**Institutionen för Medicin, Enheten för Infektionssjukdomar,
Karolinska Institutet, Stockholm**

Aetiology in community-acquired pneumonia

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Welandersalen, ingång B2, plan 00, Karolinska Universitetssjukhuset, Solna

Tordagen den 29 november 2012, kl 09.00

av

Niclas Johansson

Leg. Läkare

Huvudhandledare:
Doc. Jonas Hedlund
Karolinska institutet
Institutionen för Medicin, Solna
Enheten för infektionssjukdomar

Bihandledare:
Prof. Mats Kalin
Karolinska institutet
Institutionen för Medicin, Solna
Enheten för infektionssjukdomar

Fakultetsopponent:
Med. Dr. Martin Laurell
Lunds universitet
Enheten för infektionssjukdomar

Betygsnämnd:
Prof. Annelie Brauner
Karolinska Institutet
Institutionen för mikrobiologi,
tumör och cellbiologi

Prof. Lars Lindqvist
Karolinska institutet
Institutionen för medicin, Huddinge
Enheten för infektionssjukdomar

Doc. Karlis Pauksens
Uppsala universitet
Institutionen för medicinska vetenskaper,
infektionssjukdomar

Stockholm 2012

ABSTRACT

Background: Although community-acquired pneumonia (CAP) is a common and well-known disease, its microbial aetiology is still not well characterized. During the past few years nucleic acid detection using real-time polymerase chain reaction (PCR) has been developed for detection of many bacterial and viral pathogens causing respiratory tract infections.

Objectives: 1) to estimate the accuracy of the quantitative real-time PCR (RQ-PCR) method for identifying pneumococci in sputum; 2) to determine the aetiology of CAP by implementing new diagnostic PCR techniques combined with conventional methods; 3) to compare CAP patients with a pure bacterial aetiology with those with both bacterial and viral findings regarding severity of illness and length of hospital stay; 4) to study the inflammatory response, especially procalcitonin (PCT) levels, in patients with CAP and the correlation to different respiratory pathogens.

Material and methods: Adults admitted to Karolinska University Hospital were studied during a 12-month period. All patients were tested with an extensive panel of conventional methods and in addition sputum samples were analysed with RQ-PCR for *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*; and nasopharyngeal specimens were analysed with real-time PCR for viruses common in the airways. Serum samples were collected within 24 hours of admission for subsequent measurement of PCT, C-reactive protein, transthyretin and interleukin-6. The pneumonia severity index (PSI) was used to assess the severity of illness.

Results: In sputum samples, culture was significantly positive in 19/128 (15%), whereas a significant concentration of DNA was found with RQ-PCR in 34/127 (27%) cases ($p < 0.001$). Seventeen of the 34 RQ-PCR–positive sputum samples were negative by sputum culture, of which 14 were from patients treated with antibiotics prior to sampling. A microbial aetiology was found in 67% of all patients (n=124). The most frequently detected pathogens were *S. pneumoniae* (70 patients [38%]) and respiratory virus (53 patients [29%]). Multiple pathogens were present in 43 (35%) of those with a determined aetiology. The likelihood of getting a score corresponding to PSI classes IV or V was higher in patients with combined bacterial-viral findings than in those with a bacterial pathogen alone (odds ratio 4.98, 95% confidence interval 2.09 – 11.89; $p < 0.001$). The median length of hospital stay was seven days among patients with mixed infections and four days among those with a bacterial aetiology alone (p=0.018). Median serum concentrations of PCT were higher in patients with bacteraemia than in those without bacteraemia (6.11 µg/L vs. 0.34 µg/L, P=0.0002), in those with non-bacteraemic pneumococcal aetiology than in those infected with other classic bacteria (1.18 vs. 0.18, P=0.038), in patients with pneumococcal as compared to viral aetiology (2.43 vs. 0.24, P=0.017), and in patients with PSI classes 4-5 (2.07) than in those with PSI classes 1-3 (0.52, P=0.03).

Conclusions: The sensitivity of sputum RQ-PCR was higher than that of sputum culture, especially after antibiotic therapy had been initiated. By supplementing traditional diagnostic methods with new PCR-based methods, a high microbial yield was achieved. Mixed bacterial-viral infections were frequent and these patients developed severe CAP more often and stayed longer in hospital than those with a bacterial aetiology alone. High PCT seems to be a good marker of invasive as well as severe disease and of pneumococcal aetiology, but for localised bacterial infections caused by other pathogens the test is less sensitive.

ISBN 978-91-7457-951-2