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HYPOTHESIS AND AIMS

This thesis includes 3 separate projects that examine more in detail the relationship between inflammatory changes at exacerbation and non-recovery of exacerbations, the role of circulating leucocytes in COPD and the role of the detection of bacteria by standard cultures and by polymerase chain reaction in a group of patients with well characterized COPD.

This thesis examined the following hypotheses:

1. The course of COPD is characterized by exacerbations that are major cause for health care utilisation. Exacerbations may require recurrent hospital admission and are often recurrent. They are associated with rapid deterioration in the patients' symptoms and heightened airway and systemic

inflammation. Our group has previously demonstrated that in up to 25% of exacerbations symptoms and lung function do not return to baseline after 35 days. We also showed that the length of the exacerbation was related to symptom and physiological changes at onset. Patients with more severe disease experience more frequent and severe exacerbations with prolonged recovery time. Patients with frequent exacerbations are known to have higher levels of airway inflammation and more frequent lower airway bacterial colonisation whilst in the stable state. A faster decline in lung function has also been observed in patients with frequent exacerbations. However, it is not known whether this is related to non-recovery of the exacerbation or to the associated airway inflammation.

We hypothesized that the change in airway and systemic inflammation during an exacerbation was directly related to exacerbation recovery and recurrences. Our study will address the following questions:

- What is the relationship between the intensity of change in airway inflammation at exacerbation and symptom recovery time?

- What is the relationship between the time course of airway and systemic inflammation at exacerbation of COPD and non-recovery?

- Can the time course of airway and systemic inflammation predict who has a recurrent exacerbation?

- Is treatment with oral steroids related to airway and systemic inflammation?

- How does the presence of a common cold at onset of exacerbation affect the time course of airway and systemic inflammation?

- Are there differences in the time course of inflammatory changes between patients who are frequent or infrequent exacerbators?

2. Patients with COPD have increased numbers of neutrophils and T lymphocytes in the airways and lung parenchyma. These cells have been linked to the pathogenesis and progression of COPD. The number of lung neutrophils and T lymphocytes is linked to severity of the airway obstruction. Neutrophils and T cells play an essential role in the host defences against infection. They are both produced by the bone marrow and circulate in the systemic circulation before homing into the lungs. Bacterial toxins and presentation of bacterial antigens on the surface antigen presenting cells are major stimuli for increases in the number of leucocytes. Airway inflammatory cells and epithelial cells produce cytokines such as IL-6, IL-8, neutrophil elastase and LTB-4 that attract these cells into the lungs. We also know that the lower airways of patients with COPD are frequently colonized by bacteria. The severity of the airway disease is a major risk factor for bacterial colonisation. There is a direct relationship between lower airway colonization and lower airway inflammation.

We hypothesized that there was a relationship between the circulating leucocytes (neutrophils and T cells) and lower airway bacterial colonization in patients with COPD. We addressed the following questions:

- What is the relationship between the severity of COPD and circulating leucocytes?

- Is there a relationship between the circulating leucocytes and the lower airway bacterial load in patients with COPD?

- Are there changes in circulating leucocytes at exacerbation and are they related to lower airway bacteria?

3. Between 25% and 50% of COPD patients have lower airways bacterial colonization in the stable state. The presence of bacteria in the lower airways implies a breach of host defence mechanism. This breach leads to

a vicious cycle of epithelial cell damage, impaired mucociliary clearance, mucus hypersecretion, increased sub-mucosal vascular leakage and inflammatory cell infiltration of the lungs. This colonization is also associated with heightened neutrophilic airway inflammation in the stable state and is known to modulate the character and severity of exacerbations. The most frequently isolated organism in COPD are Haemophilus influenzae, Streptococcus pneumonieae and Moraxella catarrhalis. Routine microbiological cultures are currently the gold standard for the detection of these bacteria from the sputum samples of patients with COPD. However cultures have multiple pitfalls. More sensitive, specific and rapid diagnostic methods are necessary for a better understanding of the complex relationship present between bacteria and the COPD lung.

We set out to establish a multiplex quantitative real time polymerase chain reaction assay for the simultaneous detection of Haemophilus influenzae, Streptococcus pneumonia and Moraxella cattarhalis from sputum samples. This allowed us to address the following questions:

- What are the differences in the detection rates of bacteria by the quantitative real time PCR assay and conventional microbiological cultures?

- Is there a relationship between the detection of micro-organisms by PCR and the degree of airway inflammation in patients with COPD?

- Is there a relationship between bacterial eradication by PCR and airway inflammation?