29th ECCMID Amsterdam, Netherlands 13 – 16 April 2019

The congress of ESCMID

P2838 Deciphering networks of collateral sensitivity/resistance of antibiotic-resistant *Streptococcus pneumoniae*

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Background: *Streptococcus pneumoniae* is the leading cause of community-acquired pneumonia and meningitis, responsible for high morbidity and mortality. Treatment efficacy is threatened by the global dissemination of multi-resistant *S. pneumoniae* clones. A promising approach to address this problem is collateral sensitivity (CS) cycling. The aim of this study was to determine the CS and collateral resistance (CR) networks of antibiotic-resistant *S. pneumoniae*.

Materials/methods: Isogenic antibiotic-resistant mutants of *S. pneumoniae* R6 were selected at drug concentrations equal to EUCAST ECOFFs for ciprofloxacin, co-trimoxazole, fusidic acid, linezolid, and rifampicin. Six to ten independent antibiotic-resistant mutants were obtained for each antibiotic. Minimal inhibitory concentrations (MICs) of 13 commonly used antibiotics were determined for each strain via broth microdilution. CS/CR was determined by comparing the MICs of resistant strains to the isogenic antibiotic-sensitive wild type strain. Whole genome sequencing of parental and mutant strains using Illumina MiSeq is underway to identify resistance mechanisms and causal factors underlying CS/CR.

Results: We observed widespread CS and CR; however, independently isolated resistant strains for each antibiotic varied in their collateral responses. Among co-trimoxazole-resistant mutants, 67% showed CS to fusidic acid and daptomycin, while 100% showed CS to rifampicin, tetracycline and clindamycin; 33% had CR to chloramphenicol and 67% to ciprofloxacin. 60% of ciprofloxacin-resistant mutants exhibited CS to linezolid, and 40% to rifampicin, chloramphenicol and gentamicin. All linezolid-resistant mutants showed CS to vancomycin and CR to chloramphenicol and clindamycin. CS was found for fusidic acid-resistant mutants towards rifampicin (20%), linezolid (50%), co-trimoxazole (50%), erythromycin (60%), chloramphenicol (90%), daptomycin (90%) and clindamycin (100%), as well as for rifampicin-resistant mutants towards linezolid (10%), tetracycline (30%), fusidic acid (40%) and chloramphenicol (100%). Reciprocal CS responses were observed between ciprofloxacin and linezolid, co-trimoxazole and fusidic acid, co-trimoxazole and rifampicin, as well as fusidic acid and rifampicin.

Conclusions: This is the first report on CS/CR networks of *S. pneumoniae*. Although CS and CR responses are highly variable for strains with resistance to the same antibiotic, we identified several pairs of antibiotics with reciprocal CS responses. These results suggest that CS cycling may be a promising approach to treat antibiotic-resistant *S. pneumoniae* infections.