370. Biomarkers and exacerbations of asthma and COPD

P3348

Monitoring PGD_2 production in airway disease

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Introduction: Prostaglandin (PG) D_2 is a major mast cell mediator implicated in asthma and airway disease. Measurement of the urinary levels of 9α,11β-PGF_2 has been established to monitor PGD_2 production. Tetranor prostaglandin D (PGDM) is however the major urinary metabolite of PGD_2.
Aims and objectives: To evaluate the use of urinary levels of 9α,11β-PGF_2 vs. PGDM. In addition, the use of enzyme immune assay (EIA) was compared with LC-MS/MS.
Methods: Urinary samples from four studies were used; bronchoprovocation using allergen (n=9) and aspirin in aspirin-intolerant asthma (n=11), effect of celecoxib on baseline excretion (n=19), and excretion in patients with mastocytosis or anaphylaxis (M/A) during exacerbation (n=15). Urinary excretion of 9α,11β-PGF_2 and PGDM were measured by specific EIAs (Cayman Chemical) and LC-MS/MS, and data expressed as ng/mmol creatinine.
Results: The levels of PGDM (mean±SEM) before allergen challenge were 1330±348 and 1236±192 after ($p>0.05$), the corresponding values of 9α,11β-PGF_2 were 40±4 and 77±10 ($p=0.002$), respectively.
With aspirin challenge levels of PGDM were 516±82 before and 609±95 after ($p>0.05$), whereas the levels of 9α,11β-PGF_2 were 56±16 and 75±24 ($p=0.002$), respectively.
In M/A the levels of PGDM and 9α,11β-PGF_2 were 1977±886 ($p<0.05$ for PGDM vs baseline in healthy subjects) and 251±66 respectively, with values mildly correlated ($r=0.698$, $p=0.00382$).
Bland-Altman analysis showed good agreement between PGDM measurements with MS and EIA.
Conclusion: The earlier metabolite 9α,11β-PGF_2 may be more suitable to follow the dynamics of release during challenges whereas the higher levels of PGDM may be more appropriate for monitoring global differences in baseline production of PGD_2.

P3349

Antibiotics in exacerbations of asthma

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Introduction: Current guidelines explicitly do not recommend prescribing antibiotics for asthma exacerbations in order to avoid overprescription. We aimed to assess the prescription rate of antibiotics related to asthma exacerbations in primary care and which clinical patient characteristics are associated with antibiotic treatment.
Methods: We retrieved all electronic patient records concerning acute asthma in adults during 2008 recorded amongst 149,279 patient contacts by the centralized out-of-hours General Practice (GP) service in Amsterdam. Through uni- and multivariate analyses we analyzed the clinical parameters documented by GP's of patients who received antibiotics.
Results: Of 540 identified exacerbations, 108 (20%) were treated with antibiotics, of which in 16 cases (15%) a suspicion of pneumonia was documented. Univariate analysis showed that antibiotic prescription was positively associated with age ($p=0.006$) and clinical signs (Table 1). Multivariate analysis yielded a Nagelkerke R^2 of 0.331 for the variables age, ill appearence, sputum, rhonchi and fever. Antibiotic prescription was not associated with other treatments of exacerbation.

Table 1. Clinical associates of antibiotic treatment

History	p-value	Examination	p-value
Cough	0.002	Ill appearance	<0.001
Sputum	<0.001	Fever	0.023
Common cold	0.178	Rhonchi	<0.001
Symptoms of flue	0.019	ENT-problems	0.650
Symptoms >3 days	0.261	Focal abnormalities on auscultation	<0.001
Fever	<0.001	Wheezing	0.086

Conclusion: Antibiotics are prescribed more often for asthma exacerbations by GP's than proposed by international guidelines. Fever appears to be a major trigger for antibiotic therapy, in contrast to recommended care. This suggests that overprescription of antibiotics for asthma exacerbations is prevalent.

P3350

Monitoring free serum IgE in severe asthma patients treated with omalizumab

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It is stated that benefit of omalizumab treatment in severe IgE-dependent asthma requires serum free IgE concentrations below 50 ng/ml. It is unclear if monitoring free serum IgE is clinically meaningful once omalizumab treatment is initiated.
Free IgE and omalizumab serum concentrations were quantified in 22 patients with severe asthma (68% female, 47±11 yrs., mean (±SD) pre-bronchodilator FEV_1 62±13%, baseline mean (±SEM) free serum IgE 652±136 ng/ml) treated with omalizumab for 4 months using a Recovery-ELISA.
Omalizumab treatment reduced free serum IgE prior to the second omalizumab injection by 73%, after 16 weeks by 81% to 58±12 ng/ml ($p<0.001$ vs. baseline). 17 patients responded to anti-IgE therapy as judged by physician-rated global evaluation of treatment effectiveness. There was no relation between free serum IgE concentrations and treatment response. 41% of responders had free IgE levels above 50 ng/ml and 40% of non-responders below 50 ng/ml. There was no significant or clinically relevant difference regarding changes in lung function, exhaled NO, asthma control, and quality of life between patients with free IgE below or above 50 ng/ml.
Monitoring free IgE and omalizumab serum concentrations in patients treated with omalizumab does not predict clinical response or add to the decision to continue or

stop treatment. The relevance of free IgE measurements is limited to demonstrating an adequate reduction in non-responders. These results question the free IgE target range postulated to be necessary for a treatment response.

P3351

Serum immunoglobulin level is a useful marker for the risk of opportunistic infection in steroid dependent patients with chronic inflammatory airway diseases

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Aim: Patients with chronic inflammatory airway diseases such as severe asthma, pulmonary fibrosis often need to have long-term oral corticosteroids (O-CS). Patients who are administered O-CS, even a small amount, are susceptive for opportunistic infection (OI) such as pneumocystis pneumonia, fungal infection, herpes-zoster infection. The aim of this study is to clarify the usefulness of serum IgG as a marker for risk of OI in patients with long-term O-CS therapy.
Methods: Seventeen patients with respiratory diseases (severe asthma 11, pulmonary fibrosis 5, Churg-Strauss syndrome 1) taking regular-use of O-CS were enrolled to this study. We retrospectively reviewed the medical records and collect the data about incidence of OI and serum IgG levels of the patients.
Results: Seven out of 17 patients suffered from OI. The average IgG level in patients with OI (623±154 mg/dl, n=7) was significantly lower than patients without OI (879±188 mg/dl, p-value<0.01). The area under the ROC curves was 0.87. The most reliable cut-off level was 725 mg/dl with specificity 89%, sensitivity 75%, positive predictive value 86% and negative predictive value 80%.
Conclusion: Serum IgG need to be monitored when patients were given O-CS. It is crucial to keep serum IgG levels more than 725 mg/dl to prevent OI.

P3352

Effects of omalizumab on markers of eosinophilic inflammation in patients with severe allergic asthma

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Allergic asthma is a chronic inflammatory airway disease in which immunoglobulin E (IgE) and eosinophils play important pathogenetic roles.
We investigated the effect of the anti-IgE antibody omalizumab on markers of eosinophilic inflammation in patients with severe allergic asthma eligible for omalizumab treatment according to current guidelines. In 31 consecutive GINA step 4/5 patients (19 female, 48±11 yrs., 78±12 kg, 274±238 IU/ml total IgE, FEV1 at baseline 1.8±0.6 L, 61.8±19.5% pred.) omalizumab (median 450 mg/month) was administered s.c. as add-on therapy. Exhaled nitric oxide (NO), peripheral blood eosinophils and serum interleukin-5 were measured before and after 16 weeks of treatment. In all patients total daily doses of inhaled and oral corticosteroids remained stable during treatment.
23 (74%) patients responded to therapy (GETE). Baseline NO was 43±8 ppb (mean±SEM) for responders (R) and 23±6 ppb for non-responders (NR), blood eosinophils were 0.38±0.07/nl (R) and 0.25±0.06/nl (NR), and IL-5 was 7.5±1.13 (R) and 1.9±1.3 pg/ml (NR, R vs. NR p=0.030). After 16 weeks NO decreased by 3±6 ppb (R, p=0.804) and 12±18 ppb (NR, p=0.375), blood eosinophils were unchanged (R week0-week16: -0.14±0.16/nl, p=0.687; NR: 0.01±0.04/nl, p=1.000), and IL-5 decreased by 3.7±1.0 pg/ml (R, p=0.012) and 0.3±1.4 pg/ml (NR, p=0.625).
In conclusion, patients with a clinical response to omalizumab had higher pretreatment serum IL-5 levels and a pronounced decrease in serum IL-5 following omalizumab. Blood eosinophils were unchanged, and exhaled NO was low prior and on treatment with omalizumab, consequent to high-dose ICS treatment.

P3354

Reduction in incidence of exacerbations in patients with Alpha 1 antitrypsin deficiency (A1ATD) treated with concentrates of Alpha 1 antitrypsin (A1AT): REXA study

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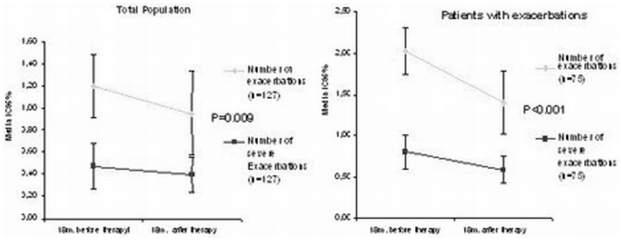
Introduction: Augmentation therapy with plasma derived Alpha 1 Antitrypsin represents the only specific treatment for patients with Alpha 1 Antitrypsin Deficiency. The aim of this study was to demonstrate that augmentation therapy can reduce the number of exacerbations in patients with A1ATD.
Material and methods: Retrospective multicentric study. We included 127 patients who received augmentation therapy for 18 months and with clinical follow-up for 18 months before treatment. We compared the incidence of exacerbations into the two periods.
Results: 127 patients, 63% male, age:52y, former smokers:79,4%, never smokers:17,4%, PiZZ:93.6%. Basal FEV1:1.24L (±0.5). Patients were treated with Prolastin® (53.5%) or Trypsone® (46.5%), 78% every 21 days. 52 patients did not present exacerbations in pretreatment period.
Augmentation therapy was associated with reduction of 2.4 exacerbations for every ten treated patients in total population and 6 exacerbations for every 10 treated patients in those with previous exacerbations.(Figure 1) Untreated patients have between 1.4 and 4 times more risk of exacerbation than treated patients.
We didn't observe differences between both available A1AT products.



Conclusions: Augmentation therapy in the A1ATD reduces the total number of exacerbations with low frecuency of adverse events.
Study realized with Grifols support.

P3355

Efficacy of roflumilast in the frequent exacerbation COPD phenotype

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Background: COPD exacerbations (EXs) are associated with increased morbidity, mortality and disease progression. The ECLIPSE study showed the best predictor of future EXs is a history of EXs, identifying a frequent exacerbator phenotype maintained over time. Roflumilast (ROF) reduces EX rate in frequent exacerbators, but its relative effect in this phenotype is not known.
Methods: In a post-hoc pooled analysis of two 1-yr studies of ROF 500μg in pts with severe COPD, chronic bronchitis and a history of EXs, pts were classified as frequent (≥2 events) or infrequent (1 event) exacerbators based on moderate/severe EX history in the previous yr. EX frequency status was analysed in ROF- and placebo (PBO)-treated pts at baseline and at yr 1.
Results: Among ROF-treated frequent exacerbators (n=413), 32.0% still had frequent EXs at yr 1 vs 40.8% of PBO-treated pts (n=417; RR=0.799, p=0.0148). Among infrequent exacerbators, 17.5% of ROF-treated pts (n=1124) had ≥2 EXs at yr 1 vs 22.9% of PBO-treated pts (n=1137; RR=0.768, p=0.0018). This reduction was similar when considering concomitant LABA, previous ICS treatment or severe EXs leading to hospitalisation/death. When analysed by COPD severity, 26.4% of ROF-treated frequent exacerbators with severe COPD (FEV_1 30–50% predicted, n=246) still had frequent EXs at yr 1 vs 38.9% of PBO-treated pts (n=239; RR=0.683, p=0.0042); the percentage of frequent exacerbators was similar between treatments in pts with very severe COPD (FEV_1 <30%).
Conclusions: This analysis shows that ROF shifts pts from the frequent to the more stable infrequent exacerbator state. This effect was not seen in frequent exacerbators with very severe COPD, highlighting the need for early treatment initiation.

P3356

Modelling and simulation in successful drug development programmes: Characterisation of exacerbation reduction with roflumilast to corroborate the importance of defining patient subsets in COPD

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Background/Rationale: Roflumilast (ROF), an oral, selective PDE4 inhibitor, reduces the rate of exacerbations and improves lung function in severe COPD. During clinical development, modelling and simulation techniques were used to identify and confirm a paradigm to explore patient, disease and treatment covariates. This approach identified patient populations that will benefit most from ROF, and was used to help design confirmatory clinical trials.
Methods: Data from two 1-year, randomised, double-blind, placebo-controlled, parallel-group trials [Rennard S, *et al*. *Respir Res* 2011;12(1):18] in 2686 patients were used to build exacerbation and lung function models to identify patient characteristics that significantly impacted the clinical endpoints.
Results: Patients with chronic bronchitis, higher cough/sputum scores, concomitant ICS use and low predicted FEV_1 at baseline were identified as having a higher rate of exacerbations and treatment effect. Patient characteristics as defined by the models were used, in addition to a history of exacerbations, to simulate the design of two other 1-year clinical trials [Calverley PMA, *et al*. *Lancet* 2009;374:685–94],

with the inclusion criteria described in the trial protocols. The models predicted that the two trials would show a 17% reduction in exacerbation rate and a 47mL gain in FEV_1 with ROF; observed results were 17% reduction and a 48mL gain.
Conclusions: This modelling and simulation approach showed the importance of defining COPD subsets for drug development, and helped support phase III studies confirming exacerbation reduction with ROF.

P3357
Clinical implications of serum procalcitonin in acute exacerbations of chronic obstructive pulmonary disease
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Background: A reliable test for differentiation between bacterial and nonbacterial AECOPD would be extremely helpful in management of AECOPD.
Objective: To explore the diagnostic and prognostic role of serum procalcitonin (PCT) in AECOPD.
Methods: A total of 100 patients with AECOPD and 20 of healthy individuals were studied. On presentation, serum PCT concentration was measured, and quantitative sputum culture was performed for AECOPD. The patients were reevaluated when they had reached their stable clinical state.Pathogenic bacterial microorganism (PBM) was regarded as significant if they were $\geq 10^5$ CFU/ml. The patients were classified into two subgroups: group A; patients with bacterial AECOPD (n = 40), and group B; patients with nonbacterial AECOPD (n = 60).
Results: On presentation, The levels of PCT for patients of group A [1.59±0.52 μg/L] were significantly > group B [0.11±0.02 μg/L] and control group [0.75±0.03 μg/L]. When they had reached their stable state, the levels of PCT for patients of group A decreased to [0.12±0.04 μg/L], which was significantly < that in exacerbation [[1.59±0.52 μg/L]; but in patients of group B the levels of PCT did not change [0.1±0.01 μg/L]. In the stable state, there were no differences in the PCT measurement between the two subgroups as well as between patients and control. Furthermore; a significant correlation was recorded between PCT levels in group A at time of presentation and temperature (r=0.988, p<0.05), leucocytic count (r=0.897,p<0.05), and FEV1% of predicted (r=0.889, p<0.05).
Conclusion: In patients presented with AECOPD, PCT is an excellent diagnostic and prognostic marker of bacterial infection.

P3358
Efficacy and safety of bacterial lysates in patients with chronic obstructive pulmonary disease and exacerbation
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Objective: This study was a double-blind, placebo-controlled, randomized clinical trial to evaluate the preventive effect of bacterial lysates (Broncho-Vaxom, OM-85 BV) on acute exacerbation in patients with COPD or chronic bronchitis in China.
Methods: 428 patients recruited from 13 centers were randomly allocated into BV or placebo. 384 patients completed the study (192 in OM-85 BV group and 192 in the placebo group). Patients received medications for 10 days per month during 3 months with a 10-week follow-up.
Results: This study revealed that the proportion of patients with recurrent exacerbation in OM-85 BV group was significantly lower than that in placebo group within 12-week treatment period (23.4% vs. 33.3%, p<0.05). Among all subjects having exacerbation (≥1 time), the percentage of patients with recurrent exacerbations (≥2 times) was significantly lower in OM-85 BV group than that in placebo group during the 12-week treatment period (38.7% vs. 73.1%, p<0.01). The percentage of concomitant antibiotics was significantly lower in OM-85 BV group than that in placebo group (37.0% vs. 63.0%, p<0.05). In terms of safety, there was no significant difference between the two groups in the incidence of adverse events (27.9% in BV group vs. 27.7% in placebo group, p>0.05).
Conclusions: OM-85 BV significantly reduced the rate of recurrent exacerbations in patients with chronic bronchitis or COPD in therapy period. It also significantly reduced the frequency of exacerbations in individual patients in active therapy period and decreased the usage of antibiotics, with a good safety profile.

P3359
β-blockers and risk of COPD exacerbation requiring hospitalisation in patients with COPD
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Background: In the past, β-blockers were contra-indicated in COPD. Recent evidence, including a cohort study by Rutten et al. (Arch Intern Med 2010), suggests that β-blockers produce good outcomes in COPD. This degree of protection might be biased.
Objectives: To study the effect of β-blockers on the risk of severe COPD exacerbations.
Methods: We conducted several analyses to study the effect of β-blockers on COPD exacerbations by: 1) mimicking the cohort design of Rutten 2) avoiding immortal time and exposure bias through a nested case-control study in a COPD cohort and 3) reducing confounding by indication by restricting the case-control analyses to users of β-blockers during follow-up. Data from the Dutch IPCI GP database (2000 to 2007) were used. Cases were all COPD patients with a first COPD exacerbation requiring hospitalization. To each case, controls were matched on age, sex and indexdate. Cox proportional hazard and conditional logistic regression analyses were used.
Results: Within the cohort of 6788 COPD patients, 619 patients had a COPD exacerbation requiring hospitalization. Current use of β-blockers significantly reduced the risk of severe COPD exacerbation in the cohort analysis (HR_{adj} 0.73, 95%CI 0.60-0.90). In the case-control analysis, use of β-blockers reduced the risk of exacerbations by 40% (OR_{adj} 0.60, 95% CI 0.44-0.82). When controlling for confounding by indication, the protective effect was clearly attenuated (OR_{adj} 0.87, 95% CI 0.52-1.45). In patients with co-existing heart failure, a significant protective effect was observed (OR_{adj} 0.15, 95% CI 0.03-0.80).
Conclusions: The choice of studydesign is crucial when assessing the effect of β-blockers on COPD outcomes.

P3360
Skin sensitivity to corticosteroids is associated with COPD susceptibility
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Introduction: Inhaled corticosteroids (ICS) improve symptoms, exacerbation rates and quality of life in COPD. However, not all COPD patients benefit from ICS treatment. Corticosteroid sensitivity can be tested with the skin blanching test, where topical corticosteroids cause local vasoconstriction. We investigated in young and old individuals if skin response to corticosteroids is associated with susceptibility to develop COPD.
Methods: Young (18 – 40 years) healthy subjects who were non-susceptible or susceptible to develop COPD (n=9 and 14 resp.), and older (40-75 years) subjects without and with COPD (n=15 and 47 resp.) were included. Susceptibility in young subjects was based on a high prevalence of COPD in smoking family members of these subjects. Budesonide dissolved in 95% ethanol was applied to the skin in eight concentrations (0-1000 μg/ml). Blanching was scored with a 7-point scale: 0-3 (0 = no blanching and 3 = intense blanching).
Results: Young non-susceptible subjects showed higher blanching scores compared to all groups (figure 1). In COPD patients, a lower blanching score correlated with lower FEV_1/FVC ratio (B=.017, p<0.01) and higher GOLD stage (figure 2).

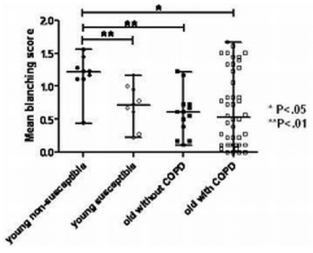

Figure 1

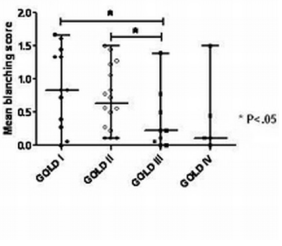

Figure 2

Conclusion: These preliminary data suggest that relative corticosteroid insensitivity contributes to COPD development and progression.

P3361
Inhaled corticosteroids in patients with mild to moderate COPD with and without airway hyperresponsiveness to mannitol: A randomized placebo controlled trial
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Background: Based on former data airway hyperresponsiveness (AHR) to mannitol challenge could allow to identify a subgroup of subjects who will respond to treatment with ICS.
Methods: We investigated 68 subjects with mild to moderately severe COPD. All subjects were treated with tiotropium initiated 4 weeks prior to randomisation. Subjects were randomized to either budesonide (daily dose of 1600 mcg) or placebo for 3 months. At all visits lung function, quality of Life (SGRQ), AHR to mannitol, exhaled nitric oxide (NO) and MRC were assessed. AHR was defined as a 15% fall in FEV1 at < or = 635 mg (PD15). RDR was calculated as the percent fall in FEV1 at the last dose divided by totally dose of mannitol administered.
Results: There was no significant change from baseline of FEV1% pred. (2.46 95% CI [-1; 5.9] p= 0.162), quality of life (SGRQ) (-3.21 95% CI [-8.5; 2.1] p= 0.227), nitric oxide (-5.48 95% CI [-11.2; 0.2] p=0.058) and MRC (0.4 95% CI

[0.1; 1.7] p= 0.22) after budesonid treatment. AHR to mannitol was present in 56% of subjects. Steroid treated subjects with AHR showed a significant improvement in quality of life (SGRQ) (8.64 95% CI [1.17; 16.11] p= 0.024), which was not observed in absence of AHR. Concomitantly AHR responded to steroid treatment showing a significant decline in log10 RDR as compared to placebo (0.27 95% CI [-0.04; 0.58] p= 0.09). Our findings were independent from smoking status.
Conclusion: AHR to mannitol improves and seems to result in a better quality of life after ICS treatment in mild to moderate COPD.

P3362
Double blind, placebo controlled crossover study in COPD patients to assess the acute effect of budesonide/formoterol using HRCT and lung function tests
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The aim of this study was to assess the acute effect of inhalation of budesonide/formoterol combination and placebo using lung function tests and imaging in COPD patients and to compare both. A total of 10 patients was assessed in a double blind cross over study. Airway volumes were analysed using segmentation of the HRCT images. Results showed that distal airway volume significantly increased in patients four hours after receiving budesonide/formoterol combination. No other lung function parameters showed a significant change. When considering the effect of placebo a significant decline in distal airway volume and peak expiratory flow was observed. A downward trend was depicted by forced expiratory volume in one second. The bodyplethysmography showed a significant increase in specific airway resistance. In addition it was shown that imaging was the only parameter that was able to predict correctly the visit at which the combination product was administered for all patients.

	budesonide/formoterol			placebo		
	pre	post	p	pre	post	p
iVaw (cm3)	9,6±4,67	10,14±4,81	0,011	9,6±4,67	9,16±4,37	0,025
FEV1 (L)	0,95±0,33	0,98±0,33	0,34	0,96±0,31	0,93±0,33	0,07
FEV1 (%p)	34,8±7,69	35,9±7,89	0,34	34,9±6,71	33,7±7,24	0,09
FEV1/VC	34,32±6,99	34,72±6,67	0,51	33,68±7,36	33,89±6,8	0,74
PEF (L/s)	3±1,26	3,12±1,22	0,71	3,07±0,95	2,77±1,03	0,025
Raw (kPas/L)	1±0,5	0,92±0,45	0,20	0,94±0,46	1,01±0,43	0,07
sRaw (kPas)	5±2,87	4,65±2,29	0,14	4,89±2,72	5,33±2,48	0,026

This study showed that imaging is a sensitive, complementary tool to describe changes in airway structure and function. Future uses could include the assessment of anti-inflammatory compounds as standard lung function test might lack the sensitivity to describe the more subtle changes.

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Antibiotic prescription in asthma exacerbations in the admitting and emergency (A&E) department
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Aim: To assess the appropriateness of antibiotic prescription in patients diagnosed with asthma exacerbations in the A&E department.
Method: All adult patients presenting at the A&E department over 10 consecutive months (January to October 2010) were included in a prospective study. Comparative statistical analysis was carried out using the t-test.
Results: A total of 244 patients were included. Forty-eight patients (19.7%) had been prescribed antibiotics by their general practitioner prior to presentation to A&E. A chest X-ray was done in 201 patients (82.4%). A radiological infiltrate suggestive of pneumonia was reported in 12 patients (6%). A white cell count (WCC) was available in 165 patients (67.6%). Antibiotics were prescribed in 65.9% of admitted patients (n=126). Of these patients 9.5% had a radiological pneumonia, 30.2% had a raised WCC (mean 10.42×10^9/L), 23% were febrile at presentation and 73% had symptoms of a respiratory tract infection including a cough and/or sputum. Antibiotics were administered to 28 patients (11.5%) at the A&E Department, 3 (10.7%) of whom had a radiological pneumonia. Antibiotics were prescribed to 39.7% of discharged patients (n=118). Of these, 11% had a fever at presentation, 46.6% had symptoms of a respiratory tract infection, and 12.7% had a raised WCC (mean 9.01×10^9/L). None had evidence of pneumonia. There was no significant correlation in the WCC and antibiotic prescription in admitted and discharged patients (p=0.013).
Conclusion: There is a tendency towards unnecessary antibiotic prescription in asthma exacerbations as few patients have evidence of radiological pneumonia or concomitant bacterial infection of the respiratory tract.

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Roflumilast in Asian patients with COPD: A randomised placebo-controlled trial
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Background/Rationale: Roflumilast (ROF) is the first oral, selective phosphodiesterase 4 inhibitor licensed for the treatment of severe COPD associated with chronic bronchitis and a history of frequent exacerbations. This study (NCT00242320) examined the efficacy, safety and tolerability of ROF in Asian patients with COPD.
Methods: Patients with moderate to severe COPD (post-bronchodilator FEV_1 30–80% predicted) were recruited from 32 outpatient centres in Hong Kong, Malaysia, the Philippines, South Korea and Taiwan. Patients were randomly assigned (1:1) to oral ROF, 500μg once daily, or placebo, in a 12-week treatment period, following a single-blind baseline period in which all patients received placebo for 4 weeks. The primary endpoint was mean change in post-bronchodilator FEV_1 from baseline to each post-randomisation visit. Safety endpoints included clinical laboratory tests, vital signs, physical examination (including electrocardiogram) and monitoring of adverse events (AEs).
Results: Of 551 patients recruited, 410 were randomised and treated (ROF, n=203; placebo, n=207). ROF improved post-bronchodilator FEV_1 by 79mL vs placebo ($p<0.0001$) at final scheduled visit. Pre-bronchodilator FEV_1, pre-and post-bronchodilator FEV_6, forced vital capacity and peak expiratory flow also significantly favoured ROF over placebo. In both groups, >90% patients completed treatment without exacerbations. AEs were more common with ROF than placebo, but were comparable with those in previous studies.
Conclusions: ROF, 500μg once daily, improves lung function in Asian patients with COPD. The safety and tolerability of ROF was similar to that observed in a Caucasian population.