Combination antimicrobial treatment for MDR Gram-positive infections

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Potential advantages of combination antimicrobial treatment

- Increased effectiveness (mainly due to synergistic antimicrobial activity)
- Wider spectrum of antimicrobial activity
- Inhibition or delay of emergence of antimicrobial resistance

Potential disadvantages of combination antimicrobial treatment

- Increased adverse events
- Increased pressure for development / selection of antimicrobial resistance
- Increased cost of antimicrobial treatment

- The significance of the combination of antibiotics has been proven in the treatment of patients with tuberculosis

- Also, the combination of anti-retroviral drugs has been proven as a life saving strategy in patients with HIV infection

- However, various combinations of antibiotics, although commonly used in clinical practice for the treatment of various infections in many patient populations, are not supported by clear, evidence based data from clinical trials

Combination antimicrobial treatment

- Available data from studies using various methods
- Laboratory in vitro antimicrobial susceptibility studies (synergism, indifference, antagonism)
- Experimental studies of comparative efficacy of combination treatment (animal models)
- Clinical studies using various methods

- We tried to contribute to the relevant literature by generating evidence based data on the role of combination of antibiotics with a series of meta-analyses and systematic reviews of clinical trials (mainly randomized controlled trials)

Value of combination antimicrobial treatment for bacterial infections

There are several important clinical questions

- Is combination antimicrobial treatment beneficial for patients with infections due to common bacterial pathogens?
- Is the addition of an aminoglycoside to a beta-lactam associated with reduction of emergence of resistance?
- Could a quinolone replace an aminoglycoside in the combination treatment with a beta-lactam?

Is combination antimicrobial treatment beneficial for serious bacterial infections?

- Most relevant analyses have not shown better results with combination antimicrobial treatment compared with broad-spectrum beta-lactam monotherapy
  - Paul M. *et al*. *BMJ* 2004;328:668 (beta-lactam monotherapy versus beta-lactam – aminoglycoside combination therapy in immunocompetent patients)
  - Cunha BA. *Crit Care* 2006;10:141 (ventilator associated pneumonia: monotherapy is optimal if chosen wisely)
- A specific population that deserves further study on this issue is patients with *P. aeruginosa* bacteremia

Is there a way to decrease the rate of emergence of resistance when administering a beta-lactam?

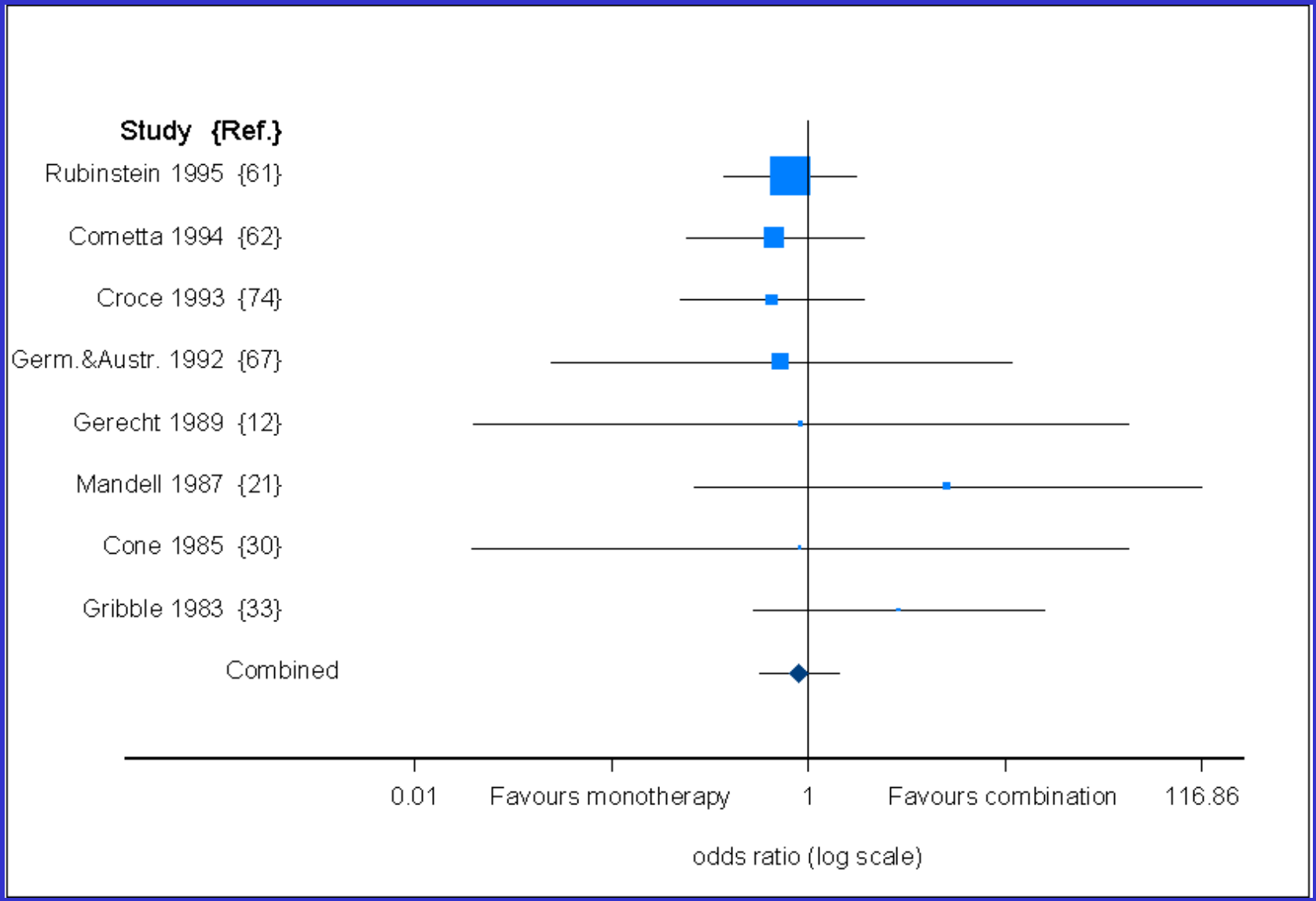
A frequently stated position is that the addition of an aminoglycoside to a beta-lactam antibiotic leads to a decrease in the development of antimicrobial resistance

Effect of aminoglycoside/beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: A meta-analysis of randomised controlled trials

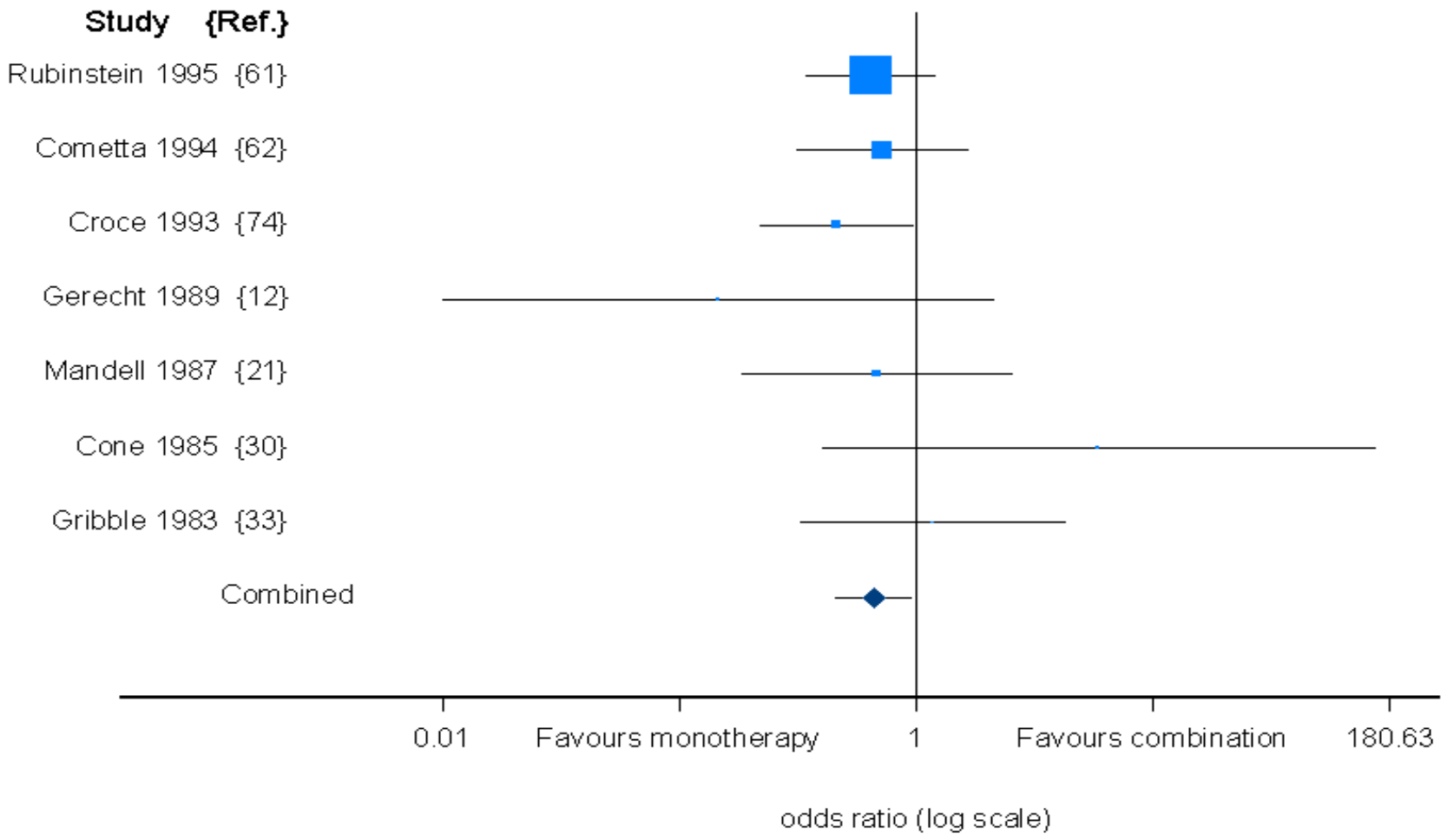
Bliziotis IA, *et al*.

Clin Infect Dis 2005;41:149-58.

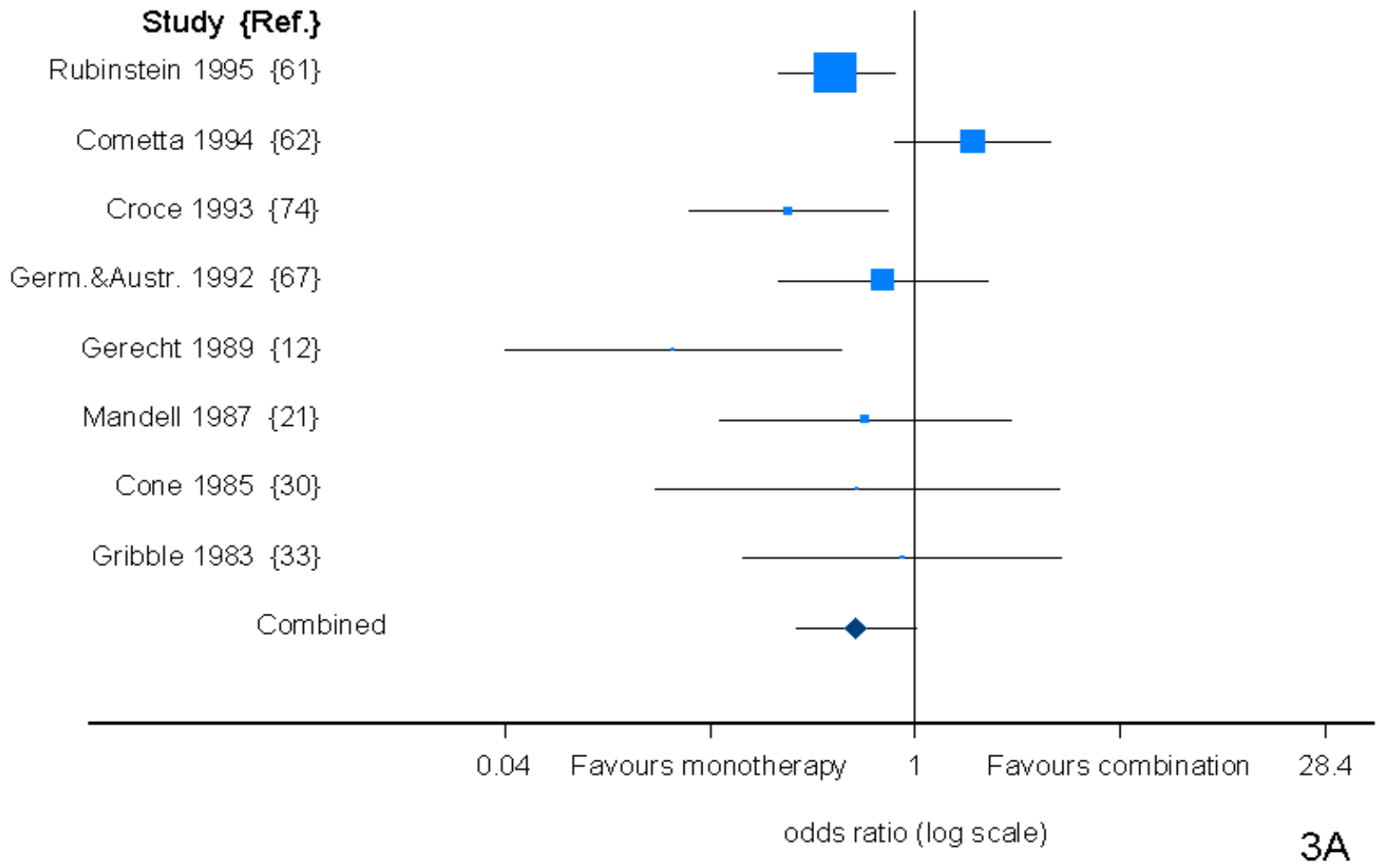
Emergence of antimicrobial resistance



Development of superinfections



Treatment failure due to any reason



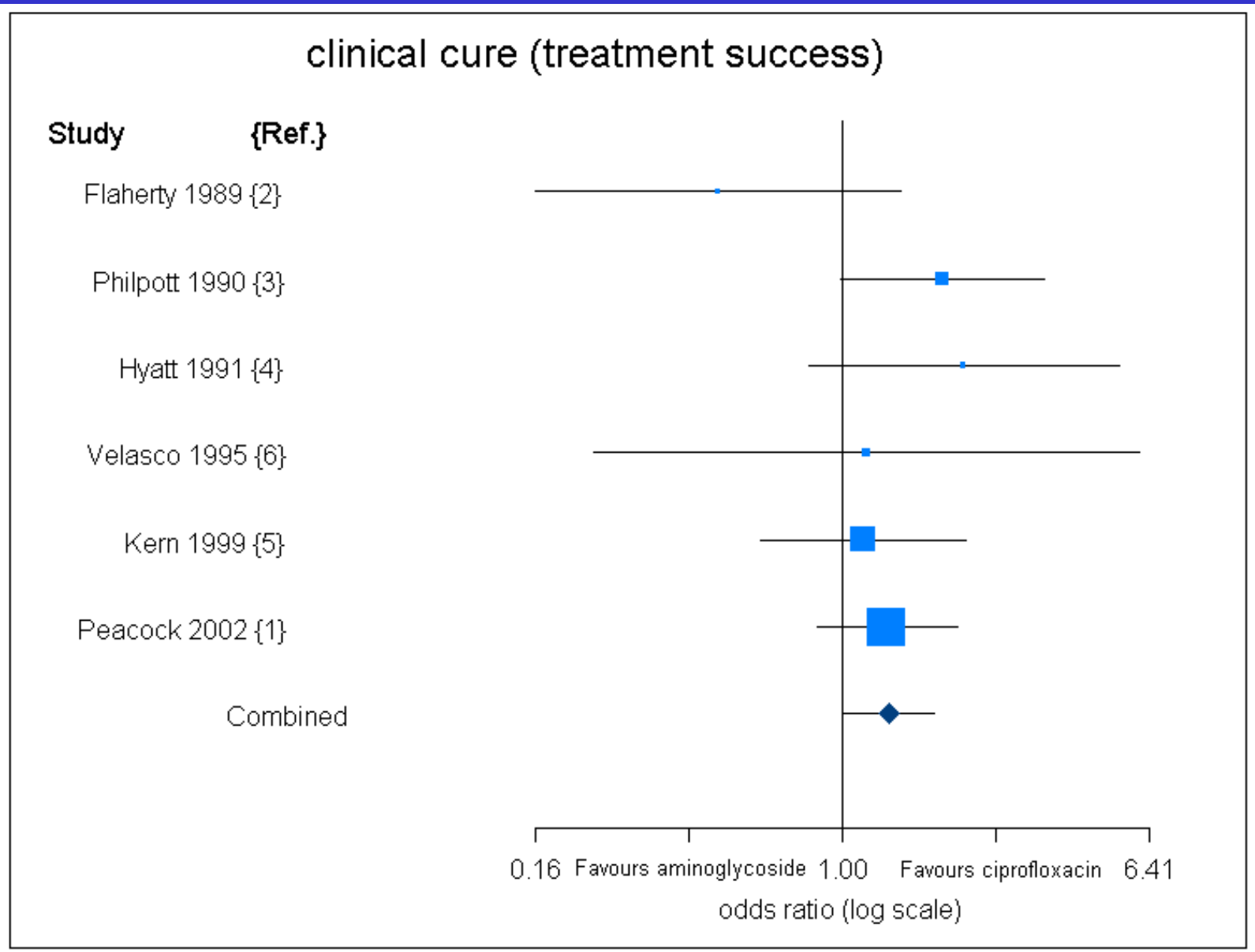
In neutropenic patients with fever, could a quinolone replace an aminoglycoside as a companion to a beta-lactam antibiotic?

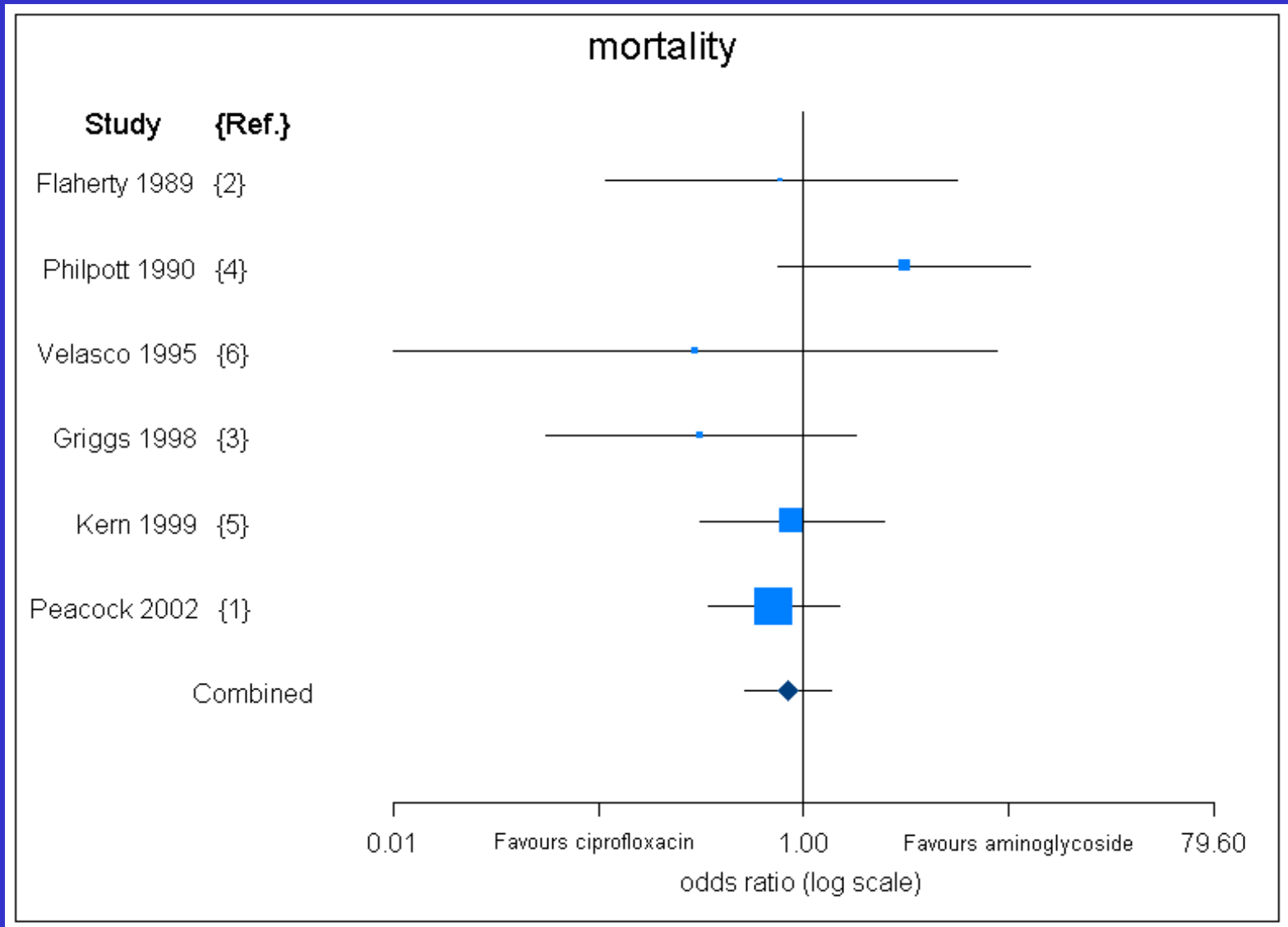
We performed a meta-analysis of 8 relevant RCTs to try to answer this question

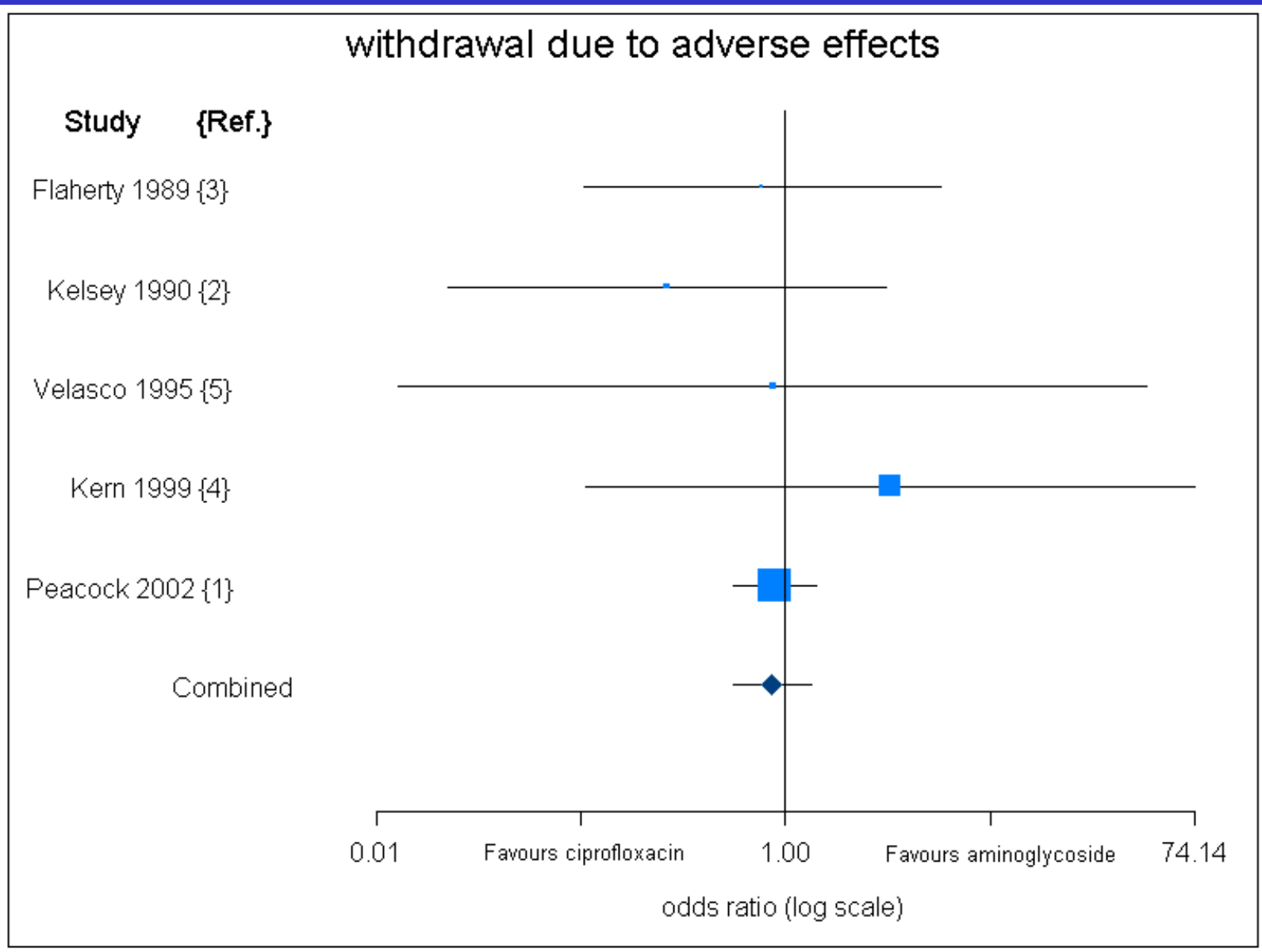
Ciprofloxacin versus an aminoglycoside as combination therapy to a beta-lactam for the treatment of febrile neutropenia: A meta-analysis of randomised controlled trials

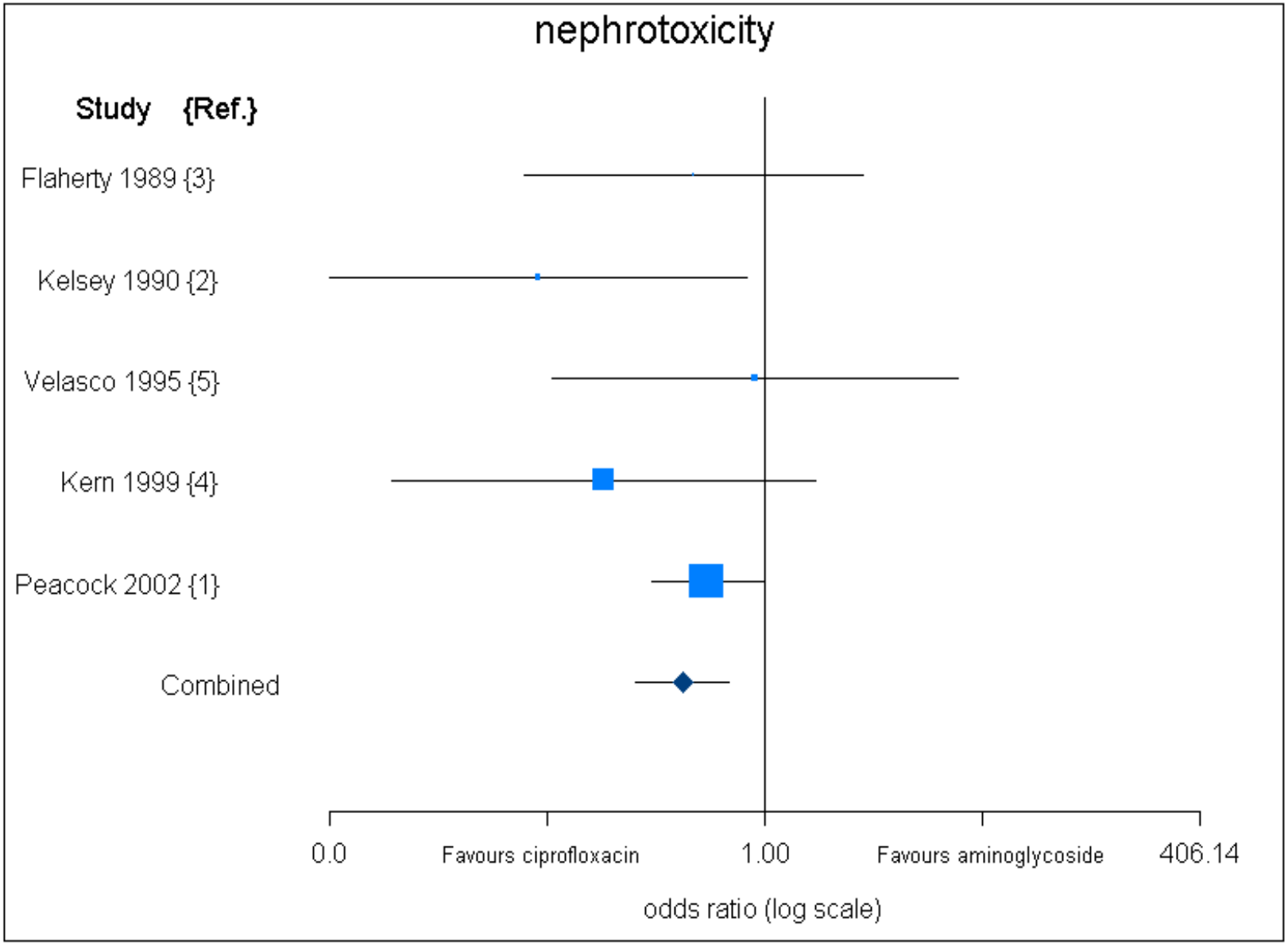
Bliziotis IA, *et al*.

Mayo Clin Proc 2005;80:1146-56.


clinical cure (treatment success)
Study {Ref.}
Flaherty 1989 {2}
Philpott 1990 {3}
Hyatt 1991 {4}
Velasco 1995 {6}
Kern 1999 {5}
Peacock 2002 {1}
Combined
0.16 Favours aminoglycoside 1.00 Favours ciprofloxacin 6.41
odds ratio (log scale)


mortality
Study
{Ref.}
Flaherty 1989 {2}
Philpott 1990 {4}
Velasco 1995 {6}
Griggs 1998 {3}
Kern 1999 {5}
Peacock 2002 {1}
Combined
0.01
Favours ciprofloxacin
1.00
Favours aminoglycoside
79.60
odds ratio (log scale)


withdrawal due to adverse effects
Study {Ref.}
Flaherty 1989 {3}
Kelsey 1990 {2}
Velasco 1995 {5}
Kern 1999 {4}
Peacock 2002 {1}
Combined
0.01
Favours ciprofloxacin
1.00
Favours aminoglycoside
74.14
odds ratio (log scale)


nephrotoxicity
Study {Ref.}
Flaherty 1989 {3}
Kelsey 1990 {2}
Velasco 1995 {5}
Kern 1999 {4}
Peacock 2002 {1}
Combined
0.0
Favours ciprofloxacin
1.00
Favours aminoglycoside
406.14
odds ratio (log scale)

Main finding

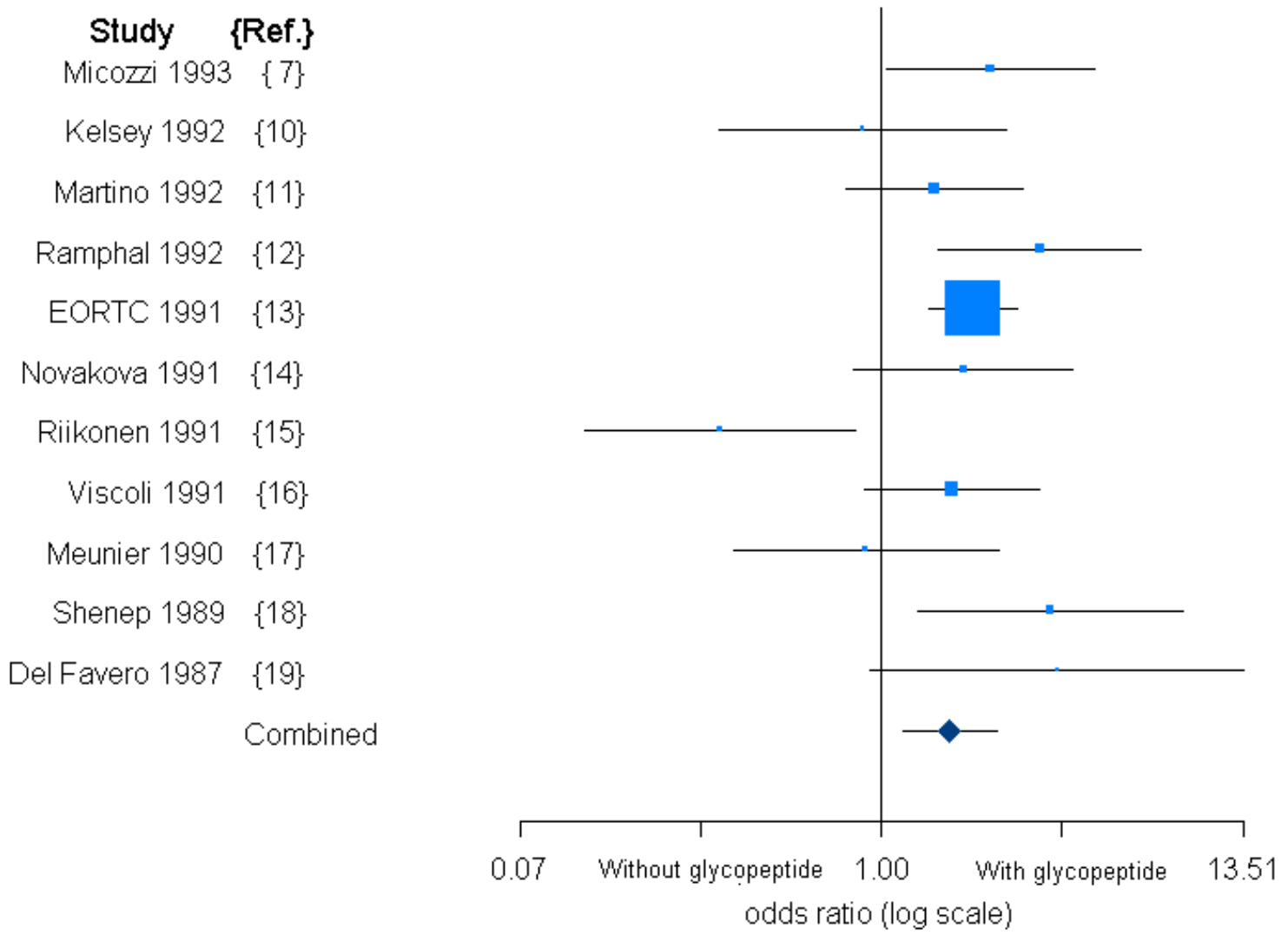
The available evidence suggests that when a combination of an antibiotic with a beta-lactam is considered necessary in hospitalized febrile neutropenic patients, use of ciprofloxacin (instead of an aminoglycoside) is an important therapeutic option, especially for patients who have not been receiving a quinolone for prevention of infections

The role of glycopeptides as part of initial empirical treatment of febrile neutropenic patients: a meta-analysis of randomized controlled trials

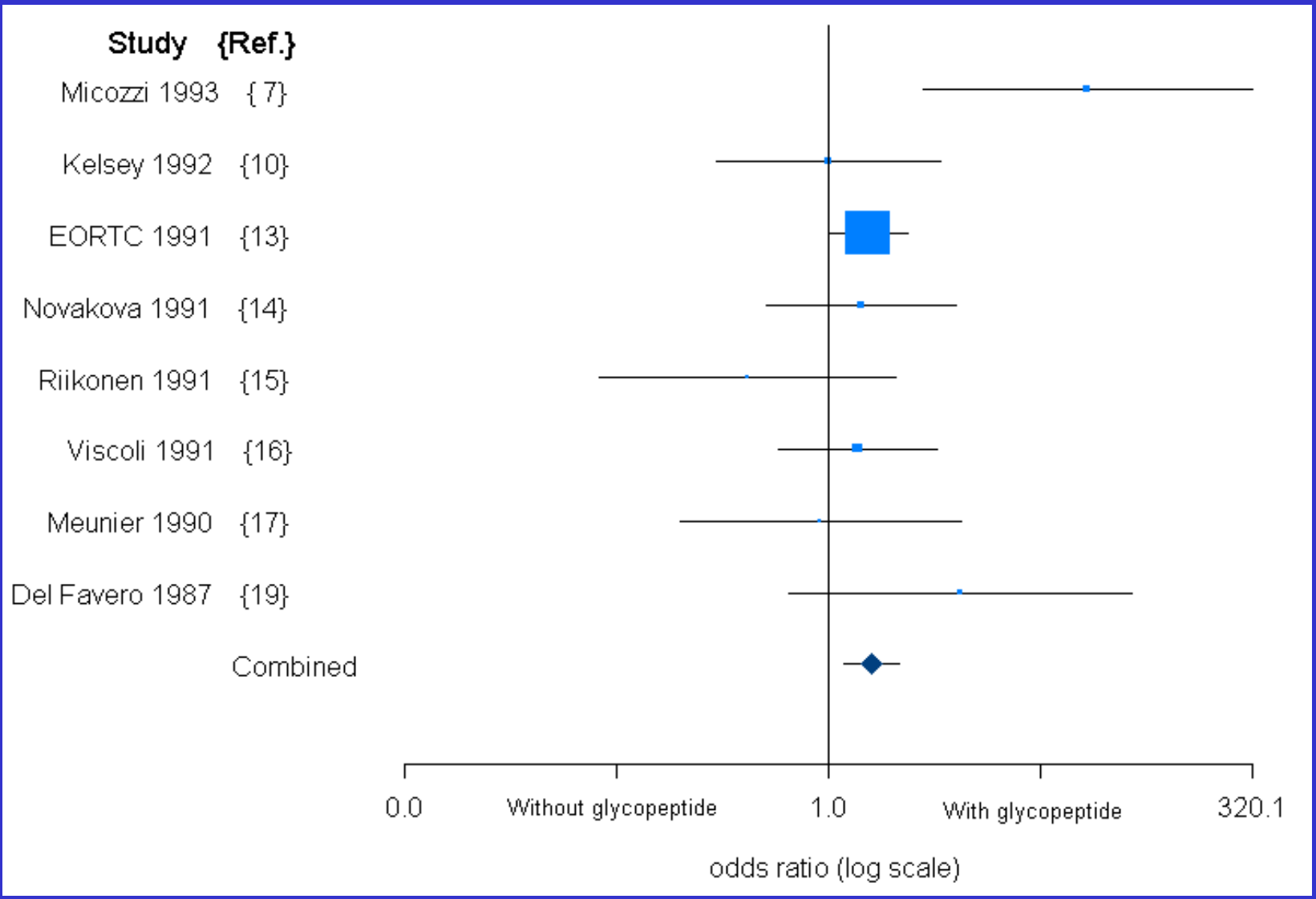
Vardakas KZ, *et al*.

Lancet Infect Dis 2005;5:431-9.

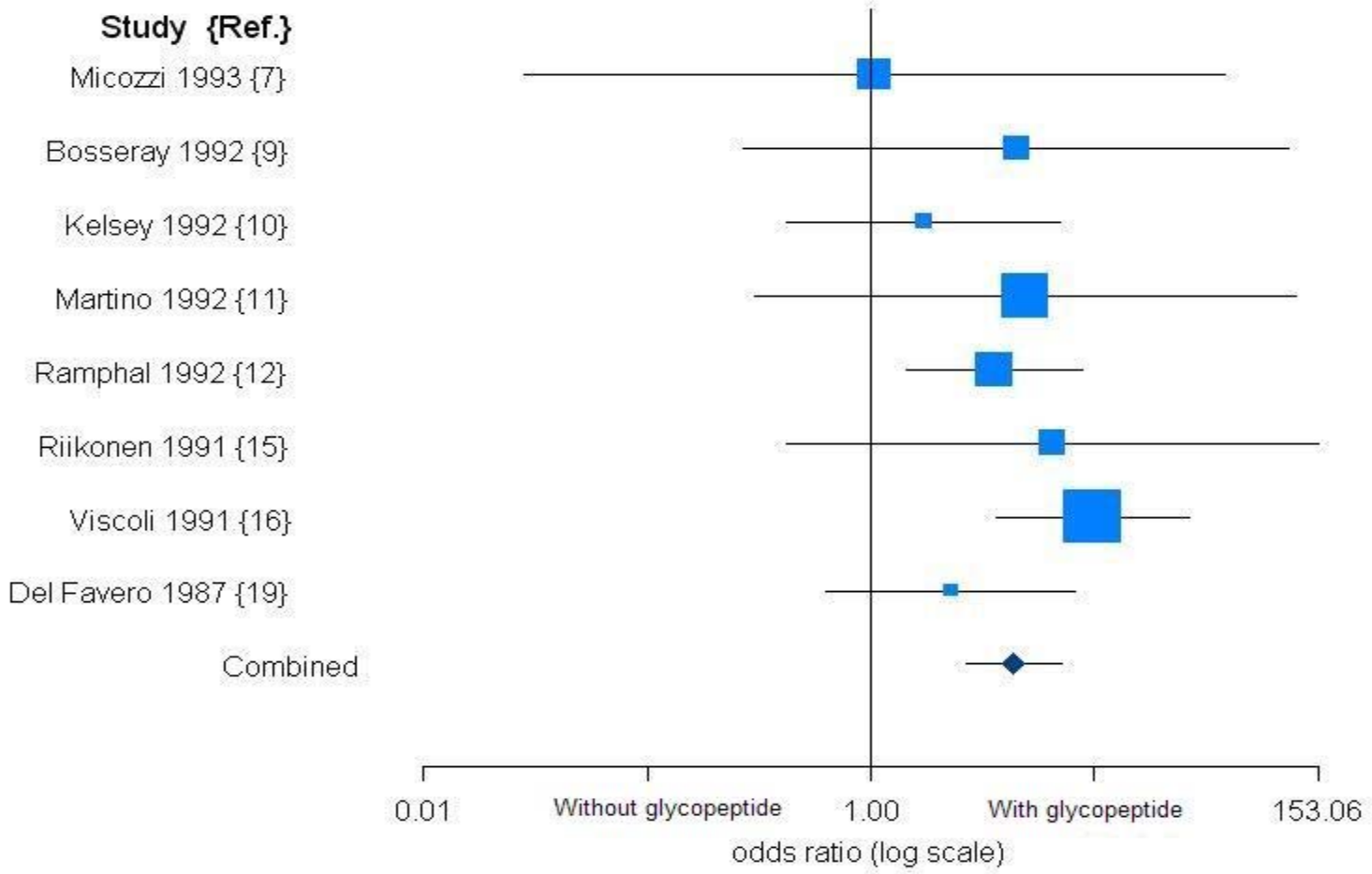
Treatment success



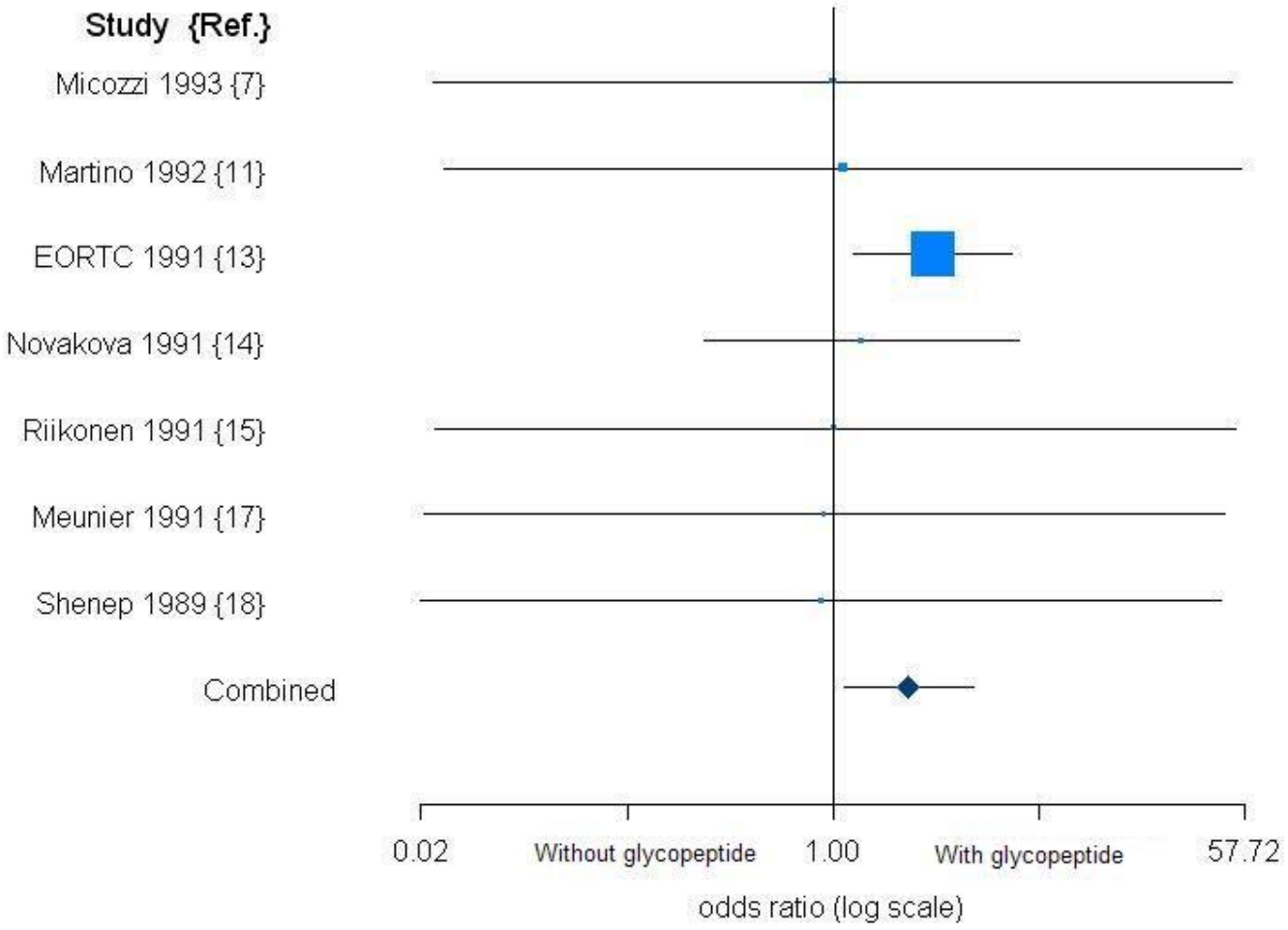
Patients with bacteremia



Adverse events



Nephrotoxicity

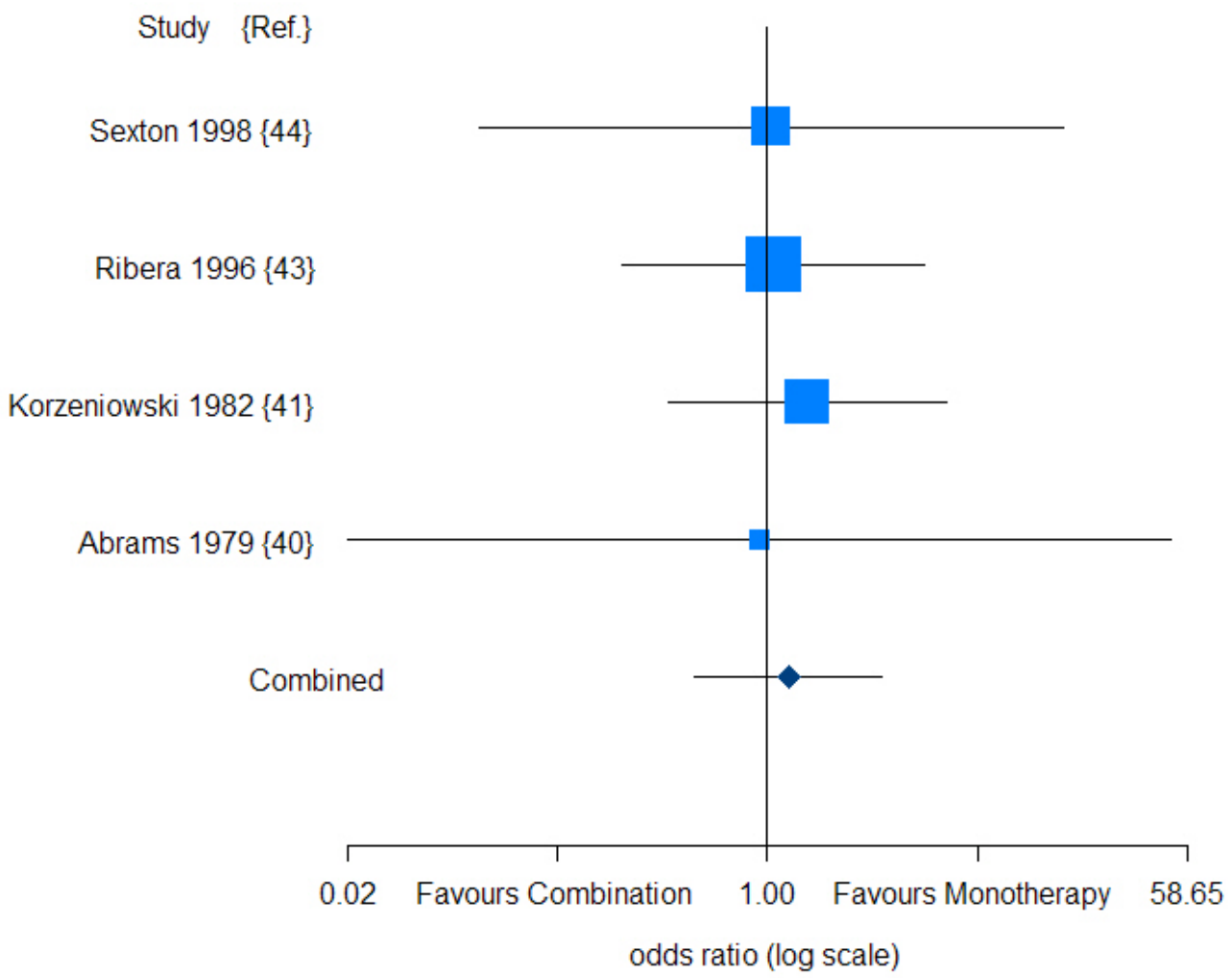


The role of aminoglycosides in combination with a β-lactam for the treatment of bacterial endocarditis: a meta-analysis of comparative trials

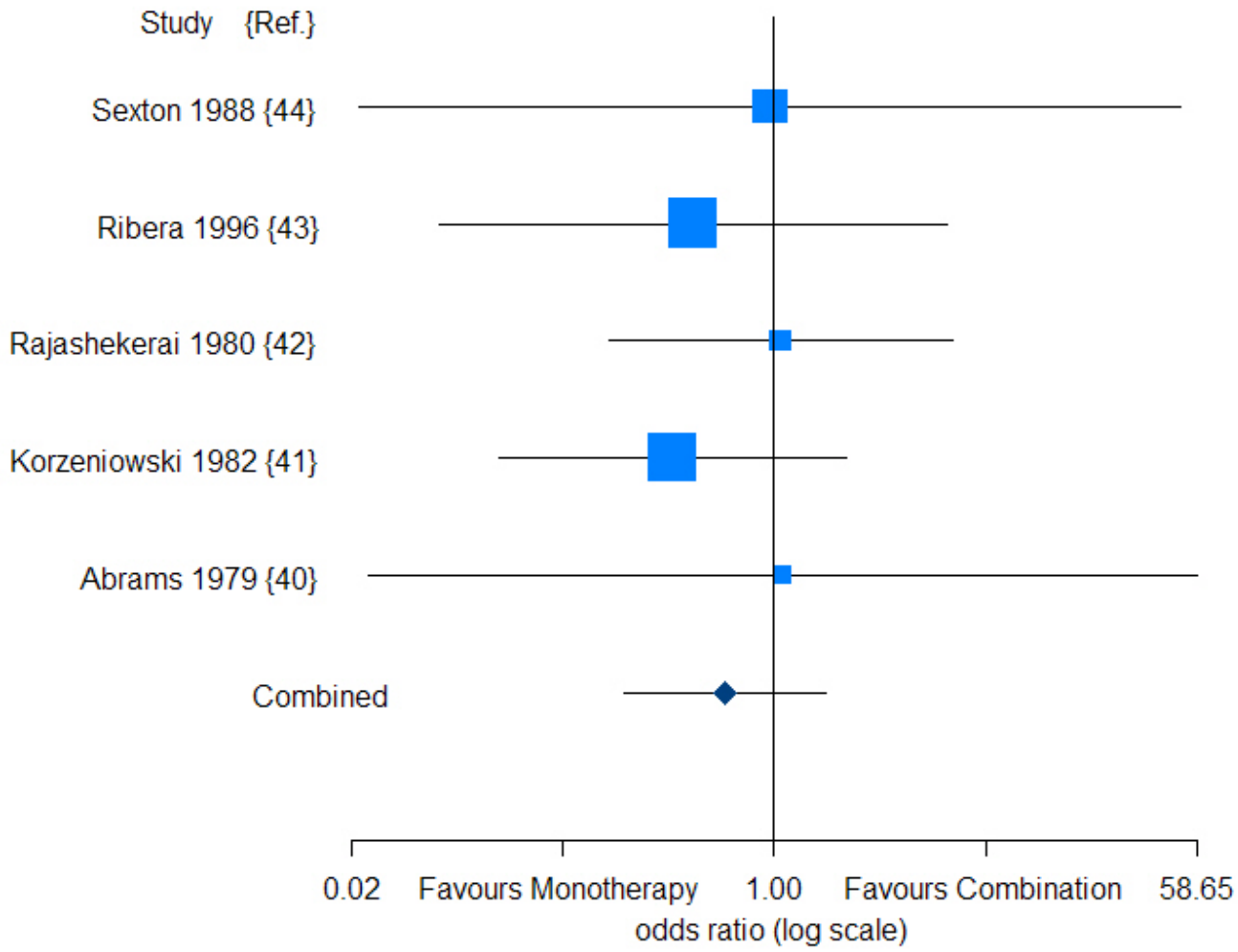
Falagas ME, *et al.*

J Antimicrob Chemother 2006;57:639-47.

Clinical cure



All cause mortality



The role of rifampin

- Supportive data from synergistic in vitro antimicrobial susceptibility studies
- Common use of combination treatment including rifampin against staphylococcal infections
- Limited available clinical data (published)
- Main role in combination antimicrobial treatment of infections related to foreign bodies

Bliziotis IA, *et al*.
Eur J Clin Microbiol Infect Dis 2007;26:849-56.

Fosfomycin

- Among the recommended options for urinary and gastrointestinal tract infections
- A potential option for infections in other sites also
- Emergence of resistance during treatment is a concern

Falagas ME, *et al.*

Clin Infect Dis 2008;46:1069-77.