68. Late breaking results: Asthma from phenotyping to emerging new treatments

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Developing obstructive change over time is dominant in small airways in severe asthma

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Background: The clinical features, physiology, and pathology of severe asthma are poorly understood. Recently, the forced vital capacity (FVC) has been shown to be reduced in severe asthma compared to mild asthma, possibly due to air trapping. However, the natural history of airway obstructive change for such asthmatic patients has not been fully elucidated.
Objective: To assess the pattern and risk factors of developing airway obstruction over time in severe asthma.
Methods: We examined the data of a retrospective analysis of lung function changes over a 10-year period in 54 patients with severe asthma. The risk factors that might contribute to the progression of obstructive changes were also investigated.
Results: The rate of change in both FVC and FEV1 (forced expiratory volume in one second) was highly variable among the patients with severe asthma. The faster obstructive changes detected by decline in FEV1 were accompanied by excessive loss of FVC ($r = 0.85$, $p < 0.0001$) and the reduction in FVC was 1.2 times larger than the FEV1 decline. Age, baseline FVC, annual exacerbation rate and

use of oral corticosteroids showed significantly negative correlations with the rate of annual change in FVC.
Conclusions: These data indicate that the decline in FVC is more evident than FEV1 in severe asthma, suggesting that small airway susceptibility may be the cause of rapid disease progression. Aging, exacerbations of asthma, and use of systemic corticosteroids are associated with excess FVC decline, particularly if FVC is still normal.

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Distinct phenotypic and pathophysiologic features of elderly asthma
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Background: Recent epidemiologic evidence suggests that asthma is prevalent in the elderly population. Majority of elderly asthma develops in later life, and thus is considered patho-physiologically distinct from young adult asthma.
Objective: To investigate whether elderly asthmatics may have different phenotypic or pathophysiologic features from young adult asthmatics
Methods: Young adult (18-45 years) and elderly (≥65 years) non-smoking, treatment-naive asthmatics were compared cross-sectionally. Asthma was defined if they had typical symptoms and methacholine PC20 ≤ 8 mg/mL. They completed baseline spirometry, induced sputum analyses, inhalant allergen skin prick tests, and anthropometric measurements. As indices of small airway involvements, a FEF25-75% and FEF25-75/FVC were used.
Results: A total of 103 young adult (mean age: 29.9 year) and 120 elderly (mean age: 71.1 year) asthmatics were included. Two age groups had similar degrees of airway hyperresponsiveness (methacholine PC20; 2.7±2.2 mg/mL in the elderly vs. 2.7±2.5 mg/mL in young adults). They also did not differ in gender distribution, FVC%, or FEV1%. However, the elderly asthmatics had higher body mass index (24.9 kg/m^2 vs. 23.3 kg/m^2, P<0.05), and lower atopy prevalence (40.0% vs. 95.5%, P<0.001), and slightly lower sputum eosinophils (7.1% vs. 10.3%, P<0.1) than young adult asthmatics. In addition, the elderly had significantly reduced FEF25-75% (43.1% vs. 61.6%) and FEF25-75/FVC (0.52 vs. 0.72) than the younger subjects at baseline (all P<0.001).
Conclusions: Elderly asthmatics had different phenotypic and pathophysiologic features from young adult asthmatics, suggesting their distinct pathogenic mechanisms and therapeutic considerations.

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Asthma phenotypes associated with vocal cord/laryngeal dysfunction
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Aim: To identify asthma phenotypes in patients with refractory and non-refractory asthma in whom inappropriate vocal cord closure and laryngeal dysfunction (LD) may occur (Low *et al*, AJRCCM, 2011).
Methods: We evaluated 57 patients with mild to moderate non-refractory asthma (N=31) or refractory asthma (N=26). Dynamic 320 slice computerised tomography (CT) of larynx was done and a validated algorithm was used to accurately measure vocal cord lateral diameter during inspiration and expiration. Excessive narrowing of the airways was diagnosed if a predetermined lower limit of normal was exceeded. The asthma groups were compared by semi-supervised cluster analysis to identify asthma phenotypes associated with laryngeal dysfunction.
Results: Overall vocal cord diameter was reduced below the lower limit of normal in 26 of 57 cases (46%). There was no relationship with asthma severity (LD) in refractory asthma: 12/26 (46%) versus non-refractory 14/31 (45%). Laryngeal dysfunction was associated with increased age (P < 0.034) bronchodilator (BD) responses <12% (P < 0.009) and difficult speech when breathless (P<0.019). There were 3 unique phenotype clusters associated with abnormal vocal cord narrowing and determinants of cluster membership were:
1. age > 40 years, female, bronchodilator response < 12%, difficulty speaking when breathless;
2. age > 40 years, bronchodilator response < 12%, BMI > 30kgs/m^2;
3. female, bronchodilator response < 12%, BMI > 30kgs/m^2.
Conclusion: Our results indicate that vocal cord behaviour is abnormal in asthma, irrespective of severity. However, laryngeal dysfunction may often be associated with particular patient phenotypes and contribute to their overall symptomatic burden of disease.

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Urinary proteomics in asthma: Search for a biomarker
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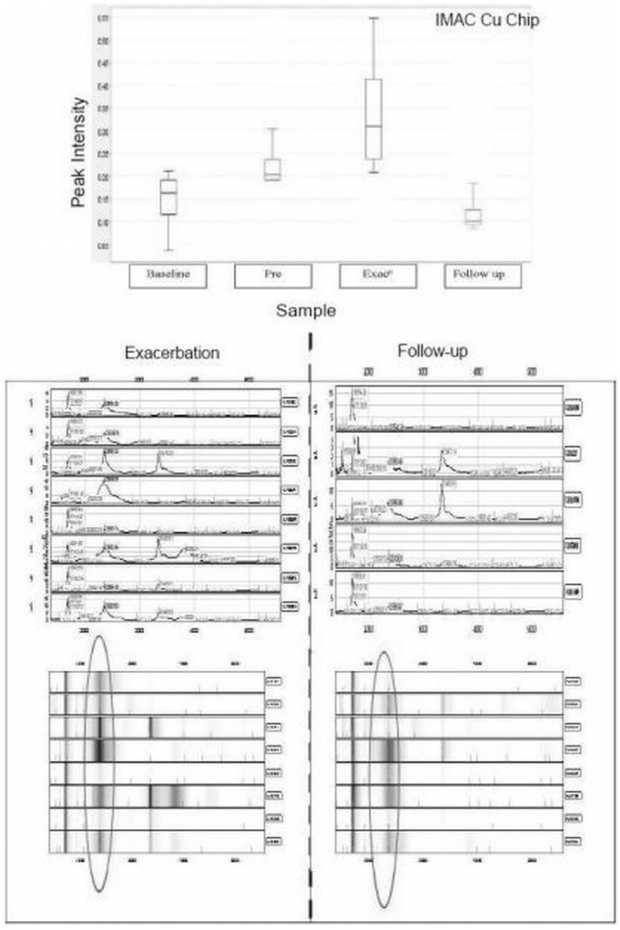
Background: The use of inflammatory indices such as sputum eosinophilia to guide anti-inflammatory treatment in asthma has been shown to reduce the frequency and severity of exacerbations.
Aims: Sputum induction can be unpleasant for patients and analysis is costly and labour intensive necessitating alternative methods to differentiate inflammatory phenotypes, guide anti-inflammatory treatment and predict exacerbation risk.
Method: Performing Surface Enhanced Laser Desorption/Ionisation Time of Flight Mass Spectrometry utilising 6 different "chips" we analysed spectra from 3 groups, the first (exacerbation vs recovery *(n=16)*, second (prospective patient samples thrice weekly, before, during and after an exacerbation *(n=3)*, and third (patients with different inflammatory phenotypes (eosinophilic, neutrophilic, mixed granulocytic and paucigranular) *(n=10)*
Results: Differential protein signatures were found between inflammatory phenotypes (p=<0.05) and between exacerbation and recovery states (p=<0.05). The IMAC Cu chip identified a signature which delineated onset, exacerbation and recovery states. Protein signatures were able to distinguish patients in each comparative group (P=<0.05)



Conclusion: Further work is warranted with a larger sample size to corroborate our findings and identify the proteins these signatures represent. This may ultimately identify a urinary marker indicating pre-exacerbation states in asthma enabling early intervention.

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Nasal and bronchial levels of Th2 cytokines correlate during a virus induced asthma exacerbation
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Asthma is a heterogeneous condition and it is vital to accurately predict responders to targeted therapies. However, difficulties in measuring IL5 and IL13 have forced reliance on indirect markers of Th2 inflammation with limited success. Using the human model of experimental rhinovirus (RV) induced asthma exacerbation (AE) and new techniques to absorb nasal (nasosorption) and bronchial (bronchosorption) mucosal lining fluid (MLF), we explored Th2 inflammation during a RV-induced AE.

Methods: 32 mild-to-moderate asthmatics and 14 healthy subjects were inoculated with RV-16. Bronchoscopies were performed 2 weeks prior to inoculation and on d4 post-inoculation. Cytokines were measured in both bronchial and nasal samples at baseline and on d4 with further nasal sampling on days 2,3,5,7,10 and 42.
Results: Nasal IL5 and IL13 were significantly increased in asthma during infection compared to baseline ($p<0.001$) and increased compared to healthy subjects ($p<0.01$). In the lung, there were relationships between bronchial IL13 ($p<0.05$) and IL5 ($p=0.059$) and total chest symptom score in asthma. Nasal IL5 and IL13 correlated with bronchial levels during infection ($p<0.01$) whilst baseline levels in the nose correlated strongly with infection levels ($p<0.001$).
Conclusion: RV induced Th2 inflammation correlated with AE severity. Nasal Th2 inflammation correlated with bronchial levels whilst baseline Th2 levels predicted the magnitude of Th2 induction during the AE. Nasosorption is a non-invasive, rapid technique capable of measuring Th2 inflammation directly. It may be possible to use this technique as a biomarker to guide therapy with anti-IL5 and anti-IL13 mAb treatments.

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The effects of interferon beta on cold-induced asthma exacerbations

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In vitro studies show that asthmatic bronchial epithelial cells produce insufficient interferon beta (IFNb) when infected with rhinovirus (RV), whilst exogenous IFNb restores their capability to stop viral replication. This has provided pre-clinical POC for innate immune deficiency in asthma and a rationale for a randomised placebo controlled clinical trial of aerosolised IFNb. The trial involved 21 centres and 147 asthmatics, with the sACQ (shortened Asthma Control Questionnaire) as the primary outcome. Patients commenced treatment at the onset of common cold symptoms and, following baseline assessment, were treated daily for 2 wks with IFNb (6MIU) or placebo.134 patients fulfilled the Jackson criteria for a cold (mITT population): in these, respiratory viruses were detected in nasal lavage by PCR in 63% of patients (68% RV+). In the placebo group, cold symptoms correlated strongly with those of asthma and only patients with difficult to treat asthma (BTS steps 4 and 5) had a clinically relevant (>0.5) increase in sACQ, whilst step 2 or 3 asthmatics did not. In the difficult to treat patients the difference in sACQ during the first week was 0.63 ($p=0.004$) in favour of treatment and the % experiencing an exacerbation was significantly ($p=0.012$) lower. Treatment with IFNb also resulted in significantly faster recovery of PEF and less use of β2-agonists ($p<0.05$). This trial suggests that treatment with inhaled IFNb significantly attenuates the adverse effects of the common cold in difficult to treat asthma patients whose needs for such treatment are greatest. The study provides rationale for follow on clinical trials.
The trial was funded by Synairgen plc and supported by NIHR.

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Increased cytotoxic T cells, CX3CR1+, γδ and IL17+ T cells in severe asthma during exacerbation

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Background: Asthma is a chronic inflammatory disease affecting up to 10% of the general population. In most cases, asthma symptoms are controlled by long term treatment without side effects. However, for severe asthmatics, therapy is often insufficient to gain control of the disease and symptoms progress to exacerbations. Recently, T cells populations such as cytotoxic T cells, CX3CR1+, γδ and IL-17+ T cells have been correlated to asthma severity. Our aim was to longitudinally study these cells populations in severe asthma, to better understand immune mechanism that underlies exacerbations.
Methods: 23 severe refractory asthmatics were enrolled in the EXPRESA study, with a longitudinal follow-up of 12 months, compring blood sampling and nasal swab. 40 exacerbations were documented. T cell phenotype was assessed by flow cytometry in samples obtained at baseline, before, during and after exacerbations. Viral colonization was also studied in nasal swab by PCR.
Results: We highlight increased cytotoxic T cells (CD8+perforine+), CD4+CX3CR1+ cells, γδ T cells and IL-17+ T cells ($p<0,03$) associated to increased Th2 cells (IL-5) during exacerbation. This increase in inflammatory profile is associated to decreased T regulatory population and Th1 cells (IFN-γ), which appears before exacerbation ($p<0,007$). Concerning viral colonization, the lack of virus identification failed to separate exacerbations of viral origins from others.
Conclusion: These results defined a T cell activation profile, specific for exacerbation outcome in severe asthma which seems to be crucial for inflammatory response which develops during exacerbation.

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Mepolizumab (anti-IL-5) reduces exacerbations in patients with refractory eosinophilic asthma

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Background: Proof-of-concept studies have shown that mepolizumab reduces eosinophilic airway inflammation and asthma exacerbations in patients with refractory eosinophilic asthma. We investigated the effect of three doses of mepolizumab on asthma exacerbations in a larger population of patients.
Methods: This 52-week randomised, double-blind, placebo-controlled study (NCT01000506) compared mepolizumab (75, 250 and 750mg; intravenous infusion) with placebo in 616 patients (≥12 years) with refractory asthma, ≥2 exacerbations in the previous year and evidence of eosinophilic inflammation. The primary outcome measure was the rate of clinically significant asthma exacerbations; defined as episode of acute asthma requiring use of systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visit. Safety and immunogenicity assessments were also conducted.
Results: The exacerbation rate with placebo (2.4/subject/year) was reduced by 48% (95% CI: 31, 61%), 39% (19, 54%), and 52% (36, 64%) with mepolizumab 75, 250 and 750 mg respectively ($p<0.001$ for all comparisons). Exacerbations requiring hospitalisation or ED visits were also reduced. The overall incidence of adverse and serious adverse events was similar across groups (mepolizumab 75mg, 82% and 13%; 250mg, 82% and 16%; 750mg 78% and 12%; placebo, 77% and 16%). No serious life-threatening anaphylactic reactions were reported and the immunogenicity profile was unremarkable.
Conclusion: Mepolizumab, as an add-on therapy in patients with uncontrolled severe refractory eosinophilic asthma, produced a significant reduction in exacerbation rate over one year compared with standard of care, and was generally well tolerated.