Clinical effectiveness and *in-vitro* activity of meropenem+ertapenem and colistin+meropenem+ertapenem combinations against carbapenemase-producing *Klebsiella pneumoniae* infections.

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Objectives

Therapeutic options against carbapenem-resistant *K. pneumoniae* (CR-Kp) are worringly limited and innovative approaches have been recently investigated. The aim of the study was to evaluate the clinical effectiveness of the double carbapenem regimen [meropenem (MEM) + ertapenem (ERT)] with or without colistin (COL) against CR-Kp infections. Furthermore, synergistic and bactericidal activity of the combinations MEM+ERT and COL+MEM+ERT were investigated.

Methods

Over a 3-years period (2012-2015), 32 subjects with CR-Kp infections were included in the study: 18 were treated with MEM+ERT (Group A), 14 with COL+MEM+ERT (Group B). The double carbapenem regimen consisted of ERT 1g (1-h infusion) followed by high-doses of MEM (2g every 8h, 3-h infusion) whereas COL was administered as 9.000.000 IU (loading dose) followed by 4.500.000 IU every 12h. Synergistic and bactericidal analyses were performed on 22 strains throughout checkerboard method and killing curves.

Table 1. Study design.

32 patients with carbapenem-resistant *Klebsiella pneumoniae* infection (2012-2015)

Group A (n=18)
Double-carbapenem regimen

Ertapenem
1g every 24h (1-hour infusion)
+
Meropenem
2g every 8h (3-hours infusion)

Group B (n=14)
Colistin+ Double-carbapenem regimen

Ertapenem
1g every 24h (1-hour infusion)
+
Meropenem
2g every 8h (3-hours infusion)
+
Colistin
9.000.000 UI loading dose, then 4.500.000 UI every 12 hours

Results

Table 2. General characteristics of study population

	Study population (n=32)	DC group (n=18)	COL+DC group (n=14)	*p-value*
Demographic characteristics				
• Age (years), M ± SD	55.09 ± 15.2	55.6 ± 13.6	54.4 ± 17.5	0.74
• Sex (M:F)	23:9	14:4	9:5	0.45
• APACHE III score, M ± SD	64.9 ± 29.6	50.7 ± 28.1	83.2 ± 20.3	**0.001**
• ≥2 Comorbidities	14 (43.7)	5 (27.7)	9 (64.2)	**0.07**
Classification of infection, n (%)				
• CA:HCA:HA	0:6:26	0:6:12	0:0:14	**0.0001**
• Length of hospitalization before infection, days Ω	17.5 (2-437)	14 (2-65)	23 (5-437)	**0.005**
Risk factors for infection (previous 12 months), n (%)				
• Previous hospitalization	22 (68.7)	15 (83.3)	7 (50)	**0.02**
• Intensive Care Unit	22 (68.7)	10 (55.5)	12 (85.7)	**0.06**
• Vescical catheter	18 (56.2)	12 (66.6)	6 (42.8)	0.12
• Central venous catheter (CVC)	11 (34.3)	9 (50)	2 (14.2)	0.28
• Tracheostomy	8 (25)	6 (33.3)	2 (14.2)	0.06
Risk factors for infection (previous 72h), n (%)				
• Intestinal endoscopy	2 (6.2)	2 (11.1)	0 (0)	0.49
• Naso-gastric tube	18 (56.2)	6 (33.3)	12 (85.7)	**0.004**
• Fibroroncoscopy	14 (43.7)	4 (22.2)	10 (71.4)	**0.01**
• Parenteral Total Nutrition	14 (43.7)	4 (22.2)	10 (71.4)	**0.01**
• CVC	20 (62.5)	7 (38.8)	13 (92.8)	**0.002**
Previous antibiotic therapy (90 days), n (%)	29 (90.6)	15 (83.3)	14 (100)	0.23
• Cephalosporin	10 (31.2)	3 (16.6)	7 (50)	0.06
• Penicillins	18 (56.2)	7 (38.8)	11 (78.5)	**0.03**
• Carbapenems	15 (46.8)	6 (33.3)	9 (64.2)	0.45
• Beta-lactams (overall)	27 (84.3)	13 (72.2)	14 (100)	**0.05**
• Fluoroquinolones	10 (31.2)	5 (27.7)	5 (35.7)	0.71
• Colistin	9 (28.1)	4 (22.2)	5 (35.7)	0.45
CR-Kp rectal colonization, n (%)	27 (96.4)	13/14 (92)	14/14 (100)	0.37
Colistin-resistance, n (%)	11 (34.3)	8 (44.4)	3 (21.4)	0.26
Clinical presentation, n (%)				
• Sepsis	5 (15.6)	3 (16.6)	2 (14.2)	0.99
• Severe sepsis	13 (40.6)	7 (38.8)	6 (42.8)	0.99
• Septic shock	8 (25)	2 (11.1)	6 (42.8)	**0.09**
• Type of infection				
Pneumonia	9 (28.1)	4 (22.2)	5 (35.7)	0.99
EVD infection	3 (9.3)	2 (11.1)	1 (7.1)	0.87
UTI	9 (28.1)	8 (44.4)	1 (7.1)	**0.04**
CVC infection	6 (18.7)	0 (0)	6 (42.8)	**0.003**
Primary bacteremia	6 (18.7)	4 (22.2)	2 (14.2)	0.67
• Presence of bacteremic infection	18 (56.2)	8 (44.4)	10 (71.4)	**0.16**
Definitive therapy, n (%)				
• Response at 5th day of therapy	23 (71.8)	11 (61.1)	12 (85.7)	**0.23**
• Length of definitive therapy, days Ω	21 (7-150)	18.5 (7-150)	25 (7-34)	**0.04**
• Clinical response (giorni) Ω	4 (2-15)	4 (2-15)	4 (3-12)	0.68
• Adverse events, n (%)**	6 (18.7)	3 (16.6)	3 (21.4)	1.00
Outcome at 60 days, n (%)				
• *Exitus*	6 (18.7)	3 (16.6)	3 (21.4)	0.99
• Relapse	2 (6.2)	2 (11.1)	0 (0)	0.49
• Improvement	24 (75)	13 (72.2)	11 (78.5)	0.89

Figure 1. Killing curves of MEM+ERT and COL+MEM+ERT in Group A (1A) and Group B (1B).
Dashed line represents bactericidal activity.

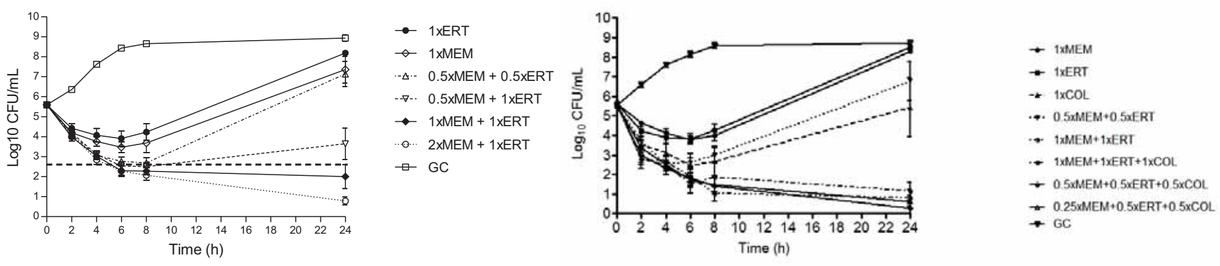

Table 3. Synergistic and bactericidal activity of DC (A) and colistin+DC (B).

A)

DC group (n=18)	Bactericidal activity (2h), n (%)	Bactericidal activity (4h), n (%)	Bactericidal activity (6h), n (%)	Bactericidal activity (8h), n (%)	Bactericidal activity (24h), n (%)	Synergistic activity (24h), n (%)
1xMIC MEM	0 (0)	1 (6.2)	4 (25)	3 (18.7)	2 (12.5)	n.a.
1xMIC ERT	0 (0)	0 (0)	1 (6.2)	1 (6.2)	0 (0)	n.a.
1xMIC MEM+ 1xMIC ERT	1 (6.2)	5 (31.2)	8 (50)	12 (75)	14 (87.5)	14 (87.5)
2xMIC MEM+ 1xMIC ERT	1 (6.2)	5 (31.2)	9 (56.2)	15 (93.7)	16 (100)	16 (100)
GC	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

B)

DC+COL group (n=14)*	Bactericidal activity (2h), n (%)	Bactericidal activity (4h), n (%)	Bactericidal activity (6h), n (%)	Bactericidal activity (8h), n (%)	Bactericidal activity (24h), n (%)	Synergistic activity (24h), n (%)
1xMIC MEM	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	n.a.
1xMIC ERT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	n.a.
1xMIC COL	0 (0)	3 (25)	4 (33)	4 (33)	2 (16.6)	n.a.
1xMIC MEM + 1xMIC ERT	4 (33)	6 (50)	10 (83.3)	10 (83.3)	11 (91.6)	11
1xMIC MEM+ 1xMIC ERT+ 1xMIC COL	4 (33)	8 (66.6)	9 (75)	12 (100)	12 (100)	n.a.
0.5xMIC MEM+ 0.5xMIC ERT+ 0.5xMIC COL	2 (16.6)	8 (66.6)	8 (66.6)	11 (91.6)	12 (100)	n.a.
0.25xMIC MEM+ 0.5xMIC ERT+ 0.5xMIC COL	2 (16.6)	9 (75)	11 (91.6)	11 (91.6)	12 (100)	n.a.
GC	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Conclusions

MEM+ERT and COL+MEM+ERT combinations showed clinical efficacy and high bactericidal activity.
MEM+ERT might be a valid therapeutic option when COL use is discouraged whereas COL+MEM+ERT might be considered in subjects presenting with more severe conditions (i.e. septic shock).