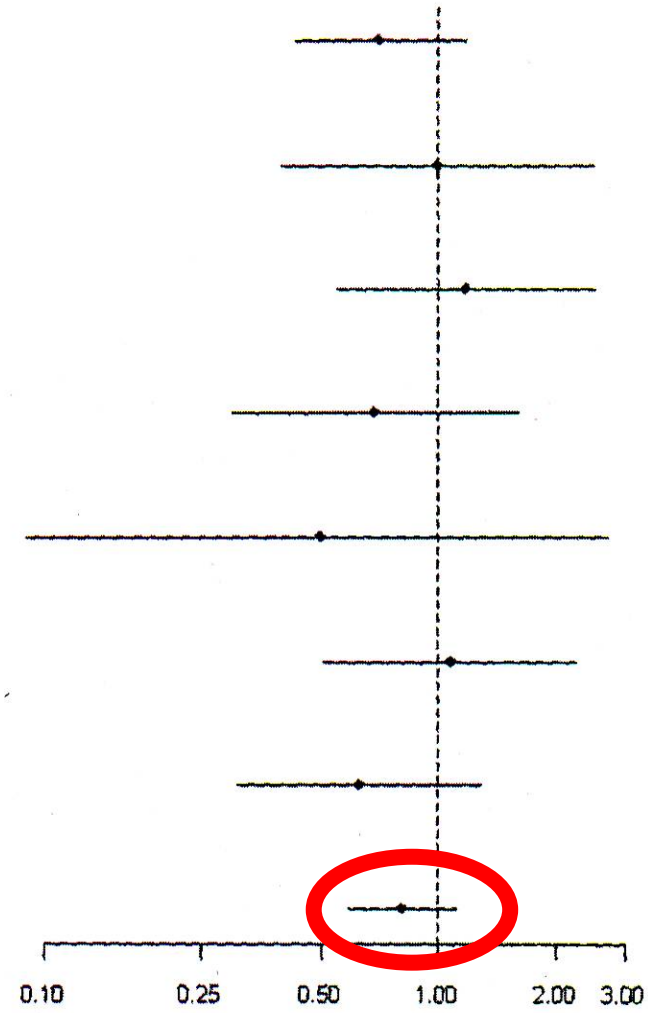
Measurements and Main Results: Baseline characteristics and etiologies of ventilator-associated pneumonia were similar in the two groups. There was no difference in 28-day mortality between the combination and monotherapy groups (relative risk = 1.05, 95% confidence interval 0.78–1.42, $p = .74$). Duration of intensive care unit and hospital stay, clinical and microbiological treatment response, emergence of antibiotic-resistant bacteria, isolation of *Clostridium difficile* in stool, and fungal colonization were also similar in the two groups. In a subgroup of patients who had infection due to *Pseudomonas* species, *Acinetobacter* species, and multidrug-resistant Gram-negative bacilli at enrollment (n = 56), the adequacy of initial antibiotics (84.2% vs. 18.8%, $p < .001$) and microbiological eradication of infecting organisms (64.1% vs. 29.4%, $p = .05$) was higher in the combination group compared with the monotherapy group, but there were no differences in clinical outcomes.

Conclusions: For critically ill patients who have suspected late ventilator-associated pneumonia and who are at low risk for difficult-to-treat Gram-negative bacteria, monotherapy is associated with similar outcomes compared with combination therapy. For those patients at high risk of difficult-to-treat Gram-negative bacteria, combination therapy is safe and may be associated with better microbiological and clinical outcomes. (Crit Care Med 2008; 36:737–744)

KEY WORDS: ventilator-associated pneumonia; antibiotics; empirical therapy; combination therapy; randomized controlled trial; outcomes; broad spectrum antimicrobials

Table 5. Frequency of organisms acquired after randomization

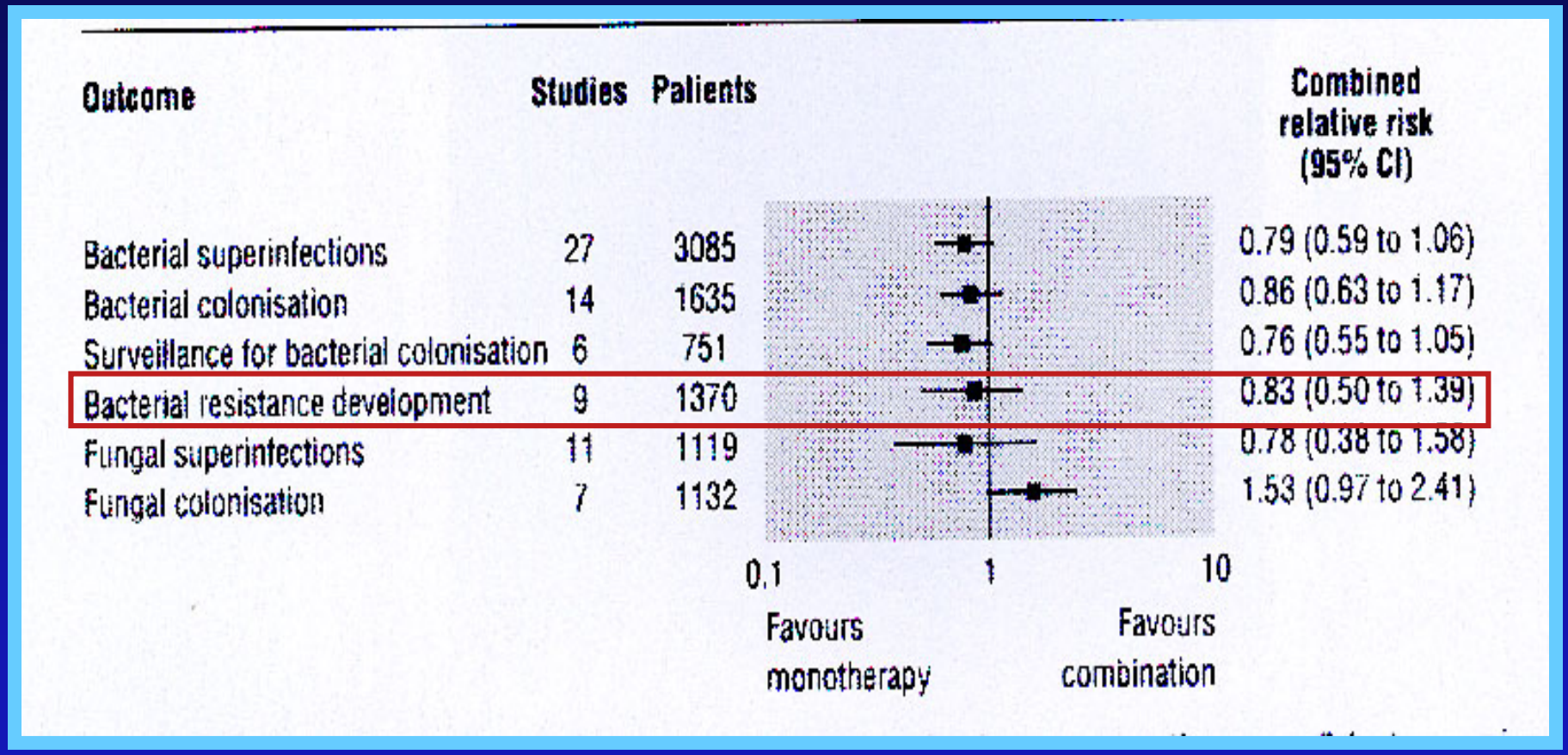
Organism	Combination Therapy (n = 369)	Monotherapy (n = 370)	All (n = 739)	Combo/Mono RR (95% CI)[a]
Pseudomonas species	25 (6.8)	35 (9.5)	60 (8.1)	
Acinetobacter species	9 (2.4)	9 (2.4)	18 (2.4)	
Methicillin-resistant *Staphylococcus aureus*	14 (3.8)	12 (3.2)	26 (3.5)	
Stenotrophomonas maltophilia	9 (2.4)	13 (3.5)	22 (3.0)	
Vancomycin-resistant *Enterococcus*	2 (0.5)	4 (1.1)	6 (0.8)	
Yeast species	14 (3.8)	13 (3.5)	27 (3.7)	
Multidrug-resistant Gram-negative bacteria	12 (3.3)	19 (5.1)	31 (4.2)	
Total high risk[b]	57 (15.4)	71 (19.2)	128 (17.3)	



RR, relative risk; CI, confidence interval.

[a]RR and 95% CI estimated by the Mantel-Haenszel method stratified by Acute Physiology and Chronic Health Evaluation II score (≤24 vs. >24) and diagnostic technique (endotracheal aspirates vs. bronchoalveolar lavage); [b]includes *Acinetobacter* species, *Pseudomonas* species, methicillin-resistant *S. aureus, S. maltophilia* and multiresistant organisms. They do not add up to the individual row totals, because some of the *Pseudomonas* species and *Acinetobacter* species are multidrug-resistant pathogens as well. Values are n (%).

Bacterial Resistance Development ?



Paul et al BMJ 2004, Online First bmj.com

Treatment of serious infections

Contract with the patient : to give the most appropriate empirical therapy.

Contract with the community : reevaluate therapy; de-escalate to antibiotics :

- **. cheaper**
- **. narrow spectrum**
- **. lower toxicity**

Take Home Messages

- High expected mortality : >25 %
- Septic shock and severe sepsis
- AMG > quinolones
- Pseudomonas ???
- Re - evaluation on day 3 – 5
- In the ICU never exceed 5 days

Broad-spectrum Empirical Therapy for 72h Does not Lead to Emergence of resistance

- Prospective study. 19 - month study period
- Imipenem + gentamicin for 72 hours for suspected sepsis, while awaiting culture

Namias et al
J. Trauma
1998, 45,
887

Early period	Late period
Imipenem sensitive	**Imipenem sensitive**
All bacteria 76% P. aeruginosa 62%	80% 88% $p < 0.007$
Genta sensitive	**Genta sensitive**
All bacteria 70%	79%
Cefta sensitive	**Cefta sensitive**
All bacteria 74%	73%