Are polymyxins effective? A meta-analysis of polymyxin use

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Outcomes to examine in observational studies

- Clinical failure
- Microbiological failure
- Infection-related mortality
- Mortality
- Nephrotoxicity

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Literature review

- Comparative clinical studies
  - Covering systemic colistin/ polymyxin B vs. comparator/s
  - Examining patients with sepsis
  - Reporting on mortality
- Regardless of types of infection, bacteria, dosing
- Published in the last decade
- PubMed search

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Description of studies I

Study	Location	Infection	Bacteria
Betrosian 2008	Greece	VAP	Acinetobacter
Durakovic 2010	Croatia	P. aeruginosa infections / hematology	P. aeruginosa
Garnacho-Montero 2003	Spain	VAP	A. baumannii
Gounden 2009	South Africa	ICU infections	A. baumannii
Hachem 2007	US, Texas	P. aeruginosa infections/ cancer	P. aeruginosa
Kallel 2007	Tunisia	VAP	A. baumanii or P. aeruginosa
Ku 2012	US, Detroit	any nosocomial	Acinetobacter, Klebsiella
Kvitko 2011	Brazil	P. aeruginosa bacteremia	P. aeruginosa
Oliveira 2008	Brazil	any nosocomial	Acinetobacter
Paul 2010	Israel	any nosocomial	Acinetobacter, Klebsiella
Reina 2005	Argentina	ICU infections	A. baumanii or P. aeruginosa
Rigatto 2013	Brazil	VAP or VAT	A. baumanii or P. aeruginosa
Rios 2007	Argentina	VAP	A. baumanii or P. aeruginosa

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Description of studies II

Study	P	Dose	Combi	Comparator
Betrosian 2008	C	9 MU	No	Ampicillin/ sulbactam
Durakovic 2010	C	9 MU	Yes	Beta-lactams
Garnacho-Montero 2003	C	2.5–5.0 mg/kg	NR	Imipenem
Gounden 2009	C	4 MU	NR	Tobramycin
Hachem 2007	C	5 mg/kg	Yes	Antipseudomonal
Kallel 2007	C	6 MU	NR	Imipenem
Ku 2012	C	NR	NR	Tigecycline
Kvitko 2011	P	141+-54 mg	NR	Antipseudomonals
Oliveira 2008	C or P	NR	NR	ampicillin/sulb
Paul 2010	C	6 MU	NR	Imipenem, meropenem or ampicillin/ sulbactam
Reina 2005	C	5 mg/kg	No	Any
Rigatto 2013	P	med 150 mg	NR	Beta-lactams
Rios 2007	C	5 mg/kg	NR	Imipenem or meropenem

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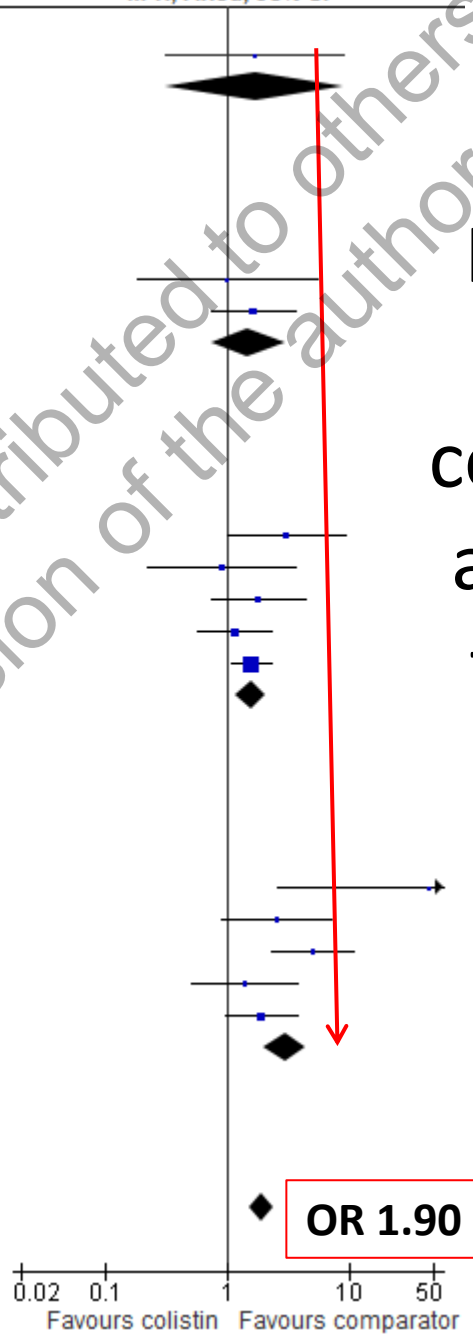
Study or Subgroup	Colistin Events	Total	Comparator Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Pseudorandomized						
Betrosian 2008 J Infect	5	15	3	13	1.9%	1.67 [0.31, 8.93]
Subtotal (95% CI)		**15**		**13**	**1.9%**	**1.67 [0.31, 8.93]**
Total events	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.2.2 Matched retrospective						
Durakovic 2011 Intern Med	3	26	3	26	2.3%	1.00 [0.18, 5.48]
Kallel 2007 Int CM	21	60	15	60	8.5%	1.62 [0.73, 3.56]
Subtotal (95% CI)		**86**		**86**	**10.8%**	**1.48 [0.73, 3.03]**
Total events	24		18			
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
1.2.3 Non-matched prospective						
Rigatto 2013 Infection	24	45	6	22	3.3%	3.05 [1.01, 9.21]
Garnacho-Montero 2003 CID	13	21	9	14	3.6%	0.90 [0.22, 3.68]
Hachem 2007 AAC	19	31	30	64	6.6%	1.79 [0.75, 4.30]
Reina 2005 Int CM	16	55	34	130	12.4%	1.16 [0.57, 2.34]
Paul 2011 JAC	78	200	85	295	36.3%	1.58 [1.08, 2.31]
Subtotal (95% CI)		**352**		**525**	**62.1%**	**1.56 [1.16, 2.08]**
Total events	150		164			
Heterogeneity: Chi² = 2.79, df = 4 (P = 0.59); I² = 0%						
Test for overall effect: Z = 2.97 (P = 0.003)						
1.2.4 Non-matched retrospective						
Ku 2012 AJIC	26	45	0	16	0.3%	44.85 [2.53, 793.82]
Gounden 2009 BMC Infect	16	32	9	32	3.9%	2.56 [0.91, 7.20]
Kvitko 2011 (polyB) JAC	30	45	25	88	4.9%	5.04 [2.32, 10.93]
Rios 2007 Eur Resp	16	31	13	30	5.5%	1.39 [0.51, 3.83]
Oliveira 2008 (polyB) JAC	63	82	54	85	10.7%	1.90 [0.97, 3.75]
Subtotal (95% CI)		**235**		**251**	**25.2%**	**2.96 [1.99, 4.39]**
Total events	151		101			
Heterogeneity: Chi² = 9.10, df = 4 (P = 0.06); I² = 56%						
Test for overall effect: Z = 5.36 (P < 0.00001)						
Total (95% CI)		**688**		**875**	**100.0%**	**1.90 [1.53, 2.37]**
Total events	330		286			
Heterogeneity: Chi² = 16.80, df = 12 (P = 0.16); I² = 29%						
Test for overall effect: Z = 5.76 (P < 0.00001)						
Test for subgroup differences: Chi² = 7.07, df = 3 (P = 0.07), I² = 57.6%						



IV colistin vs. comparator antibiotics for sepsis

all-cause mortality

OR 1.90 (95% CI 1.53-2.33)

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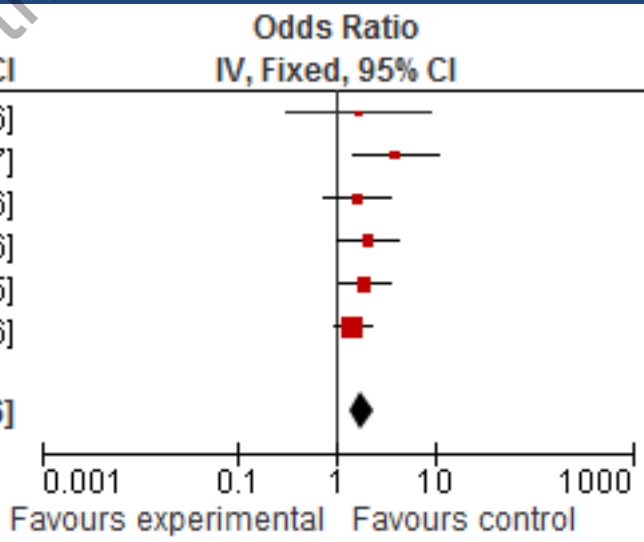
IV colistin vs. comparator antibiotics for sepsis

all-cause mortality - adjusted analysis

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Betrosian 2008 J Infect	0.512824	0.857296	2.8%	1.67 [0.31, 8.96]
Rigatto 2013 Infection	1.360977	0.51843	7.6%	3.90 [1.41, 10.77]
Kallel 2007 Int CM	0.4796	0.4027	12.6%	1.62 [0.73, 3.56]
Oliveira 2008 (polyB) JAC	0.7275	0.3561	16.1%	2.07 [1.03, 4.16]
Kvitko 2011 (polyB) JAC	0.6471	0.3017	22.4%	1.91 [1.06, 3.45]
Paul 2011 JAC	0.3646	0.23	38.6%	1.44 [0.92, 2.26]
Total (95% CI)			**100.0%**	**1.79 [1.35, 2.36]**

Heterogeneity: $Chi^2 = 3.44$, $df = 5$ ($P = 0.63$); $I^2 = 0\%$

Test for overall effect: $Z = 4.06$ ($P < 0.0001$)



Adjusted OR 1.79 (95% CI 1.35-2.36)

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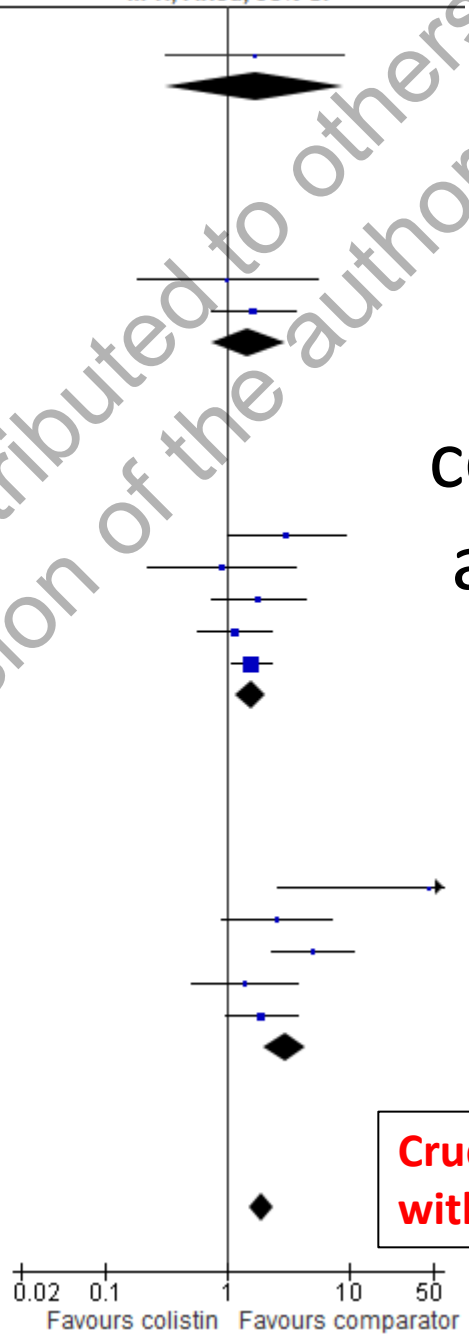
Total (95% CI)		**688**		**875**	**100.0%**	**1.90 [1.53, 2.37]**
Total events	330		286			
Heterogeneity: Chi² = 16.80, df = 12 (P = 0.16); I² = 29%						
Test for overall effect: Z = 5.76 (P < 0.00001)						
Test for subgroup differences: Chi² = 7.07, df = 3 (P = 0.07), I² = 57.6%						



IV colistin vs. comparator antibiotics for sepsis

all-cause mortality

Crude mortality 48% with colistin

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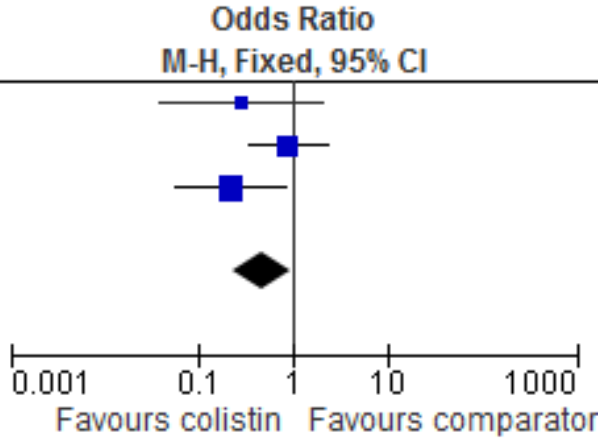
Colistin vs. inappropriate antibiotics

all-cause mortality - unadjusted

Study or Subgroup	Colistin Events	Colistin Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Qureshi 2012 AAC	5	14	4	6	15.6%	0.28 [0.04, 2.09]
Lim 2011 J Korean med	11	31	15	39	37.3%	0.88 [0.33, 2.34]
Koomanachai 2007 Int J	36	78	12	15	47.1%	0.21 [0.06, 0.82]
Total (95% CI)		**123**		**60**	**100.0%**	**0.47 [0.23, 0.96]**
Total events	52		31			

Heterogeneity: $Chi^2 = 3.15$, $df = 2$ ($P = 0.21$); $I^2 = 37\%$

Test for overall effect: $Z = 2.07$ ($P = 0.04$)



OR 0.47 (95% CI 0.23-0.96)

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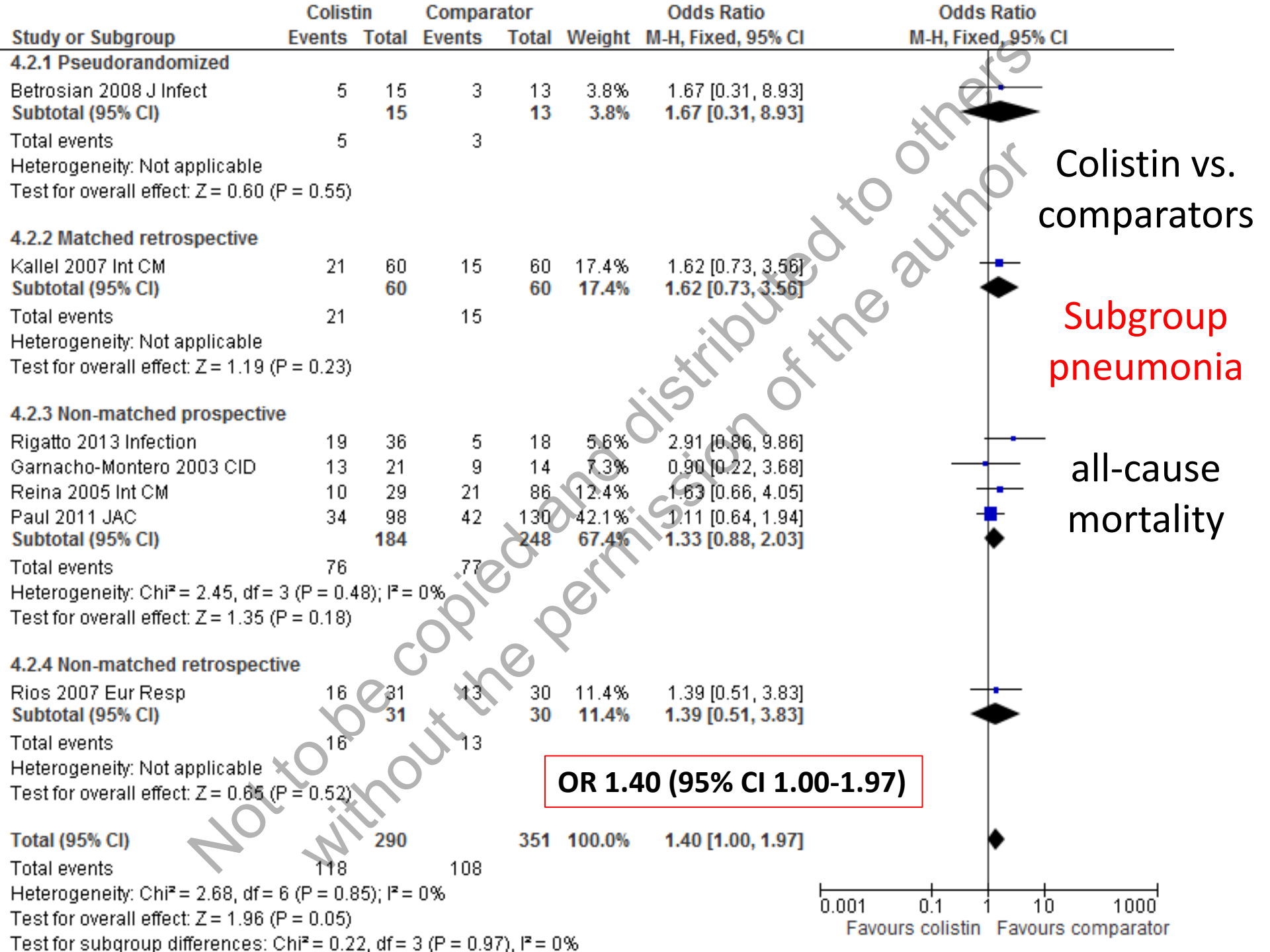

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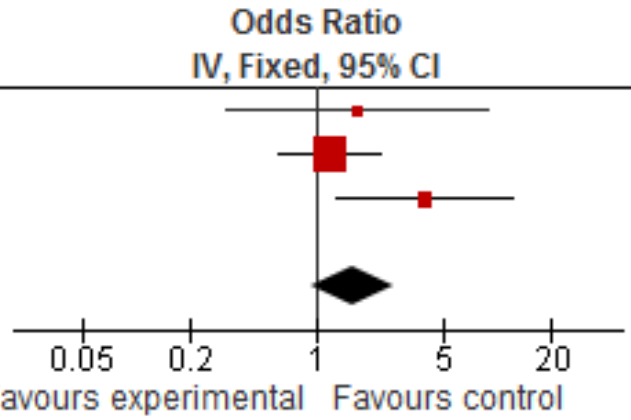
IV colistin vs. comparator antibiotics for pneumonia

all-cause mortality - adjusted analysis

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Betrosian 2008 J Infect	0.512824	0.857296	9.9%	1.67 [0.31, 8.96]
Paul 2011 JAC	0.165514	0.328477	67.7%	1.18 [0.62, 2.25]
Rigatto 2013 Infection	1.376244	0.571904	22.3%	3.96 [1.29, 12.15]
Total (95% CI)			**100.0%**	**1.60 [0.94, 2.72]**

Heterogeneity: Chi² = 3.37, df = 2 (P = 0.19); I² = 41%
Test for overall effect: Z = 1.74 (P = 0.08)



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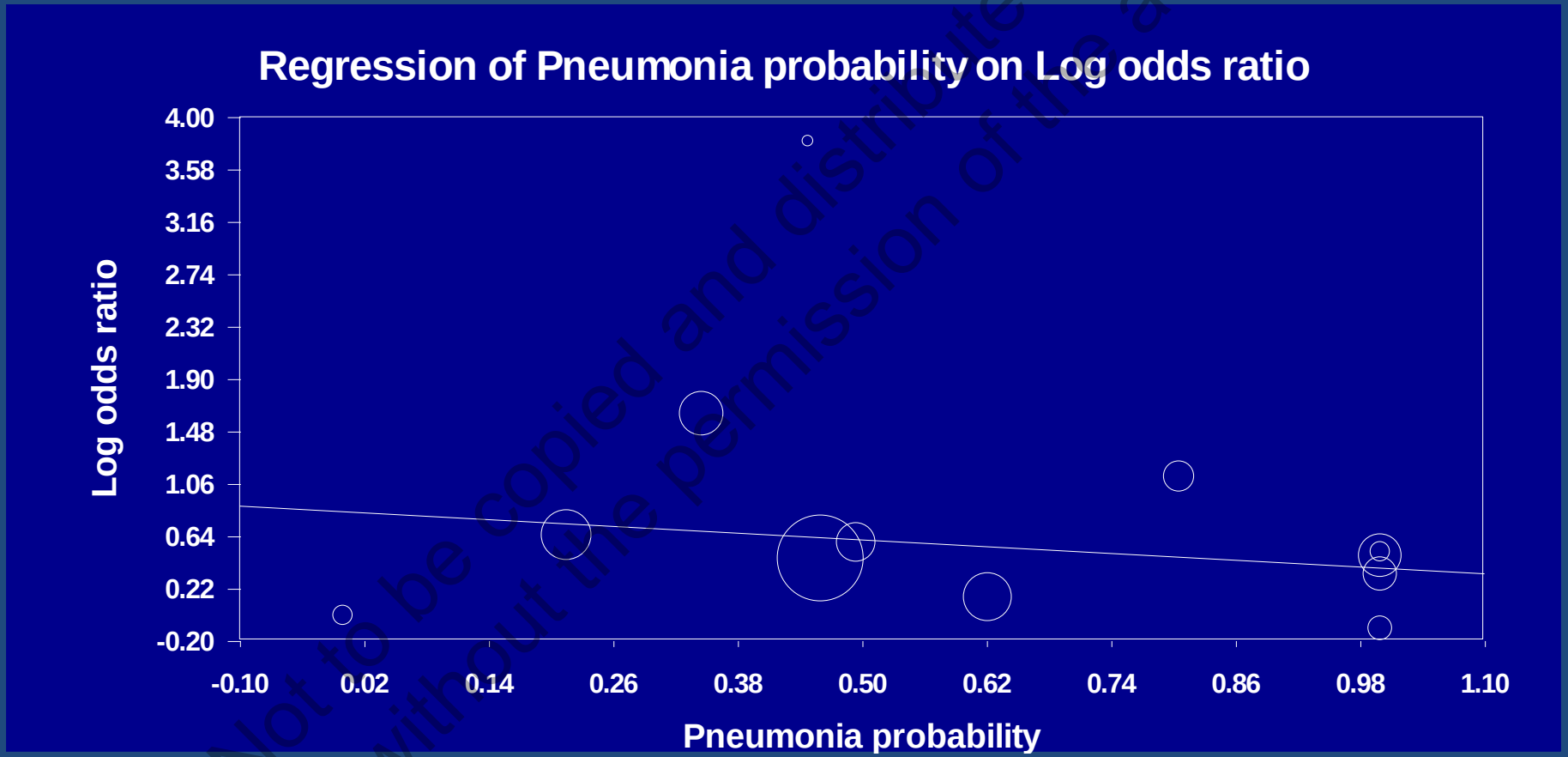
Adjusted OR 1.60 (95% CI 0.94-2.72)

IV colistin vs. comparator antibiotics for sepsis, all-cause mortality

Meta-regression pneumonia rate



Slope non-significant

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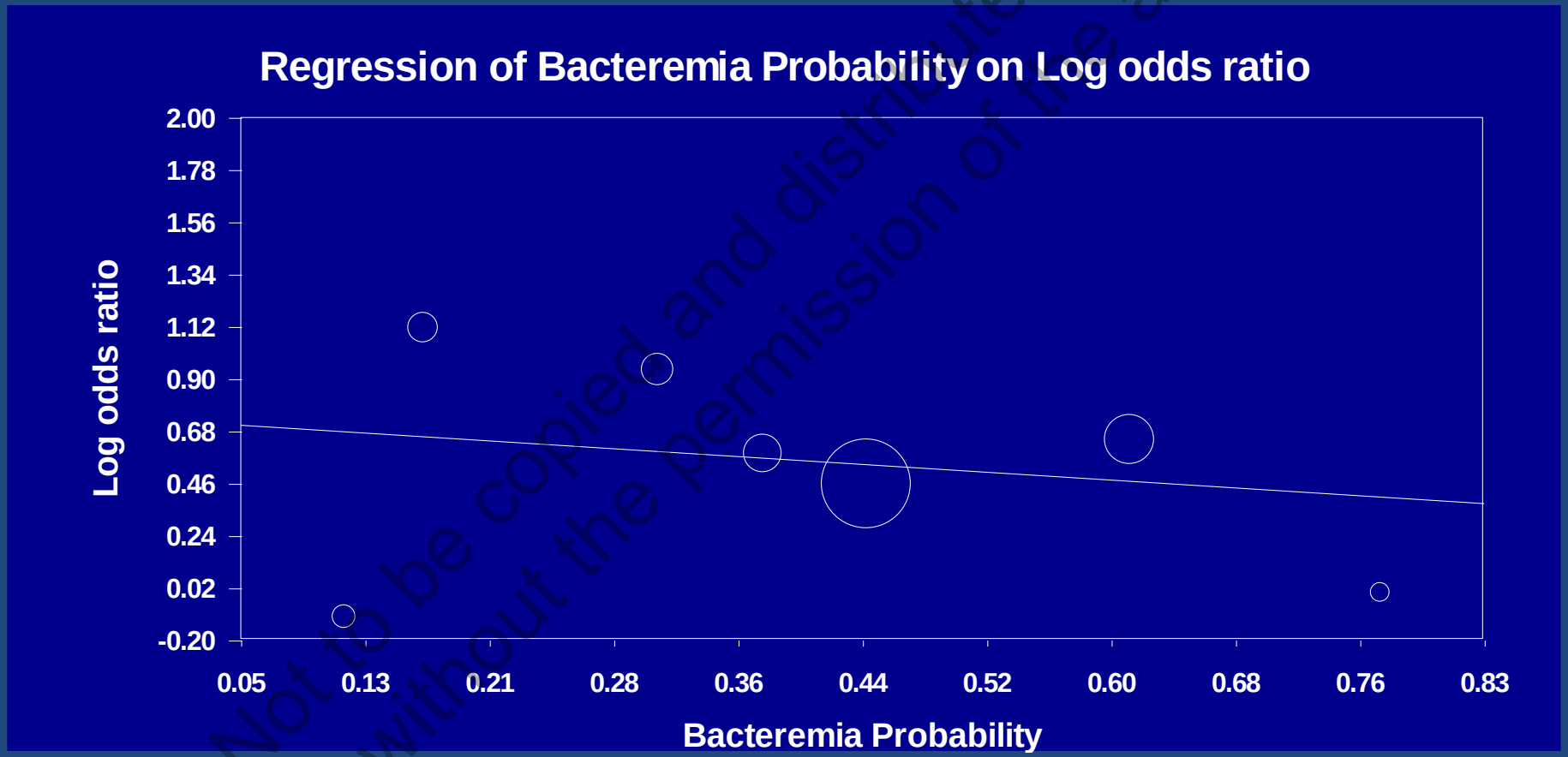
IV colistin vs. comparator antibiotics for sepsis, all-cause mortality

Meta-regression bacteremia rate



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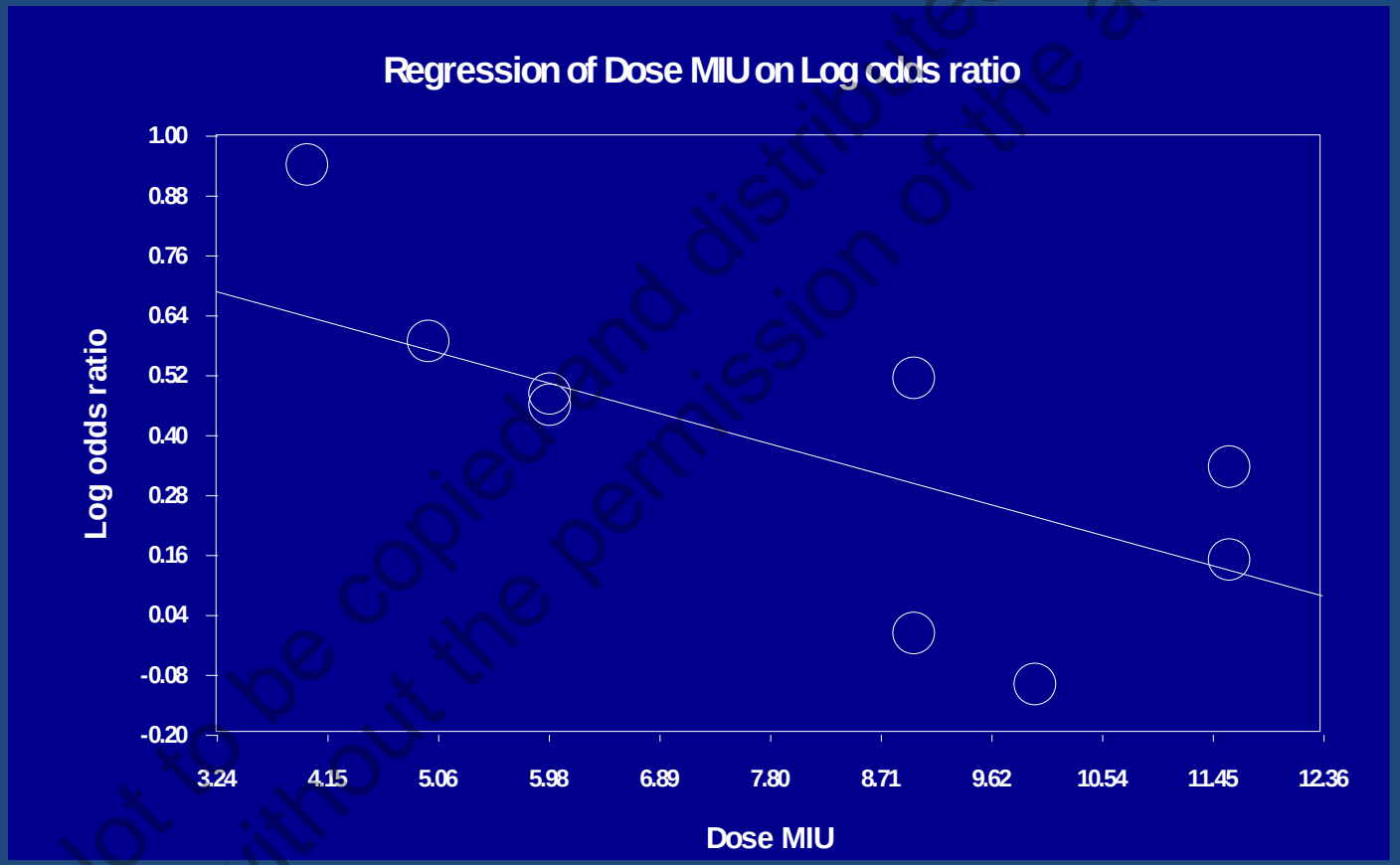
Slope non-significant

IV colistin vs. comparator antibiotics for sepsis, all-cause mortality

Meta-regression colistin dose



P=0.21

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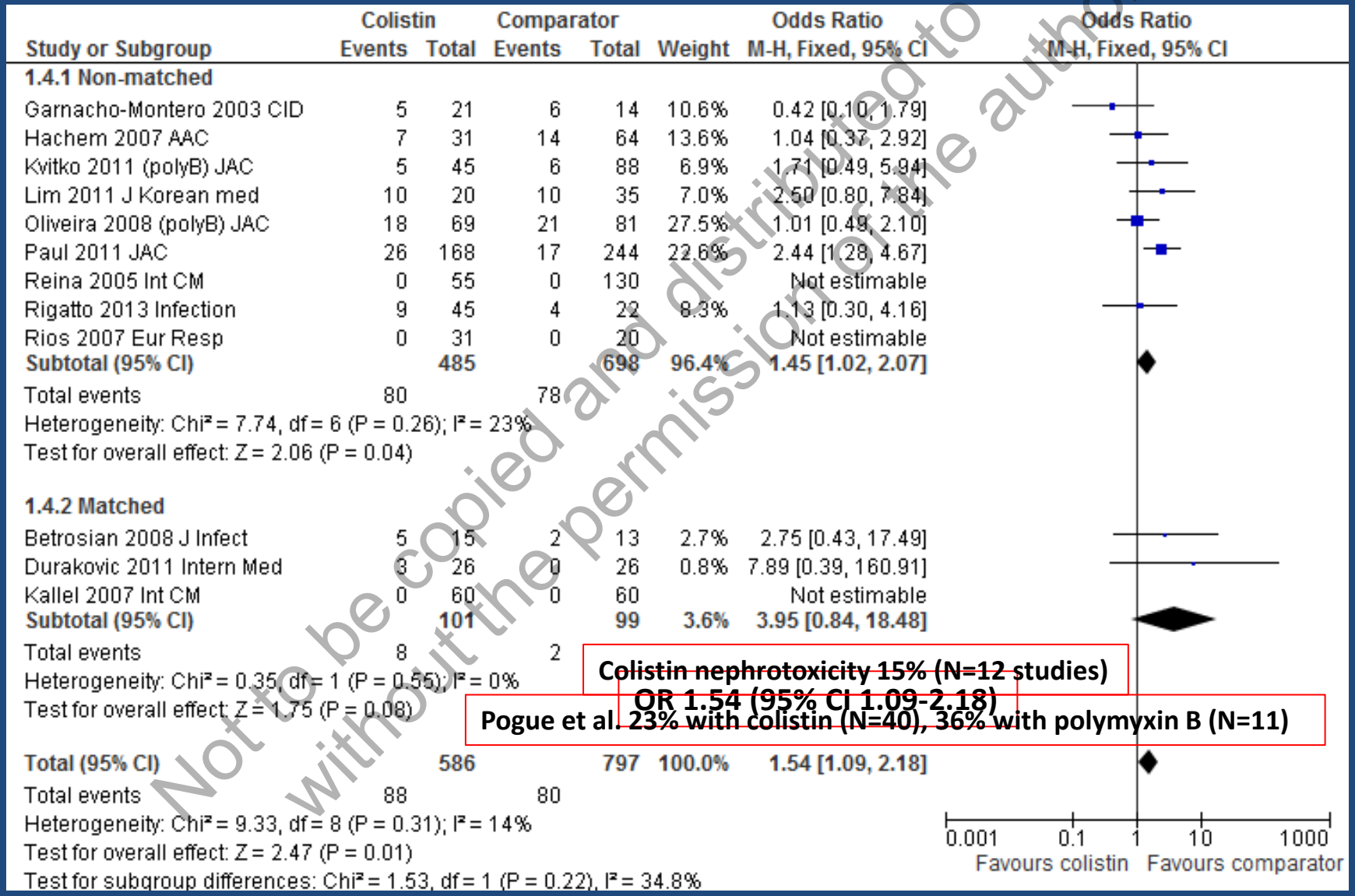
Nephrotoxicity for colistin vs. comparators in sepsis



Colistin nephrotoxicity 15% (N=12 studies)

OR 1.54 (95% CI 1.09-2.18)

Pogue et al. 23% with colistin (N=40), 36% with polymyxin B (N=11)

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Limitations

- Non-randomized
- Large difference in the adequacy of empirical antibiotic treatment
- Mix of bacteria
  - Acinetobacter
  - Pseudomonas
  - Enterpbacteriaceae
- Antibiotics administered concomitantly with polymyxin
- Variable colistin dosing
- Mortality timing variable
- Overlap of cases in different publications

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Limitations - biological

- Non-randomized
- Large difference in the adequacy of empirical antibiotic treatment
- Mix of bacteria
  - Acinetobacter
  - Pseudomonas
  - Enterpbacteriaceae
- Antibiotics administered concomitantly with polymyxin
- Variable colistin dosing
- Mortality timing variable
- Overlap of cases in different publications

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Limitations - methodological

- Non-randomized
- Large difference in the adequacy of empirical antibiotic treatment
- Mix of bacteria
  - Acinetobacter
  - Pseudomonas
  - Enterpbacteriaceae
- Antibiotics administered concomitantly with polymyxin
- Variable colistin dosing
- Mortality timing variable
- Overlap of cases in different publications

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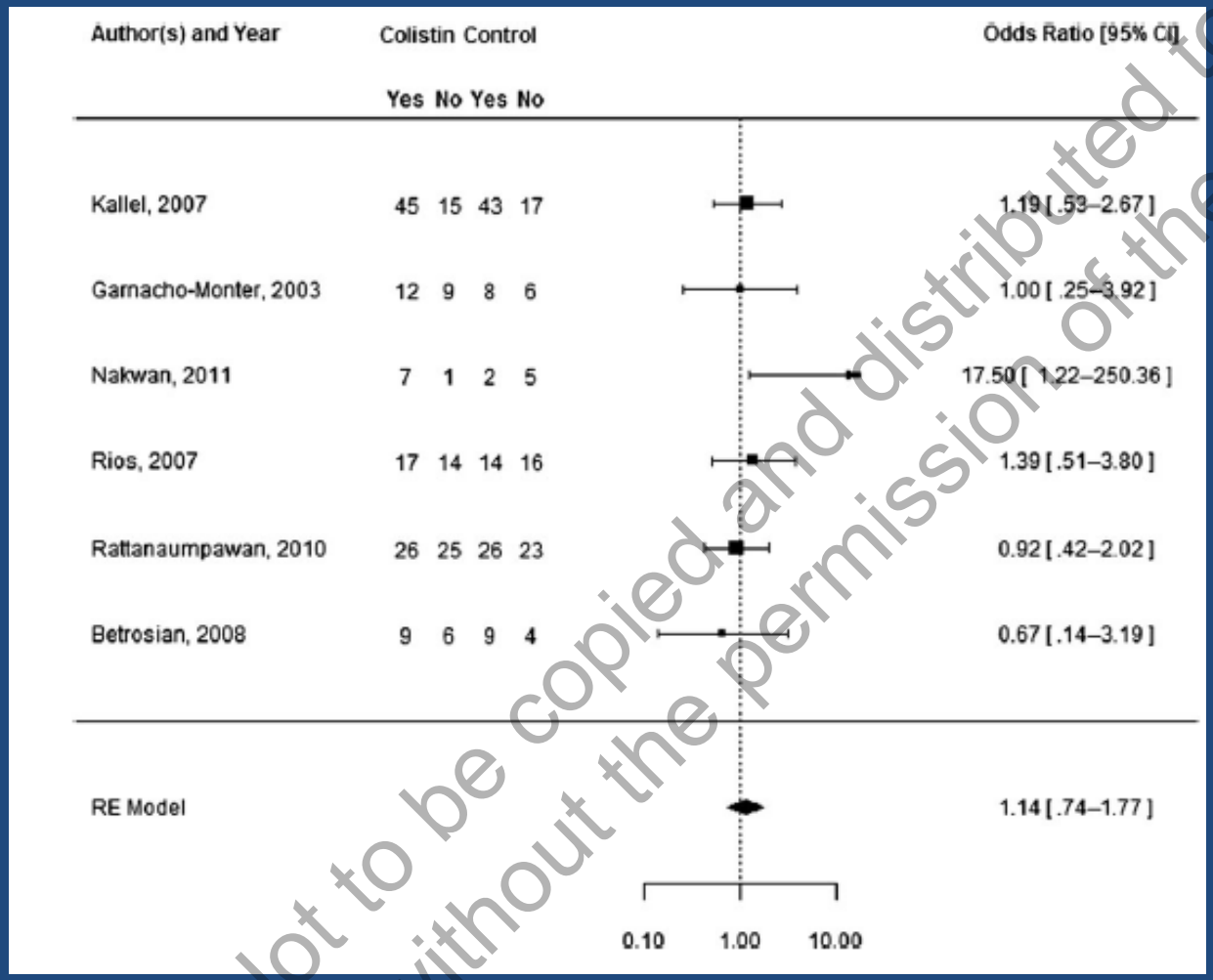
Comparing to published results



"Conclusions. Our results suggest that colistin may be as safe and as efficacious as standard antibiotics for the treatment of VAP"

Clinical response
OR 1.14
(95% CI 0.74-1.77)

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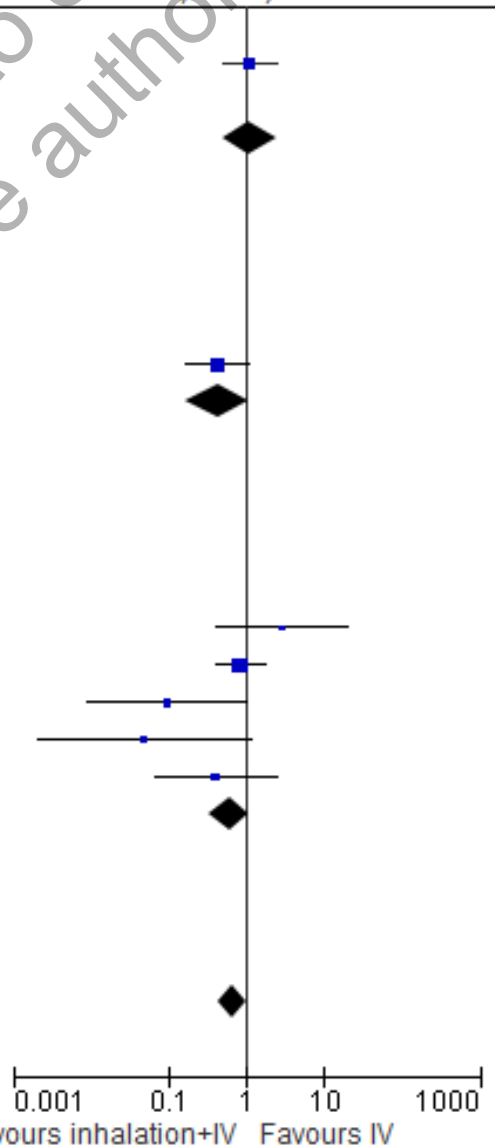
Florescu et al. What Is the Efficacy and Safety of Colistin for the Treatment of Ventilator-Associated Pneumonia? A Systematic Review and Meta-Regression. Clin Infect Dis 2012

Systemic + inhalation colistin vs. systemic antibiotics

all-cause mortality

Study or Subgroup	Inhalation+IV Events	Total	IV Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1.1 Randomized						
Rattanaumpawan 2010 JAC	22	51	20	49	21.0%	1.10 [0.50, 2.44]
Yilmaz polymyxins 2013	0	0	0	0		Not estimable
Subtotal (95% CI)		**51**		**49**	**21.0%**	**1.10 [0.50, 2.44]**
Total events	22		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
3.1.2 Matched						
Kofteridis 2011 CID	10	43	18	43	25.0%	0.42 [0.17, 1.07]
Subtotal (95% CI)		**43**		**43**	**25.0%**	**0.42 [0.17, 1.07]**
Total events	10		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
3.1.3 Non-matched						
Ganapathy 2010 Burns	10	17	2	6	2.2%	2.86 [0.41, 20.14]
Korbila 2010 CMI	31	78	19	43	26.7%	0.83 [0.39, 1.77]
Livermore 2010 Int J	1	8	9	15	9.9%	0.10 [0.01, 0.98]
Naesens 2011 BMC Infect	3	9	5	5	8.1%	0.05 [0.00, 1.17]
Perez 2011 Med Intensiva	2	15	5	18	7.1%	0.40 [0.07, 2.45]
Subtotal (95% CI)		**127**		**87**	**54.0%**	**0.61 [0.34, 1.08]**
Total events	47		40			
Heterogeneity: Chi² = 8.14, df = 4 (P = 0.09); I² = 51%						
Test for overall effect: Z = 1.71 (P = 0.09)						
Total (95% CI)		**221**		**179**	**100.0%**	**0.66 [0.44, 1.00]**
Total events	79		78			
Heterogeneity: Chi² = 10.51, df = 6 (P = 0.10); I² = 43%						
Test for overall effect: Z = 1.95 (P = 0.05)						
Test for subgroup differences: Chi² = 2.57, df = 2 (P = 0.28), I² = 22.1%						

?



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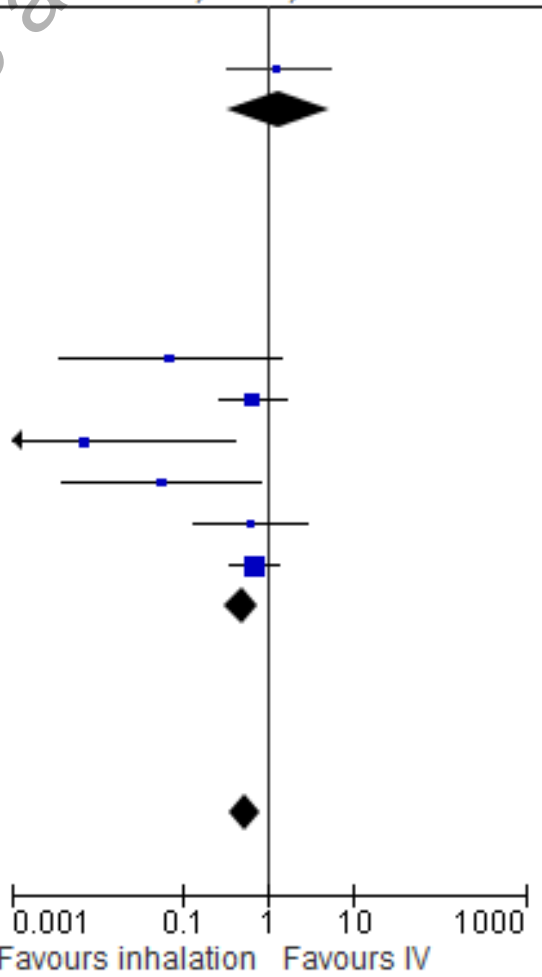
Inhalation colistin alone vs. systemic antibiotics

all-cause mortality

Study or Subgroup	Inhalation Events	Inhalation Total	IV Events	IV Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Matched						
Kuo 2012 CMI	5	39	4	39	6.2%	1.29 [0.32, 5.20]
Subtotal (95% CI)		**39**		**39**	**6.2%**	**1.29 [0.32, 5.20]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.72)						
2.1.2 Non-matched						
Ganapathy 2010 Burns	0	6	12	23	9.3%	0.07 [0.00, 1.40]
Lu 2012 Anesthesiology	7	43	28	122	21.6%	0.65 [0.26, 1.63]
Naesens 2011 BMC Infect	0	6	5	5	9.7%	0.01 [0.00, 0.41]
Nakwan 2011 Pediatr Pulm	1	8	5	7	8.2%	0.06 [0.00, 0.82]
Perez 2011 Med Intensiva	4	21	5	18	7.7%	0.61 [0.14, 2.74]
Trottier 2007 Surg Infect	16	78	35	127	37.4%	0.68 [0.35, 1.33]
Subtotal (95% CI)		**162**		**302**	**93.8%**	**0.48 [0.30, 0.77]**
Total events	28		90			
Heterogeneity: Chi² = 9.69, df = 5 (P = 0.08); I² = 48%						
Test for overall effect: Z = 3.03 (P = 0.002)						
Total (95% CI)		**201**		**341**	**100.0%**	**0.53 [0.34, 0.83]**
Total events	33		94			
Heterogeneity: Chi² = 11.04, df = 6 (P = 0.09); I² = 46%						
Test for overall effect: Z = 2.80 (P = 0.005)						
Test for subgroup differences: Chi² = 1.70, df = 1 (P = 0.19), I² = 41.1%						



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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
  - Dosing/ schedule
  - Combination therapy
  - Prevention of nephrotoxicity
- Compare colistin with aminoglycoside

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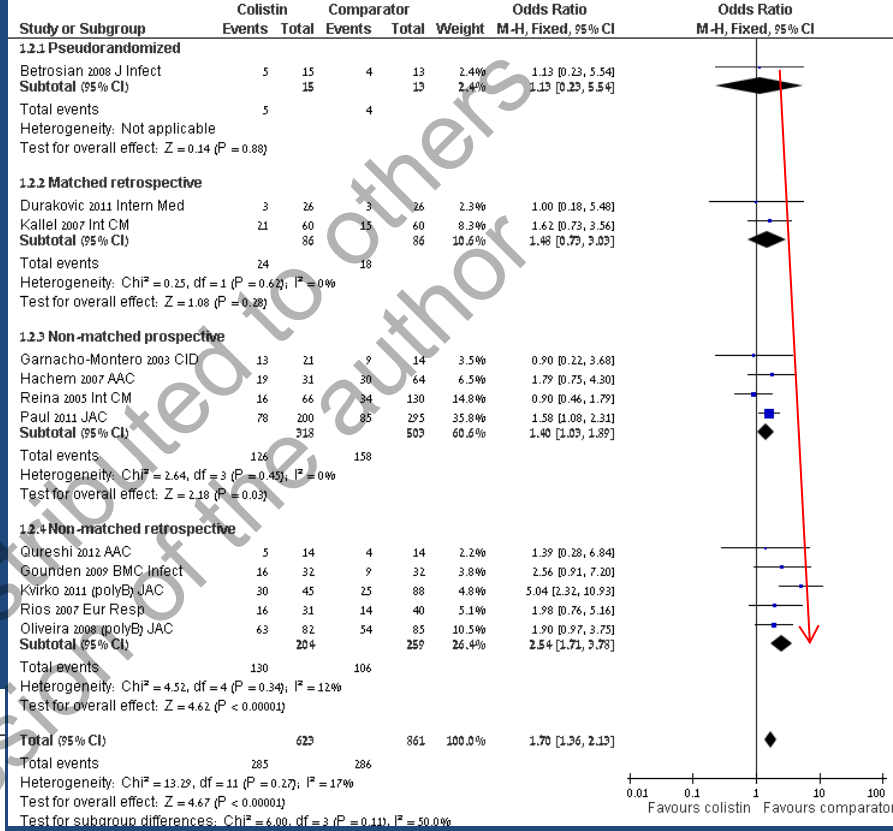
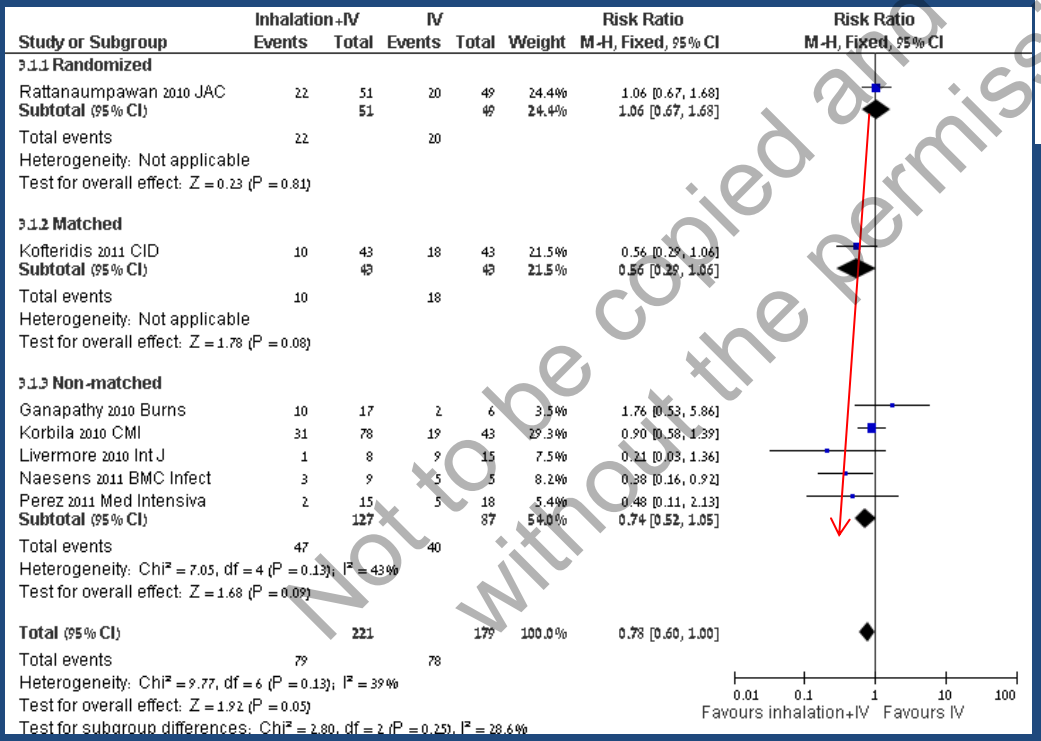
Finally





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We need randomized controlled trials

The Future: NIH registered RCTs

Colistin efficacy

- Colistin vs. carbapenem/ conventional treatment – 2 trials

Colistin combination therapy

- Colistin - imipenem/ meropenem (2 trials, AIDA, NIH)
- Colistin - fosfomycin (1 trial)
- Colistin –rifampin (2 trials)

Inhalation colistin

- IV vs. nebulized+IV colistin for VAP/ HAP (2 trials)

Prevention of nephrotoxicity

- Colistin - ascorbic acid (1 trial)

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Thank you

Conflicts of interests: none

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