63. Mechanism and monitoring of airway diseases

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Longitudinal analysis of lung function decline with eosinophilic clustering in severe asthma

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Background: Lung function decline over time is an important variable for patients with severe/difficult asthma and it is unclear how granulocytic cell counts in sputum are associated with this variable as few longitudinal studies include both biomarkers.
Aims and objectives: To analyse lung decline, post bronchodilator FEV1 was recorded over time in order to determine the best fitting mixed effect model to determine the role of granulocytes.
Methods: Data was collected form the Glenfield Hospital Severe asthma clinic, the mean duration of follow up and number of visits were 6 years and 2.7/years. A mixed effect model was applied to the data. Using individual patient mean and standard deviation over time, a statistical mixture/cluster analysis was implemented.
Results: For the best fitting mixed effects model FEV1 decline was -25.7ml/year, p=0.0001. The significant independent fixed effects included exacerbations, age of onset, log eosinophils (p<0.001). Three clusters were found in the log eosinophil cluster analysis. Cluster 1 described a low grade eosinophilic group. Cluster 2, a hyper eosinophilic group and cluster 3, a neutrophilic/non-eosinophilic group. The clusters differed in their frequency of exacerbation/decline.
Conclusions: Eosinophils were found to be a significant predictor for FEV1 decline. Clustering eosinophil variables found that patients are either consistently eosinophilic over time, consistently non eosinophilic over time or have a large amount of eosinophilic variation.

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Sputum eosinophilia identifies systemic corticosteroid responsiveness in acute exacerbations of COPD

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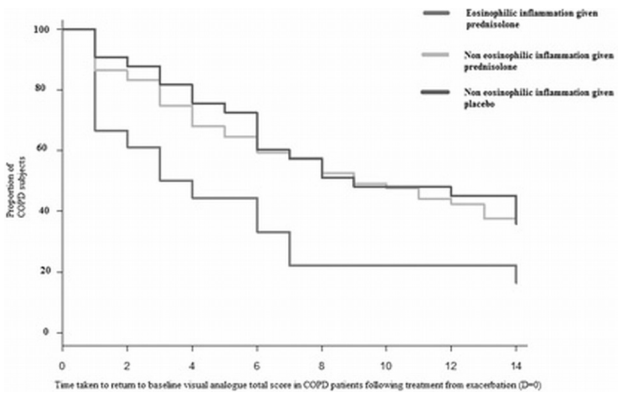
Introduction: Eosinophilic airway inflammation (EA, >3% sputum eosinophils) during stable chronic obstructive pulmonary disease is associated with corticosteroid responsiveness. Whether this is true during exacerbations remains unknown.
Methods: COPD patients were entered into a double blind prednisolone placebo controlled trial. Measurements of airway inflammation, lung function and health status using the chronic respiratory questionnaire (CRQ) and visual analogue scale (VAS) were assessed at baseline, exacerbation and 2 weeks after treatment.



Results: 166 exacerbations were captured from 109 patients (69 men, 40 women). All eosinophilic exacerbations (n=31) were treated with prednisolone. Non eosinophilic airway inflammation (NEA) occurred in 135 exacerbations, of which 70% (n=94) were treated with prednisolone and 30% (n=41) with placebo. Two weeks after prednisolone treated exacerbations, quality of life and lung function improved significantly in those with EA compared to NEA (mean change, 95%CI) in CRQ and FEV_1 was 1.5 units (1.1 to 1.9) vs. 0.8 units (0.5 to 1.0) (p<0.001) and 335mL (219 to 451) vs. 102mL (52 to 152) (p<0.001) respectively. VAS returned to baseline earlier in EA exacerbations treated with prednisolone (p=0.016, see figure)
Conclusion: Corticosteroid responsiveness during exacerbations of COPD can be identified by a sputum eosinophilia.

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Tapering oral corticosteroids in severe asthma is associated with a decrease in fractional exhaled nitric oxide

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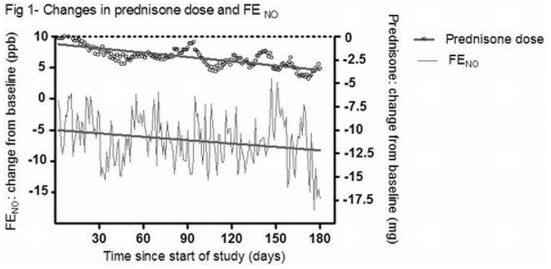
Rationale: In a recent oral corticosteroid tapering study in patients with severe asthma (Hashimoto ATS 2010), we observed high levels of exhaled nitric oxide (FE_{NO}) despite high doses of oral corticosteroids, and, unexpectedly (Smith NEJM 2005), only a minor role of FE_{NO} in adjusting the dose.
Hypothesis: Changes in FE_{NO} values in patients with severe prednisone-dependent asthma are not associated with changes in corticosteroid dose or clinical parameters.
Aim/Method: 48 adult patients with severe, prednisone dependent asthma (mean (SD) age 49.4 (12.2) y; 18 male) were included in this 6 months follow-up study. Relationships between changes in daily $FE_{NO\ and}$ oral corticosteroid dose, asthma control (ACQ), and FEV_1 were assessed. Pearson correlation and regression analyses were used.
Results: Baseline median (range) FE_{NO} and prednisone were 38 (5-300) pbb and 10 (0-60) mg/day. Daily changes in FE_{NO} from baseline were positively associated with daily changes in prednisone dose (r=0.22, p=0.003) but not with FEV_1 (r=-0.02, p=0.77) or ACQ (r=-0.03, p=0.65).

Fig 1- Changes in prednisone dose and FE_{NO}



Conclusion: In contrast to patients with mild-moderate asthma, patients with severe, prednisone dependent asthma show a decrease in FE_{NO} levels when prednisone is tapered.
Implication: This suggests that oral corticosteroids may contribute to persistently high levels of FE_{NO} in severe asthma.

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Sputum eosinophil levels in corticosteroid-treated asthmatic patients

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We have shown that asthmatic patients, despite being asymptomatic after 1-month treatment with inhaled corticosteroids (ICS), may have persistent sputum eosinophilia associated with higher degrees of bronchial hyperresponsiveness (Bacci et al., ATS meeting 2010). In order to test the effects of longer treatment periods, we treated 116 symptomatic, steroid-naive, mild-to-moderate asthmatic patients with different doses of ICS (50 to 500 mcg bid) for three to six months. Before and after treatment, all patients underwent spirometry, methacholine test, sputum analysis, and recorded symptom score (SS) and Peak Expiratory Flow (PEF) throughout the study period. Regardless of treatment dose and duration, some patients (n=56) still had high (≥ 2%) sputum eosinophils after ICS treatment; they were no different from patients with low sputum eosinophils as regards clinical and functional data after treatment, but had higher baseline SS (1.5 [0.1-3.6] vs 1.0 [0.1-3.1], p=0.04). After treatment, some patients still had high sputum eosinophils despite being totally controlled (SS=0); they were no different from totally controlled patients with low sputum eosinophils.
We conclude that, in patients with greater symptom levels before treatment, sputum eosinophilia may persist despite ICS treatment. Also, sputum eosinophilia may persist even in patients with totally controlled asthma, but after 6 months the

	Totally controlled patients	
	Eos <2%, n=31	Eos ≥2%, n=35
FEV1, %	101±12	101±12
PEF, %	90±15	92±15
PD20FEV1, mcg[§]	202	130

[§]Geometric mean; all comparisons ns.

relationship with bronchial hyperresponsiveness is lost, maybe because ICS also affect mechanisms involved in bronchial hyperresponsiveness other than sputum eosinophilia.

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A double-blind randomised control trial of peripheral blood eosinophils to direct prednisolone use in COPD exacerbations

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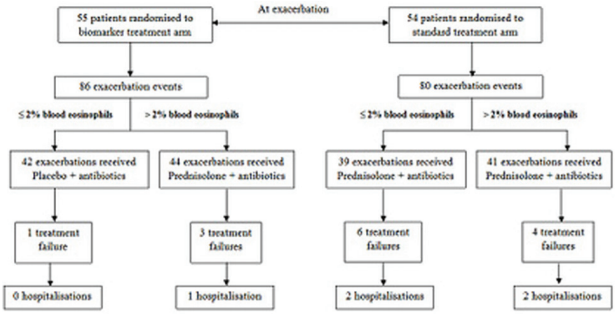
Introduction: COPD exacerbations and treatment responses are heterogeneous. Prednisolone therapy is associated with adverse events. Identifying steroid responsive subgroups maybe beneficial

Aims: To compare biomarker-directed prednisolone therapy to current standard treatment during COPD exacerbations

Methods: Patients with COPD exacerbations were randomised to receive standard therapy (ST) or a biomarker directed therapy (BT). BT patients were given prednisolone when the blood eosinophil count was >2% (biomarker positive) and placebo when ≤ 2% (biomarker negative) (see figure).



Results: From 109 patients; 86 exacerbations were treated in the BT group and 80 in the ST group. Prednisolone prescription was reduced by 49% (95% CI 38 to 59, p<0.001) in the BT compared to ST group. There was no difference between groups in health status or FEV_1 after 14 days treatment. Placebo administration did not result in excess treatment failure (hospitalisation or readmission) which occurred in 15% and 2% of biomarker negative patients in ST and BT groups (p=0.04). Improvements in health status after 14 days were greater in placebo treated patients compared to those in the ST group who were biomarker negative (mean change 1.01 vs. 0.56; mean difference 0.45; 95% CI 0.01 to 0.90; p=0.04)

Conclusions: A phenotype-specific biomarker approach can safely and effectively be applied to prednisolone therapy during exacerbations.

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Relationship between exhaled nitric oxide and exacerbation frequency in COPD patients: A longitudinal study

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We previously demonstrated that fractional exhaled nitric oxide (FENO) level determined at hospital admission predicts response to treatment in COPD patients hospitalized with acute exacerbations. The optimum cut point for FENO was 27 ppb. In this longitudinal study we assessed the relationship between FENO and frequency of hospitalization-associated exacerbations in patients with COPD.

66 COPD patients (mean age: 65.6±1.4 years; 31 males, 35 females) with FENO level lower (n=39, group 1) or higher (n=27, group 2) than 27 ppb were followed over a 33.9±1.1 months period of time. In patients in group 2 the exacerbation frequency (1.0±0.19 vs. 0.37±0.09 exacerbations/patient-year; p<0.05) and the number of hospitalization days due to exacerbations (18.5±3.9 vs. 6.9±1.0 hospitalization days/patient-year; p<0.05) were reduced compared to group 1. Moreover, there was a trend towards increased time-to-first exacerbation (6.9±1.5 vs. 8.2±2.3 months, p>0.05) in these patients. In patients in group 1 positive sputum culture results were more often obtained (group 1: 24 pos. and 15 neg. vs. group 2: 9 pos. and 18 neg.; p<0.05) and the need for intensive care was more frequently indicated. Severity of COPD as assessed by GOLD stages was not significantly different between the two subgroups of patients (p>0.05).

Our data suggest that the rate of exacerbations requiring hospitalization is reduced in COPD patients who have higher (>27 ppb) FENO level during exacerbation. FENO may have a role in detecting different COPD phenotypes.

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Expression of superoxide dismutases and its association to inflammatory cells in small airways of COPD patients

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Background and aims: Chronic obstructive pulmonary disease (COPD) is predominantly a result of the cumulative exposure to tobacco smoke and its progress is stimulated by oxygen-derived free radicals from tobacco smoke or activated structural and inflammatory cells. Superoxide dismutases (SODs) are the first line of antioxidants defence system. The present study investigates the expressions of SOD and their association to inflammatory cells and local destructive index (DI) in small airways of non-smokers and patients with severe COPD.

Methods: Expression of macrophages, mast cells, neutrophils, and SODs (CuZn-SOD, Mn-SOD, EC-SOD) was evaluated by immunochemistry using formalin-fixed, paraffin-embedded sections from non-smoking controls (n=9) and COPD patients (n=10). Histological and immunohistochemical analyses were performed using the same Region-of-Interest within each small airway.

Results: The mean percentage and intensity of CuZn-SOD-immunoreactive cells were greater in COPD patients (p< 0.05) and with a predominant expression in the small airway epithelium whereas epithelial Mn-SOD and EC-SOD expression was not altered. The DI was negatively correlated with SODs immunoreactivity. Macrophages were prominently present in the alveolar region and neutrophils in small bronchioles. Mast cells were prominent in both small airways and alveolar parenchyma, although the total numbers were decreased in COPD.

Conclusions: We demonstrate overexpression of CuZn-SOD and the elevated number of inflammatory cells. A correlation has been shown between SODs immunoreactivity and DI.

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Disease expression in patients with primary ciliary dyskinesia (PCD), CF and pancreatic sufficiency (CF-PS) and insufficiency (CF-PI)

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In both CF and PCD, lung disease is caused by impaired mucociliary clearance. In CF it is a result of airway surface liquid depletion and in PCD, of ciliary defects in the structure and/or function. CF-PS patients are diagnosed at a later age, have better nutritional status and survival compared to CF-PI. PCD patients do not have PI and are diagnosed at a later age than patients with CF-PI; hence, are expected to have a disease similar to CF-PS.

Aim: To correlate clinical status, microbiological, FEV_1, and HRCT-Total Brody Score (CT-TBS) between patients with PCD, CF-PI and CF-PS.

Methods: Patients with CF-PI, CF-PS and PCD were included. Data on FEV_1, HRCT, sputum cultures and BMI were collected as part of their routine assessment.

Results: Overall, 145 patients (79-CF-PI, 43-CF-PS, 23-PCD) participated in this study. The age of the CF-PS group was markedly higher compared to the other groups. BMI was notably lower in the PCD group compared to both CF groups. FEV_1 had a strong negative correlation with age in the CF groups, not in the PCD group. Sputum colonization rates of *P. aeruginosa* (PA) were similar in the CF-PI and PCD groups, lower in the CF-PS group. CT-TBS showed the most severe structural disease in CF-PI, followed by the PCD and the CF-PS group. In both CF groups there was a strong negative correlation between TBS and FEV_1, not observed in the PCD group.

Conclusion: In PCD, FEV_1 does not correlate with age, BMI, rate of PA infection and CT-TBS. Therefore, opposed to CF, in PCD, FEV_1 is not a reliable predictor of severity of lung disease. Further studies are needed to delineate the pathogenesis and progression of lung disease in PCD