Improved Diagnosis and Prediction of Community-Acquired Pneumonia

Alicia Edin

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt förvar i Bergasalen (Qo), Norrlands universitetssjukhus, fredagen den 25:e maj kl. 09:00.

Avhandlingen kommer att förvaras på engelska.

Fakultetsopponent: Docent, Thomas Schön,
Institutionen för klinisk och experimentell medicin, Linköpings universitet.
Clinical Microbiology

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Abstract
Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide. Although there is wide variation in the microbial etiology, CAP may manifest with similar symptoms, making institution of proper treatment challenging. Therefore, etiological diagnosis is important to ensure that correct treatment and necessary infection control measures are instituted. This provides a challenge for conventional microbial diagnostic methods, typically based on culture and direct antigen tests. Moreover, existing molecular biomarkers have poor prognostic value. Few studies have investigated the global metabolic response during infection and virtually nothing is known about early responses after the start of antimicrobial treatment. The aim of this work was to improve diagnostic and predictive methods for CAP.

In paper I, a qPCR panel targeting 15 pathogens known to cause CAP was developed and evaluated. It combined identification of bacterial pathogens and viruses in the same diagnostic platform. The method proved to be robust and the results consistent with those obtained by standard methods. The panel approach, compared to conventional, selective diagnostics, detected a larger number of pathogens. In Paper II, whole blood samples from 65 patients with bacteremic sepsis were analyzed for metabolite profiles. Forty-nine patients with symptoms of sepsis, but later attributed to other diagnoses, were matched according to age and sex and served as a control group. Six metabolites were identified, all of which predicted growth of bacteria in blood culture. One of the metabolites, myristic acid, alone predicted bacteremic sepsis with a sensitivity of 100% and a specificity of 95%. Paper III and IV were based on a clinical study enrolling 35 patients with suspected CAP in need of hospital care. The aim was to study the metabolic response during the early phase of acute infection. The qPCR panel developed in Paper I was used to obtain the microbial etiological diagnosis. Paper IV focused on the global metabolic response and highlighted the dynamics of changes in major metabolic pathways during early recovery. A specific metabolite pattern for M. pneumoniae etiology was found. Four metabolites accurately predicted all but one patient as either M. pneumoniae etiology or not. Paper III looked at phospholipid levels during the first 48 hours after hospital admission. It was found that all major phospholipid species, especially the lysophosphatidylcholines, were pronouncedly decreased during acute infection. Levels started to increase the day after admission, reaching statistical significance at 48 hours. Paper II-IV showed that metabolomics might be used to study a number of different aspects of infection, such as etiology, disease progress and recovery. Knowledge of the metabolic profiles of patients may not only be utilized for biomarker discovery, as proposed in this work, but also for the future development of targeted therapies and supportive treatment.

Keywords
Community-acquired pneumonia, infection, diagnosis, qPCR, metabolites, metabolomics