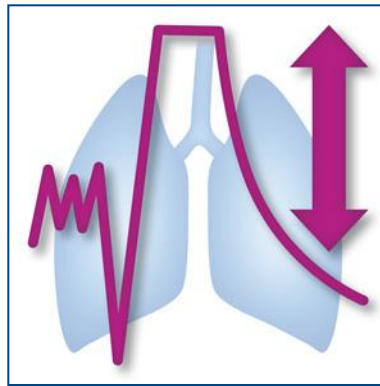


Pneumo Update Europe 2017

9-10 June, Vienna

Pneumonia



Mark Woodhead, UK

Contents

- **PPIs and Pneumonia risk**
- **Diagnosis of pneumonia**
- **Empirical antibiotic therapy**
 - **β -lactam + macrolide or β -lactam alone for CAP**
 - **Duration of treatment**
- **Steroids in CAP**
- **ECMO in CAP**
- **HAP & VAP guidelines**

PPIs and Pneumonia Risk

PPIs and Pneumonia Risk

State of the Art

- Gastric acid inhibits bacterial growth
- Acid suppression may lead to bacterial overgrowth
- Aspiration of gastric contents causes pneumonia

PPIs and Pneumonia Risk

State of the Art

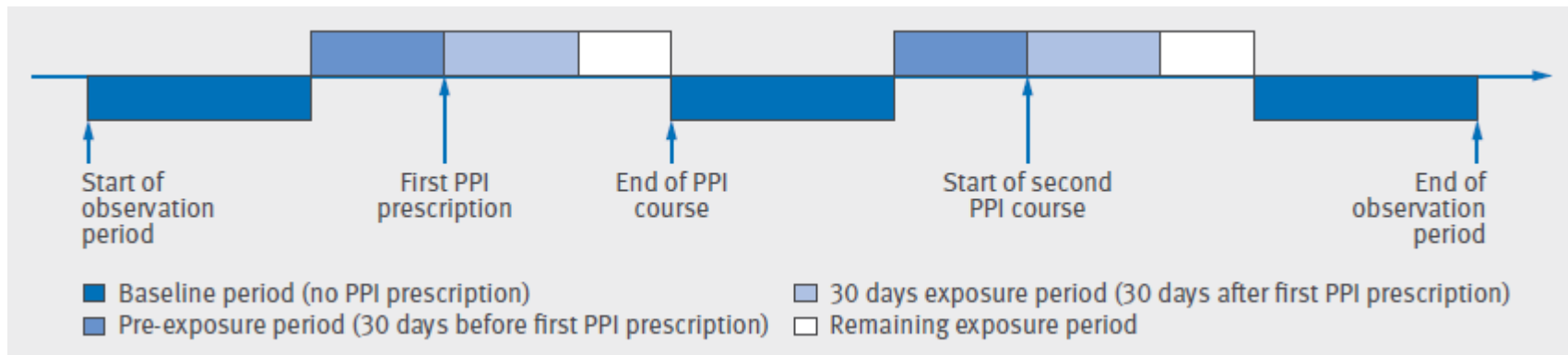
- Gastric acid inhibits bacterial growth
- Acid suppression may lead to bacterial overgrowth
- Aspiration of gastric contents causes pneumonia
- Meta-analyses suggest association between PPI use and HAP in the critically ill
- Results in CAP studies inconsistent
- PPIs very widely prescribed and used!!!!
- Does PPI use increase risk of CAP?

Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study

Fatmah Othman,^{1,2} Colin J Crooks,¹ Timothy R Card^{1,3}

Othman et al *BMJ* 2016;355:i5813

- large UK based electronic database of primary care records (www.cprd.com).
- Adults > 1 yr of registration between 1990 and 2013
- 160,000 commencing PPI use
- Pneumonia – Read code from CPRD (included chest infection and LRTI)
- coded within Hospital Episode Statistics/Office for National Statistics data.
- self controlled case series



- cohort study – exposed matched to unexposed 1 : 1

Othman et al *BMJ* 2016;355:i5813

PPIs and Pneumonia Risk

Pneumonia definition

Broad

Narrow

admission/death

Unexposed Exposed Unexposed Exposed Unexposed Exposed

Unexposed = did not receive PPI; Exposed = received PPI

Othman et al *BMJ* 2016;355:i5813

PPIs and Pneumonia Risk

| Pneumonia definition | Broad | | Narrow | | admission/death | |
|-------------------------|--------------------|---------|--------------------|---------|--------------------|---------|
| | Unexposed | Exposed | Unexposed | Exposed | Unexposed | Exposed |
| Pneumonia events | 1582 | 3798 | 74 | 392 | 234 | 1090 |
| Pneumonia rate | 30.34 | 76.13 | 1.37 | 7.31 | 5.48 | 25.74 |
| Unadjusted Hazard ratio | 2.51 (2.36 – 2.67) | | 5.44 (4.23 – 6.99) | | 4.76 (4.12 – 5.49) | |
| Adjusted Hazard ratio | 1.65 (1.53 – 1.77) | | 3.87 (2.75 – 5.44) | | 3.54 (3.02 – 4.16) | |

Unexposed = did not receive PPI; Exposed = received PPI

Othman et al *BMJ* 2016;355:i5813

PPIs and Pneumonia Risk

Pneumonia definition

| | Broad | | | Narrow | | | admission/death | | |
|-----------------------|--------|--------------|------|--------|--------------|------|-----------------|--------------|------|
| | Events | Person years | IRR | Events | Person years | IRR | Events | Person years | IRR |
| Baseline unexposed | 74121 | 531201 | 1.0 | 3083 | 46254 | 1.0 | 7212 | 41172 | 1.0 |
| Post-exposure 30 days | 1679 | 9067 | 1.19 | 151 | 791 | 2.70 | 393 | 802 | 2.69 |
| Remaining exposure | 17557 | 83720 | 1.49 | 1430 | 9263 | 3.18 | 3134 | 8824 | 2.44 |

Unexposed = did not receive PPI; Exposed = received PPI
IRR = Incidence rate ratio

Othman et al *BMJ* 2016;355:i5813

PPIs and Pneumonia Risk

| Pneumonia definition | Broad | | | Narrow | | | admission/death | | |
|-----------------------|--------|--------------|------|--------|--------------|------|-----------------|--------------|------|
| | Events | Person years | IRR | Events | Person years | IRR | Events | Person years | IRR |
| Baseline unexposed | 74121 | 531201 | 1.0 | 3083 | 46254 | 1.0 | 7212 | 41172 | 1.0 |
| Pre-exposure 30 days | 2698 | 9099 | 1.92 | 212 | 798 | 3.72 | 642 | 816 | 4.16 |
| Post-exposure 30 days | 1679 | 9067 | 1.19 | 151 | 791 | 2.70 | 393 | 802 | 2.69 |
| Remaining exposure | 17557 | 83720 | 1.49 | 1430 | 9263 | 3.18 | 3134 | 8824 | 2.44 |

Unexposed = did not receive PPI; Exposed = received PPI
IRR = Incidence rate ratio

Othman et al *BMJ* 2016;355:i5813

PPIs and Pneumonia Risk

| | PPI Exposed | PPI Unexposed % |
|---|----------------|-----------------------|
| a history of smoking | 42.9 | 33.7 |
| alcohol use | 29.1 | 23.9 |
| a higher burden of comorbidity Charlson Index ≥ 3 | 7.6 | 15.1 |
| used more corticosteroids | 3.6 | 9.9 |
| and opioids | 0.9 | 5.9 |

Othman et al *BMJ* 2016;355:i5813

Take-Home Message

- PPI users have increased CAP risk
- This is present before use starts
- Explained by co-morbid factors
- PPIs do NOT increase risk of CAP

Diagnosis of Pneumonia

Diagnosis of Pneumonia

State of the Art

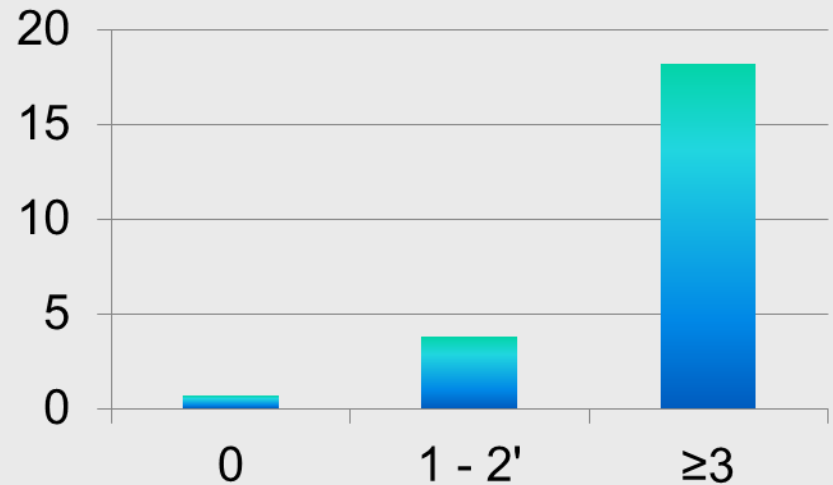
- LRTI is common, pneumonia is rare
- LRTI is self-limiting, Pneumonia=antibiotic
- Overuse of antibiotic for LRTI=resistance
- Diagnosis of pneumonia outside hospital is difficult especially when no CXR
- GPs rely on signs and symptoms
- Prediction rules may assist diagnosis

Van Vugt Model for CAP Prediction

Score x 1 for each of

- Absence of runny nose
- Raised pulse ($>100/\text{min}$)
- Breathlessness
- Fever (temperature $>37.8^{\circ}\text{C}$)
- Crackles
- Raised CRP ($>30 \text{ mg/L}$).
- Diminished vesicular breathing

| Score | No of Patients | Pneumonia |
|----------|----------------|-----------|
| 0 | 572 (20.3) | 4 (0.7) |
| 1-2 | 1902 (67.4) | 73 (3.8) |
| ≥ 3 | 346 (12.3) | 63 (18.2) |



van Vugt et al. BMJ. 2013; 346:f2450–f2450. doi: 10.1136/bmj.f2450

Meta-analysis: 6 'Rules'; 8 Datasets

Pneumonia (%): 5,5,12,13,13,20,21,43

| | pooled AUC (95% CIs) |
|-------------------|----------------------|
| van Vugt et al. | 0.79 (0.74–0.85) |
| Heckerling et al. | 0.72 (0.68–0.76) |
| Diehr et al. | 0.65 (0.61–0.68) |
| Singal et al. | 0.64 (0.61–0.67) |
| Melbye et al. | 0.56 (0.49–0.63) |
| Hopstaken et al. | 0.53 (0.5–0.56) |

Schierenberg A, et al. (2016) PLoS ONE 11(2):
e0149895. doi:10.1371/journal.pone.0149895

Take-Home Message

- Pneumonia diagnosis remains difficult
- Prediction rules may help
- Van Vugt model may be the best
- ? Guides when to withhold antibiotic
- CXR remains *gold standard*

Antibiotic

**β -lactam + macrolide
or β -lactam alone for
CAP**

β -lactam + macrolide or β -lactam alone for CAP

State of the Art

- Cohort studies consistently suggest better outcome for β -lactam + macrolide
- Bias due to intention to treat
- Guidelines mostly recommend dual therapy
- UK monotherapy for non-severe
- Two RCTs suggest, at best, little benefit from addition of macrolide
- Is illness severity an issue?

SYSTEMATIC REVIEW

Beta-lactam plus macrolides or beta-lactam alone for community-acquired pneumonia: A systematic review and meta-analysis

NOBUYUKI HORITA,¹ TATSUYA OTSUKA,² SHUSAKU HARANAGA,³ HO NAMKOONG,⁴ MAKOTO MIKI,⁵
NAOYUKI MIYASHITA,⁶ FUTOSHI HIGA,⁷ HIROSHI TAKAHASHI,⁸ MASAHIRO YOSHIDA,⁹
SHIGERU KOHNO¹⁰ AND TAKESHI KANEKO¹

Horita et al *Respirology* 2016;21:1193-1200

β -lactam + macrolide or β -lactam alone for CAP

14 studies identified

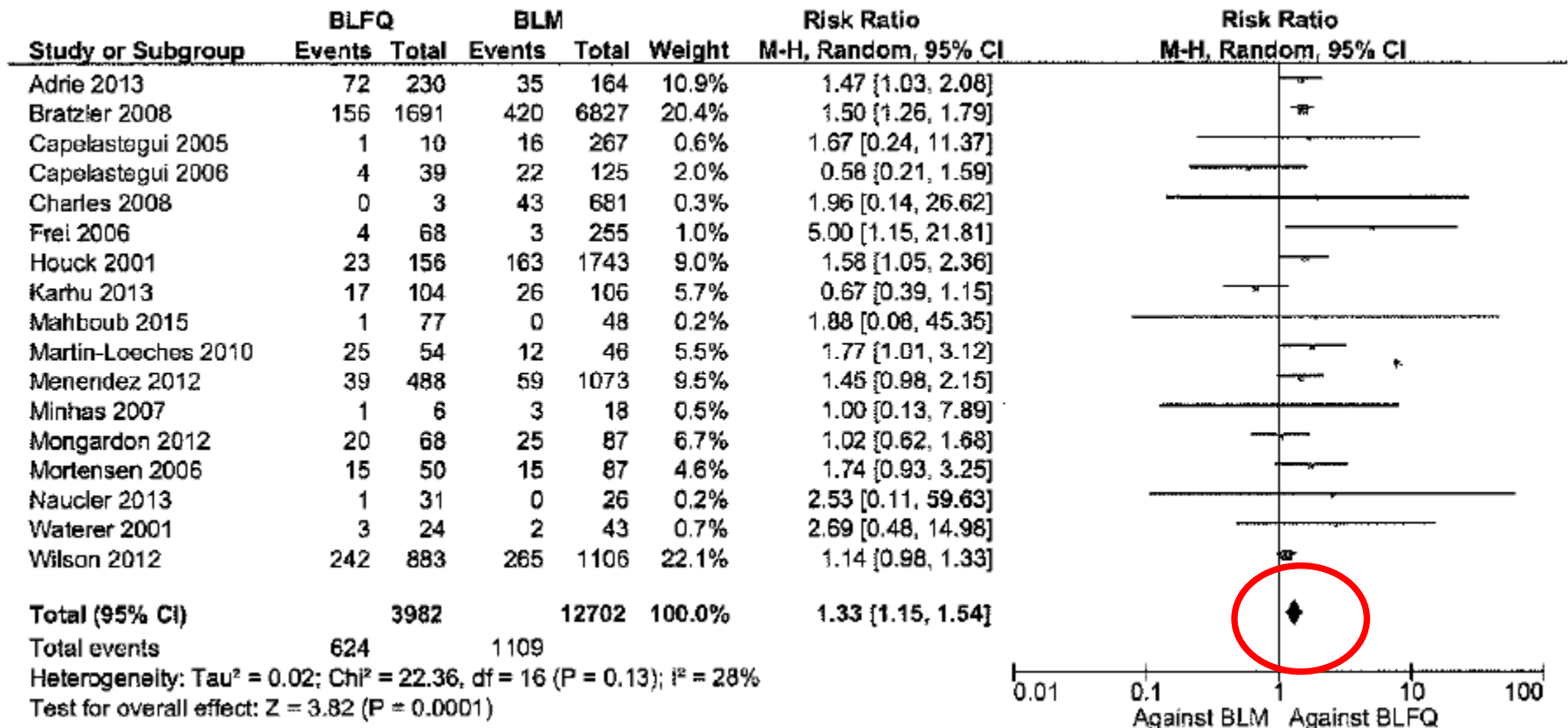
12 cohort, 2 RCTs

10 used PSI, 1 CURB65, 1 CRB65, 2 none

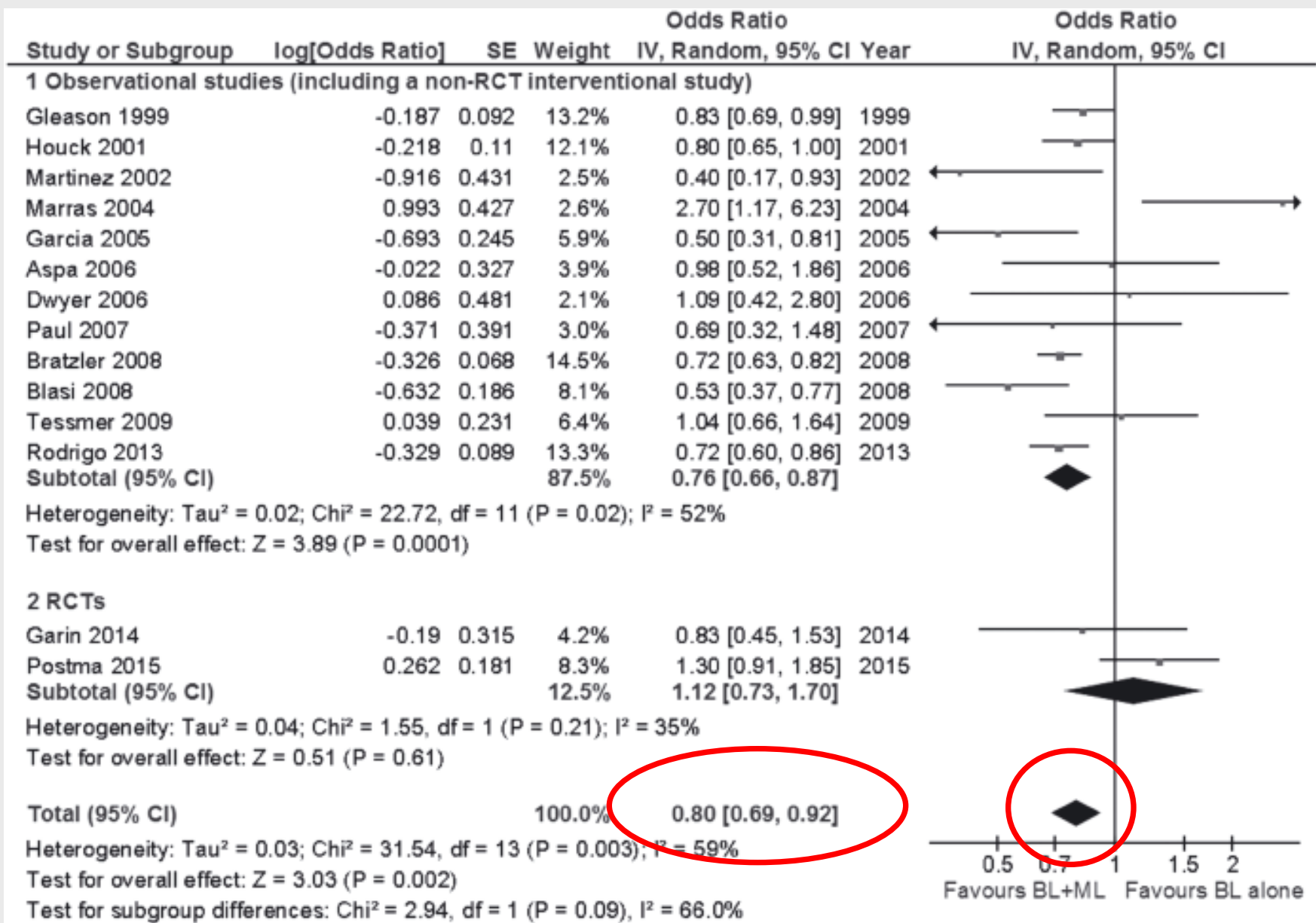
Outcome = All-cause mortality

Horita et al *Respirology* 2016;21:1193-1200

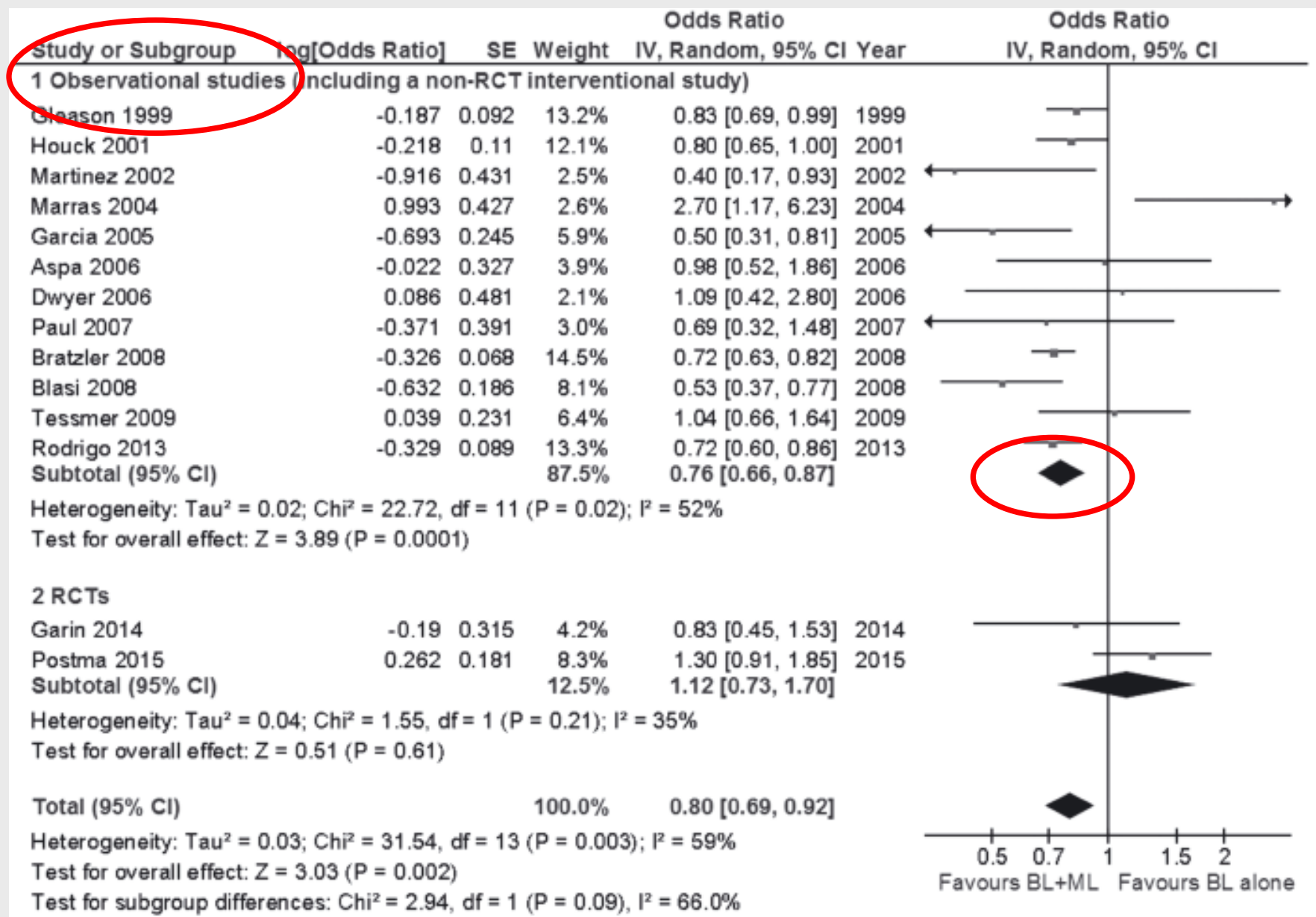
β -lactam + Macrolide (BLM) or β -lactam + Fluoroquinolone (BLFQ)



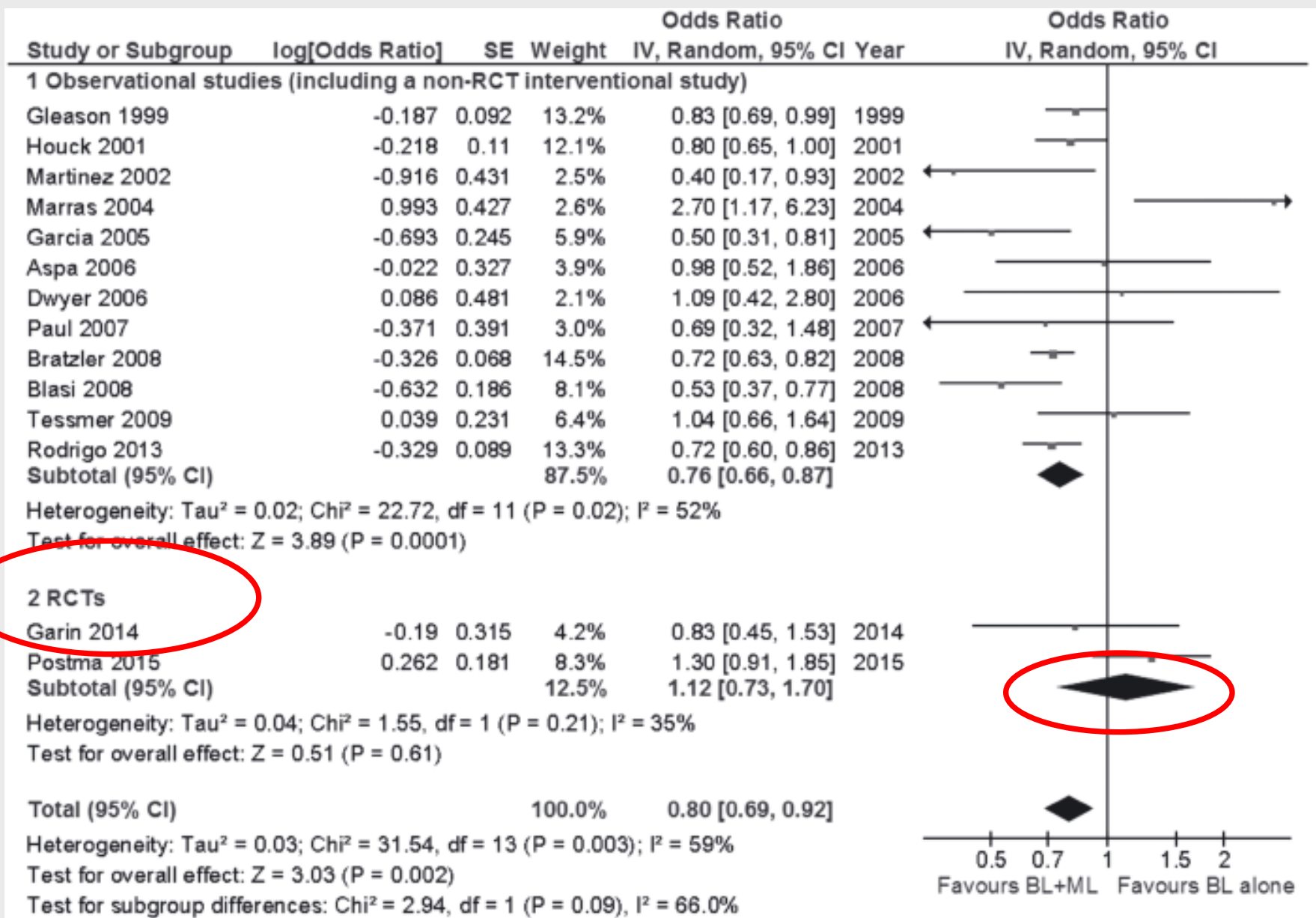
Vardakas et al *Clin Microbiol Infect* 2017;23:234-241



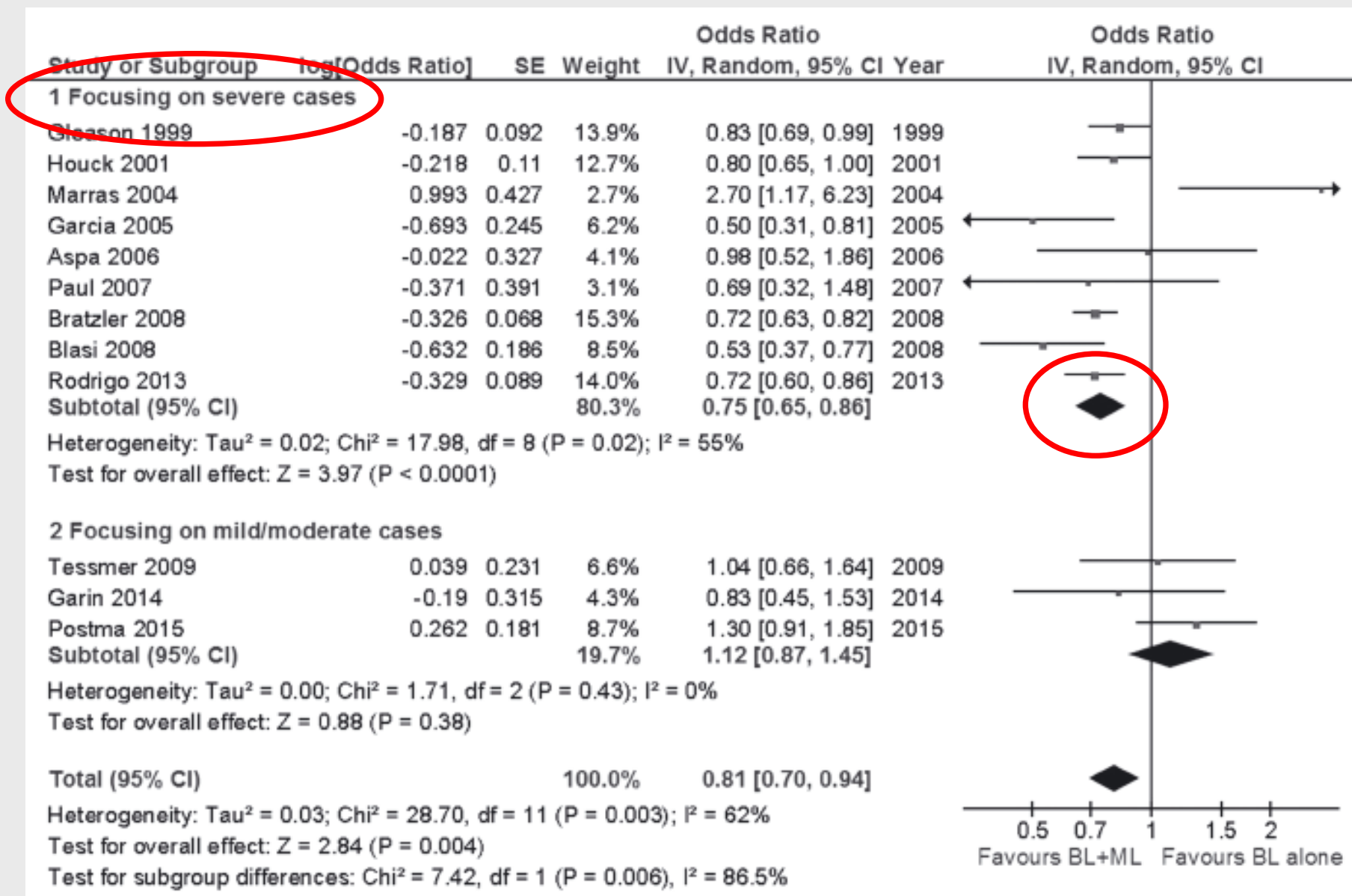
Horita et al *Respirology* 2016;21:1193-1200



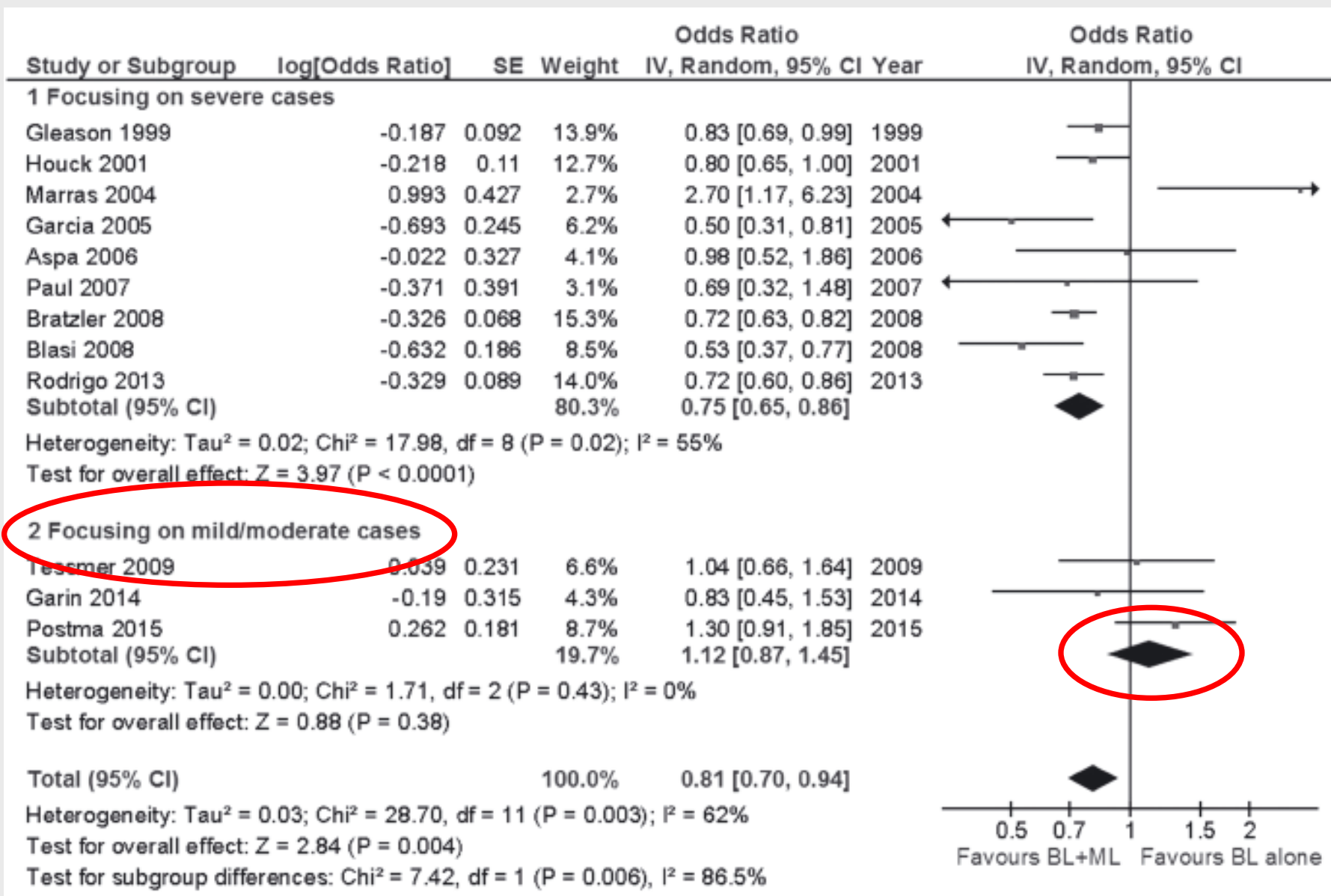
Horita et al *Respirology* 2016;21:1193-1200



Horita et al *Respirology* 2016;21:1193-1200

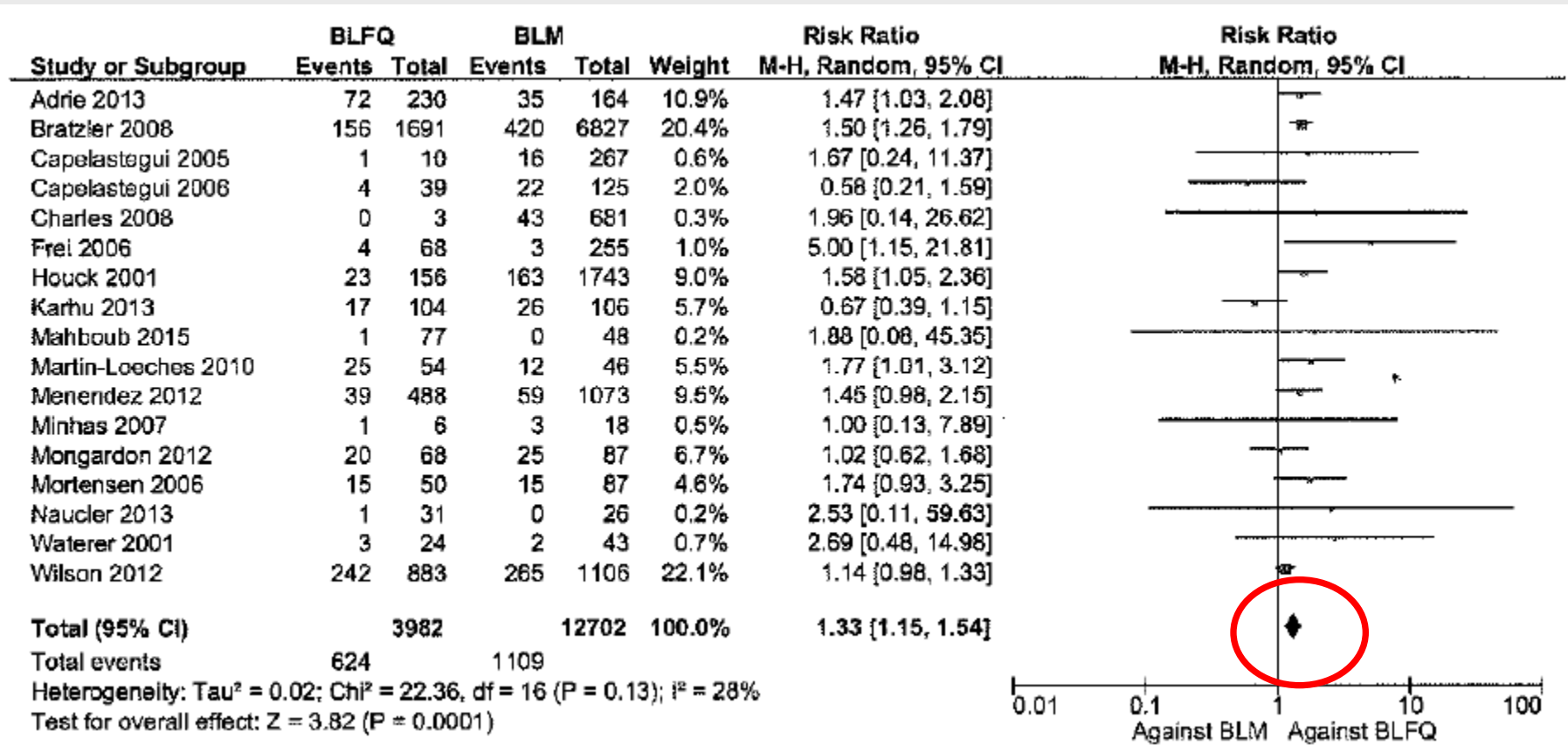


Horita et al *Respirology* 2016;21:1193-1200



Horita et al *Respirology* 2016;21:1193-1200

β -lactam + Macrolide (BLM) or β -lactam + Fluoroquinolone (BLFQ)



Vardakas et al *Clin Microbiol Infect* 2017;23:234-241

β -lactam + macrolide or β -lactam alone for CAP

Take-Home Message

- macrolide to β -lactam appropriate for severely ill
- β -lactam alone adequate for non-severe CAP
- Limited assessment of harms
- Further RCTs would be helpful

Antibiotic

Duration of Treatment

Duration of Antibiotics

State of the Art

- Few clinical trials
- Decision usually guided by historical practice

- **ERS Guidelines 2011**

The duration of treatment should generally not exceed **8 days** in a responding patient .

Biomarkers, particularly PCT, may guide shorter treatment duration.

Woodhead et al Clin Microbiol Infect 2011; 17(Suppl. 6): E1–E59

- **England NICE Guidelines 2014**

Offer a **5-day** course of a single antibiotic to patients with low-severity community-acquired pneumonia.

Consider a **7- to 10-day** course of antibiotic therapy for patients with moderate- or high-severity community-acquired pneumonia.

Eccles et al BMJ 2014;349:g6722 doi: 10.1136/bmj.g6722;

www.nice.org.uk/guidance/cg191

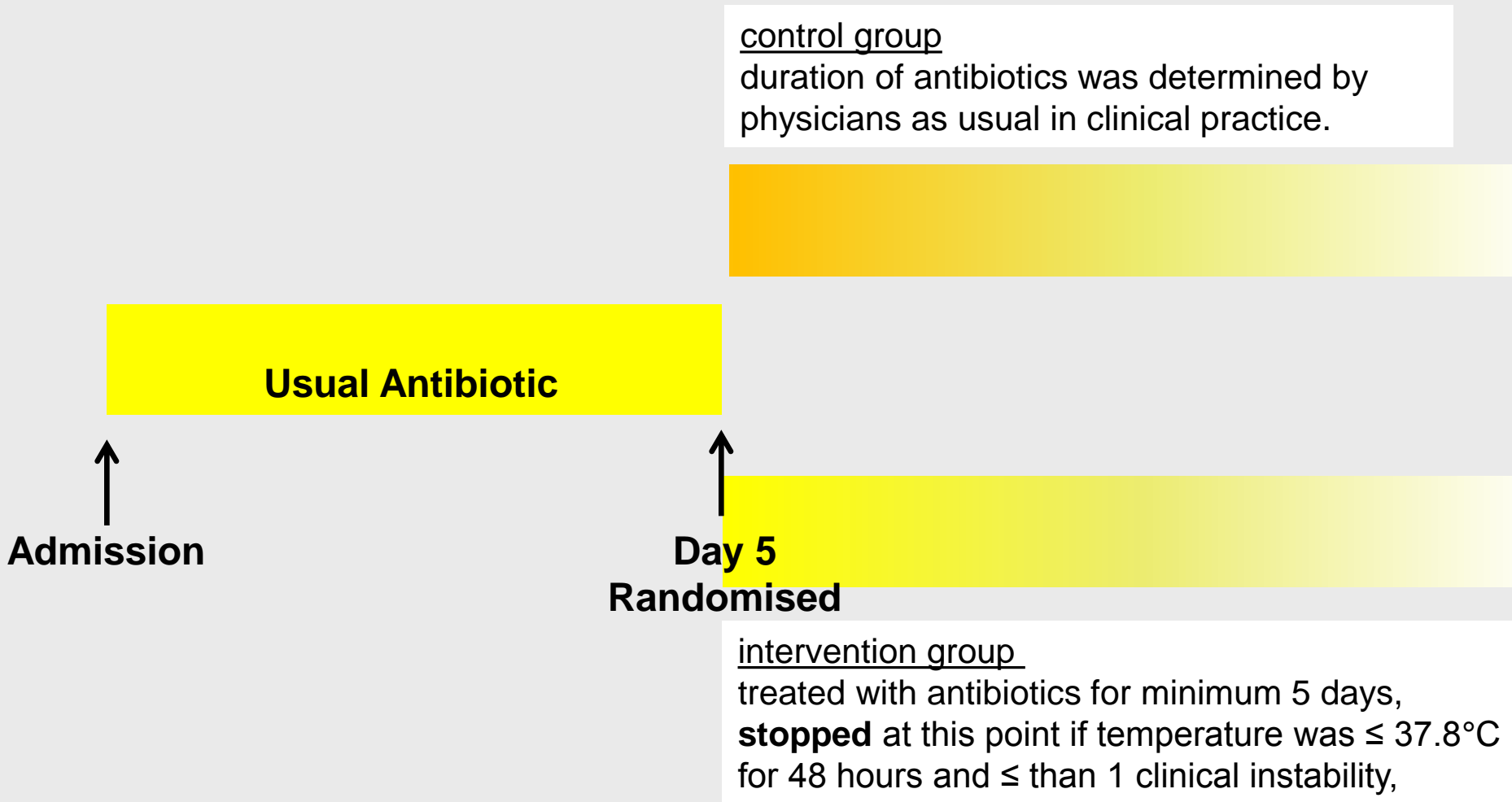
Original Investigation | LESS IS MORE

Duration of Antibiotic Treatment in Community-Acquired Pneumonia A Multicenter Randomized Clinical Trial

Ane Uranga, MD; Pedro P. España, MD; Amaia Bilbao, MSc, PhD; Jose María Quintana, MD, PhD;
Ignacio Arriaga, MD; Maider Intxausti, MD; Jose Luis Lobo, MD, PhD; Laura Tomás, MD; Jesus Camino, MD;
Juan Nuñez, MD; Alberto Capelastegui, MD, PhD

Uranga et al *JAMA Intern Med.* 2016 Sep 1;176(9):1257-65

- Multicentre, non-inferiority randomized clinical trial
- Hospitalized patients diagnosed as having CAP 4 teaching hospitals in Spain



Uranga et al *JAMA Intern Med.* 2016 Sep 1;176(9):1257-65

- Multicentre, non-inferiority randomized clinical trial
- Hospitalized patients diagnosed as having CAP 4 teaching hospitals in Spain

| PSI Class | | Control | Intervention |
|----------------------------|------------|--------------------|---------------------|
| I – III | (%) | 89 (59.3) | 102 (63.0) |
| IV – V | | 61 (40.7) | 60 (37) |
| PSI Score Mean (SD) | | 83.7 (33.7) | 81.8 (33.8) |

Uranga et al *JAMA Intern Med.* 2016 Sep 1;176(9):1257-65

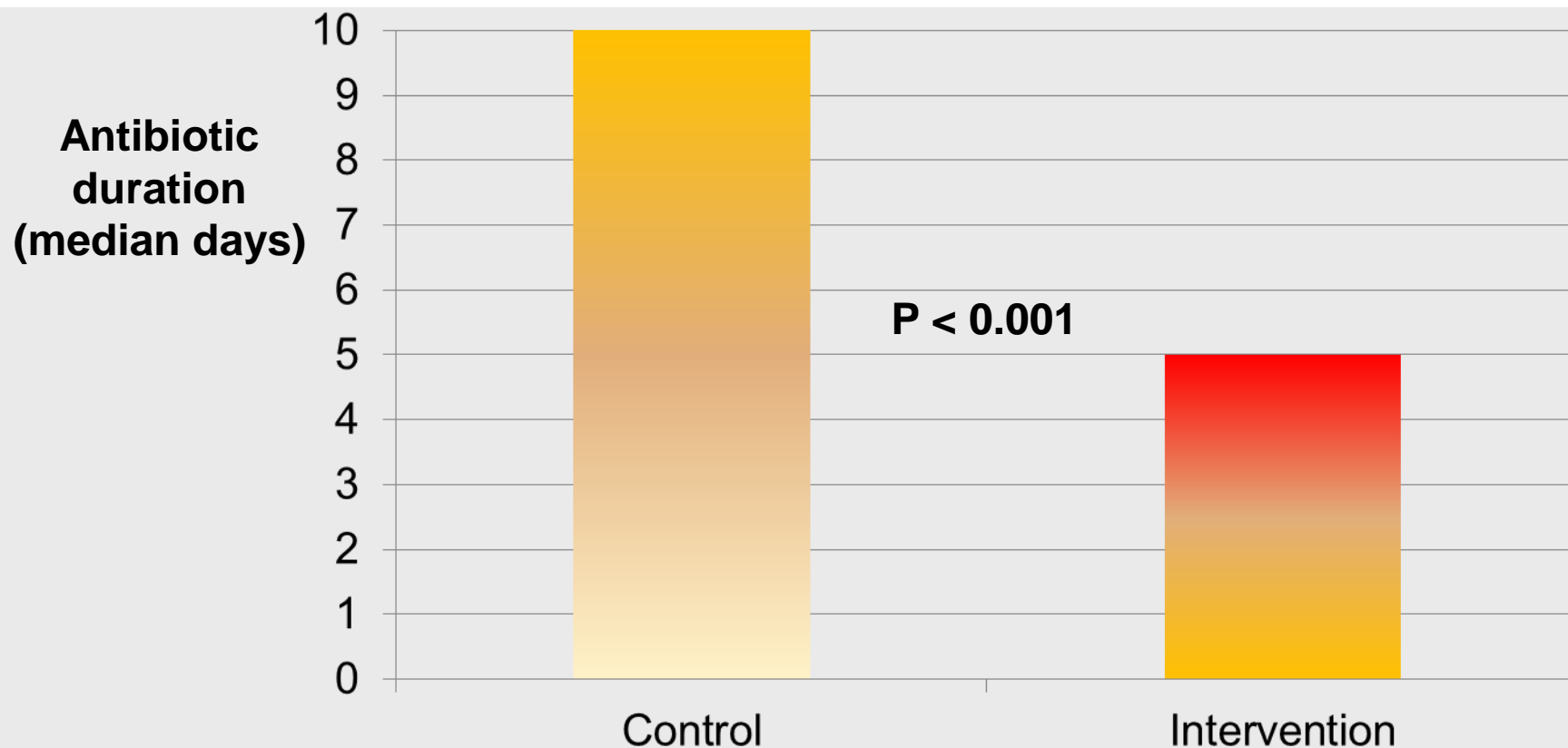
| n | 150 | 162 | p |
|----------------------------|------|------|-----|
| 30-day mortality (%) | 2.2 | 2.1 | NS |
| Day 10 clinical success(%) | 48.6 | 56.3 | .18 |
| Day 30 clinical success(%) | 88.6 | 91.9 | .33 |
| Day 10 Mean symptom score | 18.6 | 17.9 | .69 |

Control

Intervention

Uranga et al *JAMA Intern Med.* 2016 Sep 1;176(9):1257-65

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Uranga et al *JAMA Intern Med.* 2016 Sep 1;176(9):1257-65

Take-Home Message

- 5 days is sufficient (for non-severe CAP)
- Duration for Severe ?

Steroids in CAP

State of the Art

- Not a current standard of care
- Widely used ? as rescue when Rx failing
- Meningitis and Pneumocystis
- ? benefit in severe CAP, but trials small and biased
- 4 systematic reviews inconclusive

RESEARCH ARTICLE

Efficacy and Safety of Adjunctive Corticosteroids Therapy for Severe Community-Acquired Pneumonia in Adults: An Updated Systematic Review and Meta-Analysis

Jirui Bi^{1☯}, Jin Yang^{1☯}, Ying Wang¹, Cijiang Yao², Jing Mei¹, Ying Liu², Jiyu Cao³, Youjin Lu^{1*}

Bi et al *PLOS One* 11(11): e0165942. doi:10.1371/journal.

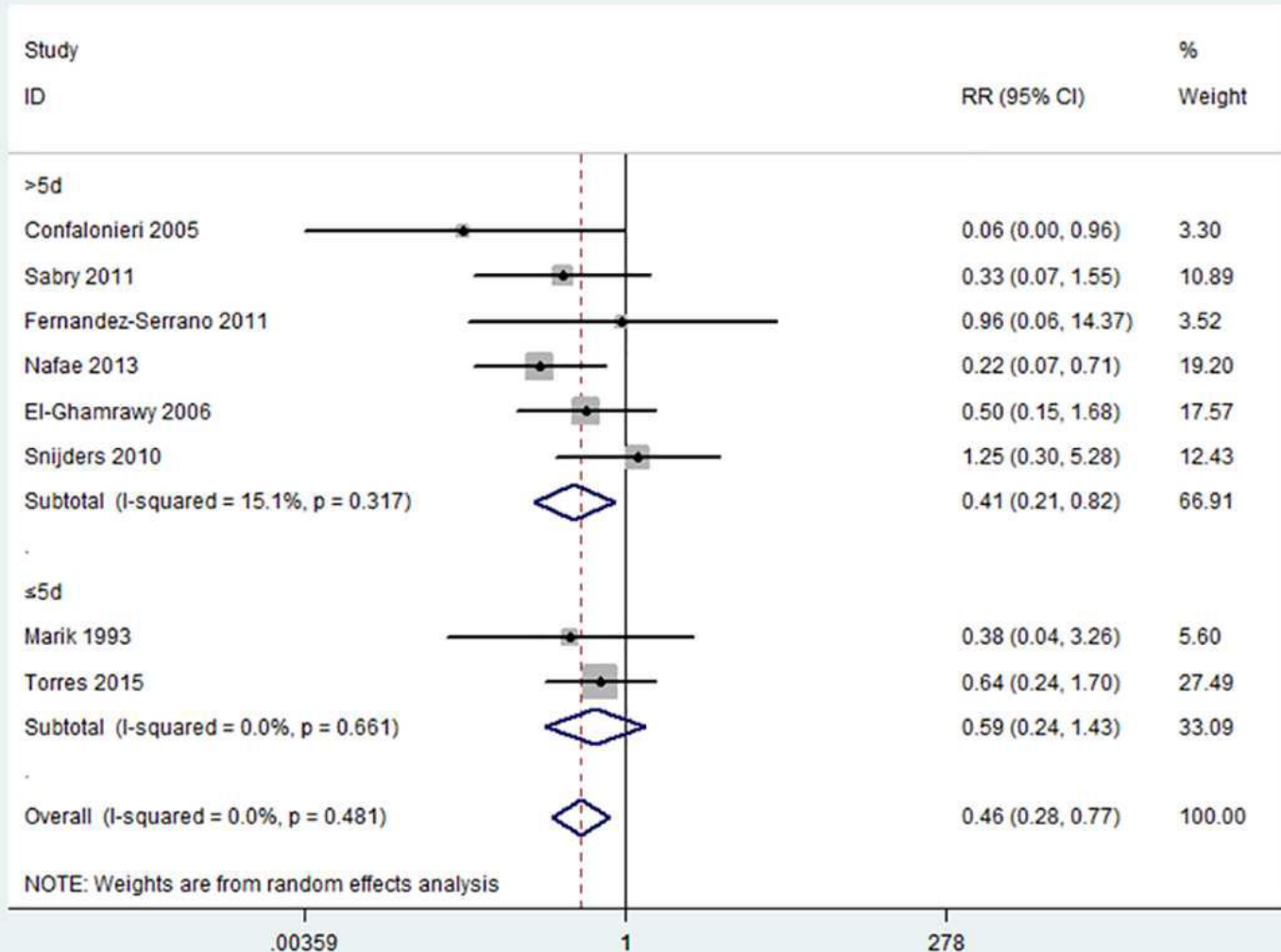
Steroids in CAP: 2015 Systematic Reviews

| | | Horita | Marti | Siemieniuk |
|------------------|------|--------|-------|------------|
| Wagner | 1955 | . | ✓ | ✓ |
| Bennett | 1963 | . | ✓ | . |
| Klustersky | 1971 | . | ✓ | . |
| McHardy | 1972 | ✓ | ✓ | ✓ |
| Marik | 1993 | ✓ | ✓ | ✓ |
| Confalonieri | 2005 | ✓ | ✓ | ✓ |
| El Ghamrawy | 2006 | . | . | ✓ |
| Mikami | 2007 | ✓ | ✓ | . |
| Snijders | 2010 | ✓ | ✓ | ✓ |
| Fernandez-Serano | 2011 | ✓ | ✓ | ✓ |
| Meijvis | 2011 | ✓ | ✓ | ✓ |
| Sabry | 2011 | ✓ | ✓ | ✓ |
| Nafae | 2013 | . | ✓ | ✓ |
| Blum | 2015 | ✓ | ✓ | ✓ |
| Torres | 2015 | ✓ | ✓ | ✓ |

Steroids in CAP:

| | | Horita | Marti | Siemieniuk | Bi |
|------------------|------|--------|-------|------------|----|
| Wagner | 1955 | . | ✓ | ✓ | . |
| Bennett | 1963 | . | ✓ | . | . |
| Klustersky | 1971 | . | ✓ | . | . |
| McHardy | 1972 | ✓ | ✓ | ✓ | . |
| Marik | 1993 | ✓ | ✓ | ✓ | ✓ |
| Confalonieri | 2005 | ✓ | ✓ | ✓ | ✓ |
| El Ghamrawy | 2006 | . | . | ✓ | ✓ |
| Mikami | 2007 | ✓ | ✓ | . | . |
| Snijders | 2010 | ✓ | ✓ | ✓ | ✓ |
| Fernandez-Serano | 2011 | ✓ | ✓ | ✓ | ✓ |
| Meijvis | 2011 | ✓ | ✓ | ✓ | . |
| Sabry | 2011 | ✓ | ✓ | ✓ | ✓ |
| Nafae | 2013 | . | ✓ | ✓ | ✓ |
| Blum | 2015 | ✓ | ✓ | ✓ | . |
| Torres | 2015 | ✓ | ✓ | ✓ | ✓ |
| | | 10 | 14 | 12 | 8 |

Steroids in CAP:



Bi et al *PLOS One* 11(11): e0165942. doi:10.1371/journal.

Steroids in CAP:

| | | Mortality (%) |
|-------------------|-------------------|---------------|
| Confalonieri | ICU admitted | 25 |
| Sabry | ICU admitted | 10 |
| Fernandez Serrano | ICU admitted | 50 |
| Nafae | | |
| El-Ghamrawy | | |
| Snijders | Hospital admitted | 5 |
| Marik | ICU admitted | 13 |
| Torres | ATS Criteria | 15 |

Bi et al *PLOS One* 11(11): e0165942. doi:10.1371/journal.

Steroids

Take-Home Message

- Evidence does not support use of corticosteroids in CAP
- ? Benefit in severely ill, ?dose
- Do not use routinely in CAP

ECMO in CAP

ECMO in CAP

State of the Art

- Increasing use for refractory respiratory failure
- Effect of Influenza pandemic
- Single specialist centre experiences published
- Outcomes and prognostic factors?

ECMO in CAP

- Extracorporeal Life Support Organization Database
- Data from > 250 International centres
- Adults (≥ 18 years) with CAP
- Aspiration and post-procedure cases excluded

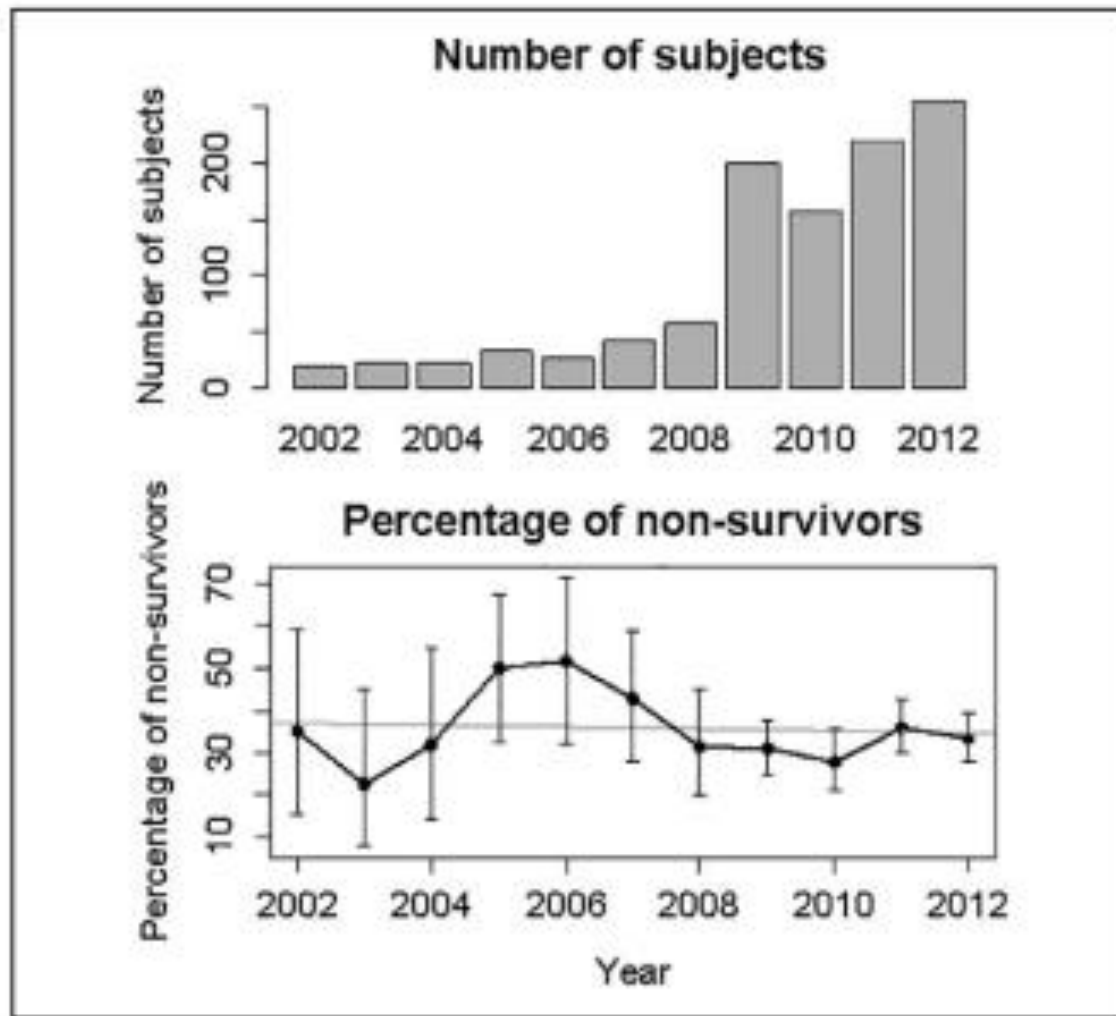
Ramanathan et al *Crit Care Med* March 2017 (epub) PMID:28252534

ECMO in CAP

- Extracorporeal Life Support Organization Database
 - Data from > 250 International centres
 - Adults (≥ 18 years) with CAP
 - Aspiration and post-procedure cases excluded
-
- N = 1055
 - 699 (66%) survived until hospital discharge
 - Median 197 hours of ECMO
 - Influenza (32%), *S pneumoniae* (14%),
Staph aureus (11%), Legionella sp (9%)
 - Multivariate analysis of factors related to outcome

Ramanathan et al *Crit Care Med* March 2017 (epub) PMID:28252534

ECMO in CAP



Ramanathan et al *Crit Care Med* March 2017 (epub) PMID:28252534

ECMO in CAP

| | | OR | p |
|-----|---------|------------------|--------|
| Age | 18-30 | 1 | 0.004 |
| | 30-4 | 0.85 (0.5 -1.44) | |
| | 41-53 | 1.45 (0.88-2.38) | |
| | >53 | 2.05 (1.24-3.39) | |
| SBP | ≤87 | 1 | <0.001 |
| | 87-105 | 0.38 (0.23-0.62) | |
| | 105-120 | 0.37 (0.22-0.62) | |
| | >120 | 0.53 (0.32-0.87) | |

Ramanathan et al *Crit Care Med* March 2017 (epub) PMID:28252534

ECMO in CAP

| | | OR | p |
|------------------------------------|--------|------------------|--------|
| Ventilation Pre-ECMO (hours) | ≤24 | 1 | <0.001 |
| | 24-62 | 1.59 (0.94-2.69) | |
| | 62-145 | 2.26 (1.34-3.83) | |
| | >145 | 3.42 (1.99-5.88) | |
| Complication Number | 1 | 1 | 0.002 |
| | 2-3 | 1.31 (0.79-2.17) | |
| | 4 | 2.61 (1.36-5.01) | |
| | ≥5 | 3.82 (1.73-8.43) | |

Also duration of ECMO, Neurological complications and fungal aetiology

Ramanathan et al *Crit Care Med* March 2017 (epub) PMID:28252534

ECMO in CAP

Take-Home Message

- Good outcome in selected patients
- Worse outcome with:
 - Prolonged pre-ECMO ventilation
 - Low arterial pressure
 - Fungal pneumonia
 - Advancing age

VAP & HAP

VAP & HAP

State of the Art

IDSA / ATS 2005

Healthcare Associated Pneumonia (HCAP)

Identified those likely to have **MDR-bacteria**

- hospitalized in an acute care hospital for two or more days within 90 days of the infection;
- residence in a nursing home or long-term care facility;
- received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection;
- or attended a hospital or hemodialysis clinic

Am J Respir Crit Care Med Vol 171. pp 388–416, 2005

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Andre C. Kalil,^{1,a} Mark L. Metersky,^{2,a} Michael Klompas,^{3,4} John Muscedere,⁵ Daniel A. Sweeney,⁶ Lucy B. Palmer,⁷ Lena M. Napolitano,⁸ Naomi P. O'Grady,⁹ John G. Bartlett,¹⁰ Jordi Carratalá,¹¹ Ali A. El Solh,¹² Santiago Ewig,¹³ Paul D. Fey,¹⁴ Thomas M. File Jr,¹⁵ Marcos I. Restrepo,¹⁶ Jason A. Roberts,^{17,18} Grant W. Waterer,¹⁹ Peggy Cruse,²⁰ Shandra L. Knight,²⁰ and Jan L. Brozek²¹

- Formal evidence base using GRADE criteria
- **Removal of Health-care Associated Pneumonia concept**
- Base antibiotics on local antibiogram
- Use clinical criteria to decide antibiotic commencement
- Procalcitonin guided antibiotic discontinuation
- Empirical VAP antibiotic duration 7 days

Clinical Infectious Diseases 2016;63(5):e61–111

Recommended Initial Empiric Antibiotic Therapy for **Hospital-Acquired Pneumonia** (Non-Ventilator-Associated Pneumonia)

Low risk death
Low risk MRSA

One of:

Piperacillin-tazobactam
Cefipime
Levofloxacin
Imipenem
Meropenem

Low risk death
Increased risk MRSA

One of:

Piperacillin-tazobactam
Cefipime/ceftazidime
Levofloxacin/ciprofloxacin
Imipenem
Meropenem
Aztreonam

**High risk death or
Iv Antibiotic within 90 d**

Two of:

Piperacillin-tazobactam
Cefipime/ceftazidime
Levofloxacin/ciprofloxacin
Imipenem
Meropenem
Amikacin/gent/tobra micin
Aztreonam
+
Vancomycin or Linezolid

Clinical Infectious Diseases 2016;63(5):e61–111

VAP & HAP

Take-Home Message

- **Do not use Health-care Associated Pneumonia concept**
- Base antibiotics on local antibiogram
- Use clinical criteria to decide antibiotic commencement
- Use Procalcitonin to guide antibiotic discontinuation
- Empirical VAP antibiotic duration 7 days

List of References

- Othman et al *BMJ* 2016;355:i5813
- van Vugt et al. *BMJ*. 2013; 346:f2450–f2450. doi: 10.1136/bmj.f2450
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- Ramanathan et al *Crit Care Med* March 2017 (epub) PMID:28252534
- *Am J Respir Crit Care Med* Vol 171. pp 388–416, 2005
- *Clinical Infectious Diseases* 2016;63(5):e61–111

List of Abbreviations

- PPI Proton pump inhibitor
- CAP Community-acquired Pneumonia
- HAP hospital-acquired Pneumonia
- VAP Ventilator-associated Pneumonia
- HCAP Healthcare-associated Pneumonia
- CPRD Clinical Practice Research Database
- LRTI Lower respiratory Tract Infection
- IRR Incident rate Ratio
- CXR Chest X-ray
- GP general practitioner
- CRP C-reactive Protein
- RCT Randomised Controlled Trial
- ERS European Respiratory Society
- NICE National Institute for Health and Care Excellence
- ECMO Extra-corporeal membrane Oxygenation