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O0930 Minimum inhibitory concentrations of pyrazinamide for *Mycobacterium tuberculosis* in relation to lineage, genotypic and phenotypic drug resistance

Johanna Kuhlin[1], Mikael Mansjö[2], Lina Davies Forsman[1], Maria Wijkander[2], Michaela Jonsson Nordvall[3], Jim Werngren[2], Jan W. C. Alffenaar[4], Judith Bruchfeld[1], Thomas Schön*[5]

[1] Unit of Infectious Diseases, Department of Medicine and Department of Infectious Diseases, Solna, Sweden, [2] Department of Microbiology, The Public Health Agency of Sweden, Solna, Solna, Sweden, [3] Department of Clinical and Experimental Medicine, Division of Clinical Microbiology, Linköping, Sweden, [4] Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [5] Department of Clinical Microbiology and Infectious Diseases, Kalmar County Hospital, Linköping University, Linköping, Sweden

Background: Pyrazinamide (PZA) is an important sterilizing drug in the treatment of both multidrug resistant (MDR) and drug-susceptible tuberculosis (TB). However, antimicrobial susceptibility testing (AST) for PZA requires special test conditions and is rarely performed. Consequently, even less is known regarding susceptibility levels for PZA quantified by minimum inhibitory concentrations (MIC) which are needed for phenotype-genotype correlations, individualized therapy based on therapeutic drug monitoring (TDM) and for setting adequate clinical breakpoints.

Materials/methods: From a collection of consecutive MDR- and drug susceptible TB patients in Sweden (n=112), MIC determinations (BACTEC 960 MGIT) were compared to routine DST (critical concentration (CC) of 100 mg/L), mutations in *pncA* as well as to *Mycobacterium tuberculosis* (Mtb) lineage by Ion-torrent based whole genome sequencing (NGS). Mtb H37Rv ATCC 27294 and ATCC 25618 were included as quality controls (QC).

Results: In total, 28.1% (25/89) isolates showed PZA resistance among MDR-TB patients and routine AST correlated well with MIC determination at the CC (94.6%). The QC (Mtb H37Rv ATCC 27294) showed a median of 32 mg/L and a variability less than ±one MIC dilution step. MICs in the putative wild type were distributed between ≤8mg/L to 64 mg/L and lacked *pncA* mutations in contrast to resistant isolates with MICs≥128mg/L. Within the wild type, lineages 4.2.2 (n=9) and 3 (n=10) both showed median MICs ≤8mg/L with a distribution significantly and systematically lower than for lineage 1 (64 mg/L, n=10 $p<0.01$; Mann Whitney U-test).

Conclusions: In this Swedish cohort of MDR-TB patients, only around one third of patients were infected with a PZA resistant Mtb isolate. As previously shown, *pncA* mutations correlated to drug resistance and current breakpoints. A novel observation was a trend for lineage specific differences in the level of PZA susceptibility which may have implications for the reproducibility of PZA testing, efficacy of PZA in different geographical areas and constitutes a potential WGS based strategy to individualize treatment for PZA by TDM.