**P0226**
**Poster Session I**
**Antibacterial drug activity and interactions in Gram-negative bacteria**

# TIGECYCLINE-COLISTIN IS ACTIVE AGAINST ST258, KPC-PRODUCING KLEBSIELLA PNEUMONIAE WITH MAJOR OMPK36 PORIN MUTATIONS, WHICH DO NOT RESPOND TO DORIPENEM-COLISTIN.

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Objective. We have demonstrated that doripenem-colistin (DOR-COL) is active against KPC-*K. pneumoniae* strains with wild-type (WT) ompK36 porin, but not against insAA134-135DG or IS*5* ompK36 mutants (major mutants). Our objective was to evaluate the susceptibility of KPC-*K. pneumoniae* strains with diverse ompK36 porin genotypes to tigecycline (TGC) *in vitro*, alone or in combination with DOR and COL.

Methods. We measured TGC MICs against 50 ST258, KPC-producing strains by broth microdilution (BMD) and E-test (rounded to next doubling dilution). MIC discrepancies were resolved by time kill assays (TKA) with TGC at 0.25, 0.5, 1, 2, 4 µg/mL. TKA MIC was defined as the concentration that prevented growth at 24 hrs (static activity). We then performed TKA for TGC (2 µg/mL), COL (2 µg/mL) and DOR (8 µg/mL) against 12 ST258, KPC-2-producing *K. pneumoniae* strains.

Results. TGC MICs by BMD and E-test showed essential and categorical agreement (EA, CA) of 84% (42/50) and 50% (25/50), respectively. Among the 8 strains that did not show EA, BMD and E-test MICs were consistently lower and higher than TKA MIC, respectively. E-test MICs correlated more closely than BMD with TKA MICs. The ompK36 genotypes of the 12 strains in TKA were insAA134-135DG, IS*5*, and WT/other (n=4 each). Thirty-three percent (4/12), 42% (5/12) and 100% of strains were TGC-, COL- and DOR-resistant, respectively. TGC alone showed >1-log kill against 62.5% (5/8) and 0% (0/4) of strains with E-test MIC ≤2 and >2 µg/mL, respectively (p=0.08). COL and DOR did not demonstrate >1-log kill against any strain. TGC-COL, DOR-TGC and DOR-COL were synergistic (>2-log kill in combo *vs* alone) against 83% (10/12), 33% (4/12) and 33% (4/12) of strains, respectively. DOR-TGC was antagonistic against 17% (2/12). TGC-COL, DOR-TGC and DOR-COL were bactericidal (> 2-log kill) against 42% (5/12), 17% (2/12), and 33% (4/12), respectively. The activity of TGC-containing combinations did not correlate with TGC MICs. In contrast, COL-containing combinations were less active against strains with COL MICs>2 µg/mL. TGC-DOR-COL activity was similar to TGC-COL (mean log-kill = -3.23 *vs* -3.25 (p=0.98)). The most effective combination against insAA134-135DG mutants was TGC-COL, which achieved mean synergistic and bactericidal activity. TGC-COL was also most effective against IS*5* mutants, achieving mean synergistic and bacteriostatic activity. DOR-COL and TGC-COL were equally effective against WT stains, achieving mean synergistic and bactericidal activity.

Discussion. TGC-COL may be a useful treatment option against infections caused by KPC-*K. pneumoniae* with insAA134-135DG and IS*5* ompK36 porin mutations, which do not respond to DOR-COL. TGC-DOR-COL did not offer any advantage over TGC-COL *in vitro*, and may be limited by antagonism against some strains. TGC MICs by E-test may more accurately reflect *in vitro* drug activity than MICs by BMD.