27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: OS183 Clinical studies on MDR Gram-negatives

Category: 3b. Resistance surveillance & epidemiology: Gram-negatives

25 April 2017, 11:42 - 11:52
OS0890

Predictors of mortality in infections caused by non-carbapenemase-producing carbapenem-resistant Klebsiella pneumoniae

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Background: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections are associated with high mortality despite appropriate therapy. The mechanisms of CRKP involved the overexpression of extended spectrum β-lactamase (ESBL) or AmpC β-lactamase with decreased membrane permeability, and the presence of carbapenemases. The outcome analysis of CRKP infection almost comes from infections caused by carbapenemases-producing isolates, and several reports demonstrated the superiority of combination therapy. We demonstrated the efficacy of single active antimicrobial agents in treating infections caused by non-carbapenemase producing CRKP in our preliminary study. We aims to investigate the predictors of mortality in patients with non-carbapenemase-producing CRKP infections treated with appropriate therapy in this study. Particular attention is given to the impact of the combination therapy and microbiological characteristics of the CRKP isolates on the outcome of these patients.

Material/methods: We retrospectively collected clinical and microbiological data of patients with non-carbapenemase-producing CRKP infections from 16 hospitals in Taiwan during 2013 to 2014. Carbapenem resistance was defined as reduced susceptibility with a minimum inhibitory concentration (MIC) of ≥ 2 mg/L for imipenem or meropenem. The resistance mechanisms were analysed. Patients

who received appropriate antimicrobial therapy were included. Combination therapy was defined as use of at least two active agent, or carbapenem with one active agent. Multivariate cox regression analysis was used to determine independent risk factors of 14-day morality.

Results: A total of 67 patients with non-carbapenemase-producing CRKP infections who received appropriate antimicrobial therapy were enrolled. The 14-day mortality was 22.4%. Thirty-five isolates (52.2%) lost the expression of both OmpK35 and OmpK36, and the others (47.8%) preserved at least one of the porin. Forty isolates (59.7%) harbored the genes encoded both ESBL and AmpC beta-lactamases, and the others (40.3%) had ESBL beta-lactamases only. Thirty-two isolates (47.8%) had MIC ≥ 8 for imipenem. There was no difference in 14-day mortality between patients treated with monotherapy or treated with combination therapy (23.2% versus 18.2%, *P* = 0.714). The number of lost porins, types of beta-lactamases, and MIC for imipenem were not associated with 14-day mortality. In multivariate Cox regression analysis with backward selection process, APACHE II score (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.03-1.19; *P* = 0.004) was the only independent predictor of 14-day mortality.

Conclusions: Among patients with non-carbapenemase-producing CRKP infections treated with appropriate antibiotics, APACHE II score was the only independent predictor of 14 day mortality. Combination therapy was not associated with additional benefit compared with monotherapy. The microbiological characteristics of CRKP had no significant impact on treatment response. Our results suggest that carbapenemase testing may have therapeutic implications in CRKP and give some insight on future stewardship interventions.