DIAGNOSIS OF ACUTE AND CHRONIC ENTERIC FEVER USING METABOLICOMICS

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt förvar i KB.E3.03 (Stora hörsalen, Carl Kempe-salen), KBC-huset, Umeå universitet fredagen den 27:e oktober, kl. 10:00. Avhandlingen kommer att förvaras på engelska.

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Abstract
Enteric (or typhoid) fever is a systemic infection mainly caused by *Salmonella* Typhi and *Salmonella* Paratyphi A. The disease is common in areas with poor water quality and insufficient sanitation. Humans are the only reservoir for transmission of the disease. The presence of asymptomatic chronic carriers is a complicating factor for the transmission. There are major limitations regarding the current diagnostic methods both for acute infection and chronic carriage. Metabolomics is a methodology studying metabolites in biological systems under influence of environmental or physiological perturbations. It has been applied to study several infectious diseases, with the goal of detecting diagnostic biomarkers. In this thesis, a mass spectrometry-based metabolomic approach, including chemometric bioinformatics techniques for data analysis, has been used to evaluate the potential of metabolite biomarker patterns for diagnosis of enteric fever at different stages of the disease.

In *Paper I*, metabolite patterns related to acute enteric fever were investigated. Human plasma samples from patients in Nepal with culture-confirmed *S.* Typhi or *S.* Paratyphi A infection were compared to afebrile controls. A metabolite pattern discriminating between acute enteric fever and afebrile controls, as well as between the two causative agents of enteric fever was detected. The strength of using a panel of metabolites instead of single metabolites as biomarkers was also highlighted. In *Paper II*, metabolite patterns for acute enteric fever, this time focusing only on *S.* Typhi infections, were investigated. Human plasma from patients in Bangladesh with culture-positive or -negative but clinically suspected *S.* Typhi infection were compared to febrile controls. Differences were found in metabolite patterns between the culture-positive *S.* Typhi group and the febrile controls with a heterogeneity among the suspected *S.* Typhi samples. Consistencies in metabolite patterns were found to the results from *Paper I*. In addition, a validation cohort with culture-positive *S.* Typhi samples and a control group including patients with malaria and infections caused by other pathogens was analysed. Differences in metabolite patterns were detected between *S.* Typhi samples and all controls as well as between *S.* Typhi and malaria. Consistencies in metabolite patterns were found to the primary Bangladeshi cohort and the Nepali cohort from *Paper I*. *Paper III* focused on chronic *Salmonella* carriers. Human plasma samples from patients in Nepal undergoing cholecystectomy with confirmed *S.* Typhi or *S.* Paratyphi A gallbladder carriage were compared to non-carriage controls. The *Salmonella* carriage samples were distinguished from the non-carriage controls and differential signatures were also found between the *S.* Typhi and *S.* Paratyphi A carriage samples. Comparing metabolites found during chronic carriage and acute enteric fever (in *Paper I*) resulted in a panel of metabolites significant only during chronic carriage. This work has contributed to highlight the potential of using metabolomics as a tool to find diagnostic biomarker patterns associated with different stages of enteric fever.

Keywords
Enteric fever, *Salmonella*, chronic carriers, metabolomics, diagnosis, biomarkers, multivariate data analysis, GCxGC-MS, GC-MS, LC-MS.