Development of an Diagnostic Antibiotic Stewardship (ABS) Strategy combining Therapeutic Drug Monitoring (TDM) with Culture-Independent Fast Antimicrobial Susceptibility Testing (AST) in Patients Suffering From Pneumonia

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Introduction:

- Fast antimicrobial susceptibility testing (AST), minimal inhibitory concentration (MIC) detection and therapeutic drug monitoring (TDM) with consecutive adapted antibiotic drug dosing is of vital importance for clinical outcome in patients suffering from pneumonia.

What is „Diagnostic Stewardship" ?: coordinated guidance and interventions to improve appropriate use of microbiological diagnostics to guide therapeutic decisions. It should promote appropriate, timely diagnostic testing, including specimen collection, and pathogen identification and accurate, timely reporting of results to guide patient treatment

Methods (1):

- At ECCMID 2018, we reported very prominsing evaluation results for a new, fully automated, culture-independent diagnostic FISH/ microscopy-based method used for pathogen identification (ID), antimicrobial susceptibility testing (AST) and minimal inhibitory concentration (MIC) detection (Accelerate Pheno™, Tucson, AZ, USA) in patients suffering from sepsis (1)
- Susceptibility reports are generated by microscopic observation of individual, live, growing immobilized bacterial cells in real time in the presence/absence (control) of antimicrobial agents.
- Antimicrobials for AST are selected based on the respective identified pathogen.

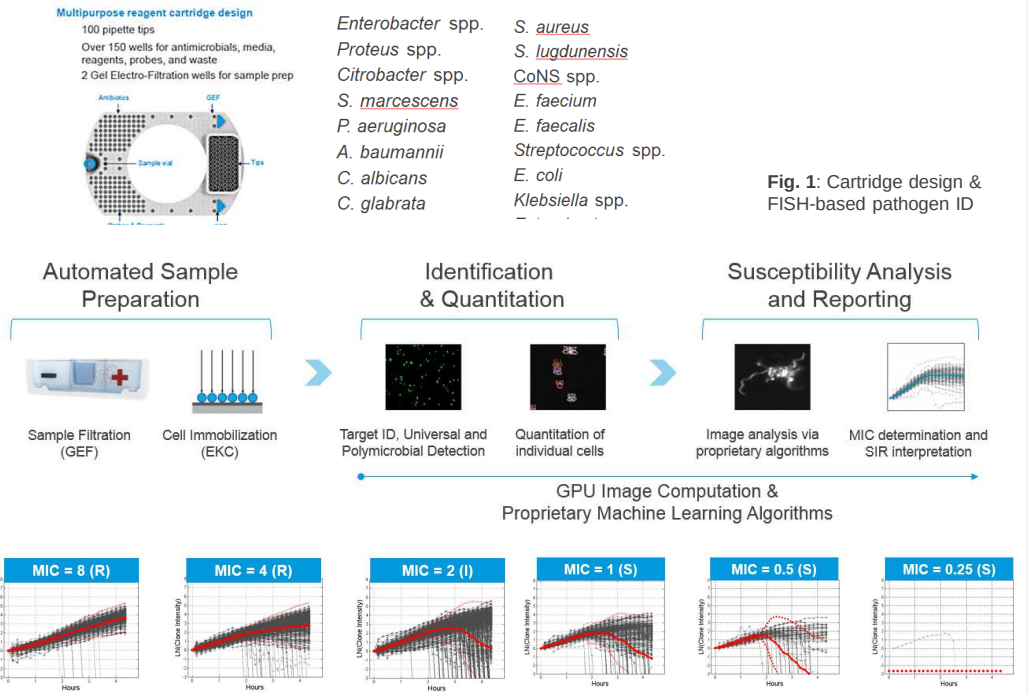

Fig. 1: Cartridge design & FISH-based pathogen ID

Fig. 2: Identification, quantification & morphokinetic cellular analysis: Distinct morphokinetic features are translated into a growth response profile and converted to a Minimum Inhibitory Concentration (MIC) value

Methods (2):

- High-performance liquid chromatography (HPLC) using UV detection is frequently used for TDM.
- We developed a more sensitive and selective method using HPLC coupled with tandem mass spectrometry (LC-MS/MS) for TDM of eight antimicrobials (ampicillin, cefuroxime, ciprofloxacin, meropenem, metronidazole, piperacillin, rifampicin, tazobactam) plus one nucleoside antiviral drug (acyclovir) in lithium-heparin plasma with a chromatographic run time of ten minutes (2).
- Analyses were performed using an Agilent 1200 series system (Santa Clara, CA), consisting of a thermostatic autosampler, a binary solvent delivery manager, and a thermostated column compartment. Chromatographic separation was achieved using a Kinetex F5 core–shell reverse-phase column (50 × 2.1 mm, 100 Å pore size, 2.6 µm particle size; Phenomenex, Aschaffenburg, Germany) and a corresponding F5 precolumn with a 2.1-mm internal diameter (Phenomenex, Aschaffenburg, Germany).
- detection was conducted with an API4000 LC-MS/MS System (AB SCIEX, Framingham, MA) equipped with an electrospray ionization source.

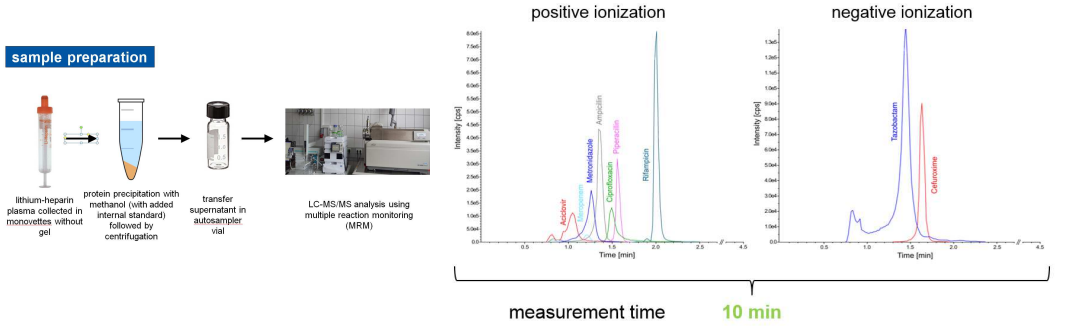

Fig. 3: Sample preparation (left) and representative MRM chromatograms (right). The peaks are shown in an overall overview of positive and negative ionization, including retention times in a sample MRM chromatogram for 10 mg/L of antimicrobials in lithium–heparin plasma. Left panel: MRM chromatogram of all antimicrobials (quantifier) with positive ionization, Right panel: MRM chromatogram of all antimicrobials (quantifier) with negative ionization.

Conclusion:

- Development of an Diagnostic Antibiotic Stewardship Strategy: We aim to combine the LC-MS/MS based TDM method with the FISH/microscopy-based ID/AST method to have a more personalized therapeutic drug dosing approach for patients suffering from pneumonia in a clinical study.

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