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P0251 Comparative resistance studies using in vitro dynamic model: amoxicillin versus azithromycin against Streptococcus pneumoniae

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Background: Despite the widespread use of aminopenicillins and macrolides in infections caused by *Streptococcus pneumoniae* (S.p.), current knowledge of the possible selection of resistant mutants during treatment is limited. To compare amoxicillin (AMX) and azithromycin (AZM) in this aspect, their pharmacokinetics were simulated in an in vitro dynamic model at clinically attainable 24-hour areas under the concentration-time curve (AUC).

Materials/methods: The MICs and MPCs (mutant prevention concentrations) of AMX and AZM were determined with two ATCC and four clinical S.p strains. Five-day treatments of S.p. ATCC 49619 with AMX MIC of 0.06 µg/ml and AZM MIC 0.125 µg/ml, corresponding to the MIC_{50}s and a clinical isolate S.p. 9-5 with AMX MIC of 0.25 µg/ml and AZM MIC of 0.25 µg/ml (greater than the MIC_{50}s) were simulated in a hollow fiber model. Thrice daily dosing of AMX (500 and 1000 mg by 1.67-hour infusion) and once-daily dosing of AZM (500 and 1000 mg by 2-hour infusion) were mimicked. Mono-exponential concentration decay was simulated with AMX and bi-exponential decay with AZM. To reveal resistant mutants, samples withdrawn from the peripheral compartments of the model were plated onto agar plates containing 2× and 4×MIC of AMX or AZM. To ensure that the designed antibiotic concentrations were achieved, AMX and AZM concentrations were determined by LC-MS/MS spectrometry.

Results: MPC/MIC ratios for the studied S.p. strains varied from 8 to 266 (AZM) and from 2 to 4 (AMX), showing much wider mutant selection windows (MSWs) with AZM compared to AMX. When simulating antibiotic pharmacokinetics, AZM-resistant but not AMX-resistant S.p. mutants were enriched. This is explained by the position of pharmacokinetic profiles in the MSWs. Simulated AZM concentrations were consistently inside the MSW, whereas AMX concentrations were out of the MSW over the entire dosing interval: the times above the MPC were zero with AZM but 100% of the dosing interval with AMX.

Conclusions: The enrichment of AZM-resistant S.p. in contrast to the lack of such an enrichment of AMX-resistant mutants can be predicted by the MSW hypothesis: unlike AMX, clinically attainable AZM concentrations are inside the MSW.