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Imipenem-relebactam, ceftolozane-tazobactam and ceftazidime-avibactam against carbapenem-resistant Pseudomonas aeruginosa: surveying clinical isolates for molecular markers that correlate with minimum inhibitory concentrations

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Background: *P. aeruginosa* is a leading human pathogen notable for its intrinsic and acquired resistance to antibiotics. Carbapenem-resistant *P. aeruginosa* (CRPA) are major problems worldwide. CR mechanisms included chromosomally-encoded inducible *AmpC*, several efflux pumps and porin loss/mutatiions.

Material/methods: We used broth microdilution to test 72 *P. aeruginosa* isolates (64 CR) *in vitro* against the recently FDA-approved agents ceftolozane-tazobactam and ceftazidime-avibactam, and the pipeline agent imipenem-relabactam that is currently in clinical trials. Relabactam has activity against class A and C β-lactamases. We applied CLSI breakpoints for ceftolozane-tazobactam and ceftazidime-avibactam and defined imipenem-relabactam MIC > 2 µg/mL as resistant. We sequenced ESBL genes (*TEM, SHV, CTX-M*), carbapenemase genes (*OXA-48, KPC, VIM, NDM*), *OmpD* and *AmpC* genes for all isolates. We evaluated basal and cefoxitin-induced expression of *AmpC* and various efflux and porin genes among isolates that exhibited a range of antibiotic MICs.

Results: All carbapenem-susceptible *P. aeruginosa* (CSPA) were susceptible to all 3 agents. Among CRPA, 27%, 14% and 6% were resistant to ceftazidime-avibactam, ceftolozane-tazobactam and imipenem-relabactam, respectively. Respective MIC_{50}'s were 1, 8 and 4 µ/mL. There was low correlation between imipenem MIC and imipenem-relabactam MIC (R=0.4). The addition of relabactam reduced imipenem MIC by a median of 8-fold, and rendered 94% of isolates susceptible to imipenem. 35% (6/17) of ceftazidime-avibactam-resistant isolates were also resistant to

ceftolozane-tazobactam, and 67% (6/9) of ceftolozane-tazobactam-resistant isolates were also resistant to ceftazidime-avibactam. 25% (1/4) of imipenem-relabactam-resistant isolates were resistant to ceftazidime-avibactam, and none resistant to ceftolozane-tazobactam. None of the isolates harbored mutations within ESBL, carbapenemase or *AmpC* genes. 41% of CRPA isolates had mutations within *OprD*. There was no correlation between MICs of any of the 3 drugs with basal *AmpC, MexB, MexD, MexY* and *OprD* expression. There was also no correlation between cefoxitin-induced expression of *AmpC, MexB, MexD, MexY* and *OprD* and ceftolozane-tazobactam and ceftazidime-avibactam MICs. In contrast, imipenem and imipenem-relabactam MICs correlated with cefoxitin-induced expression of *MexY* (p=0.003), *MexD* (p=0,008), *OprD* (p=0.01) and *MexB* (p=0.09). Cefoxitin-induced *AmpC* expression did not correlate with imipenem-relabactam MIC.

Conclusions: Imipenem-relabactam has excellent *in vitro* activity against CRPA, including isolates resistant to ceftazidime-avibactam and ceftolozane-tazobactam. Imipenem-relabactam MICs did not correlate with cefoxitin-induced *AmpC* expession, suggesting that relabactam efficiently inhibits activity of this enzyme. The correlation between imipenem and imipenem-relabactam MICs and efflux and porin gene expression is concerning, and suggests that limiting access of imipenem to the periplasmic space is an important determinant of reduced imipenem-relabactam susceptibility.