Jens-Ulrik Jensen PhD Dissertation

Dynamic use of Biomarker Procalcitonin in the Intensive Care Unit

Bacterial infection remains a major cause of mortality in patients who are admitted to the intensive care unit. Diagnosis and monitoring of effects of antibacterial treatment is particularly complicated in these critically ill patients, since infections may not clinically present typically, difficulties in separating colonisation from invasive infection, patients may suffer from multiple pathologies and receive medication affecting the usual parameters to assess the treatment response. Additionally, the established biomarkers, namely C-reactive protein and white blood cell count have several limitations in these patients, because of their slow elimination kinetics and a low specificity for bacterial infection. Therefore, a need for novel methods to diagnose bacterial infections and monitor the response to antibacterial chemotherapy would be desirable. Unfortunately, results regarding the biomarkers of infection investigated so far are diverging; this is also true for the most investigated biomarker of infection, Procalcitonin.

The aim of this Ph.D. was to investigate the prognostic power of Procalcitonin measurements and, most importantly, the ability of PCT-guided antimicrobial therapy in improving survival and other outcome parameters in ICU patients. Core elements in this approach were to: 1) study outcome endpoints other than sepsis or other clinical diagnoses, 2) as a diagnostic and treatment monitoring biomarker of ongoing bacterial infection with daily sequential measurements, to investigate the potentially useful information from changes in levels of the biomarker over time after admission to ICU, 3) to apply the randomised controlled intervention methodology to assess whether procalcitonin-guided antibiotic use can reduce mortality in critically sick patients.

Paper I is an original article of 472 ICU patients and 3,642 PCT measurements, sampled on all days of the ICU admission. The main result was that one single day of PCT increase in the ICU, was an independent predictor of mortality (based on at least two measurements), and conversely, that the level of PCT at admission, was not a predictor of mortality. The hazard ratio for death, for patients who had at least one day of PCT-increase was 1.8 [95% CI 1.4-2.4]. It was also found, that increases in white blood cells or C-reactive protein were not predictors of mortality.

Paper II is the protocol for the PASS trial, a 1,200 patient randomized interventional trial, which has been developed in part on the basis of the results of paper I. Along side paper II, the data from the open reports from the so far performed interim analyzes are included. To preserve the integrity of the study, outcome data from the study remained blinded until the study had been completed (after the PhD defence). The results from the trial were later presented at the Infectious Disease Society of America meeting, Oct 28th – Nov 1st 2009, Philadelphia, USA.