191 Long-term prognostic significance of a positive BPI-ANCA test in CF − a prospective 10 year follow-up study

U. Lindberg[1], L. Mared[1], M. Carlsson[2], M. Segelmark[3]. [1]*Lund University Hospital, Dep of Pulmology, Lund, Sweden;* [2]*AstraZeneca AB, Lund, Sweden;* [3]*Lund University Hospital, Dep of Nephrology, Lund, Sweden*

Objective: Several studies have shown a high frequency of antineutrophil cytoplasmic antibodies (ANCA) in CF, especially those with anti-bactericidal/permeability increasing protein (BPI) specificity. Earlier studies have shown correlation between BPI-ANCA and poor prognosis in CF and between BPI-ANCA and factors as iv antibiotic courses, low BMI and presence of multi drug resistant *P aeruginosa*. In this study we followed 46 adult CF patients for ten years to elucidate the prognostic significance of a positive BPI-ANCA.
Methods: 46 adult CF patients were sampled for IgA-BPI-ANCA between 1995 and 1998 and followed prospectively until death, lung transplantation or ten years of follow-up. Lung function was measured as % of expected FEV 1.0 and PsA colonisation was categorised according to the Leeds classification. Patients were divided into three groups regarding lung function; FEV1 > 80%, FEV1 50–80% and FEV1 < 50%pred.
Results: 15/46 patients reached end-point, 13 of these were BPI-ANCA+. None of the 16 patients with the best preserved lung function experienced end-point, regardless of BPI-ANCA level and Leeds classification. In the 13 patients with the lowest lung function all belonged to Leeds 1 or 2 and all except one was BPI-ANCA positive, nine reached end-point. The median BPI-ANCA level of the patients with end-points was 251 ELISA units as compared to 69 for the 31 patients who did not reach end-point.
Conclusion: High BPI-ANCA level is associated with poor long-term outcome among adult CF patients. However, a positive BPI-ANCA seems to have a strong prognostic significance only among patients already having a reduced lung function and a chronic PsA infection.

192 Prevalence and mechanism of adverse reactions to colistin in patients with cystic fibrosis

P. Whitaker[1], S. Lavergne[2], J. Gooi[3], D. Naisbitt[2], K. Park[2], D. Peckham[1]. [1]*Regional Adult CF Unit, St James's Hospital, Leeds, United Kingdom;* [2]*MRC Centre for Drug Safety Science, School of Biomedical Sciences, University of Liverpool, Liverpool, United Kingdom;* [3]*Department of Immunology, St James's Hospital, Leeds, United Kingdom*

Colistin is a polymyxin antibiotic that is active against *Pseudomonas Aeruginosa*. While some patients develop allergic reactions and non specific symptoms of neurotoxicity, there is little published data on the frequency and mechanism for colistin induced allergic reactions in patients with CF.
We retrospectively reviewed the Unit's database and determined the frequency of allergic reactions to colistin. We then prospectively performed a lymphocyte transformation test (LTT) in both allergic and non allergic patients with CF and healthy controls. Supernatants from the LTT were then collected and the cytokine profiles assessed.
180 adult patients with CF had received iv colistin. Of these, 51 individuals (28%) had developed a drug reactions resulting in stopping the treatment early. Reactions included rash (14), headache (11), paraesthesia (9), swollen lips (7), dizziness (6), chest tightness (3), and arthralgia (1). An LTT was undertaken in 11 allergic patients with CF (rash 7, headache 3, paraesthesia 1). The controls included 7 tolerant patients and 5 non-CF naive subjects, in this latter group all LTT were negative. Nine patients (82%) with a history of adverse reactions, including 3 patients with a history of severe headache, were LTT positive. This suggests immunological memory and sensitisation. Supernatant levels of IL-1, IL-10, and IFN-γ were significantly elevated in patients with adverse reactions.
Allergic reaction to colistin is relatively common. Some of the neurological adverse reactions may be related to a direct effect of cytokine release. Recent studies have reported an association between IL-1 levels and cluster headaches in the general population.

193 Cytokine profiles in different matrices before and after therapy for acute exacerbation in cystic fibrosis (CF) patients

N. Faelli[1], A.S. Tirelli[2], D. Costantini[1], A. Biffi[1], V. Motta[1], M. Conese[3], C. Colombo[1]. [1]*Cystic Fibrosis Centre Fondazione IRCCS Ca Granda-Ospedale Maggiore Policlinico Milan, Milan, Italy;* [2]*Laboratory of Clinical Pathology, Fondazione IRCSS Ca' Granda-Ospedale Maggiore Policlinico Milan, Milan, Italy;* [3]*Department of Biomedical Sciences, University of Foggia, Milano, Italy*

In CF simple and non-invasive biomarkers of lung inflammation are urgently needed to monitor disease progression, identify exacerbations, and evaluate therapeutic efficacy. We studied the simultaneous presence of twelve biomarkers by a biochip array (Randox) in three different matrices (serum, sputum, exhaled breath condensate [EBC]) in 24 CF patients (age: 18.8±4.8 years [mean±SD]; range:12.0–27.5 years, 13 M) before and after antibiotics given for an acute exacerbation. In serum, there was a trend for a significant decrease in IL-2, IL-4, IL-6, IL-10, IFN-g, IL-8, MCP-1, EGF and VEGF levels. In sputum, IL-1a, IL-1b, IL-4, IL-6, IL-10, TNF-a, IL-8 and VEGF levels decreased already at 6 days of therapy and remained constantly lower than baseline, while MCP-1 and EGF levels significantly increased. In EBC, the biomarker behaviour was more heterogeneous. In one group (IL-1a, IL-2, IL-6, IL-8, EGF) they first increased and then significantly lowered at 1 month post-treatment. In the other group (IL-1b, IL-10, VEGF, IFN-g) biomarker levels were always lower at all the time points post-treatment than baseline. On the other hand, IL-4 and TNF-a appeared to change in a bimodal fashion: they first decreased at 6 days, increased to value higher than baseline at 15 days and finally decreased to levels lower than baseline at 30 days post-treatment. Overall, these results show that different biomarkers are responsive to treatment in each considered matrix and indicate that only correlation studies with FEV_1 will elucidate which of these biomarkers is more sensitive of therapeutic efficacy.

194 Different interferon gamma responses in cystic fibrosis patients with and without *Mycobacterium abscessus (M. abscessus)*

F. Perrin[1,2], R. Doffinger[3], P. Seddon[4], R.G. Ruiz[1], D. Kumararatne[3], D. Bilton[2], London and Brighton NTM Collaboration. [1]*King's College Hospital NHS Foundation Trust, London, United Kingdom;* [2]*Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom;* [3]*Addenbrooke's Hospital, Cambridge, United Kingdom;* [4]*Brighton and Sussex University Hospitals NHS Trust, Brighton, United Kingdom*

Introduction: Nontuberculous mycobacteria (NTM) are emerging CF pathogens, particularly *M. abscessus*. Non-CF patients with disseminated NTM disease associated with interferon gamma (IFN-γ) deficiency respond to IFN-γ therapy. We have been testing the ability of whole blood from CF patients with NTM lung disease to produce IFN-γ after stimulation. Anecdotally, some with impaired IFN-γ responses compared to normal controls have benefited from subcutaneous IFN-γ. It is unclear whether an impaired response is a feature of CF itself or of the *M. abscessus* disease. We present pilot data to answer this question.
Method: 7 CF patients with *M. abscessus* lung disease by ATS criteria who had had IFN-γ studies, were matched by age, disease severity (FEV1) and other gram-negative pathogens to 8 CF patients without NTM. Whole blood from each subject was stimulated with phytohaemagglutinin (PHA) (positive control), IL12/IL18 and lipopolysaccharide (LPS). IFN-γ production, determined by ELISA, was expressed as % of the response measured in blood taken simultaneously from healthy controls.
Results: IFN-γ production was lower in CF patients than healthy controls on stimulation with all activators. *M. abscessus* patients had lower IFN-γ production than non-NTM patients when stimulated with PHA – median 30.6% (range 2.4–100) vs 51.5% (2.2–100) and IL12/IL18 – 18.9% (8.9–91) vs 78.5% (50–100). Both groups had low responses to LPS – 10.95% (1.3–100) vs 14.5% (0.18–100).
Conclusion: CF patients with *M. abscessus* have significantly reduced IFN-γ production *in vitro* compared to non-NTM patients. Larger prospective studies are required to confirm this and to determine the therapeutic role of IFN-γ.