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.

### 343 Distinct phenotypic and pathophysiological 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 pathophysiological 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% 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: 27.2±2.2 mg/mL in the elderly vs. 27.1±3.5 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 (29.4 kg/m² vs. 23.3 kg/m², P<0.05), and lower airways prevalence (40.9% 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 pathophysiological features from young adult asthmatics, suggesting their distinct pathogenic mechanisms and therapeutic considerations.

### 344 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%, difficult speaking when breathless;
2. age ≥ 40 years, bronchodilator response < 12%, BMI > 30 kg/m²;
3. female, bronchodilator response < 12%, BMI > 30 kg/m².

**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.

### 345 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 three weekly, before, during and after an exacerbation (n=3)), and third (patients with different inflammatory phenotypes (eosinophilic, neutrophilic, mixed granulocytic and paucigranulat) (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).
Conclusions: 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.

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 cell count in bronchoalveolar lavage (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.

The effects of interferon beta on cold-induced asthma exacerbations
Ratko Djukanovic
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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 IL17+ T cells in severe asthma during exacerbation
Karine Botturi-Cavaillès

Methods: Three 52-week randomised, double-blind, placebo-controlled studies (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.