48. Different ways to phenotype asthma

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Identification of aspirin-induced asthma (AIA) subphenotypes using a clustering approach

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Background: AIA is a distinct asthma phenotype which symptoms are exacerbated by aspirin and other NSAIDs. It is generally recognized as a severe difficult to treat asthma accompanied by chronic rhinosinusitis, nasal polyps, blood eosinophilia, elevated levels of urinary LTE4 (uLTE4). It seems, however, that AIA phenotype is not homogenous.
Aims: To identify distinct subphenotypes in a cohort of AIA patients by applying latent class analysis.
Methods: Clinical data from 201 AIA patients (134 women, mean age 49,4 yrs) were collected using unified questionnaire. Asthma severity and control were assessed using NAEPP EPR3 guideline. Spirometry, skin tests, blood eosinophilia, uLTE4 were evaluated.
Results: Four clusters of AIA were identified. Cluster 1: severe uncontrolled atopic asthma with non-reversible or reversible airway dysfunction, high rates of health care use (HCU) for asthma. Cluster 2: moderate uncontrolled/partially controlled non-atopic asthma with non-reversible or reversible airway dysfunction, high rates of HCU. Cluster 3: mild partially controlled atopic asthma with normal airway function, lower rates of HCU. Cluster 4: intermittent well controlled atopic/non-atopic asthma with normal airway function, lower rates of HCU. Upper airway symptoms were very common in all clusters. The groups did not differ with respect to blood eosinophilia and uLTE4.
Conclusions: From clinical point of view AIA patients are not a homogenous population. Only part of them have severe uncontrolled asthma. Despite of the presence of upper airway symptoms, some subjects have mild, better controlled disease. Atopy but not blood eosinophilia and uLTE4 may discriminate patients assigned to different clusters.

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Safety of long-acting β-agonist (LABA) withdrawal in patients in two clinical asthma trials

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Background: LABAs are used with inhaled corticosteroids (ICS) for asthma treatment. Due to safety concerns, the US FDA has recommended stopping LABA therapy when asthma control is achieved. Little data exists on the effect of LABA withdrawal in patients on LABA/ICS therapy.
Objective: To evaluate safety of LABA withdrawal up to 6 months in clinical trial patients on LABA/ICS therapy.
Methods: Patients receiving LABA/ICS therapy at enrollment in Amgen AMG 317 and AMG 853 clinical trials underwent LABA withdrawal at screening. Patients who received either inefficacious treatment with study drug or placebo were analyzed. Clinical endpoints were change from screening in prebronchodilator forced expiratory volume in 1 second (FEV_1), percentage of predicted prebronchodilator FEV_1, Asthma Control Questionnaire (ACQ) score, daily rescue medication use, daily symptom eDiary, exacerbation incidence, and adverse events.
Results: A total of 366 patients were previously treated with ICS+LABA (underwent withdrawal), and 177 patients were treated with ICS only. Changes in prebronchodilator FEV_1, percentage of predicted prebronchodilator FEV_1, ACQ score, daily rescue medication use, symptoms, and exacerbation incidence were not significantly different between patients with previous LABA use and those without. Time to exacerbation did not differ between groups (log rank test P=0.4112; Cox regression analysis P=0.9755, adjusted for screening characteristics). Adverse events were similar between groups. Similar patterns were observed in placebo patients.
Conclusions: Asthma symptoms, lung function, and exacerbations were not significantly affected by LABA withdrawal in these clinical trial patients.

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Managing asthma in the outpatient clinic – Athletes with exercise-induced asthma

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Background: In athletes with exercise-induced asthma, confirmation of the disease with an objective test is required as part of the Therapeutic Use Exemption (TUE) application. An objective diagnosis often requires multiple testing with bronchial provocations and lung function measurements. Currently no guidelines exist on a diagnostic strategy in this group of subjects.
Aim: To evaluate the use of diagnostic tests in newly referred athletes with possible exercise-induced asthma in a specialized outpatient clinic.
Methods: Medical records on all patients with a suspected diagnosis of asthma referred to the outpatient clinic at Bispebjerg Hospital, Copenhagen, Denmark in 2010 where reviewed, and data on reversibility to beta2-agonist and airway hyperresponsiveness (AHR) to inhaled mannitol, methacholine and eucapnic hyperventilation was collected. Subjects with exercise-induced symptoms that reported to spend at least 10 hours a week on their sports were defined as athletes and were included in the analysis.
Results: Of 221 subjects referred with possible asthma to the outpatient clinic, 51 (23%) were athletes with possible exercise-induced asthma. A total of 39/51 (72%) was concluded to have asthma, based on a specialist's assessment. Among these subjects the final diagnosis was confirmed by an objective test in 31/39 (80%). The number of tests required to confirm the presence of disease was one in 9 (29%) subjects, two in 15 (48%) subjects, three in 6 (19%) and four in 1 (3%) subject.
Conclusion: In more than eight out of ten athletes with exercise induced asthma, more than one test for AHR or reversibility was necessary as part of the diagnostic process.

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A comparison of the frequency of cough with laughter in asthmatic and non asthmatic patients

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Cough is a frequent symptom in asthmatic patients.Cough may be induced by typical asthma triggers such as allergens, exertion or change in atmospheric temperature. This study investigates the symptom of cough with laughter as an asthmatic symptom.
Patients attending a general adult respiratory clinic were routinely asked if they experienced cough with laughter. Seventy four consecutive patients with a single respiratory diagnosis were included. The patients were divided into two groups-patients with asthma and those with another respiratory diagnosis.
The asthma group had forty three patients with a mean age of 57.7 years, twenty seven were female and sixteen male.
The non asthma group had thirty one patients with a mean age of 63.9 years, sixteen were male and fifteen female.In this second group their diagnoses were chronic obstructive pulmonary disease in eleven, pulmonary fibrosis in eight, sarcoidosis in five, bronchiectasis in two, hyperventilation in two and one each of carcinoma of bronchus, tuberculosis and sleep apnoea.
In the asthma group forty two of the forty three patients had the symptom of cough with laughter.
In the non asthma group one of the thirty one patients had the symptom of cough with laughter.
The symptom of cough with laughter is highly significantly associated with a diagnosis of asthma compared to other respiratory diagnoses ($p<0.0001$) and has a 97.6% sensitivity and a 96.8% specificity as an asthma symptom in this study.

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A retrospective analysis of methotrexate therapy as a steroid sparing agent within a UK severe asthma clinic

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Background: Treatment with Methotrexate (MTX) immunosupressive therapy in severe asthma is used in an effort to reduce corticosteroid dependancy and associated side effects. This study aimed to evaluate the effectiveness of MTX within this patient population as an efficient aid to reduce corticosteroids.
Methods: A retrospective data collection was performed within the severe asthma service. Patients whom were established on or had started MTX within the last twelve months were included. Variables explored included mean daily corticosteroid dose, exacerbation frequency, acute admission episodes and blood eosinophil count twelve months prior to and twelve months post commencement of Methotrexate therapy.
Results: n=30, 9 patients stopped MTX due to side effects. Within the ongoing sample group, corticosteroid dose was significanlty lower post MTX compared to previous treatment (mean dose 10.4mg daily post MTX compared with 16.8mg pre

MTX [p< 0.001]). The exacerbation frequency following MTX commencement was signifcantly lower (2.7) than in the year prior to treatment (6.1) (p<0.002). Reduced hospitalisation following MTX therapy was also demonstrated (0.4 episodes post treatment compared to 1.5 episodes pre treatment [p< 0.006]). There was a trend for a reduction in eosinophil level post treatment compared with prior to treatment, but this did not reach statistical significance.
Conclusion: MTX (where tolerated within this severe asthma population) was found to significantly reduce the demand for corticosteroids. A reduction in exacerbation rate and hospitalisation are also demonstrated when sufficiently monitored and supervised within a specialist setting.

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Small airways involvement is associated with bronchial hyperresponsiveness in asthma
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Background: Bronchial hyperresponsiveness (BHR) is a hallmark of asthma. Although, the role of small airways involvement in asthma has been well established, little is known about the association between BHR and small airways obstruction. We hypothesize that small airways disease contributes to BHR.
Methods: A total of 119 patients with a doctor's diagnosis of asthma were included. All subjects underwent spirometry and a BHR testing (PD_{20} histamine). Small airways involvement was defined as an $MEF_{50} \leq$ the lower limit of normal (LLN). We compared the severity of BHR between asthmatics with and without small airways involvement.
Results: We found 36 patients with and 83 patients without small airways involvement ($MEF_{50} \leq$LLN and $MEF_{50} >$LLN respectively). Patients with small airways involvement showed a more severe BHR than patients without (PD_{20} histamine 0.2 vs. 1.1 mg). In addition, FEV_1, FEV_1/FVC and reversibility were lower in patients with small airways involvement. Both a lower MEF_{50} and FEV_1 were independent predictors of more severe BHR in multivariate linear regression models.

Table 1. Differences between asthmatics with and without small airways involvement (MEF_{50} = LLN and MEF_{50} > LLN respectively

	>LLN		=LLN		p-value
	n=83		n=36		
Age (years)	45	35 - 52	47	34 - 57	0.42*
Gender (m,%)	29	34.9	14	38.9	0.68§
Smoking (n,%)					0.58§
non-smoker	43	52.4	22	61.1	
ex-smoker	29	35.4	12	33.3	
occasional smoker	3	3.7	0	0	
habitual smoker	7	8.4	2	5.6	
Packyears ‡	2.0	0.8 - 5.0	4.0	1.0 - 7.0	0.16#
Beclomethasone equivalent dose (µg/day)	600	400 - 800	800	400 - 800	0.14*
BMI (kg/m^2)	26	24 - 29	26	24 - 30	0.66#
PD_{20} methacholine (mg) £	1.1	0.1 - 9.0	0.2	0.1 - 9.0	<0.001*
FEV_1 (L)	3.4	2.9 - 4.1	2.8	2.3 - 3.1	<0.001*
FEV_1 %predicted	108.1	99.6 - 113.7	83.6	71.0 - 90.3	<0.001*
Reversibility (%)	4.0	2.2 - 6.8	8.7	5.9 - 11.1	<0.001#
FEV_1/FVC (%)	82.4	79.5 - 85.5	68.5	62.1 - 73.0	<0.001#
MEF_{50} (L/s)	3.9	2.9 - 4.6	2.1	1.6 - 2.5	<0.001#
MEF_{50} %predicted	86.5	68.8 - 100.2	46.9	39.2 - 51.5	<0.001#

Values are median with interquartile range, unless stated otherwise. £ = geometric mean with range, ‡ = without non-smokers.
Differences tested with: *Student's t-test, #Mann Whitney U test, § χ^2 test.

Conclusion: Small airways involvement is associated with more severe BHR in asthma. Since FEV_1 is used as a read-out in current BHR tests, we hypothesize that further research with small airways measurements during BHR tests will provide more insight into the relation between BHR and small airways involvement.

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Comparison of aerosol deposition pattern in healthy vs. asthmatic subjects
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Introduction: A clinical study designed to validate computational models of aerosol deposition in healthy and asthmatic subjects has been completed.
Objectives: The objective here is to compare the aerosol deposition patterns between healthy and moderate asthmatic subjects inhaling identical aerosols under identical ventilatory parameters.
Methods: 6 healthy and 6 asthmatic subjects performed two inhalations each, which differed by a single controlled parameter: particle, ventilation, or carrier gas. The same parameters were used for a healthy subject (e.g. H01) and the corresponding asthmatic patient (e.g. A01).
3D-SPECT was performed to measure aerosol deposition location, and the 3D Central to Peripheral ratios, C/P, were calculated for right and left lungs.
Results: Almost all (11/12) the asthmatics had higher central deposition than the corresponding healthy subjects. Data on deposition per airway generation show that the asthmatics have a peak around the 5th generation, which is less marked for the healthy subjects (e.g. Figure 1 for H03 and A03). The mean right and left C/P ratios are 1.56±0.45 and 1.86±0.61 for healthy subjects, vs. 2.89±1.45 and 4.04±2.22 for the asthmatics. These differences between healthy and asthmatic subjects were statistically significant (p<0.002).

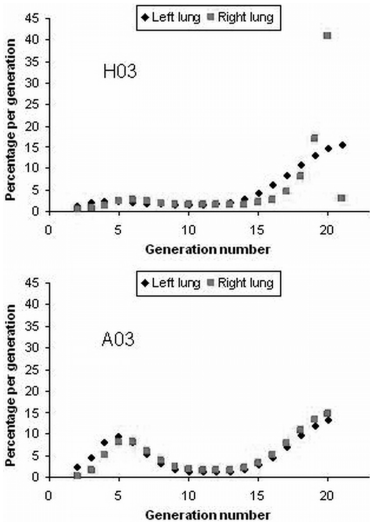

Figure 1. Generational deposition of aerosol estimated from 3D-SPECT images for subjects H03 and A03.

Conclusion: The obstruction of the upper airways in asthma disease may induce the larger deposition of aerosol in central airways of asthmatics compared to healthy subjects.

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Local coagulation activation following bronchial instillation of house dust mite allergen (HDM) and HDM/Lipopolysaccharide (LPS) in mild asthmatics
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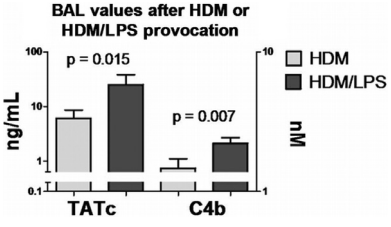
Rationale: Exposure to house dust, containing HDM and LPS, is associated with exacerbations of allergic asthma. In patients with asthma, the hemostatic balance in the lungs is often instable. We hypothesized that adding LPS to bronchial provocation with HDM increases activation of coagulation and complement pathways in asthmatics while on maintenance treatment with inhalation corticosteroids (ICS).
Aim: To assess the activation of coagulation in bronchoalveolar lavage fluid (BALF) induced by provocation with HDM +/– LPS.
Methods: We included 32 mild asthmatic patients with HDM allergy. After 2 weeks run-in with fluticasone 100µg bid, subjects underwent bronchoscopy for segmental instillation of saline in one lung followed by instillation of HDM +/– LPS in the contralateral lung. Six hours later, BAL was performed. Statistical comparisons were made by univariate analysis.
Results: Additional instillation of LPS to HDM resulted in a significant increase in levels of thrombin-antithrombin complexes (TATc) (p=0.015) and complement 4b (p=0.007) in BALF.



Conclusion: Additional instillation of LPS to a provocation with HDM in mild asthma increases pulmonary activation of coagulation and activation of the comple-

ment system. This suggests that coagulation contributes to environmentally-induced airway responses in asthma.