



Efficacy, use and dosing of colistin: what have contemporary studies taught us?

Mical Paul

Rabin Medical Center, Beilinson Hospital

Tel-Aviv University

Israel



Infectious Diseases University Research Center

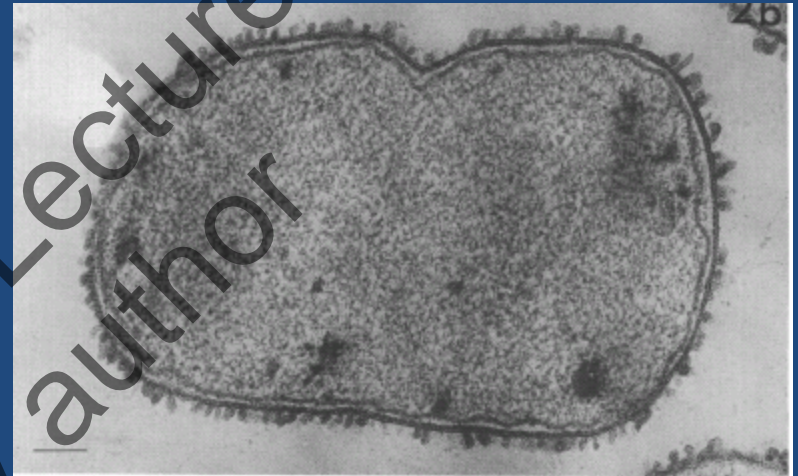
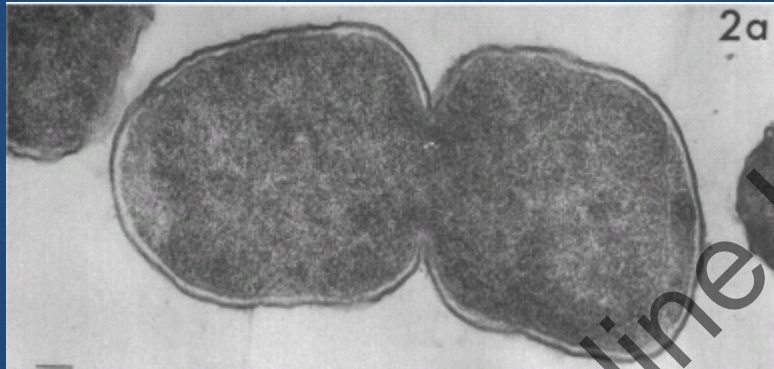
Colistin activity

- Polymyxin E1 + polymyxin E2
- Electrostatic binding to LPS molecules on the cell membrane, causing disruption of the membrane

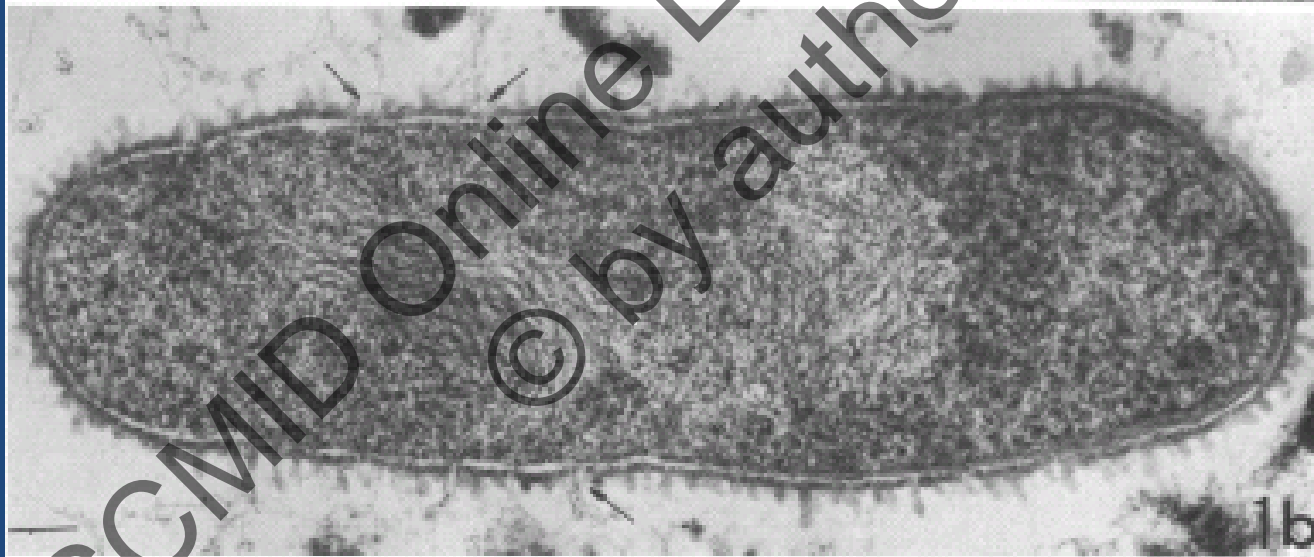
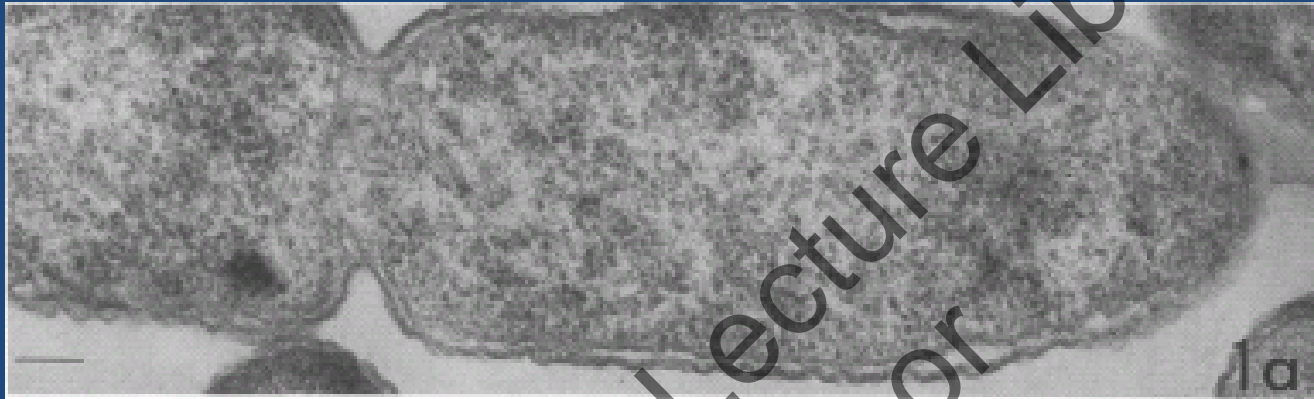
 ? Bacterial cell death

- Binding to LPS may also block the biologic effects of this endotoxin

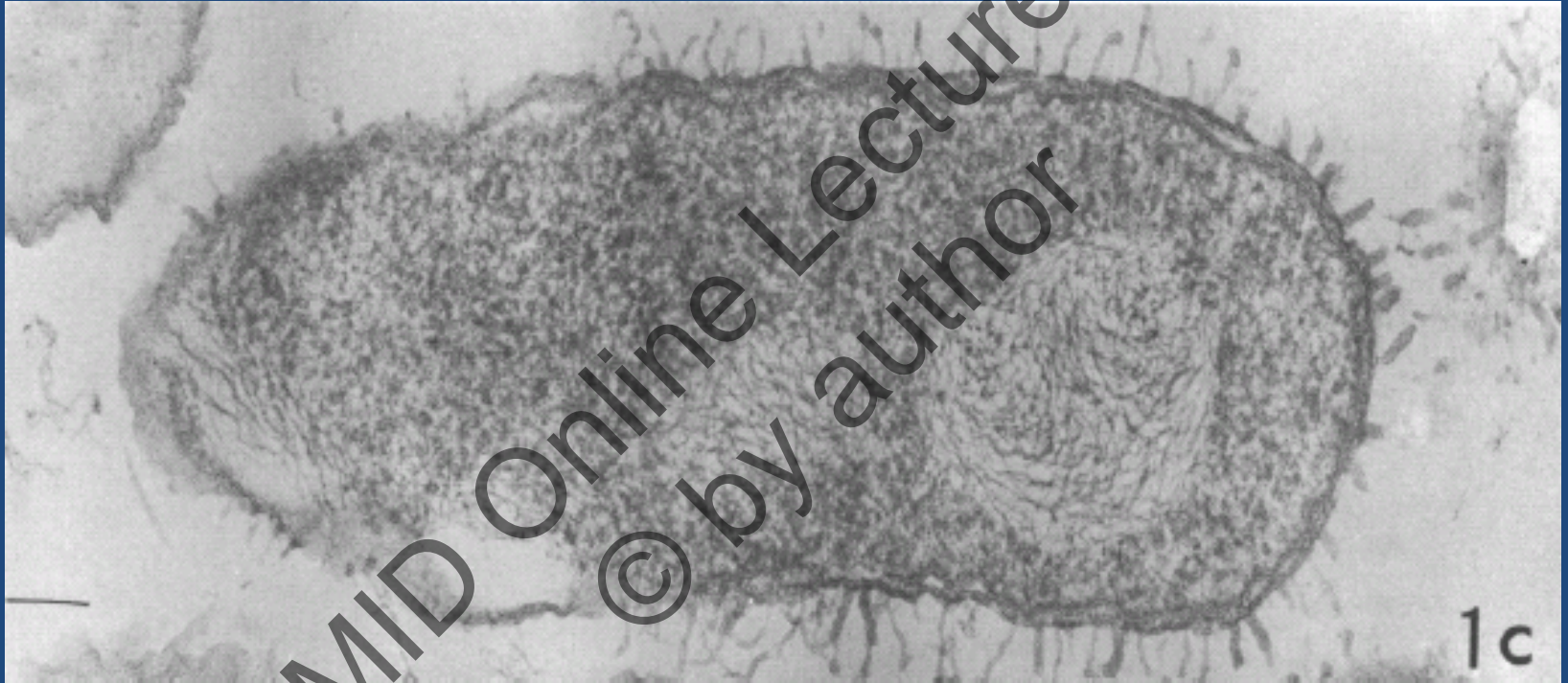
E. coli : before/ after



P. aeruginosa: before/ after



P. aeruginosa: after



Spectrum of activity

- Aerobic Gram-negative rods; exceptions
 - *Proteus*
 - *Providencia*
 - *Serratia*
 - *Brucella*
 - *Edwardsiella* species, *Pseudomonas mallei* and *Burkholderia cepacia*
- EUCAST MIC breakpoint 2 mg/L for *Acinetobacter sp.* and enterobacteriaceae, and 4 mg/L for *Pseudomonas sp.*
- No activity against Gram-positive bacteria and anaerobes

Unit conversions

1 mg colistin base activity (CBA) ~ 33,250 IU

5 mg/kg (350mg/day CBA) ~ 11.5 MIU/ day

1 mg colistimethate sodium (CMS) ~ 12,500 IU

6 MIU ~ 720 mg CMS ~ 3.9 mg/kg CBA

Systemic use of colistin

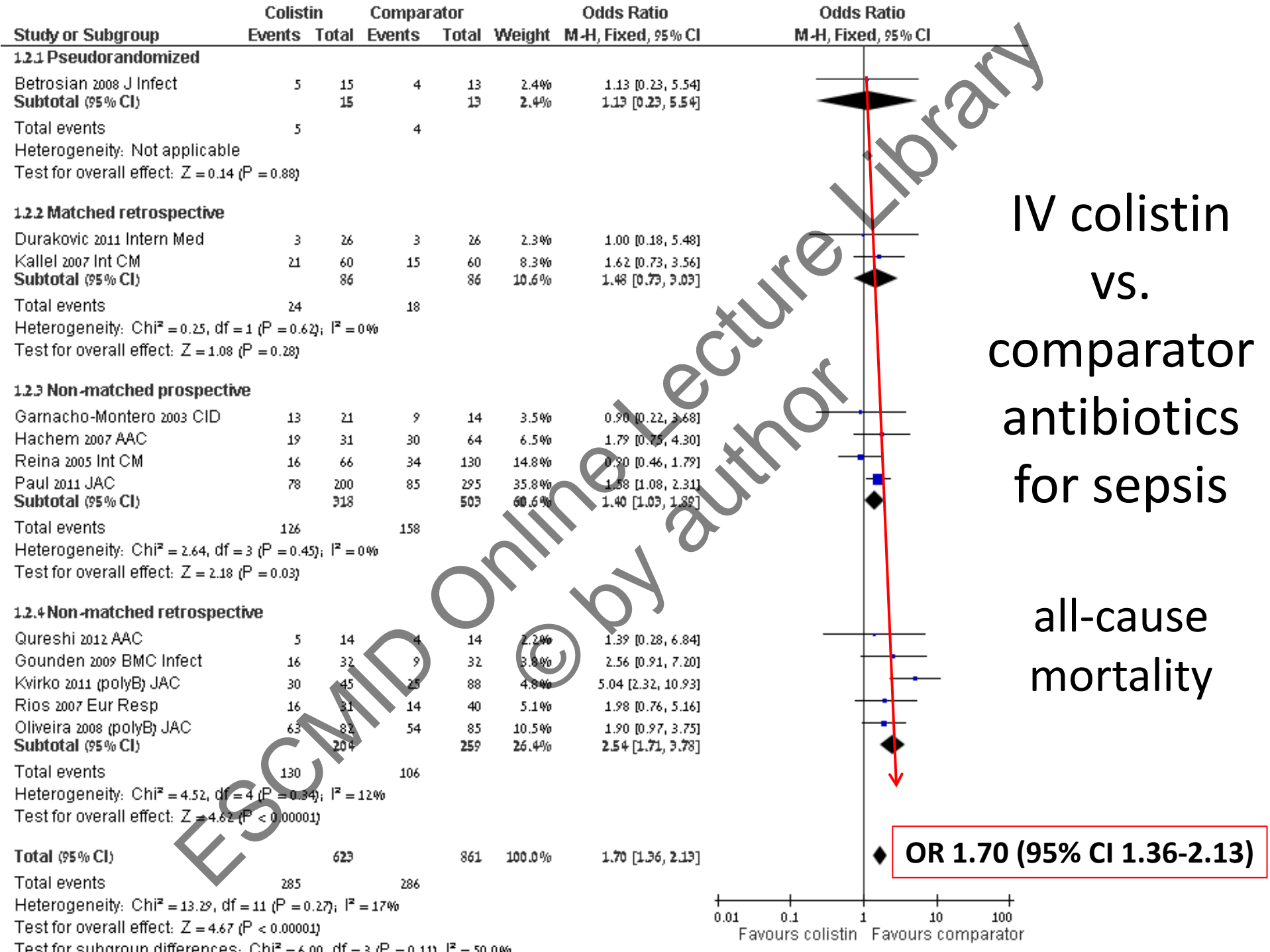
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Clinical studies

- Information relies on observational studies
- Mostly retrospective

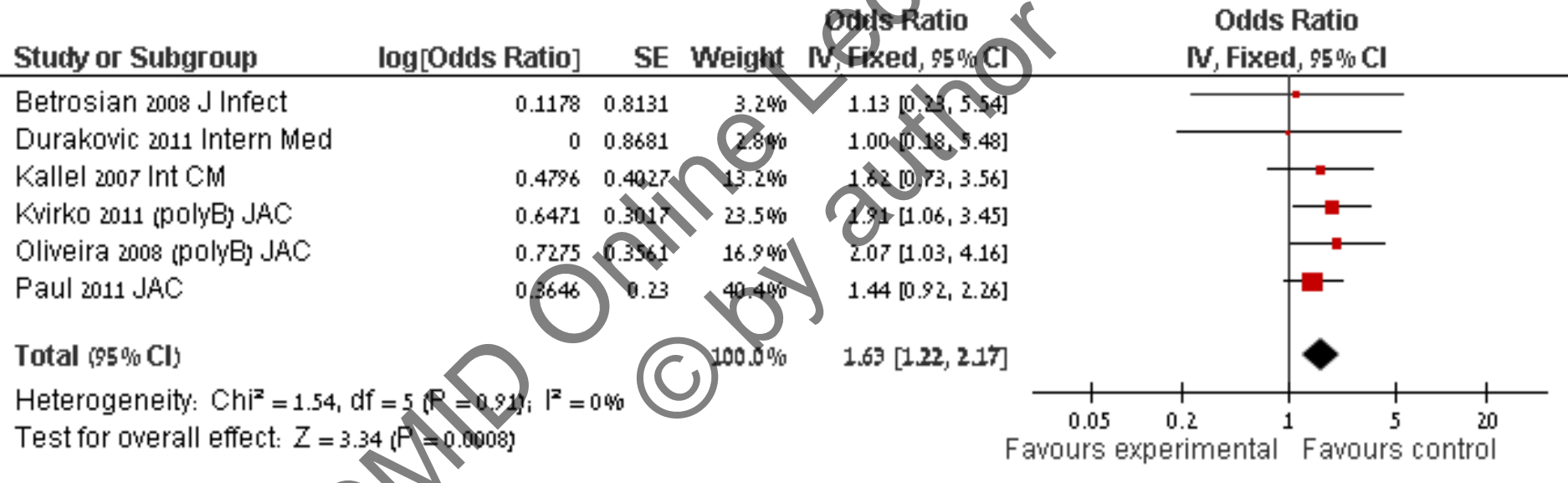
Cause and effect difficult to establish...

- Mix of infections
- Mix of bacteria
- Mix of antibiotics
- Monotherapy/ combinations



IV colistin vs. comparator antibiotics for sepsis

all-cause mortality - adjusted analysis



OR 1.63 (95% CI 1.22-2.17)



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46% 33%

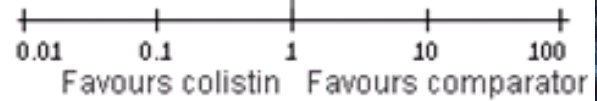
Total (95% CI) 623 861 100.0% 1.70 [1.36, 2.13]

Total events 285 286

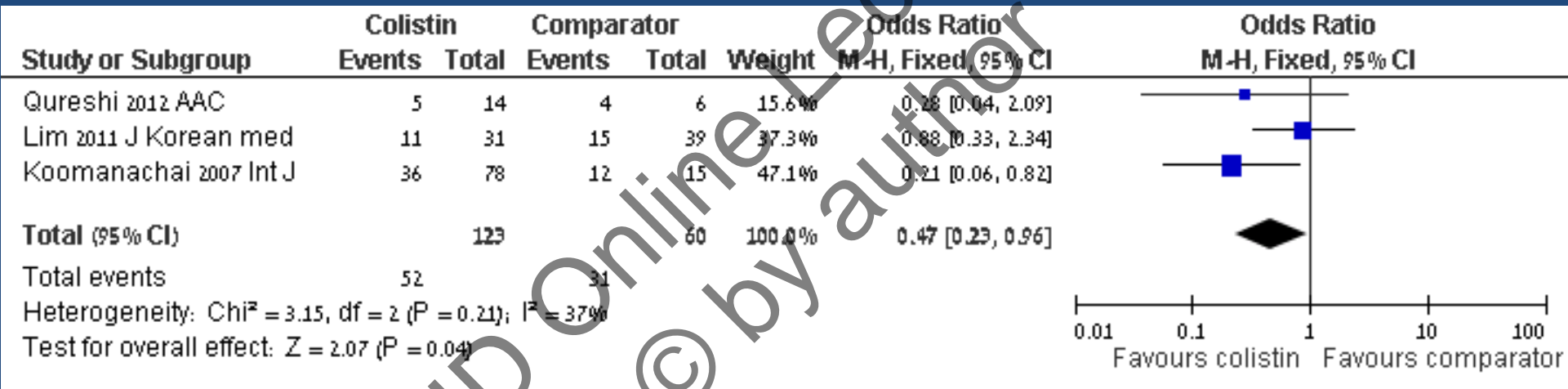
Heterogeneity: $\text{Chi}^2 = 13.29$, $\text{df} = 11$ ($I^2 = 0.27$); $I^2 = 17\%$

Test for overall effect: $Z = 4.67$ ($P < 0.00001$)

Test for subgroup differences: $\text{Chi}^2 = 6.00$, $\text{df} = 3$ ($I^2 = 50.0\%$)



Colistin vs. inappropriate antibiotics all-cause mortality



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Dosing and clinical outcomes

- Retrospective cohort study, 2000-2007, Henry Dunant Hospital, Athens, Greece
- Overall 258 patients, 222 (86%) hospitalised in the ICU

In-hospital mortality (%)	3 MIU	6 MIU	9 MIU
All	38.6%	27.8%	21.7%
Normal RF	34.3%	27.6%	19.5%



Dosing and clinical outcomes multivariate

Multivariable analysis, in-hospital survival	aOR (95% CI)
Higher daily colistin dose	1.22 (1.05-1.42)
Cure of infection	9 (3.6-23.1)
Higher APACHE II score	0.89 (0.84–0.95)
Rise in creatinine	0.21 (0.1–0.45)
Haematological disease	0.23 (0.08–0.66)



Hieronymus Bosch. Allegory of Gluttony and Lust. 1490-1500

Falagas and Karageorgopoulos
Lancet 2010

Colistin toxicity

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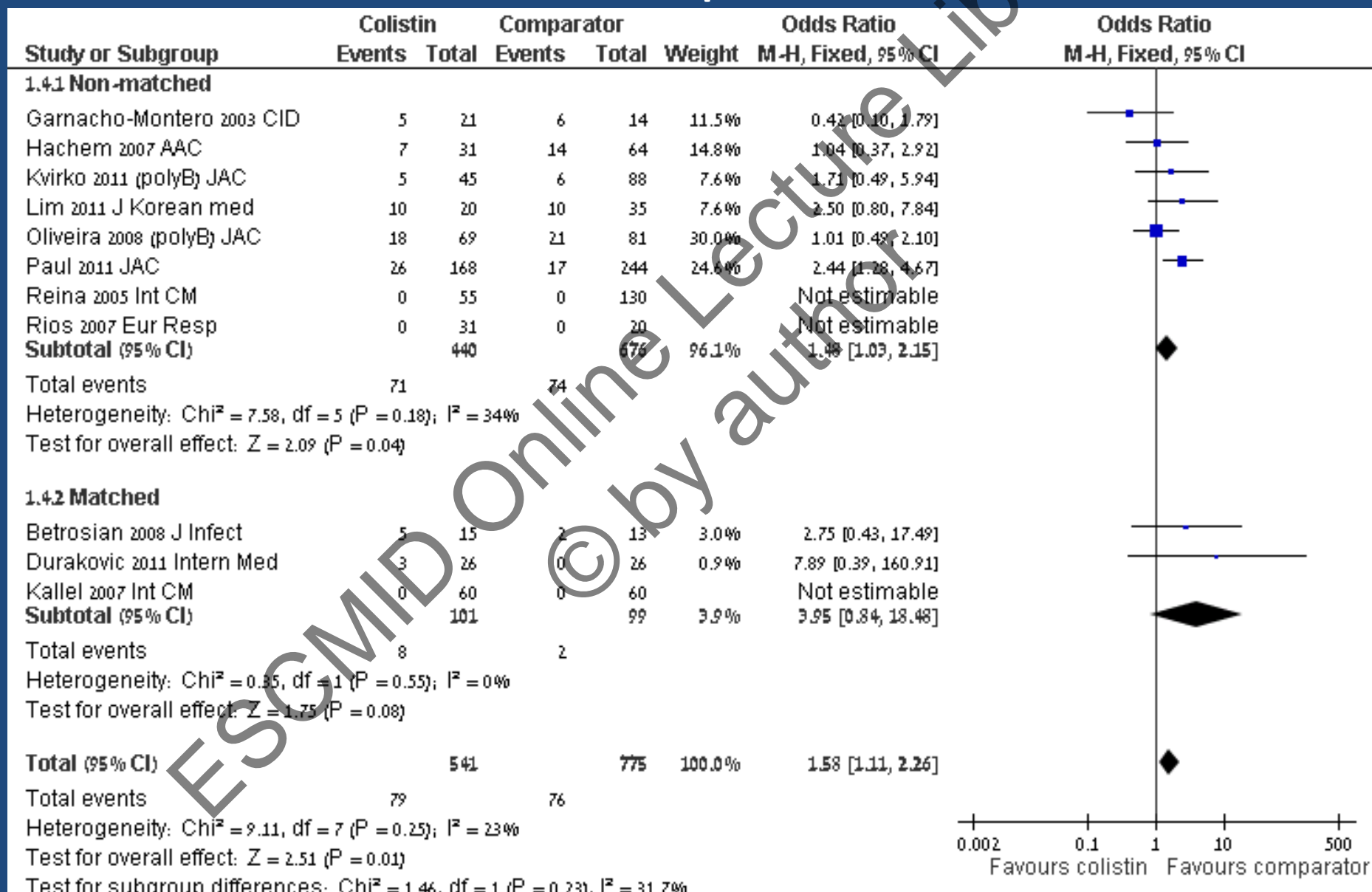
Colistin-related nephrotoxicity

Mechanism

- Increased membrane permeability, cell swelling and lysis (bladder)
- Oxidative stress



Nephrotoxicity for colistin vs. comparators in sepsis



“Interesting” risk factors for nephrotoxicity

- Obesity (BMI ≥ 31.5 kg/m²)¹
- Dosing of ≥ 5.0 mg/kg /day CBA (~ 11.5 MIU/day): adjusted OR 15.3, 23; dosing ≥ 3.0 mg/kg/day (~7 MIU/day): adjusted OR 3^{2, 3}
- Cumulative dose - duration²⁻⁵
- Male sex⁵

¹ Gauthier et al. Antimicrob Agents Chemother 2012; ² Rattanaumpawan J Infect 2011; ³ Pogue et al. Clin Infect Dis 2011 ⁴ Hartzell et al. Clin Infect Dis 2009; ⁵ Kwon et al. Int J Antimicrob Agents 2010

Protection from colistin-induced nephrotoxicity

- Avoidance of concomitant nephrotoxic agents (including IV contrast material) ¹

In-vivo studies:

- Ascorbic acid ²
- N-acetylcysteine ³
- Melatonin ⁴

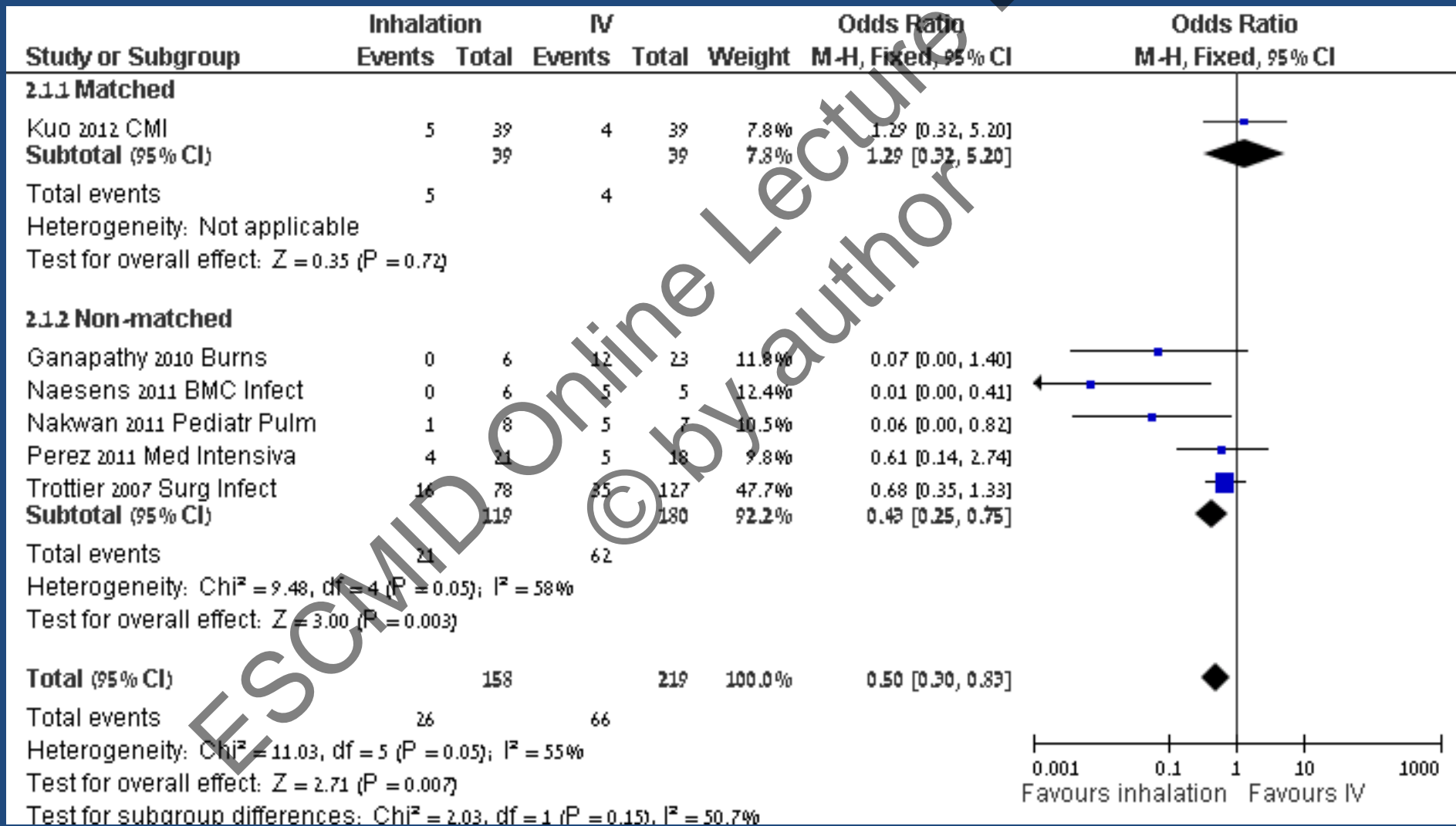
¹ Doshi et al. Pharmacotherapy 2011; ² Yousef et al. J Antimicrob Chemother 2012; ³ Ozyilmaz et al. Intensive Care Med 2011; ⁴ Yousef et al. J Antimicrob Chemother 2011

Inhaled colistin for VAP/ HAP

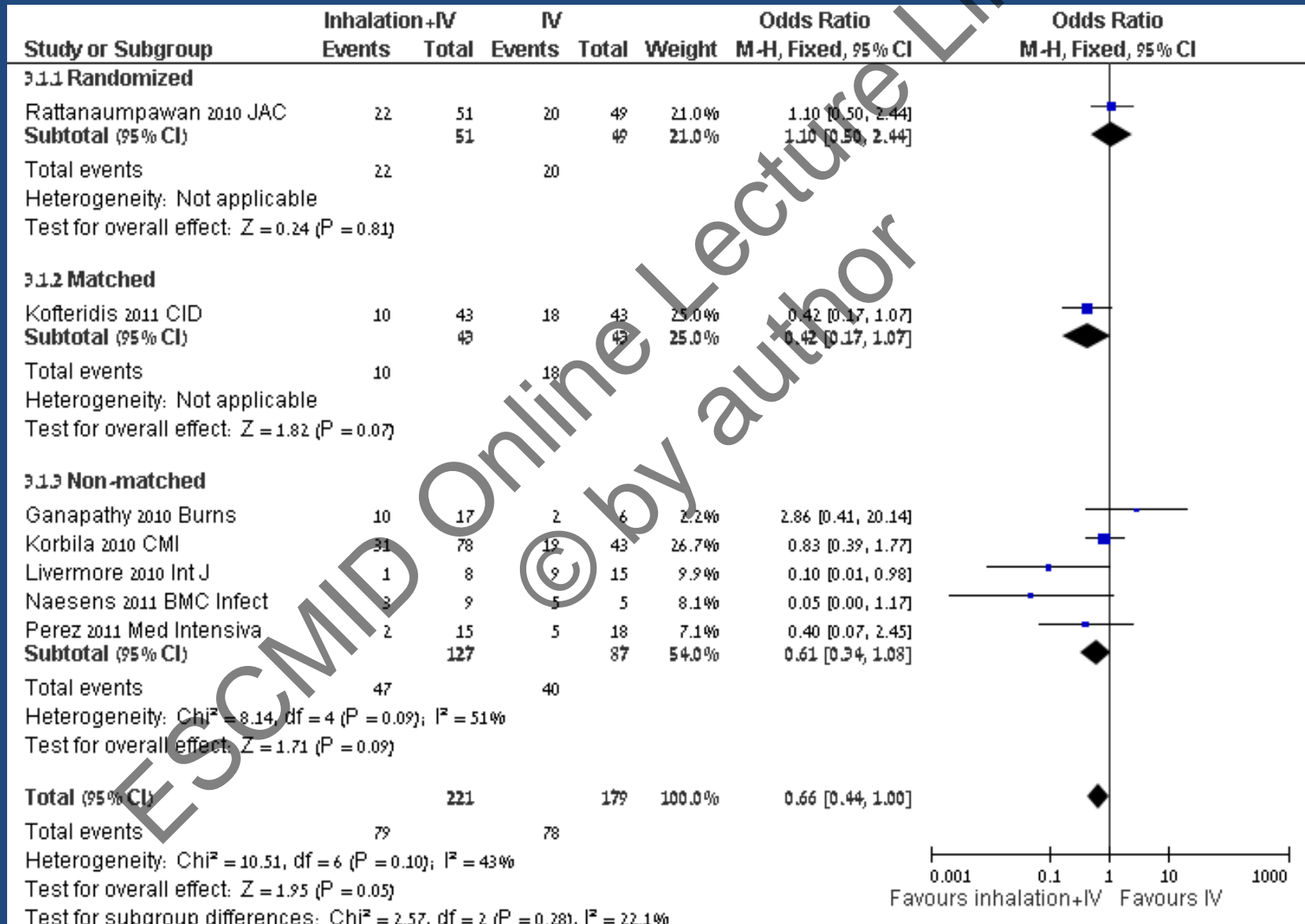
Ventilator-associated pneumonia

Hospital-acquired pneumonia

Colistin inhalation vs. systemic antibiotics all-cause mortality



Systemic + inhalation colistin vs. systemic antibiotics all-cause mortality



Administration of inhaled colistin

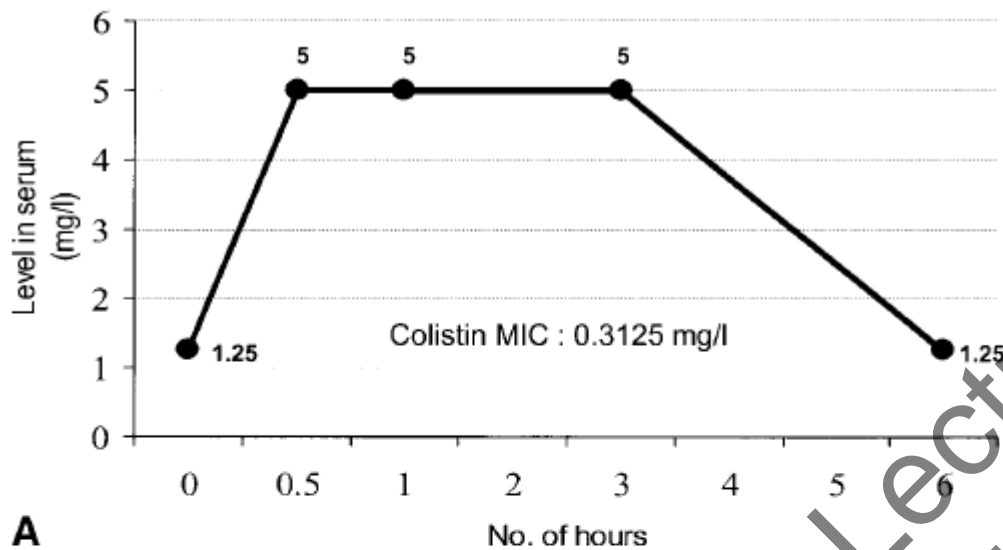
- Usual dose of 80 mg (1,000,000 IU) q12h in adults
- Up to 60 mg (2,000,000 IU) q8h
- Admixed with 4 ml of normal saline or sterile water
- Administered promptly after mixing to avoid hydrolysis of colistin in water



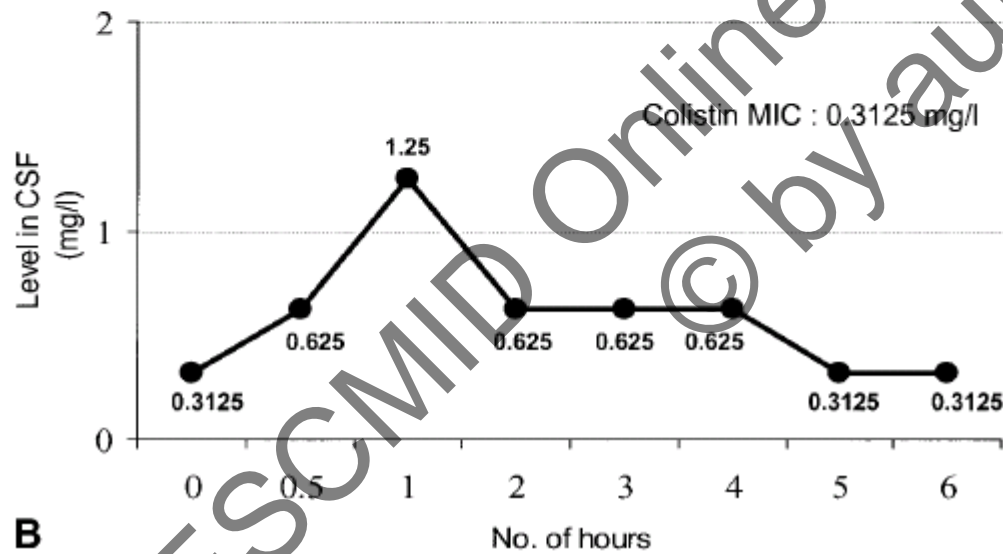
Colistin for meningitis

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Colistin penetration to CSF



A



B

Study	CMS dose mg (MIU) /kg/day	Serum µg/ml	CSF µg/ml	CSF/ serum	Serum µg/ml	CSF µg/ml	CSF/ serum
Adults ¹	30-60 min. after IV dose				Before next IV dose		
1 *	8.3 (0.1)	1.55	0.083	5.4%			
2 *	10.1 (0.13)	1.92	0.099	5.2%			
3 *	4.4 (0.05)	0.82	0.043	5.3%			
4	8.3 (0.1)	1.55	0.083	5.4%	0.82	0.042	5.1%
5	2 (0.02)	1.53	0.088	5.7%	0.87	0.048	5.5%
Children ²							
1	4.8 (0.06)	0.29	0.06	19.3%	0.19	0.05	25.2%
1	10.4 (0.13)	1.46	0.05	3.4%	0.52	0.06	11.1%
1 **	16 (0.2)	1.33	0.46	34.8%	0.73	0.50	67.7%
2 *	16 (0.2)	1.60	0.11	7.2%	0.97	0.15	16.1%
3	18 (0.23)	2.20	0.07	3.2%	2.29	0.07	3%

* Meningitis ** meningitis with inflammation. ¹ Markantonis et al. AAC 2009;

² Antachopoulos et al. AAC 2010

IV vs. IV + intrathecal colistin

- Two tertiary university hospitals in Madrid ¹
- All cases of adult neurosurgical *A. baumannii* meningitis

	N patients	N deaths (%)
IV beta-lactam *	29	11 (37.9%)
IV carbapenem + IT aminoglycoside	9	2 (22.2%)
IV colistin + IT colistin	8	0 (0%)
IT colistin/ polymyxin B ²	7 cases, 6 cures	

• Mostly carbapenems (24) or ampicillin-sulbactam (4) monotherapy. Combination with IV aminoglycoside in 2 cases. ¹Rodriguez Guardado et al. *J Antimicrob Chemother* 2008

²Falagas et al. *Int J Antimicrob Agents* 2007

Intrathecal/ intraventricular colistin

- Case series and literature review ^{1,2}
- Concomitant IV antibiotics usually

	Intrathecal N=15	Intraventricular N=24
Death	2	5
Relapse	1	1
Chemical meningitis	2	1
Other neurological toxicity	1/8	1

- In a systematic review of case reports on all IT/IV polymyxins, cure in 51/64 (80%) and major toxicity in 17/60 (28%) ³

¹ Cascio et al. Int J Infect Dis; ² Khawcharoenporn et al. Clin Microbiol Infect 2010;

³ Falagas et al. Int J Antimicrob Agents

IT/ IV colistin administration

- Usual dosing 2-20 mg (25,000 – 250,000 IU) q24 hr (sometimes divided to q12h)
- Recent series up to 40mg (500,000 IU) per day
- The most common toxicity is chemical meningitis (up to 25%) manifested by pleocytosis with negative cultures +/- clinical manifestations
- The feared toxicity is neurological (seizures)

Summary and open questions

Colistin probably somewhat less effective than beta-lactams and more toxic

Prevent carbapenem-resistant infection

Improve efficacy and safety profile of colistin

Compare colistin with aminoglycoside

Dosing/ schedule

Combination therapy

Prevention of nephrotoxicity

More questions than answers

Questionable benefit of colistin inhalations

Ecological effects?

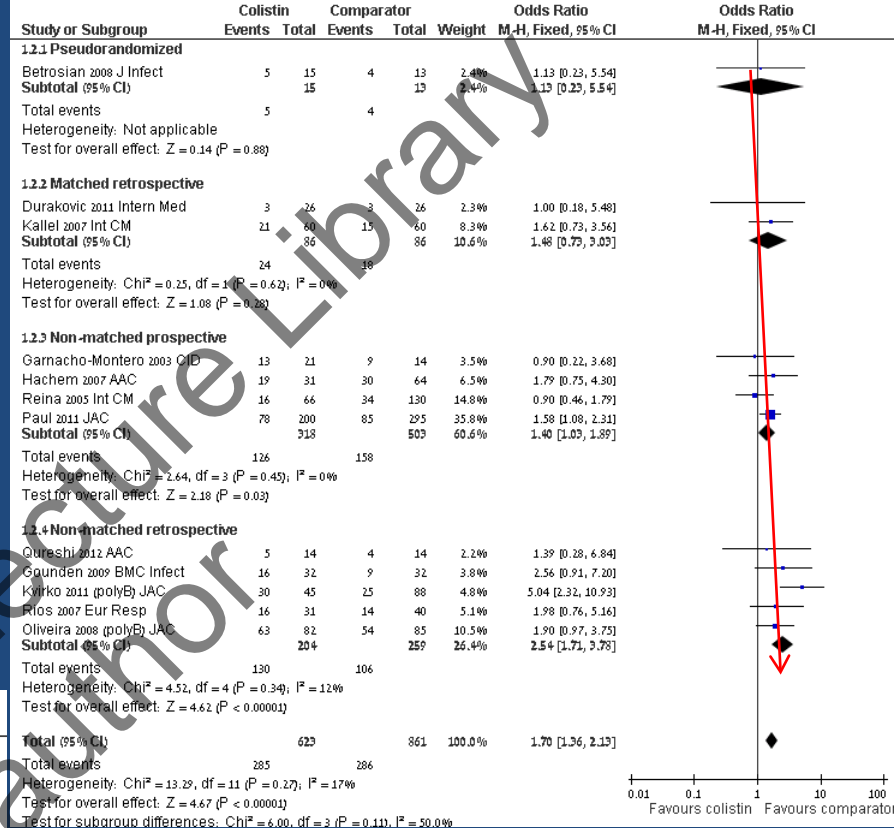
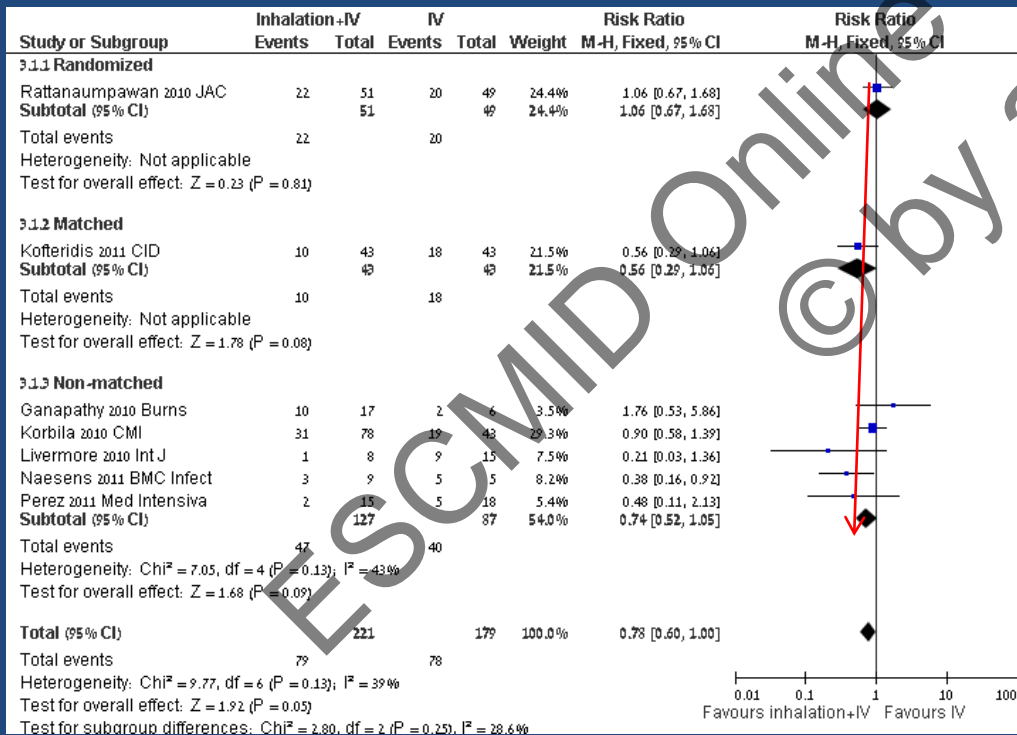
Proof needed

Probable efficacy of IT/IV colistin for Acinetobacter meningitis

With/ without systemic colistin?

IT colistin vs. aminoglycoside?

Finally



We need randomized controlled trials

The Future: registered RCTs

Combination therapy

- Colistin vs. colistin+imipenem for treatment of documented carbapenem-resistant bacteremia or VAP (2 trials, AIDA, NIH)
- Colistin vs. meropenem as empirical treatment for VAP with suspicion of multi-resistant Gram-negative bacteria (MAGIC BULLET)
- Colistin vs. colistin+fosfomycin for *A. baumannii* infections
- Colistin vs. colistin+rifampin for *A. baumannii* or *P. aeruginosa* infections

Other

- IV vs. nebulized+IV colistin for VAP/ HAP (2 trials)
- Colistin vs. colistin+ascorbic acid for prevention of colistin-associated nephrotoxicity

Thank you

Conflicts of interests: none



