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Exploring the *in vitro* activity of cefepime/taniborbactam combination against metallo beta-lactamase producing *Klebsiella pneumoniae and Pseudomonas aeruginosa* isolates

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INTRODUCTION

Taniborbactam is a novel β-lactamase inhibitor which directly inhibits all four classes of β –lactamases (Class A, C, D Serine- and VIM/NDM class B metallo-β-lactamases) and enhances the activity of cefepime against metallo-β-lactamase (MBL) producing *K. pneumoniae* and *P. aeruginosa* isolates. However, a subset of isolates remain resistant to cefepime. We therefore investigated the role of efflux pump activity and AmpC production on the *in vitro* activity of cefepime/taniborbactam combination.

METHOD

Isolates. Non-clonal molecularly characterized clinical MBL producing *K. pneumoniae* (N=19, 39% VIM, 61% NDM) and *P. aeruginosa* (N=59, 100% VIM) isolates highly resistant to cefepime with median (range) MIC >256 (64->256) and 32 (8->256) mg/L, respectively, were studied. In presence of 4 mg/L of taniborbactam, 9/19 *K. pneumoniae* and 29/59 *P. aeruginosa* remained resistantτ to cefepime.

Efflux pump activity. Efflux pump activity was concluded when cefepime MIC was reduced in presence of 25 mg/L carbonyl cyanide m-chlorophenyl hydrazone (CCCP) based on ISO-20776. Cefepime MICs were correlated with cefepime MIC reduction in presence of CCCP.

AmpC production. The presence of AmpC mediated resistance was evaluated in a Mueller Hinton agar plate inoculated with bacterial suspension where 3 disks of imipenem (10μg/disk) alone, imipenem+10μl of 0.1M EDTA, and imipenem+10μl of 0.1M EDTA + 10μl of cloxacillin 4000μg were placed. EDTA inhibits MBLs, imipenem served as an inducer of AmpC production and cloxacillin inhibits AmpC. Any difference of >4 mm between inhibition zones of the triple imipenem-EDTA-cloxacillin and the double imipenem-EDTA disk indicated AmpC activity.

RESULTS

- **An efflux-pump activity** was observed in 63% (12/19) *K. pneumoniae* and 61% (36/59) of *P. aeruginosa* isolates.
- A significant correlation was found between cefepime MICs and cefepime MIC reduction in presence of CCCP for *K. pneumoniae* (r=0.74, p=0.0003) and *P. aeruginosa* (r=0.27, p=0.03) (Figure 1).
- MIC related efflux activity was found between *K. pneumoniae* isolates with cefepime/taniborbactam MICs >4 and ≤4 mg/L [100% (9/9) and 30% (3/10), respectively] (P<0.0031) which had median (range) cefepime MICs >256 (64->256) and 64 (32->256), respectively.
- MIC inversely related efflux activity was found between *P. aeruginosa* isolates with cefepime/taniborbactam MICs >8 and ≤8 mg/L [38% (11/29) and 83% (25/30) respectively] (P<0.0005) with no difference in cefepime MICs.
- **AmpC activity** was detected in 37% (7/19) of *K. pneumoniae* and 68% (40/59) *P. aeruginosa* isolates with no differences found between isolates with cefepime/taniborbactam low and high MICs (P>0.05).

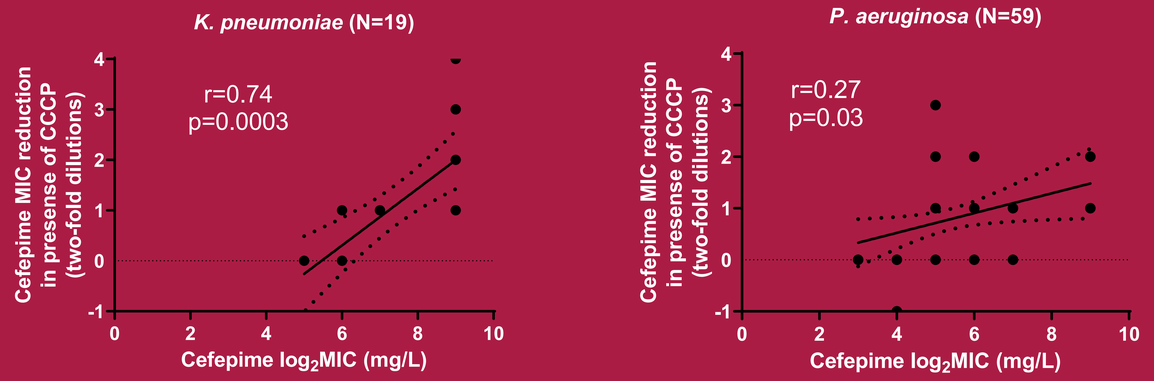

Figure 1. Correlation between cefepime MICs and cefepime MIC reduction in presence of CCCP

CONCLUSIONS

Cefepime enhancement by taniborbactam against *K. pneumoniae* isolates with high cefepime MICs was limited by efflux pump activity whereas for *P. aeruginosa* isolates a complex interplay between AmpC, MBL type and efflux pump activity may be present.

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