Talk

In vitro effect of ceftazidime-avibactam pressure on ceftazidime-avibactam resistance in KPC-producing Klebsiella pneumoniae clinical isolates.

Díaz-Roblizo, Daniel(1), Rodríguez-Villodres, Ángel(1,2), Lepe, José Antonio(2), Pachón, Jerónimo(1), Smani, Younes(1,2,*)

(1)Institute of Biomedicine of Seville (IBiS)/CSIC/University of Seville • University Hospital Virgen del Rocío, 41013, Seville, Spain.

(2)Clinic Unit of Infectious Diseases, Microbiology and Preventive Medicine, University Hospital Virgen del Rocío • University Hospital Virgen del Rocío, 41013, Seville, Spain.

Tutor académico: Flores Díaz, Amando

Keywords: Ceftazidime/avibactam; Klebsiella pneumoniae; resistance; carbapenemase; KPC

ABSTRACT

Motivation: Infections caused by KPC-producing Klebsiella pneumoniae represent a challenge due to the limited available treatement choices. In this context, ceftazidime-avibactam (CAZ-AVI) is postulated as an alternative treatment effective against class A beta-lactamases such as KPC [1]. But, recent data reported the failure of CAZ-AVI treatment of infections by KPC-producing K. pneumoniae due to the development of CAZ-AVI resistance [2]. However, little is known concernig the CAZ-AVI resistance developement by CAZ-AVI selective pressure. Here, we aimed to determinate in vitro whether the exposure of KPC-producing K. pneumoniae clinical isolates to CAZ-AVI subinhibitory concentrations could lead the selection of CAZ-AVI resistant isolates.

Methods: Seventeen KPC-producing K. pneumoniae clinical isolates (7 KPC-2, 9 KPC-3 and 1 KPC-11) were analyzed. Minimum inhibitory concentrations (MICs) of CAZ-AVI were determined by broth microdilution using a fixed AVI cocentration of 4 mg/L [3]. Moreover, these isolates were further exposed to increasing concentrations of CAZ and fixed 4 mg/L of AVI, from a sub-MIC up to 256/4 mg/L of CAZ-AVI (or the concentration able to kill the bacterial isolate) at 37ºC with shaking during 24h. New MICs to CAZ-AVI were determined in each condition and after 15 days without CAZ-AVI pressure. Therefore, in order to demonstrated that blaKPC gene is responsible for acquisition of CAZ-AVI resistance in KPC-producing K. pneumoniae, blaKPC-2 and blaKPC-3 were cloned into a reference K. pneumoniae CECT 997 strain. Resistance or susceptibility were determined according to EUCAST criteria [3].

Results: All (17/17, 100%) KPC-producing K. pneumoniae isolates were able to grow at high concentrations of CAZ-AVI (≥64/4 mg/L), increasing their resistance to CAZ-AVI ≥8-fold. Likewise, fifteen of the 17 (88.2%) resistant isolates maintained the acquired CAZ-AVI resistance 15 days after without CAZ-AVI pressure. In addition, the CECT 997 mutants with blaKPC-2 or blaKPC-3 were able to grow up to 256/4 mg/L of CAZ-AVI, displaying and maintaining CAZ-AVI MIC shift from <0.01/4 mg/L (susceptible) to 512/4 mg/L (resistant).

Conclusions: These data suggest that exposure of KPC-producing K. pneumoniae to subinhibitory CAZ-AVI concentrations could lead to the selection of CAZ-AVI resistance and this resistance is stable over the time.

REFERENCES

[1] López-Hernández, I. et al. (2016) Activity of ceftazidime-avibactam against multidrug-resistance Enterobacteriaceae expressing combined mechanisms of resistance. *Enferm. Infecc. Microbiol. Clin.*, **35(8)**, 499–504.

[2] Räisänen, K. *et al*. (2019) Emergence of ceftazidime-avibactam-resistant Klebsiella pneumoniae during treatment, Finland, December 2018. *Euro Surveill.*, **24(19)**, 1900256.

[3] European Committee on Antimicrobial Susceptibility Testing (2019). Breakpoint tables for interpretation of MICs and zone diameters. EUCAST.