Combination therapy - The solution to all problems?

ESCMID conference on revival of old antibiotics

Vienna, 22-23 October 2014

Bacteria	Carbapenem	% Synergy rate (95% CI)	% Antagonism rate (95% CI)	N Tests	N Bact	% Total synergy (I^2)
A. baumannii	Imipenem	56 (35-74)	8 (4-17)	11	82	77 (64-86), 48%
	Meropenem	86 (75-93)	7 (2-17)	9	71	
	Doripenem	88 (70-96)	9 (3-24)	6	33	
K. pneumoniae	Imipenem	41 (23-62)	24 (7-58)	5	58	44 (30-59), 51%
	Meropenem	34 (13-64)	9 (3-23)	6	39	
	Doripenem	63 (39-82)	10 (2-32)	6	19	
	Ertapenem	11 (3-29)	12 (3-42)	2	30	
P. aeruginosa	Imipenem	60 (18-91)	21 (11-38)	5	39	50 (30-69), 66%
	Meropenem	24 (15-38)	2 (0-16)	2	54	
	Doripenem	62 (38-81)	5 (1-20)	5	43	

In-vitro interactions polymyxins - carbapenems

- Results of time-kill studies summarized in table
- Bactericidality of the single best agent increased from
  - 26% to 74% for *A. baumannii*
  - 18% to 63% for *K. pneumoniae*
  - 10% to 49% for *P. aeruginosa*
- Resistance development examined in time-kill studies totaling 13isolates of AB and 14 of PA, showing prevention and delay of resistance development

Zusman et al. Antimicrob Agents Chemother. 2013

TABLE 2 Analysis of clinical variables in 34 patients that received definitive therapy

Variable	Combination therapy ($n = 15$)[a]	Monotherapy ($n = 19$)[a]	OR (95% CI)
Demographics			
Age ≥65	6 (40)	11 (57.8)	0.4 (0.09–2.35)
Male	8 (53.3)	7 (36.8)	1.7 (0.36–8.31)
Severity of illness			
In ICU at enrollment	10 (66.6)	10 (52.6)	1.8 (0.36–9.28)
APACHE II	17.4 ± 6.65	21.3 ± 8.69	
LOS[b]	35 ± 28	34.9 ± 72	
Underlying diseases			
Immunocompromised state	11 (73.3)	9 (47.3)	3.0 (0.58–17.14)
Chronic renal failure	3 (20)	3 (15.8)	1.3 (0.17–10.54)
Malignancy	3 (20)	5 (15.8)	0.7 (0.02–4.51)
Transplant	8 (53.3)	0	∞ (3.01–∞)

TABLE 1 Predictors of mortality in 41 patients with bacteremia due to KPC-producing *K. pneumoniae*

Variable	Survived ($n = 25$)[a]	Died ($n = 16$)[a]	Univariate analysis OR (95% CI)	Multivariate analysis[b] OR (95% CI)
Therapy				
Inappropriate empirical therapy	21 (65.6)	11 (34.3)	0.2 (0.07–2.33)	
Combination definitive therapy	13 (60)	2 (12.5)	0.13 (0.01–0.82)	0.07 (0.009–0.71)
Appropriate therapy at any time	18 (78.2)	10 (62.5)	0.46 (0.08–2.35)	

Qureshi et al. Antimicrob Agents Chemother. 2012

Table 1. Univariate Analysis of Factors Associated With Death Among Patients With Bloodstream Infections Due to *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*

Variable	No. (%) of Patients		
	Nonsurvivors (n = 52)	Survivors (n = 73)	OR (95% CI)
Postantibiogram antimicrobial regimens			
Monotherapy	25 (48.1)	21 (28.7)	1.59 (1.06–2.38)
Tigecycline	10 (19.2)	9 (12.3)	1.32 (.81–2.16)
Colistin	11 (21.5)	11 (15.1)	1.25 (.77–2.03)
Gentamicin	4 (7.6)	1 (1.3)	1.98 (1.21–3.23)
Combination therapy	27 (51.9)	52 (71.2)	0.62 (.41–.94)
2-drug combinations	23 (44.2)	33 (45.2)	0.97 (.64–1.48)
Tigecycline + colistin	7 (13.4)	16 (21.9)	0.68 (.35–1.32)
Tigecycline + gentamicin	6 (11.5)	6 (8.2)	1.22 (.66–2.25)
Other 2-drug combinations[e]	10 (19.2)	11 (15.1)	1.17 (.71–1.95)
3-drug combinations	4 (7.7)	19 (26.1)	0.36 (.15–.92)
Tigecycline + colistin + meropenem	2 (3.8)	14 (19.2)	0.27 (.07–1.01)
Other 3-drug combinations[f]	2 (3.8)	5 (6.8)	0.67 (.21–2.21)
Inadequate initial antimicrobial treatment	39 (75)	36 (49.3)	2.00 (1.19–3.34)
Presentation with septic shock	13 (25)	4 (5.5)	2.11 (1.47–3.04)
APACHE III score (mean ± SD)	40 ± 22	24 ± 15	…

Tumbarello et al. Clin Infect Dis. 2012

Table 3. Multivariate Analysis of Risk Factors for Mortality in Patients With Bloodstream Infection Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*

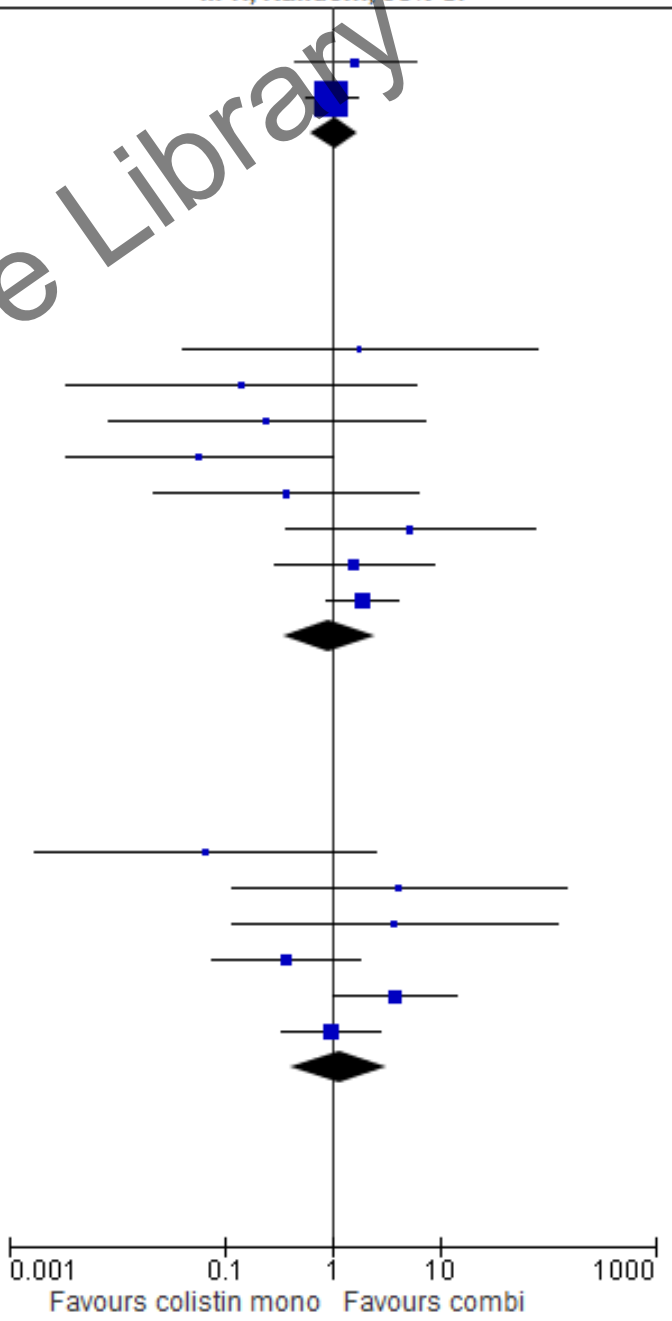
Variable	*P* Value	OR (95% CI)
Presentation with septic shock	.008	7.17 (1.65–31.03)
Inadequate initial antimicrobial treatment	.003	4.17 (1.61–10.76)
High APACHE III score	<.001	1.04 (1.02–1.07)
Postantibiogram therapy with tigecycline + colistin + meropenem	.01	0.11 (.02–.69)

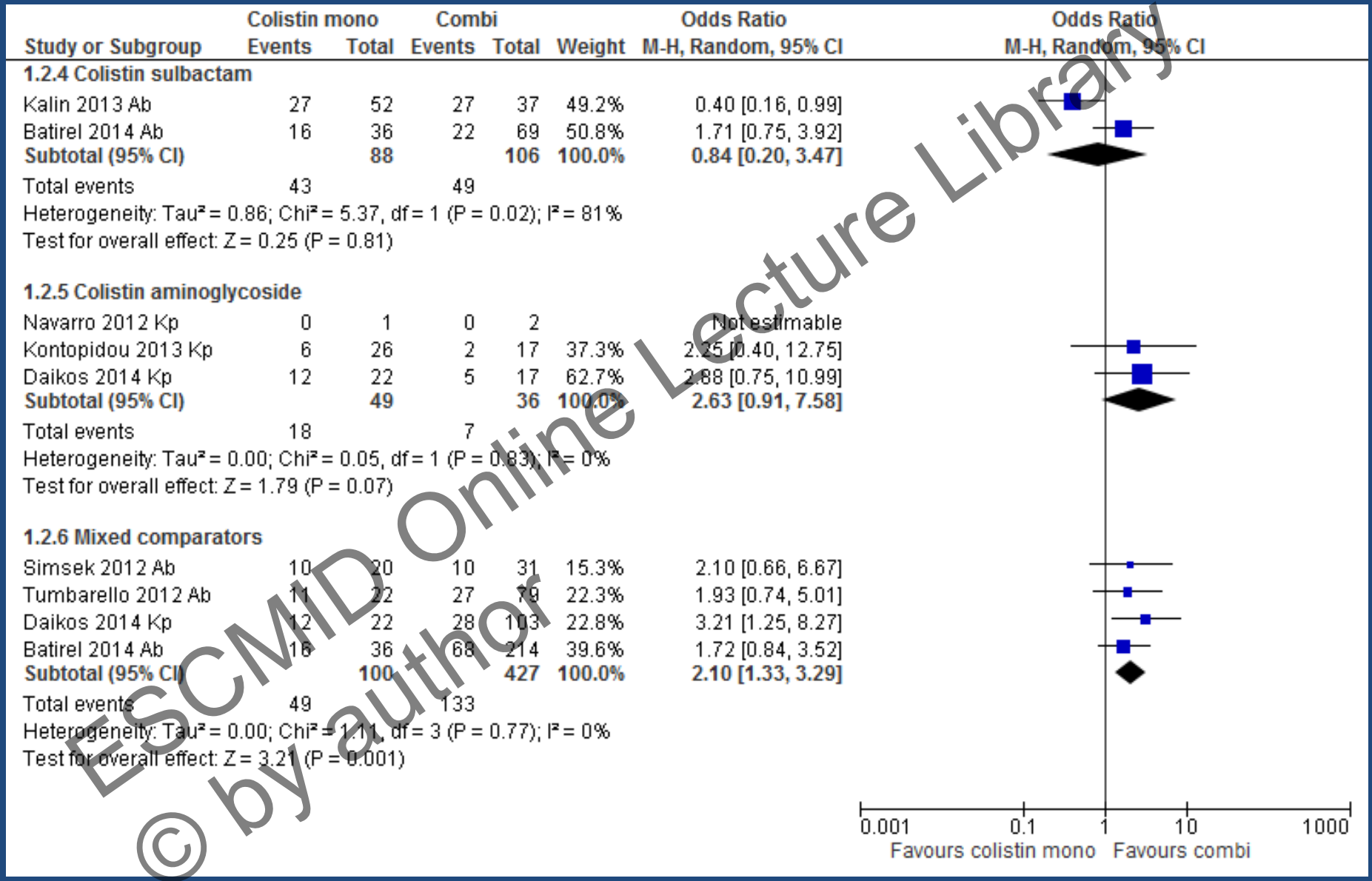
Tumbarello et al. Clin Infect Dis. 2012

Outcome	Colistin + Rifampicin Arm (n = 104)	Colistin Arm (n = 105)	*P* Value
Primary outcome			
30-d mortality			
Yes	45 (43.3%)	45 (42.9%)	.95[a]
No	59 (56.7%)	60 (57.1%)	
Secondary outcomes			
Infection-related death at 30 d			
Yes	22 (21.15%)	28 (26.6%)	.29[a]
No	23 (22.1%)	17 (16.2%)	
Acinetobacter baumannii eradication			
Yes	63 (60.6%)	47 (44.8%)	.034[a]
No	38 (36.5%)	54 (51.4%)	
Median hospitalization length, d (IQR)	41 (26–61)	44 (27–59)	.96[b]
Development of colistin resistance, %	0	0	. . .

Durante-Mangoni et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: a multicenter, randomized clinical trial. Clin Infect Dis. 2013

Study or Subgroup	Colistin mono Events	Total	Combi Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Colistin rifampin (RCTs)						
Aydemir 2013 Ab	16	22	13	21	15.3%	1.64 [0.45, 5.94]
Durante-Mangoni 2013 Ab	45	105	45	104	84.7%	0.98 [0.57, 1.70]
Subtotal (95% CI)		**127**		**125**	**100.0%**	**1.06 [0.64, 1.76]**
Total events	61		58			
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.1.2 Colistin carbapenem						
Tuon 2013 Kp	1	1	2	3	5.8%	1.80 [0.04, 79.42]
Navarro 2012 Kp	0	1	3	4	6.0%	0.14 [0.00, 5.95]
Bergamasco 2011 Kp	1	3	2	3	7.0%	0.25 [0.01, 7.45]
Falagas 2006 Ab Pa	0	14	21	57	9.2%	0.06 [0.00, 1.03]
Souli 2008 Ab	1	3	4	7	9.4%	0.38 [0.02, 6.35]
Qureshi 2012 Kp	4	7	1	5	10.4%	5.33 [0.38, 75.78]
Daikos 2014 Kp	12	22	3	7	18.6%	1.60 [0.29, 8.90]
Batirel 2014 Ab	16	36	30	102	33.5%	1.92 [0.88, 4.20]
Subtotal (95% CI)		**87**		**188**	**100.0%**	**0.95 [0.35, 2.54]**
Total events	35		66			
Heterogeneity: Tau² = 0.59; Chi² = 10.38, df = 7 (P = 0.17); I² = 33%						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.1.3 Colistin tigecycline						
Navarro 2012 Kp	0	1	7	8	6.8%	0.07 [0.00, 2.56]
Bergamasco 2011 Kp	1	3	0	3	7.0%	4.20 [0.12, 151.97]
Qureshi 2012 Kp	4	7	0	1	7.3%	3.86 [0.12, 126.73]
Kontopidou 2013 Kp	6	26	4	9	21.7%	0.38 [0.08, 1.86]
Daikos 2014 Kp	12	22	5	21	26.2%	3.84 [1.04, 14.21]
Ku 2012 Ab	26	71	7	19	30.9%	0.99 [0.35, 2.83]
Subtotal (95% CI)		**130**		**61**	**100.0%**	**1.16 [0.41, 3.27]**
Total events	49		23			
Heterogeneity: Tau² = 0.61; Chi² = 8.50, df = 5 (P = 0.13); I² = 41%						
Test for overall effect: Z = 0.29 (P = 0.77)						





Paul et al. J Antimicrob Chemother 2014

Limitations of the observational studies

- Selection bias
  - Patients with XDR bacteria, with high carbapenem MICs more likely treated with colistin monotherapy *
  - Patients with polymicrobial infections more likely treated with combination therapy
- Non-interventional design
  - No control over treatment regimens *
- Small sample size makes adjustment difficult
  - Most studies did not adjust for appropriateness of empirical antibiotic treatment
- Biological rationale of comparing “combo” vs. “mono” *
- Ecological impact in location with high prevalence of carbapenem-resistant bacteria

Letter to the editor: Polymyxin B with dual carbapenem combination therapy against carbapenemase-producing *Klebsiella pneumoniae*.
Chua et al. (Singapore), J Infect 2014

Table 4. Outcomes of the 36 Bloodstream Infections Treated With Combination Therapy Including Meropenem Stratified by Meropenem Minimum Inhibitory Concentration

		No. (%)	
Meropenem MIC (mg/L)	Total	Nonsurvivors	Survivors
1	1	0	1 (100)
2	4	0	4 (100)
4	10	2 (20)	8 (80)
8	4	1 (25)	3 (75)
≥16	17	6 (35.2)	11 (64.7)
Total	36	9 (25)	27 (75)

Tumbarello et al. Clin Infect Dis. 2012

TABLE 3 Definitive antimicrobial therapy and mortality in 17 patients who received combination therapy and 19 patients who received monotherapy

Definitive treatment	*n* (%)	Mortality *n* (%)
Combination therapy	15 (44)	2 (13.3)
Colistin-polymyxin B combined with:		
Carbapenem	5 (33)	1 (20)
Tigecycline	1 (7)	0
Fluoroquinolone	1 (7)	0
Tigecycline combined with:		
Carbapenem	3 (20)	0
Aminoglycoside	2 (12)	0
Carbapenem-fluoroquinolone	1 (7)	1 (100)
Aztreonam-fluoroquinolone	1 (7)	0
Cefepime-gentamicin	1 (7)	0
Monotherapy	19 (46)	11 (57.8)
Colistin-polymyxin B	7 (36.8)	4 (57.1)
Tigecycline	5 (26.3)	4 (80)
Carbapenem	4 (21)	2 (50)
Gentamicin	1 5.2)	0
Ampicillin-sulbactam	1 (5.2)	0
Piperacillin-tazobactam	1 (5.2)	1 (100)
Total	34 (83)	13 (38.2)

Qureshi et al. Antimicrob Agents Chemother. 2012