

Metabolic biomarkers of *P. aeruginosa* ventilator-associated pneumonia

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Facts & Figures

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Challenge

Ventilator-associated pneumonia (VAP) is the most frequent hospital-acquired infection in the intensive care unit. VAP is generally caused by opportunistic pathogens, of which *Pseudomonas aeruginosa* is one of the major causes. VAP caused by *P. aeruginosa* (VAP-PA) has been associated with higher case fatality rates than VAP caused by other bacterial aetiologies. The attributable mortality is even further increased when *P. aeruginosa* is present with other organisms, especially Staphylococcal spp., or with multi-drug resistant strains.

Despite the clinical importance of VAP-PA and the knowledge that timely *P. aeruginosa* specific treatment improves patient outcome, no predictive biomarkers are currently available to diagnose the disease. The lack of rapid diagnostic methods leading to timely treatment, the high mortality associated with *P. aeruginosa* infection and the high levels of antibiotic resistance in *P. aeruginosa* strains prompts an urgent need for diagnostic markers of VAP-PA to guide pathogen-targeted therapy.

Approach & Methodology

Samples were prospectively collected at the start of mechanical ventilation, and upon presumptive clinical diagnosis of VAP, which was confirmed by culture of bronchoalveolar lavage. Using quantitative metabolomics VAP-PA cases were compared with VAP–non-PA and with the pre-infection timepoints. Metabolites were separated on a Rapid Resolution Liquid Chromatography system coupled in-line with a quadrupole time-of-flight mass spectrometer. For VAP-PA biomarker discovery, only metabolites differentially-expressed (> 8-fold upregulated) metabolites at P < 0.05.

Results

Multivariate analyses with heat map as well as with partial least squares regression discriminant (PLS-DA) analyses accurately discriminated VAP-PA from VAP–non-PA and from the pre-infection control group (PLS-DA, R² = 0.97 and 0.98, respectively).

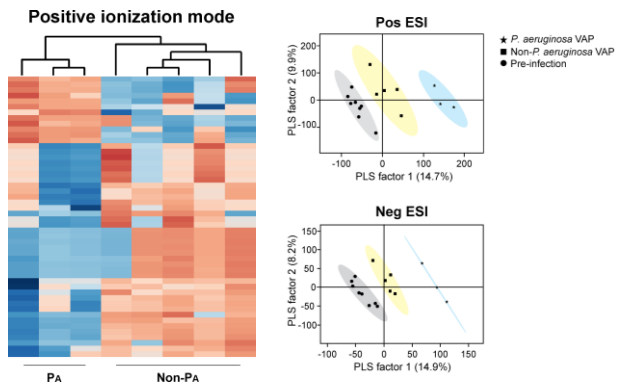


Fig. 2: Clustering of VAP patients based on aetiology

Univariate analyses identified 58 metabolites that were significantly elevated or uniquely present in VAP-PA compared to the pre-infection timepoint and to the VAP–non-PA group (P at least 0.048). Of these, 3 metabolites were highly abundant in, and specific to, VAP-PA being absent in all pre-infection timepoints and in VAP–non-PA (Fig. 3A). Two targets were exclusively present in *P. aeruginosa* and *S. marcescens* VAP (Fig. 3B).

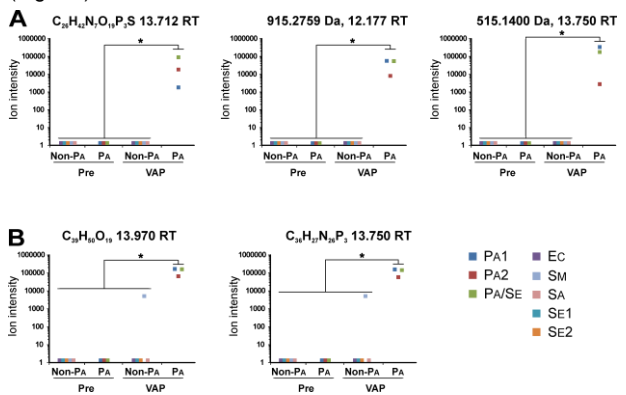


Fig. 3: Top discriminating metabolites in univariate analyses

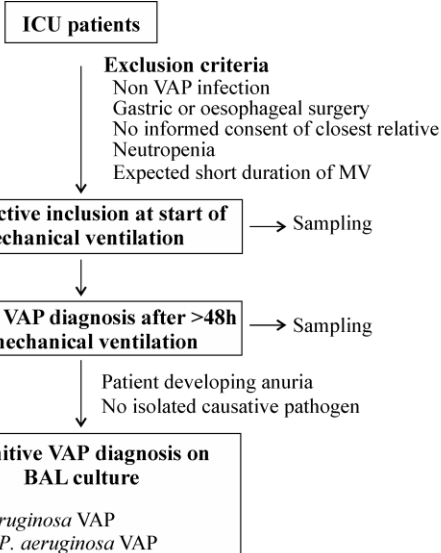


Fig. 1: Flow diagram of study design, patient inclusion and sampling

Value of IMI collaboration

IMI provides a unique framework to engage academic and industry experts in a mutually enriching collaboration, which along with fulfilling the primary goals of the project also allows capacity building. In this project we were able to closely collaborate with clinicians and mass spectrometry experts to be able to conduct this study.

Impact & take home message

This proof-of-principle study, identifying several unique metabolic biomarkers for VAP caused by *P. aeruginosa*, clearly demonstrates that metabolomic biomarkers can differentiate VAP-PA from VAP due to other bacterial aetiologies as early as the time of the clinical suspicion of VAP. These biomarkers, if further validated in large multicentre studies for their sensitivities and specificities have the potential to be developed into highly specific early VAP-PA biomarkers that could lead to an improved patient outcome.