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Poster Session V
Worldwide spread of carbapenem resistance

A TREATMENT ALGORITHM FOR CARBAPENEM-RESISTANT KLEBSIELLA PNEUMONIAE INFECTIONS BASED ON THE RESISTANCE MECHANISMS OF INFECTING STRAINS

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Objectives. We previously demonstrated that carbapenem-resistant *K. pneumoniae* infections at our center were caused overwhelmingly by KPC-2-producing, ST258 strains that were indistinguishable by conventional typing. Despite clonality, genome sequencing revealed 50-700 SNPs between strains, and several ompK36 genotypes. Doripenem-colistin (D-C) was the most active antimicrobial combination against KPC-Kp strains with wild-type (WT) ompK36, but it was inactive against insAA134-135DG or IS*5* ompK36 mutants. Our objectives were to: 1) identify antimicrobial regimens active against KPC-Kp ompK36 mutants; 2) devise a treatment algorithm for KPC-Kp infections based on *in vitro* data; and 3) determine if the algorithm predicted treatment responses among patients (pts) with KPC-Kp bacteremia.

Methods. We conducted time kill assays (TKA) against strains with various ompK36 genotypes. We performed a retrospective study of pts from 2/10-5/13 who were treated for >3 days with antimicrobial combinations recommended by our algorithm.

Results. Each ST258 strain at our center harbored mutant ompK35 (STOP-AA89), bla_{KPC-2}, bla_{SHV-12}, and bla_{TEM-1}, but was negative for bla_{CTX-M}, bla_{IMP}, bla_{NDM}, bla_{VIM}, bla_{OXA-48}, and bla_{AmpC}. insAA134-135DG or IS*5* ompK36 mutations were detected in 70% of strains, and WT ompK36 in 30%. As previously reported, insAA134-135DG and IS*5* ompK36 conferred high-level D resistance, and were independently associated with lack of response to D-C (8 and 2 µg/mL) during TKA (n=23 strains; p=0.02). Overall, 60% and 40% of strains were gentamicin (G)-susceptible and –resistant, respectively, irrespective of ompK36 genotype. During TKA, G (2 and 10 µg/mL) was bactericidal against 64% (9/14) and 100% (14/14) of G-susceptible strains, respectively. D-G (8 and 2 µg/mL) was synergistic and inhibited regrowth of 60% (3/5) of strains for which G was not bactericidal. G (2 µg/mL; median AUBC: 53-log_{10} (CFU/ml.h)) was more bactericidal than C (115-log_{10}; p=0.0008), D (221.3-log_{10}; p<0.0001), or D-C (112-log_{10}; p=0.0008). D-C did not differ significantly from G or D-G against WT ompK36 strains, but was significantly less bactericidal against ompK36 mutants (p≤0.007). In contrast, G (2 and 10 µg/mL) exerted no activity against 12 G-resistant strains. Based on these data, we devised an algorithm that uses ompK36 genotypes and G susceptibility to identify D-C or G-based regimens as likely to be effective against KPC-Kp strains. D-C treatment was successful at 28 d in 62.5% (5/8) of pts with bacteremia due to WT ompK36 strains, *vs.* 8% (1/12) of pts infected with ompK36 mutants (p=0.02). G-based treatment was successful in 67% (14/21) of pts with bacteremia due to G-susceptible strains (G, 60% (6/10); D-G 73% (8/11)).

Conclusions. Optimal antimicrobial regimens against KPC-Kp infections are determined by strain genetics and resistance mechanisms. Treatment algorithms incorporating these data may improve outcomes. Our current priority is to identify an effective antimicrobial combination against ~20% of KPC-Kp strains that are G-resistant, insAA134-135DG or IS*5* ompK36 mutants.