227. Monitoring of airway diseases: far from the airways

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Fixed airflow obstruction in asthma is related to systemic eosinophilic inflammation – Results from the Swedish GA²LEN survey

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Background: Patients with asthma and fixed airflow obstruction represent a difficult-to-treat subgroup. Increased local airways inflammation has been linked to fixed airflow obstruction, but few studies have analysed the relation to systemic eosinophilic inflammation, a component not reached by inhaled corticosteroids.
Methods: Non-smoking healthy subjects (n=130) and non-smoking asthma subjects (n=357), aged 17-76 years performed lung function, exhaled NO (FeNO) and urine eosinophil protein X (uEPX) measurements. Fixed airflow obstruction was defined as postbronchodilator FEV1/FVC under the lower limit of normality (Hankinson et al. AJRCCM 1999).
Results: Asthmatic subjects with fixed airflow obstruction (n=56) had higher uEPX levels than asthmatics without fixed airflow obstruction (n=301) ((62.4 ng/mL (51.9, 75.1)) vs. 47.2 (44.1, 50.6)) or healthy controls (40.0 (36.2, 44.2)) (geometric mean (95%CI)) (all p-values <0.05). No differences (p=0.32) were found between asthmatic subjects with or without fixed airflow obstruction in terms of FeNO, whereas both asthma groups had higher levels than controls ($p<0.01$). Increased levels of uEPX (p=0.04), use of inhaled corticosteroids (p=0.01) and increased age (p=0.05) were independently related to persistent airflow obstruction in asthmatics, after adjustments for study centre, height, atopy, sinusitis, rhinitis and time of day for measurements.
Conclusion: Persistent airflow obstruction in asthma was accompanied by increased urinary excretion of EPX. Further studies are warranted to investigate if more aggressive treatment of the systemic inflammation may be required to prevent fixed airflow obstruction.

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Prediction of new-onset wheeze based on serum inflammation biomarkers – Evaluation using univariate and multivariate techniques

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Asthma is associated with inflammation in the airways and wheeze. The hypothesis is that increased levels of inflammation biomarkers among subjects without respiratory symptoms are a sign of subclinical airways inflammation.
Objective: To evaluate if increased levels of inflammation biomarkers in serum predicts later onset of wheeze.
Methods: We followed up 2,200 subjects from a general population-based study. At baseline, the subjects were investigated with questionnaires, blood samples, spirometry and FENO. All subjects reporting tobacco smoking, wheeze, asthma, asthma symptoms, or CRP >5 at baseline were excluded. Four years later all subjects got a respiratory questionnaire, which 86.2% completed. The association between baseline levels of a panel of cytokines in serum and incident wheeze was evaluated using non-parametric statistical methods and orthogonal projection to latent structures - discriminant analysis (OPLS-DA). Subjects with FENO levels between the 45th percentile and the 55th percentile served as controls (n=101), and were compared to subjects with new-onset wheeze (n=29).
Results: The median levels of TNF, IL-1, IL-2, IL-4 and IL-12 at baseline were significantly higher among those with new-onset wheeze ($p<0.05$). This was supported by OPLS-DA, where TNF, IL-1, IL-4 and IL-12 scored the highest probability. The median levels of IL-5, IL-8, IL-10 and IL-13 at baseline were significantly lower ($p<0.05$).
Conclusions: Our results indicate that the levels of serum inflammation biomarkers in respiratorily healthy subjects were associated with an increased risk of developing wheeze.

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Vitamin D insufficiency in adult asthma: Association with asthma severity and control

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Data in asthmatic children suggest that low vitamin D levels are associated with poor asthma control, reduced lung function, and increased medication intake. To inves-

tigate the role of vitamin D insufficiency in adult asthmatics 25-hydroxyvitamin D was measured in 280 adult patients with asthma (mean±SEM: 45.0±0.8 yrs., 40% male, FEV1 74.9±1.4%) and correlated with clinical parameters of asthma control. The majority of patients had severe asthma (n=155, 55%) and were uncontrolled (n=144, 51%). Serum levels of vitamin D were significantly related to asthma severity (mean±SEM: intermittent 31.1±3.2 ng/ml, mild 27.3±1.6 ng/ml, moderate 26.5±1.5, severe 24.0±0.9, p=0.046) and asthma control (controlled 29.5±1.9, partly controlled 25.9±1.1, uncontrolled 24.2±1.0 ng/ml, p=0.030). Frequency of vitamin D insufficiency (vitamin D <30 ng/ml) was significantly higher in patients with severe or uncontrolled asthma and was associated with a lower FEV1 (vitamin D <30 vs. ≥30 ng/ml 2.3±0.1 L vs. 2.7±0.1 L, p=0.006), higher levels of exhaled NO (45±4 ppb vs. 31±4 ppb, p=0.023), a higher BMI (28.3±0.5 vs. 25.1±0.4, p<0.001), and sputum eosinophilia (5.1±1.6% vs. 0.5±0.2%, p=0.005).
Levels of serum vitamin D were associated with clinical parameters of asthma severity and control supporting the hypothesis that improving suboptimal vitamin D status might be effective in prevention and treatment of asthma.

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Asthma, upper airway disease and systemic inflammation in patients with Churg Strauss syndrome and severe chronic asthma

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Background: The bronchial and systemic eosinophilic inflammation is a well-known distinctive tract in patients with SCA (severe chronic asthma) and with CSS (Churg Strauss syndrome), where the upper airways disease is a comorbidity which strongly influences the respiratory symptoms.
Aims: To compare the functional and biological characteristics of patients with SCA and CSS in relation to systemic asset and level of therapy; to define the upper airways diseases and to characterize nasal inflammation.
Methods: 35 patients with CSS and 21 with SCA were enrolled. All patients were assessed for lung function and bronchial iperreactivity. Asthma control was established according to GINA guidelines and by ACT questionnaire, the quality of life by AQLQ. Sputum eosinophil percentages, exhaled nitric oxide, peripheral blood eosinophil counts and nasal disease and cytology were assessed.
Result: The two groups of patients were similar in lung function, asthma control and quality of life. While CSS patients showed higher sputum eosinophil percentages (38[91] vs 15[94], p<0.05) SCA patients had higher peripheral eosinophil counts (895±740 vs 592±579, p<0.05), depending probably by the different therapy (higher systemic therapy in CSS vs higher ICS dose in SCA).The majority of patients presented upper airway involvement, with eosinophilic inflammation evidence (nasal eosinophilic %: 0.5[38] CSS vs 0.6[10] CSA).
Conclusions: Both groups of patients showed partially controlled eosinophilic airway inflammation. The ICS dose in CSS patients seems not appropriate to the asthma severity. Eosinophilic upper airway inflammation may represent a limit to achieve a good asthma control.

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Airway and systemic inflammation during Churg-Strauss syndrome natural course

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Background: Asthma is a key feature in Churg-Strauss syndrome (CSS) but the relationship between airway and systemic manifestations over the follow-up have been scarcely investigated.
Aims: To compare in CSS patients asthma activity/severity and systemic disease activity/damage, sputum inflammatory markers with inflammatory disease biomarkers, asthma severity and airway inflammation.
Methods: 35 patients with CSS were enrolled. All patients were assessed for lung function and bronchial hyperreactivity. Asthma severity and control were established according to GINA guidelines and by ACT questionnaire. We measured: sputum eosinophil percentage and exhaled nitric oxide, the Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI), peripheral blood eosinophils count, and serum anti-neutrophil cytoplasmic autoantibody, eosinophil cationic protein, IgE, IL2-4-5.
Results: Despite the majority of the patients presented a complete systemic remission (BVAS:14±2 diagnosis vs 2.5±2 follow-up), 80% showed a moderate/severe chronic asthma with vasculitis damage (VDI: 0 at diagnosis vs 1.7±0.8 at follow-up). A significant correlation was detected between sputum eosinophil counts and ACT (r=-0.64, p=0.014) and sputum eosinophil counts and GINA control score (p=0.008). No statistical correlation was found between peripheral eosinophil count and asthma severity, and between sputum inflammatory markers and blood inflammatory mediators.
Conclusion: Chronic asthma negatively affects the natural history of CSS. Sputum inflammatory markers might represent a complementary tool in monitoring asthma component in CSS patients, as well as blood inflammatory disease biomarkers reflect CSS systemic activity.

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Calprotectin – A marker of mortality in COPD? Results from a prospective cohort study

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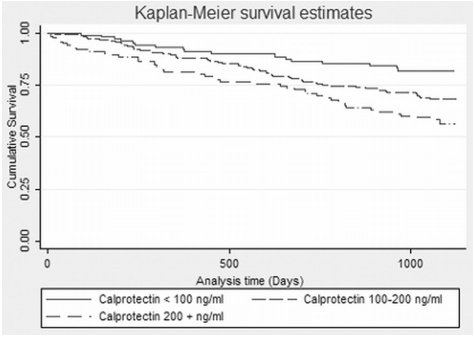
Background: Neutrophil involvement in chronic obstructive pulmonary disease (COPD) is well established. Calprotectin comprises more than 45% of the cytosolic content of neutrophils, and has been shown to be useful as a marker of inflammatory activity in inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). Since disease activity in COPD seems dependent, in part, by neutrophil driven inflammation we decided to investigate whether plasma level of calprotectin (p-calprotectin) was associated with mortality in COPD.
Methods: We measured p-calprotectin in blood samples from 458 patients suffering from moderate to very severe COPD in stable phase. Patients were stratified into three groups according to p-calprotectin. Outcome measure was mortality in a 3 year follow-up period. Analyses were adjusted for factors known to influence mortality using multivariate cox proportional hazard regression analysis (Cox PH).
Results: Absolute mortality increased from 16.2% (p-calprotectin< 100 ng/ml), to 27.8% (p-calprotectin100-200 ng/ml), and to 39.0% (p-calprotectin> 200 ng/ml). In Cox PH p-calprotectin level > 200 ng/ml [HR 2.16 (CI 95%: 1.19-3.91)] when adjusting for factors known to influence mortality.



Conclusions: p-Calprotectin levels >200 ng/ml are associated with increased mortality in patients with moderate to very severe COPD in stable phase. P-calprotectin is a potential marker of airway inflammatory activity.

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Collagen degradation profile in serum of patients with COPD or IPF

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Introduction: Fibrosis is a common consequence of COPD and IPF characterized by fibroblast proliferation and extracellular matrix (ECM) remodeling. The most representative ECM component in lungs is collagen, and an imbalance in collagen turnover rate may lead to its accumulation eventually resulting in fibrosis.
Aims and objectives: During pulmonary fibrosis collagens type I, III, IV, V, VI are deposited in the lungs and are degraded by disease relevant proteases. Thus collagen fragments (neoepitopes) are released into circulation: our aim is to investigate their potential as markers for lung ECM turnover.
Methods: Levels of serum matrix metalloprotease degraded type I (C1M), III (C3M), IV (C4M), V (C5M) and VI (C6M) collagen and ADAMTS-4 degraded type III collagen (C3A) were assessed in serum from patient with COPD or IPF and healthy controls using a competitive ELISA assay.
Results: All serum markers were significantly elevated in COPD compared to controls (p<0.05-0.01, up to +289% for C1M), and C1M, C3M, C5M and C6M were highly elevated in all severity groups of IPF (p<0.05-0.0001, up to +233% for C1M). The area under the curve calculated using the receiver operating characteristic (AUROC), describing the diagnostic power of the marker, was >85% for C1M, C3M, C5M and C6M for COPD and IPF patients versus controls, while C4M and C3A had an AUROC>89% for COPD versus controls but were unable to diagnose IPF patients.
Conclusions: Four out of six collagen degradation serum markers were elevated in patients with mild COPD and IPF, who would benefit the most from early diagnosis. This small study highlights the potential of neoepitope collagen turnover marker for separation of healthy versus COPD and IPF patients.

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Downregulation of Th 17 response after low dose clarithromycin in non-CF bronchiectasis patients

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Introduction: Th17 lymphocytes and, particularly, IL-22-secreting Th17 cells play a crucial role in neutrophilic inflammation and tissue injury. It has been shown that clarithromycin (CAM) has antiinflammatory and immunoregulatory effects. However, the effect of CAM administration on Th17 response in the setting of non-CF bronchiectasis has not yet been studied.

Aim: To evaluate the effects of CAM prophylaxis on the inflammatory process and Th17 response in patients with steady-state non-CF bronchiectasis.

Methods: Ten adult patients received CAM 500mg per day p.o. for 12 weeks. Peripheral blood Th17 cells were analyzed by flow cytometry using antibodies against CD4, IL-17 and IL-22. IL-17 concentrations in exhaled breath condensate (EBC) were quantified using a commercially available ELISA. Pulmonary function tests (PFT) and clinical data were recorded during the treatment period.

Results: Post treatment CD4+IL17+ count (cells/μl) and EBC IL-17 levels (pg/ml) decreased significantly (mean 3.2016±2.7280 vs 2.8181±1.9426, p=0.001 and 4.3560±1.5899 vs 3.2990±0.74311, p<0.001, respectively). Mean pO2 (mmHg) improved significantly (72.8±6.477 vs 79.3±10.242, p<0.001), while PFT and pCO2 remained unaltered. Notably, the decrease in CD4+IL17A+ cell count correlated with the decrease in exacerbations (r: 0.618, p=0.057) and the pO2 increase (r: 0.648, p=0.043), while the decrease of IL-22+IL-17+ effectors correlated with the decrease in EBC IL-17 levels (r: 0.852, p=0.002).

Conclusion: We report for the first time that low dose CAM in patients with non-CF bronchiectasis appears to reduce lung inflammatory process potentially via downregulating the Th17 response.