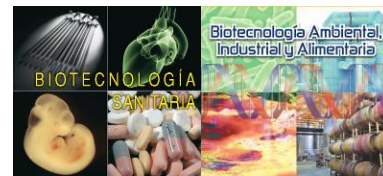


Talk

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



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ABSTRACT

Motivation: Infections caused by KPC-producing *Klebsiella pneumoniae* represent a challenge due to the limited available treatment 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 concerning the CAZ-AVI resistance development by CAZ-AVI selective pressure. Here, we aimed to determine 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 concentration 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 37°C with shaking during 24h. New MICs to CAZ-AVI were determined in each condition and after 15 days without CAZ-AVI pressure. Therefore, it was 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 ($\geq 64/4$ 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

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