

28th

ECCMID

Madrid, Spain
21–24 April 2018



ESCMID

MANAGING INFECTIONS
PROMOTING SCIENCE

Preparing the future ESCMID guideline on infections due to MDR Gram-negative bacteria - a case-based discussion

Discussion panel:

Jesús Rodríguez-Baño

Jan de Waele

Mical Paul

Pilar Retamar

Evelina Tacconelli

All panel:

**No conflicts of
interests**

Case 3

- ▶ 78 year-old man

Background:

No allergies, diabetes mellitus, smoker

Present admission:

Radical cystectomy (urothelial carcinoma), robotic, elective

Day 5: catheter-related BSI due to *Pseudomonas aeruginosa* resistant to quinolones

- Catheter removed
- Ceftazidime treatment

Case 3

- ▶ **Day 10:** new fever
- ▶ Physical examination: BP 97/54 mmHg, heart rate 92/min, respiratory rate 16 min. Suppurative wound and drainage.
- ▶ Tests:
 - WBC: 16500 leukocytes (89% neutrophils), C-reactive protein: 149 mg/dL, lactate 2 mmol/L, creatinine 1.8 mg/dL, urine (catheter) with leukocytes ++
 - Blood cultures
 - Abdomen CT: collection in operated area
 - Surgical drainage performed; sample sent for culture
 - Ceftazidime switched to piperacillin-tazobactam, vancomycin added

Case 3

Abscess and blood culture:

CULTIVO

SE AISLA:

(1) *Acinetobacter baumannii*.

Antimicrobiano	S/I/R	CMI (ug/ml)
Ampicilina/Sulbactam	R	>16/8
Piperacilina/Tazobac	R	>64
Ceftazidima	R	>16
Cefotaxima	R	>32
Imipenem	R	>=8
Meropenem	R	>=8
Gentamicina	R	>=8
Tobramicina	R	>=8
Amikacina	R	>32
Ciprofloxacino	R	>2
Levofloxacina	R	>4
Colistina	S	<=2

Tigecycline

S

=1

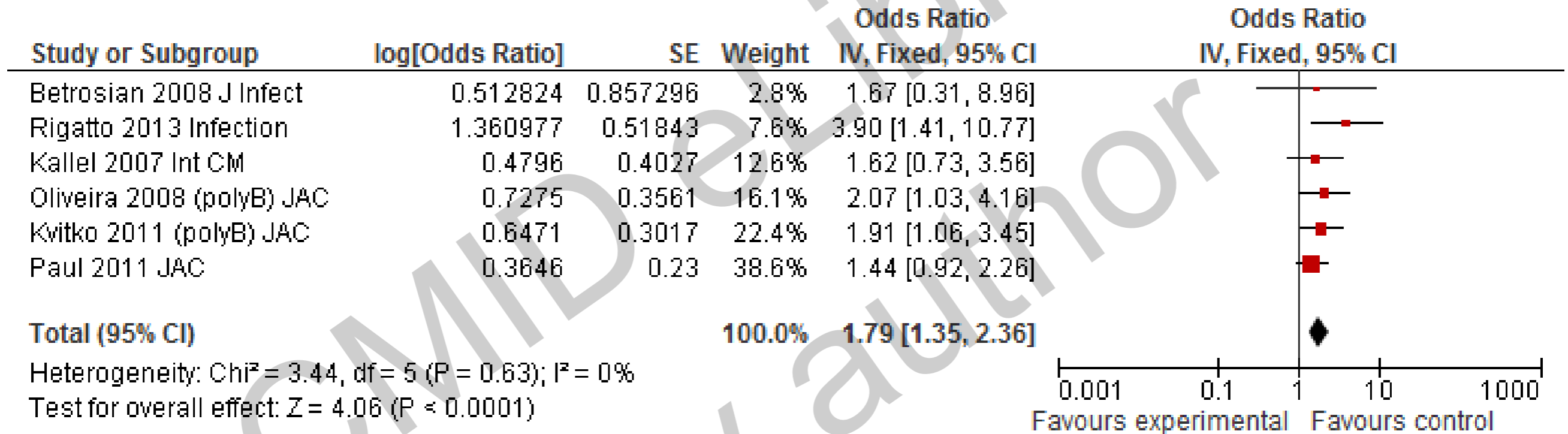
How would you treat?

1. Colistin monotherapy
2. Tigecycline monotherapy
3. Colistin and tigecycline combination
4. Colistin and meropenem combination
5. Colistin and rifampin combination
6. Colistin, meropenem and tigecycline combination

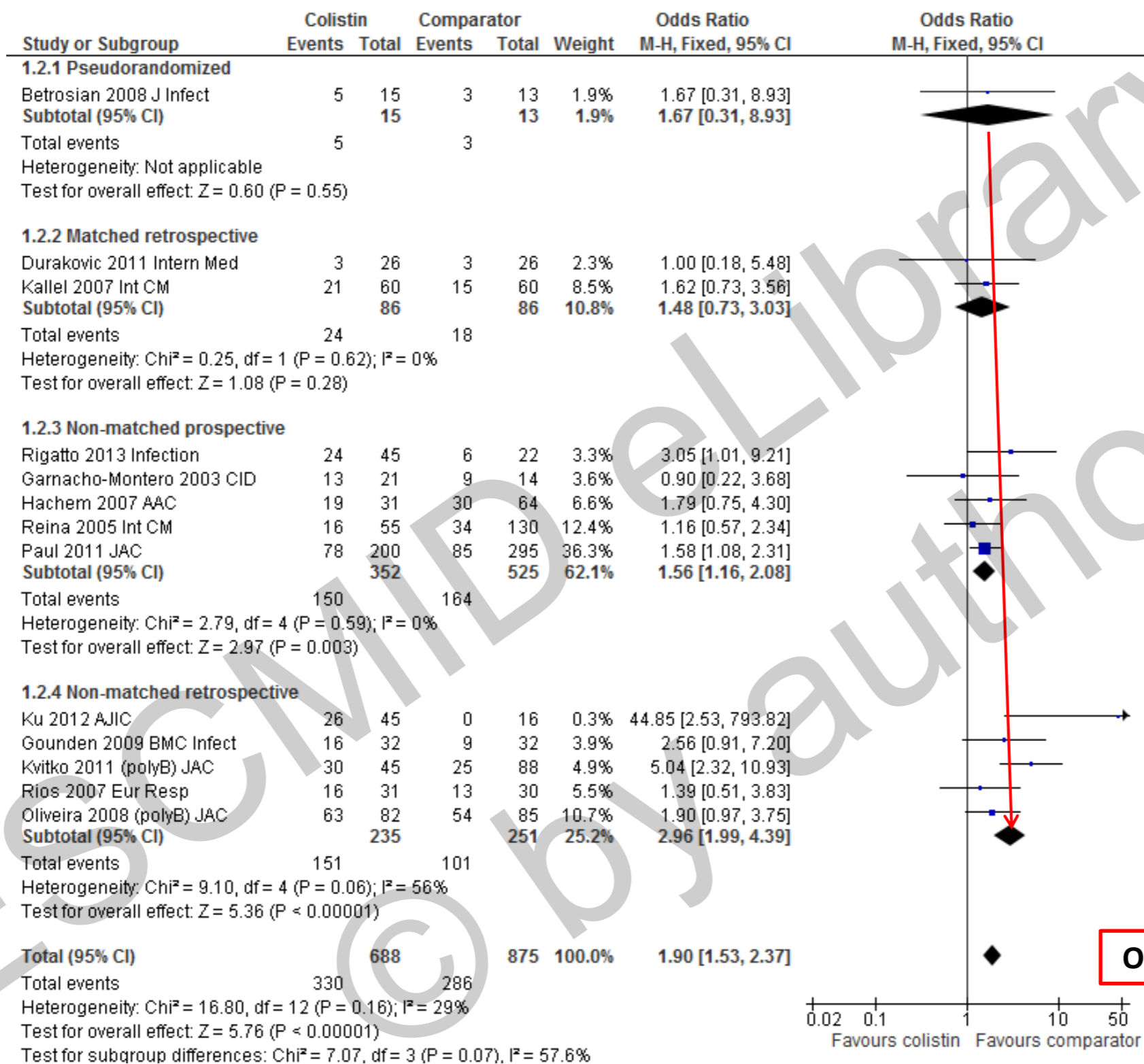
PICO questions

- ▶ Patients: with carbapenem-resistant *A. baumannii* infections
 - Bacteremia
- ▶ Intervention: colistin monotherapy, tigecycline monotherapy
 - Optimally dosed
- ▶ Comparison: other monotherapies, colistin and tigecycline, colistin and meropenem, colistin and rifampin, colistin, meropenem and tigecycline
- ▶ Outcomes:
 - Primary: all cause 30-day mortality
 - Secondary: serious adverse events, clinical cure, ecologic impact

Colistin vs. comparators: all-cause mortality, observational, adjusted



Adjusted OR 1.79 (95% CI 1.35-2.36)

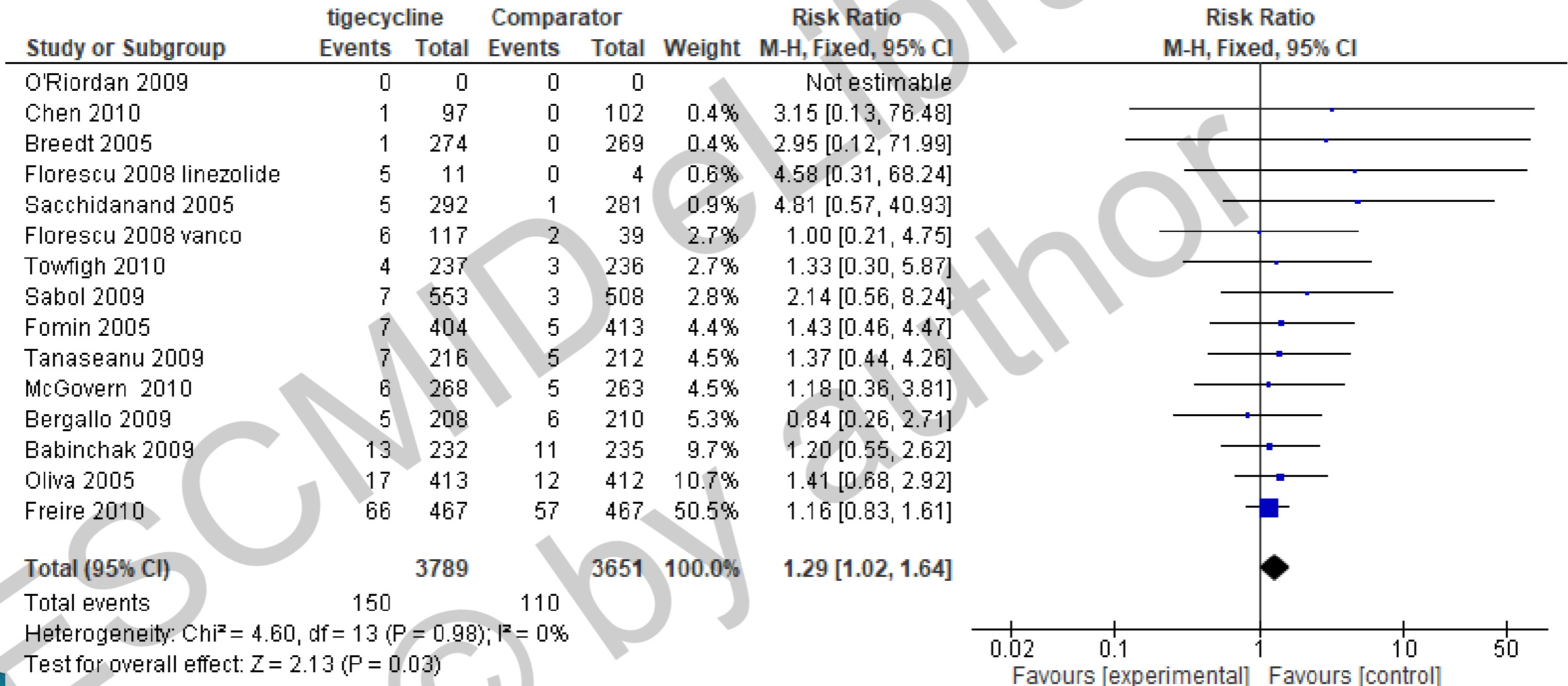


IV colistin
vs. comparator
antibiotics for
sepsis

All-cause mortality

OR 1.90 (95% CI 1.53-2.33)

Tigecycline monotherapy: all cause mortality in RCTs



Explanatory analyses

- ▶ Individual patient data meta-analysis of 13 phase 3-4 RCTs (Pfizer) reveals excess mortality in patients with HAP (mainly VAP) and bacteremia
- ▶ Possibly related to inadequate AUC/MIC ratios in this population
- ▶ A RCT comparing standard dose (150mg loading, 75mg BID) vs. high-dose (200mg loading, 100mg BID) tigecycline for HAP showed higher cure and survival with the high dose

McGovern et al. Int J Antimicrob Agents. 2013 May;41(5):463-7

Ramirez et al. Antimicrob Agents Chemother. 2013 Apr;57(4):1756-62

Colistin vs./plus tigecycline

Effectiveness and safety of high-dose tigecycline-containing regimens for the treatment of severe bacterial infections

Efficacy of Tigecycline for Secondary *Acinetobacter* Bacteremia and Factors Associated with Treatment Failure

The combined use of tigecycline with high-dose colistin might not be associated with higher survival in critically ill patients with bacteraemia due to carbapenem-resistant *Acinetobacter baumannii*

Effectiveness of tigecycline-based versus colistin-based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis

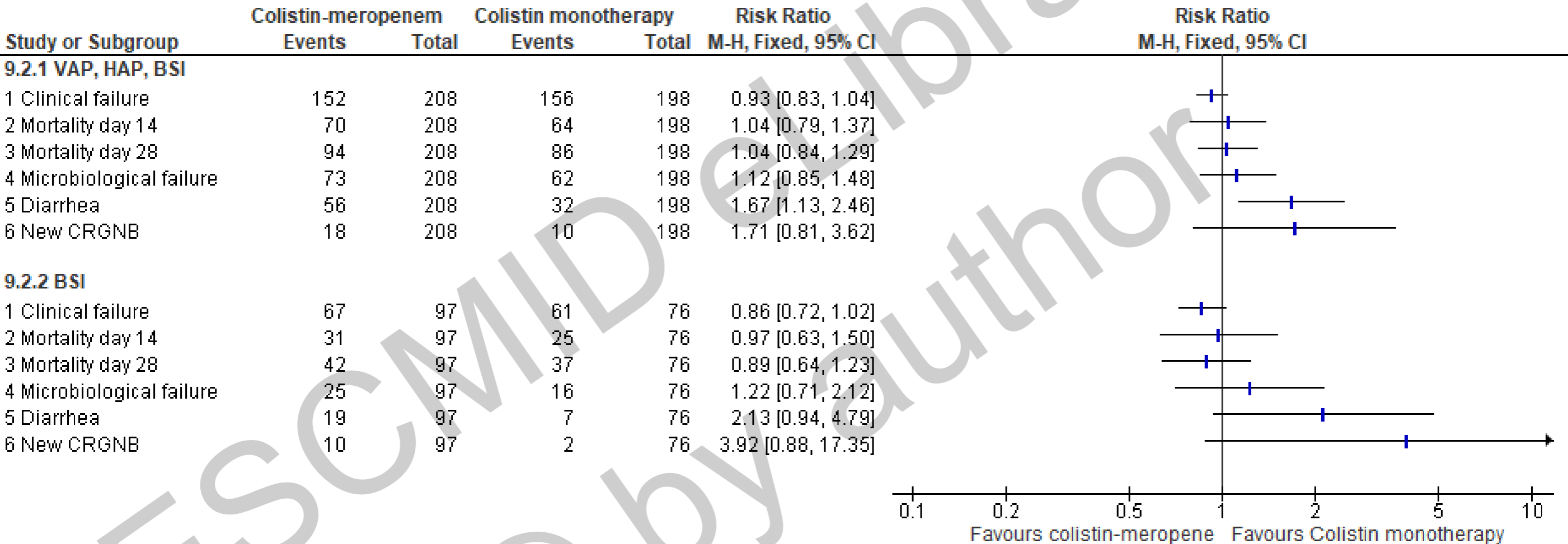
Observational studies of antibiotics against severe infections, MDR bacteria

- ▶ Heterogeneity of treatment regimens, including combination therapies
 - Intervention classification bias
- ▶ Frequent treatment modifications
 - Departure from intended intervention bias
- ▶ Treatments dictated by patient characteristics
 - Selection bias
- ▶ Sample size does not allow for adequate adjustment
 - Confounding

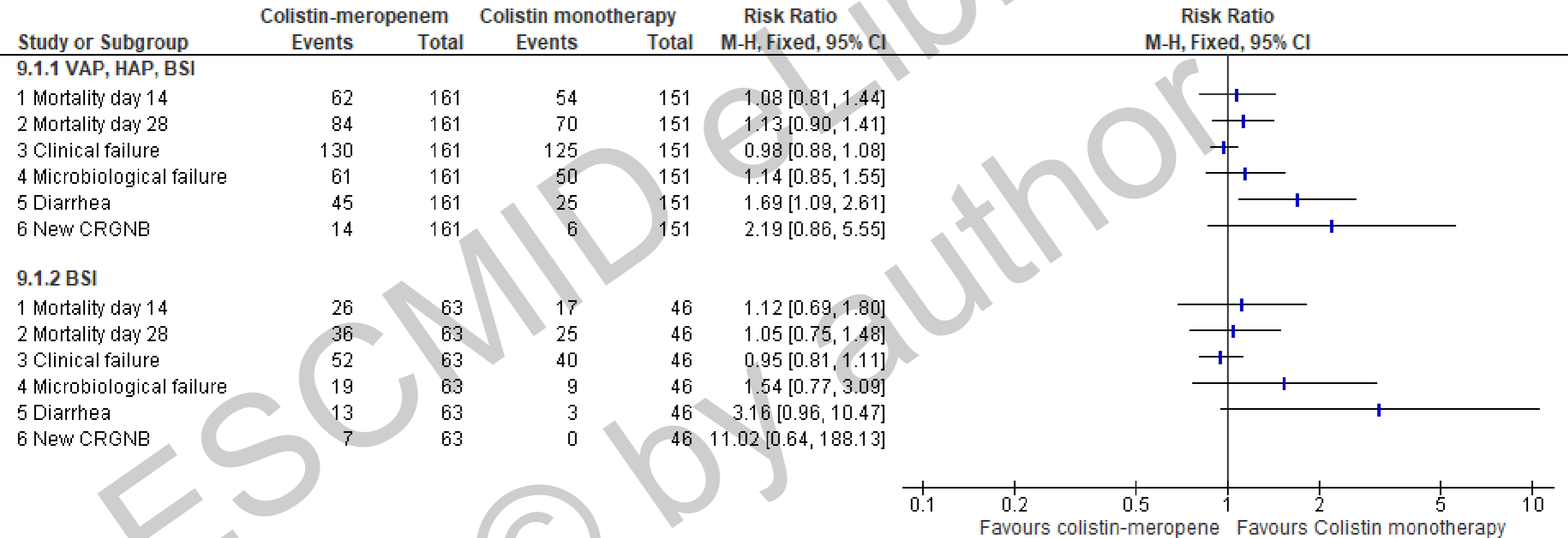
Colistin vs./plus tigecycline

- ▶ No evidence-based comparative data
- ▶ Colistin (low dose) probably worst than comparator antibiotics (observational studies)
- ▶ Tigecycline (low dose) worst than comparators (randomized controlled trials)
- ▶ PKPD considerations may direct selection between the drugs
- ▶ No data to direct combination therapy

Colistin and meropenem combination RCT

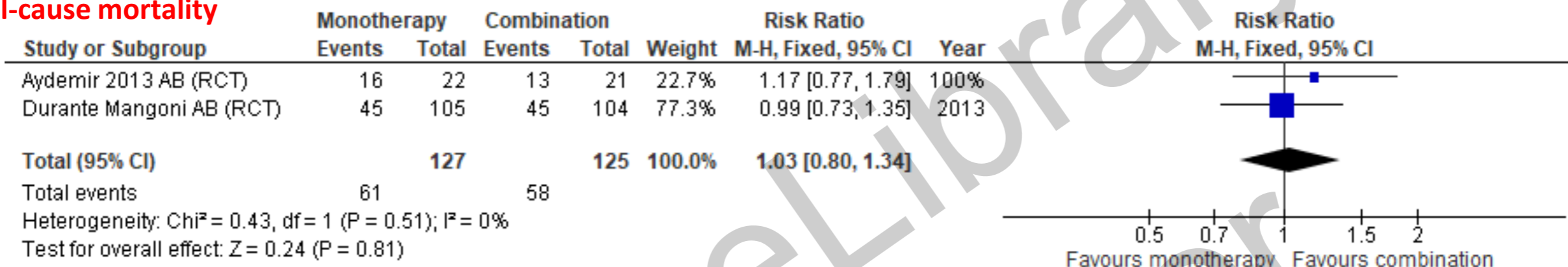


Colistin and carbapenem combination: *Acinetobacter baumannii* RCT subgroup

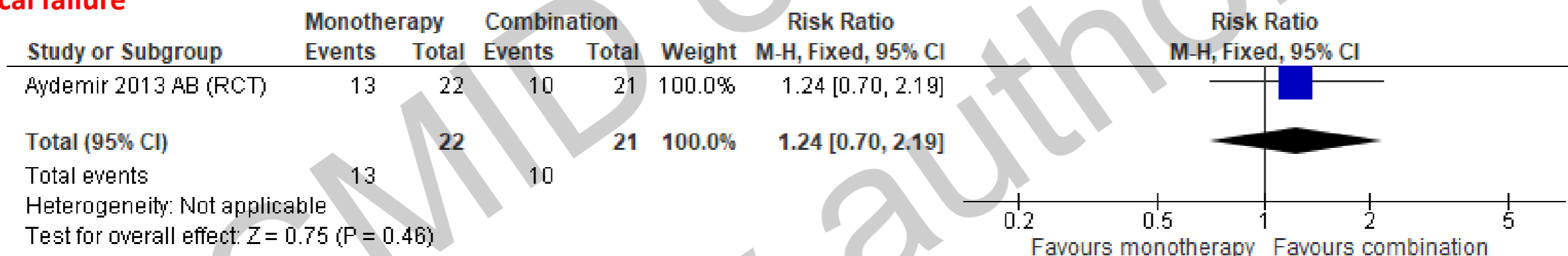


Colistin and rifampin: RCTs

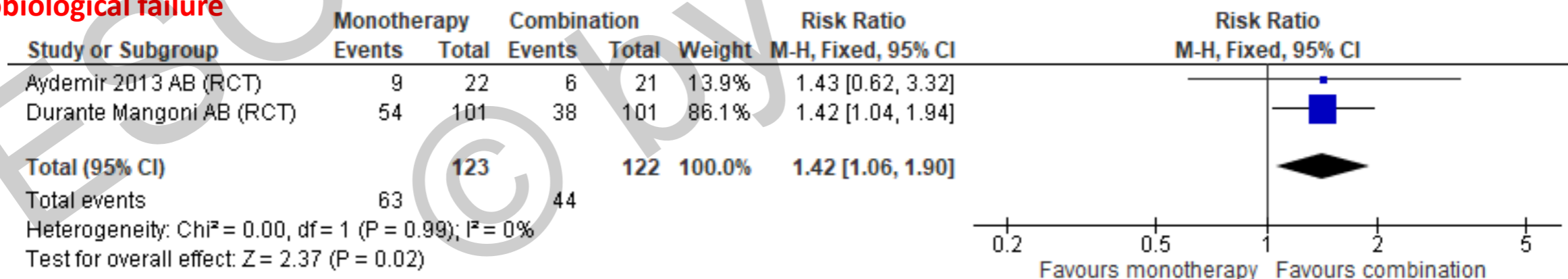
All-cause mortality



Clinical failure



Microbiological failure



Guidelines panel discussions

- ▶ A single high-quality evidence recommendation against colistin–meropenem combination therapy in CRAB
- ▶ How to interpret the benefit in microbiological cure for colistin rifampin?
- ▶ Double covering combination therapy (colistin–tigecycline)?
- ▶ Does the higher mortality seen with tigecycline in RCTs apply to MDR bacteria?
- ▶ No evidence on colistin vs. aminoglycoside, tetracyclines

Personal choice

- ▶ Drain
- ▶ Look for source of the collection
- ▶ Clarify to surgeon that antibiotics will have very little effect and outcome will depend on surgery
- ▶ Examine carefully the AST report and MICs
 - Ask for tigecycline MIC of both and repeat isolates
- ▶ Prescribe colistin monotherapy and discuss the options of colistin, tigecycline or their combination with ID staff
 - Renal function
 - *Clostridium difficile*

Case 3

Abscess and blood culture:

CULTIVO

SE AISLA:

(1) Acinetobacter baumannii.

Antimicrobiano	S/I/R	CMI (ug/ml)
Ampicilina/Sulbactam	R	>16/8
Piperacilina/Tazobac	R	>64
Ceftazidima	R	>16
Cefotaxima	R	>32
Imipenem	R	>=8
Meropenem	R	>=8
Gentamicina	R	>=8
Tobramicina	R	>=8
Amikacina	R	>32
Ciprofloxacino	R	>2
Levofloxacina	R	>4
Colistina	S	<=2

Tigecycline

S

=1

What do you advise the panel?

1. Colistin monotherapy
2. Tigecycline monotherapy
3. Colistin and tigecycline combination
4. Colistin and meropenem combination
5. Colistin and rifampin combination
6. Colistin, meropenem and tigecycline combination

Take home message

- ▶ We can direct practice only based on RCTs
 - Statins for sepsis, AIDA trials, Magic Bullet
- ▶ All efforts should be directed at patient recruitment into well-conducted RCTs
 - Assessing specific and optimized interventions
 - Efficient study design
 - Examining patient relevant outcomes
- ▶ The discussion on the relevant outcome in RCTs of MDR Gram-negative bacteria is open

Thank you

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