29th ECCMID Amsterdam, Netherlands 13 – 16 April 2019

The congress of ESCMID

P2785 *In vitro* synergy does not predict treatment outcome with colistin plus meropenem in patients with carbapenem-resistant Gram-negative infections

Amir Nutman*[1], Jonathan Lellouche[1], George Daikos[2], Anna Skiada[2], Emanuele Durante Mangoni[3], Yael Dishon, Johan W. Mouton[4], Lena Friberg[5], Leonard Leibovici, Mical Paul[6,7], Ursula Theuretzbacher[8], David Schwartz[9,10], Yehuda Carmeli

[1] National Center for Infection Control and Antibiotic Resistance, Tel-Aviv Sourasky Medical Center, Israel, [2] Greece, [3] Monaldi Hospital, Napoli, Italy, [4] Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, Rotterdam, Netherlands, [5] Dep of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, [6] Infectious Diseases Unit, Rambam Health Care Campus, Haifa, Israel, [7] Technion, The Ruth and Bruce Rappaport Faculty of Medicine, Haifa, Israel, [8] Center for Anti-Infective Agents, Vienna, Austria, [9] Tel Aviv-Yafo sourasky medical center, Tel Aviv-Yafol, Israel, [10] National Laboratory for Antibiotic Resistance and Investigation of Outbreaks in Medical Institutions, National Institute for Antibiotic Resistance and Infection Control Ministry of Health , Tel Aviv-Yafo, Israel

Background: Combination therapy with a carbapenem and polymyxin against Gram-negative bacterial infections is supported by *in vitro* studies demonstrating synergy. However, colistin-meropenem did not result in better outcomes compared to colistin monotherapy in AIDA, a randomized controlled trial of patients with severe carbapenem-resistant Gram-negative infections. We aimed to test the association between *in vitro* synergy and mortality in patients in the AIDA trial who were treated with colistin-meropenem.

Materials/methods: This secondary analysis of the AIDA trial includes only patients who received combination therapy and excludes patients with polymicrobial infections. The checkerboard method was used to detect the minimum inhibitory concentration (MIC) of colistin-meropenem. To evaluate the combined antibacterial effect, the fractional inhibitory concentration index (ΣFIC) was calculated. The results were classified as follows: synergy for ΣFIC ≤0.5; additivism/indifference for ΣFIC between 0.5 and ≤4; and antagonism for values above 4. We tested the association between synergy group and 14-day mortality using chi-square and multivariate logistic regression.

Results: The sample included 153 patients. In 68 (44.4%) patients, bacterial isolates showed *in vitro* synergy; in 69 (45.1%) additivism/indifference; and in 16 (10.5%) antagonism. *In vitro* synergy varied by species: for *Acinetobacter baumannii*, 63/116 (54.3%) demonstrated synergy, 50/116 (43.1%) additivism/indifference, and 3/116 (2.6%) antagonism; for Enterobacteriaceae 4/34 (11.8%) synergy, 19/34 (55.9%) additivism/indifference, and 11/34 (32.4%) antagonism; and for *Pseudomonas* 1/3 (33.3%) synergy and 2/3 (66.65) antagonism (Table 1). Overall 14 day-mortality did not differ between groups: 24/68 (35.3%) in the synergy group, 18/69 (26.1%) in the additivism/indifference group, and 2/16 (12.5%) in the antagonism group (p=0.16). In the multivariate model, the association between synergy group and 14-day mortality remained nonsignificant after adjusting for age, Charlson score, SOFA score, and bacterial species (p=0.53). The associations between 14 day-mortality and synergy group at the species level are presented in Table 1. Synergy was more common for *Acinetobacter baumannii*, and antagonism was more common for Enterobacteriaceae, but these *in vitro* findings did not affect mortality.

Conclusions: The combination of colistin and meropenem for Gram-negative infections is supported by *in vitro* synergy testing; however, in this clinical trial *in vitro* results did not predict mortality.

Table 1: Association between *in* vitro synergy testing and 14-day mortality in patients treated with colistin-meropenem for carbapenem-resistant Gram-negative infections.

Species	Synergy group	Survived, n (%)	Died, n (%)	p-value
All (N=153)	Synergy (n=68)	44 (64.7%)	24 (35.3%)	0.16
	Additivism/indifference (n=69)	51 (73.9%)	18 (26.1%)	
	Antagonism (n=16)	14 (87.5%)	2 (12.5%)	
Acinetobacter baumannii (N=116)	Synergy (n=63)	39 (61.9%)	24 (38.1%)	0.19
	Additivism/indifference (n=50)	37 (74%)	13 (26%)	
	Antagonism (n=3)	1 (33.3%)	2 (66.7%)	
Enterobacteriaceae (N=34)	Synergy (n=4)	4 (100%)	0 (0%)	0.1
	Additivism/indifference (n=19)	14 (73.7%)	5 (26.3%)	
	Antagonism (n=11)	11 (100%)	0 (0%)	
Pseudomonas (N=3)	Synergy (n=1)	1 (100%)	0 (0%)	NA
	Additivism/indifference (n=0)	NA	NA	
	Antagonism (n=2)	2 (100%)	0 (0%)	